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Blood pressure targets for the treatment of people with hypertension and cardiovascular disease (Review)

Saiz LC, Gorricho J, Garjón J, Celaya MC, Erviti J, Leache L

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[Intervention Review]

Blood pressure targets for the treatment of people with hypertension and cardiovascular disease

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ABSTRACT

Background

This is the second update of the review first published in 2017.

Hypertension is a prominent preventable cause of premature morbidity and mortality. People with hypertension and established cardiovascular disease are at particularly high risk, so reducing blood pressure to below standard targets may be beneficial. This strategy could reduce cardiovascular mortality and morbidity but could also increase adverse events. The optimal blood pressure target in people with hypertension and established cardiovascular disease remains unknown.

Objectives

To determine if lower blood pressure targets (135/85 mmHg or less) are associated with reduction in mortality and morbidity as compared with standard blood pressure targets (140 to 160/90 to 100 mmHg or less) in the treatment of people with hypertension and a history of cardiovascular disease (myocardial infarction, angina, stroke, peripheral vascular occlusive disease).

Search methods

For this updated review, the Cochrane Hypertension Information Specialist searched the following databases for randomized controlled trials (RCTs) up to November 2019: Cochrane Hypertension Specialised Register, CENTRAL, MEDLINE (from 1946), Embase (from 1974), and Latin American Caribbean Health Sciences Literature (LILACS) (from 1982), along with the World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov. We also contacted authors of relevant papers regarding further published and unpublished work. We applied no language restrictions.

Selection criteria

We included RCTs with more than 50 participants per group that provided at least six months' follow-up. Trial reports had to present data for at least one primary outcome (total mortality, serious adverse events, total cardiovascular events, cardiovascular mortality). Eligible interventions involved lower targets for systolic/diastolic blood pressure (135/85 mmHg or less) compared with standard targets for blood pressure (140 to 160/90 to 100 mmHg or less).

Participants were adults with documented hypertension and adults receiving treatment for hypertension with a cardiovascular history for myocardial infarction, stroke, chronic peripheral vascular occlusive disease, or angina pectoris.

Data collection and analysis

Two review authors independently assessed search results and extracted data using standard methodological procedures expected by Cochrane. We used GRADE to assess the quality of the evidence.

Main results

We included six RCTs that involved 9484 participants. Mean follow-up was 3.7 years (range 1.0 to 4.7 years). All RCTs provided individual participant data. None of the included studies was blinded to participants or clinicians because of the need to titrate antihypertensives to reach a specific blood pressure goal. However, an independent committee blinded to group allocation assessed clinical events in all trials. Hence, we assessed all trials at high risk of performance bias and low risk of detection bias. Other issues such as early termination of studies and subgroups of participants not predefined were also considered to downgrade the quality evidence.

We found there is probably little to no difference in total mortality (risk ratio (RR) 1.06, 95% confidence interval (CI) 0.91 to 1.23; 6 studies, 9484 participants; moderate-quality evidence) or cardiovascular mortality (RR 1.03, 95% CI 0.82 to 1.29; 6 studies, 9484 participants; moderate-quality evidence). Similarly, we found there may be little to no differences in serious adverse events (RR 1.01, 95% CI 0.94 to 1.08; 6 studies, 9484 participants; low-quality evidence) or total cardiovascular events (including myocardial infarction, stroke, sudden death, hospitalization, or death from congestive heart failure) (RR 0.89, 95% CI 0.80 to 1.00; 6 studies, 9484 participants; low-quality evidence). The evidence was very uncertain about withdrawals due to adverse effects. However, studies suggest more participants may withdraw due to adverse effects in the lower target group (RR 8.16, 95% CI 2.06 to 32.28; 2 studies, 690 participants; very low-quality evidence). Systolic and diastolic blood pressure readings were lower in the lower target group (systolic: mean difference (MD) -8.90 mmHg, 95% CI -13.24 to -4.56; 6 studies, 8546 participants; diastolic: MD -4.50 mmHg, 95% CI -6.35 to -2.65; 6 studies, 8546 participants). More drugs were needed in the lower target group (MD 0.56, 95% CI 0.16 to 0.96; 5 studies, 7910 participants), but blood pressure targets were achieved more frequently in the standard target group (RR 1.21, 95% CI 1.17 to 1.24; 6 studies, 8588 participants).

Authors' conclusions

We found there is probably little to no difference in total mortality and cardiovascular mortality between people with hypertension and cardiovascular disease treated to a lower compared to a standard blood pressure target. There may also be little to no difference in serious adverse events or total cardiovascular events. This suggests that no net health benefit is derived from a lower systolic blood pressure target. We found very limited evidence on withdrawals due to adverse effects, which led to high uncertainty. At present, evidence is insufficient to justify lower blood pressure targets (135/85 mmHg or less) in people with hypertension and established cardiovascular disease. Several trials are still ongoing, which may provide an important input to this topic in the near future.

PLAIN LANGUAGE SUMMARY

Blood pressure targets in people with cardiovascular disease

Review question

We assessed whether lower blood pressure goals are better than standard blood pressure goals for people with high blood pressure who also have heart or vascular problems.

Background

Many people with heart or vascular (blood vessels and circulatory system) problems also have high blood pressure. Some clinical guidelines recommend a lower blood pressure goal (135/85 mmHg or lower) for people with previous heart or vascular problems than for those without (140 to 160 mmHg or less systolic and 90 to 100 mmHg diastolic or less are standard blood pressure goals). It is unclear whether lower goals lead to overall health benefits.

Search date

We searched for evidence up to November 2019.

Study characteristics

For this updated review, we included six trials with 9484 participants who were followed up from one year to 4.7 years. We analyzed data to detect differences between lower and standard blood pressure goals in terms of numbers of deaths and numbers of serious side effects (leading to hospital admission).

Key results

We found little to no differences in total numbers of deaths, or heart or vascular deaths between lower and standard blood pressure goal approaches. Similar findings of little to no differences were also found for the total number of heart problems, or vascular problems and total serious harms, but the evidence was less certain. Based on very uncertain and limited information, we found more dropouts resulting from drug-related harms in the lower blood pressure target group and no overall health benefit among people in the lower target group.

Quality of the evidence

The evidence identified in this review does not support lower blood pressure goals over standard goals in people with elevated blood pressure and heart or vascular problems. More new trials are needed to examine this question. Overall, the quality of evidence was very low to moderate according to the GRADE assessment (a method for appraising clinical studies and making recommendations for reviews and guidelines).

SUMMARY OF FINDINGS

Summary of findings 1. Lower blood pressure targets compared with standard blood pressure targets for mortality and morbidity

Lower blood pressure targets compared with standard blood pressure targets for mortality and morbidity

Patient or population: cardiovascular disease with high blood pressure

Setting: outpatients (mean duration of trials 4 years)

Intervention: lower blood pressure targets ($\leq 135/85$ mmHg)

Comparison: standard blood pressure targets (≤ 140 to $160/90$ to 100 mmHg)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with standard blood pressure target	Risk with lower blood pressure target				
Total mortality	Study population		RR 1.06 (0.91 to 1.23)	9484 (6 RCTs)	⊕⊕⊕⊖ Moderate ^a	—
Follow-up: mean 1–4.7 years	68 per 1000	72 per 1000 (62 to 84)				
Total serious adverse events	Study population		RR 1.01 (0.94 to 1.08)	9484 (6 RCTs)	⊕⊕⊖⊖ Low ^{a,b}	—
Follow-up: mean 1 to 4.7 years	252 per 1000	255 per 1000 (237 to 272)				
Total cardiovascular events	Study population		RR 0.89 (0.80 to 1.00)	9484 (6 RCTs)	⊕⊕⊖⊖ Low ^{a,b}	—
Follow-up: mean 1–4.7 years	127 per 1000	113 per 1000 (102 to 127)				
Cardiovascular mortality	Study population		RR 1.03 (0.82 to 1.29)	9484 (6 RCTs)	⊕⊕⊕⊖ Moderate ^a	—
Follow-up: mean 1–4.7 years	31 per 1000	32 per 1000 (25 to 40)				
Participant withdrawals due to adverse effects	Study population		RR 8.16 (2.06 to 32.28)	690 (2 RCT)	⊕⊖⊖⊖ Very low ^{b,c}	—
Follow-up: mean 1–3.8 years	7 per 1000	60 per 1000 (15 to 239)				

***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; **RCT:** randomized controlled trial; **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 the effect.

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

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

Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^aDowngraded one level owing to serious imprecision (95% CI is wider than the minimal important difference).

^bDowngraded one level owing to high risk of bias.

^cDowngraded two levels owing to very serious imprecision (only two of the smaller studies reported this outcome).

BACKGROUND

Description of the condition

Hypertension (high blood pressure) is one of the most preventable causes of premature morbidity and mortality worldwide. Hypertension was the leading risk factor for the global burden of disease in 2017 ([GBD 2017 Risk factors](#)). Hypertension is a major risk factor for ischaemic and haemorrhagic stroke, myocardial infarction, heart failure, chronic kidney disease, peripheral vascular disease (PVD), cognitive decline, and premature death ([NICE 2019](#)).

Historically more emphasis was placed on diastolic than on systolic blood pressure (SBP) as a predictor of cardiovascular morbidity and fatal events. However, a large number of observational studies have revealed that both SBP and diastolic blood pressures (DBP) show a graded independent relationship with mortality and morbidity ([ESH-ESC 2007](#)). Untreated hypertension may be associated with a progressive rise in blood pressure, possibly culminating in a treatment-resistant state caused by associated vascular and kidney damage ([NICE 2019](#)).

Epidemiological studies suggest that the risk associated with high blood pressure is a continuous relationship, and for blood pressures above 115/70 mmHg, the risk of cardiovascular events doubles for every 20/10 mmHg (systolic/diastolic) rise in blood pressure. This suggests that for every 20 mmHg lower SBP or 10 mmHg lower DBP, the risk of a cardiovascular event is reduced by about 50% ([Lewington 2002](#)).

Blood pressure is normally distributed within a population, and there is no natural cut-off point above which hypertension definitively exists and below which it does not. In any individual person, systolic or diastolic (or both) blood pressure may be elevated. Diastolic pressure is more commonly elevated among people younger than 50 years. With ageing, systolic hypertension becomes a more significant problem as a result of progressive stiffening and loss of compliance of larger arteries ([NICE 2019](#)).

Cardiovascular disease remains the leading cause of death worldwide ([Townsend 2016](#)). Cardiovascular disease accounts for more deaths than all communicable, neonatal, maternal, and nutritional disorders combined, and almost double the number of deaths caused by cancers. Globally, cardiovascular disease accounts for nearly 17 million deaths annually – more than one-third of the total number of deaths. Despite this, between 2007 and 2017, age-standardized death rates fell by 10% for cardiovascular and circulatory diseases ([GBD 2017 Mortality](#)). Ischaemic heart disease (IHD) was the leading global cause of years of life lost (YLLs), having increased by 17.3% from 2007 to 2017. Similarly, stroke ranked third and increased its mean percentage change number of YLLs by 12.1% from 2007 to 2017 ([GBD 2017 Risk factors](#)).

Thus, cardiovascular secondary prevention is considered a key issue. People who have had atherosclerotic stroke should be included among those deemed at high risk of further atherosclerotic coronary events (20% over 10 years). A significant percentage of those who have a first myocardial infarction are expected to experience recurrent myocardial infarction, heart failure, stroke, or fatal coronary heart disease (CHD). In fact, within five years of a first myocardial infarction, around 20% to 30% of the population aged over 65 years will experience recurrent myocardial infarction or fatal CHD ([Mozaffarian 2015](#)).

Description of the intervention

Clinicians use target blood pressures in clinical practice to make treatment decisions related to the intensity of antihypertensive therapy for each patient.

The standard blood pressure target has generally been an arbitrary threshold blood pressure above which treatment is recommended. Over time, this threshold has become lower. The standard SBP target declined from a target of 160 mmHg or less to 140 mmHg or less, and the DBP target decreased from 100 mmHg or less to 90 mmHg or less in people aged up to 80 years ([ESH-ESC 2007](#)). Even lower blood pressure targets have been proposed for people with a history of cardiovascular events ([AHA 2007](#); [ESH-ESC 2007](#); [JNC-7 2003](#)).

Years later, a review of available evidence led to a reappraisal of some recommendations made by international guidelines, particularly among older people and people with diabetes or previous cardiovascular disease ([ESH-ESC 2013](#); [JNC-8 2014](#); [Joint ESC 2016](#)). However, the last updates of some US and European guidelines have turned again to recommend more intensive goals ([ACC-AHA 2017](#); [ESH-ESC 2018](#)).

How the intervention might work

Some evidence suggests that for people at high risk, thresholds for antihypertensive treatment should be lower than for those at lower risk. It has also been suggested that to maximize the cost-effectiveness of hypertension management, the intensity of the therapeutic approach should be graded as a function of total cardiovascular risk ([ESH-ESC 2007](#)). However, we noted a trend towards homogenizing blood pressure goals ([ACC-AHA 2017](#); [NICE 2019](#)).

People with a history of cardiovascular disease are considered to represent a high-risk population. The effect of lowering blood pressure values in these people could include greater absolute reduction in morbidity and mortality but could also be associated with an absolute increase in adverse events.

Reducing blood pressure to below standard targets through drug therapy has been recommended in guidelines as a strategy for people with a history of cardiovascular disease. Nevertheless, lower may not always be better. Researchers have described a J-curve for blood pressure in coronary artery disease ([Bangalore 2010](#); [Messerli 2006](#)). [Bangalore 2010](#) reported that for people with coronary artery disease, low blood pressure (less than 110 to 120/60 to 70 mmHg) was associated with increased risk of future cardiovascular events.

One cohort study explored the association between achieved blood pressure and cardiovascular events in people with hypertension and a history of coronary disease. These investigators concluded that when a goal less than 120/70 mmHg was reached, an association with more cardiovascular adverse events was detected, supporting the J-curve hypothesis ([Vidal-Petiot 2016](#)).

Uncertainty remains regarding many aspects of this controversial topic, leading to differing opinions ([Mancia 2014](#); [Verdecchia 2014](#)).

Why it is important to do this review

The arterial pressure threshold above which benefits of treatment outweigh harms in people with hypertension and cardiovascular disease is unclear.

Some, but not all, clinical guidelines have recommended blood pressure targets lower than standard targets. Following are recommendations for blood pressure targets in people with hypertension and cardiovascular disease as stated in recently published guidelines.

The Joint National Committee-7 Report recommended blood pressure targets less than 140/90 mmHg for people with uncomplicated hypertension, and blood pressure targets less than 130/80 mmHg for people with hypertension and either diabetes or kidney disease ([JNC-7 2003](#)). However, an updated statement in 2014 reflects some changes in the goals policy ([JNC-8 2014](#)). [JNC-8 2014](#) suggests treating to goals of SBP less than 150 mmHg and DBP less than 90 mmHg in the general population aged 60 years and older. In the general population aged up to 60 years, the guideline maintains the recommendation of treating to goals of SBP less than 140 mmHg and DBP less than 90 mmHg. In people with diabetes or kidney disease, new targets are similar to those for the general population. [JNC-8 2014](#) provides no direct recommendation for people with previous cardiovascular disease, although this is acknowledged as a relevant question to be assessed and answered. The latest American guideline recommends a blood pressure target less than 130/80 mmHg for adults with confirmed hypertension and known cardiovascular disease ([ACC-AHA 2017](#)).

The 2007 European Society of Hypertension and European Society of Cardiovascular Guidelines for Management of Arterial Hypertension recommended that blood pressure should be reduced to less than 140/90 mmHg and to lower values, if tolerated, in all people with hypertension ([ESH-ESC 2007](#)). The blood pressure goal was less than 130/80 mmHg for people with diabetes and others at high risk, such as people with associated clinical conditions (stroke, myocardial infarction, kidney dysfunction, proteinuria). Reappraisal of European guidelines on hypertension management remarks that the recommendation to lower blood pressure to 130/80 mmHg or less for people with diabetes or a history of cardiovascular disease is not supported by incontrovertible trial evidence ([ESH 2009](#)). The most recent update proposed an SBP goal of 120 mmHg to 129 mmHg for people younger than 65 years at low to moderate cardiovascular risk or with diabetes, and a goal of 130 mmHg to 139 mmHg, if tolerated, for older people at any level of cardiovascular risk and in people with and without established CVD. A DBP target of less than 80 mmHg is always recommended ([ESH-ESC 2018](#)).

The 2016 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice indicate that evidence was sufficient to recommend a blood pressure target less than 140/90 mmHg for all people who are hypertensive (except older people, for whom the benefit has not been tested in randomized trials) ([Joint ESC 2016](#)). According to [Joint ESC 2016](#), the recommendation to aim for a lower SBP goal less than 130 mmHg in people with diabetes and people at very high cardiovascular risk (previous cardiovascular events) is not consistently supported by trial evidence. Thus, it would be prudent to recommend lowering blood pressure to values within the range of 130 to 139/80 to 85 mmHg, and possibly closer to lower values in this range for all people with hypertension.

In its Recommendations for Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension, the 2015 Canadian Hypertension Education Program made a proposal to reach blood pressure targets less than 140/90 mmHg in most situations, including for people with previous cardiovascular disease ([CHEP 2015](#)). Nevertheless, the latest update of this guideline is prone to an intensive intervention in some people with high cardiovascular risk, including those with cardiovascular disease ([Hypertension CANADA 2018](#)). Specifically, the guideline calls for consideration of a less than 120 mmHg target, taking into account the SPRINT results (Systolic Blood Pressure Intervention Trial; [SPRINT 2015](#)).

One Cochrane Review found that treating hypertension to lower than the standard blood pressure target of 140 to 160/90 to 100 mmHg or less was not proven to reduce mortality or morbidity in the overall population ([Arguedas 2009](#)). Another Cochrane Review analyzing the same question in people with diabetes found a reduction in the incidence of stroke with the lower goal but a significant increase in the number of serious adverse events ([Arguedas 2013](#)).

Two non-Cochrane reviews on this issue have also been published ([Ettehad 2016](#); [Xie 2016](#)). [Ettehad 2016](#) combined data from all relevant clinical trials published on blood pressure reduction. The authors estimated effects of a blood pressure decrease in terms of mortality or cardiovascular morbidity, and according to different basal characteristics, such as established cardiovascular disease. There was a decrease in mortality and other cardiovascular events as blood pressure was reduced. The review found inconsistent results on safety issues. [Xie 2016](#) focused on the efficacy and safety of a blood pressure decrease for intensive strategies, including clinical trials with at least six months' follow-up that randomized participants to more intensive versus less intensive blood pressure targets, different blood pressure targets, or different blood pressure changes from baseline. Participants in the intensive group showed decreased risk in terms of less ictus and fewer relevant cardiovascular events.

Several guidelines that directly focus on the main objective of this Cochrane Review – cardiovascular secondary prevention – have been published. The 2007 guidelines for Treatment of Hypertension in the Prevention and Management of Ischemic Heart Disease from the American Heart Association recommended blood pressure targets less than 130/80 mmHg for people with demonstrated coronary artery disease or risk equivalents (carotid artery disease, peripheral arterial disease, abdominal aortic aneurysm) and for high-risk people ([AHA 2007](#)). Subsequently, when performance measures based on these recommendations were proposed, limitations were admitted because of lack of clinical trials that directly compared clinical outcomes of large populations of people with coronary disease randomized to different blood pressure targets ([Drozda 2011](#)). This guideline was updated in 2015 ([Rosendorff 2015](#)). The update concluded that blood pressure less than 140/90 mmHg would seem a reasonable target for the secondary prevention of cardiovascular events in people with hypertension and coronary artery disease.

Conversely, with less supportive evidence, a lower blood pressure target (less than 130/80 mmHg) could be appropriate for some people with coronary artery disease, previous myocardial infarction, stroke, or coronary artery disease equivalents (carotid

artery disease, peripheral artery disease, abdominal aortic aneurysm).

Limited data specifically assess the optimal blood pressure target in relation to secondary stroke prevention. American guidelines note that goals for target blood pressure level or reduction from pretreatment baseline are uncertain and should be individualized (Kernan 2014). For people who have had a recent lacunar stroke, a SBP less than 130 mmHg is accepted as reasonable; for people who have had other types of stroke, less than 140/90 mmHg is recommended.

Lowering blood pressure too much also may cause adverse cardiovascular events (Filippone 2011). Some observations have suggested that excessive lowering of blood pressure through drug treatment is associated with an increased number of deaths due to CHD (Farnett 1991), particularly among people with coronary artery disease (Bangalore 2010; Messerli 2006). Given that controversy over a potential J-curve phenomenon continues (Auer 2018; Mancia 2014; Verdecchia 2014), additional studies are expected to clarify the dilemma.

Therefore, at present, the optimal blood pressure target for reducing morbidity and mortality in people with hypertension and history of cardiovascular disease is unknown. This review aimed to establish if a more strict blood pressure target should be recommended for these people.

OBJECTIVES

To determine if lower blood pressure targets (135/85 mmHg or less) are associated with reduction in mortality and morbidity as compared with standard blood pressure targets (140 to 160/90 to 100 mmHg or less) in the treatment of people with hypertension and a history of cardiovascular disease (myocardial infarction, angina, stroke, peripheral vascular occlusive disease).

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) with more than 50 participants per group and at least six months' follow-up. In addition, 70% or more of participants had to meet all cited criteria in the [Types of participants](#) section. Studies could also be included if individual participant data were available, or if data from relevant participants were provided separately, enabling specific inclusion of this population as defined. Blinding was not possible. To be eligible for inclusion, trial reports had to present data for at least one primary outcome.

We excluded trials that used anything other than accepted randomized allocation methods such as alternate allocation, week of presentation, or retrospective controls. We placed no restrictions on publication language.

Types of participants

Participants had to be at least 18 years of age with hypertension documented in a standard way, or had to be receiving treatment for hypertension, with a positive cardiovascular history of myocardial infarction, stroke (not including transient ischaemic attack (TIA)), chronic peripheral vascular occlusive disease, or angina pectoris.

Trials were not limited by any other factor or by baseline risk.

Types of interventions

Intervention: lower blood pressure treatment target: systolic/diastolic 135/85 mmHg or less; mean blood pressure (MBP) 102 mmHg or less.

Control: standard blood pressure treatment target: systolic/diastolic 140 to 160/90 to 100 mmHg or less; MBP 107 to 120 mmHg or less.

MBP was accepted as a valid way of measuring interventions, while prespecified targets are taken into account and according to the following equation: $MBP = [(2 \times DBP) + SBP]/3$.

Types of outcome measures

All primary and secondary outcomes were measured at longest reported follow-up (except when other period indicated) in clinical trials with a minimum follow-up time of six months.

Primary outcomes

- Total mortality.
- Total serious adverse events.
- Total cardiovascular events including myocardial infarction, stroke, sudden death, hospitalization or death from congestive heart failure, and other significant vascular events such as ruptured aneurysms (excluding angina, TIA, surgical or other procedures, or accelerated hypertension). In practice, this was measured as total number of participants with at least one cardiovascular event, including fatal and non-fatal cardiovascular events.
- Cardiovascular mortality.

We defined serious adverse events according to the International Conference on Harmonisation Guidelines as any event that led to death, was life-threatening, required hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability, or was a congenital anomaly or birth defect (ICH 1995).

If a study used a different definition for serious adverse events, review authors resolved this inclusion of data by consensus.

We included all four primary outcomes in 'Summary of findings' tables.

Secondary outcomes

- Participant withdrawals due to adverse effects.
- SBP and the difference from baseline at one year, or both.
- DBP and the difference from baseline at one year, or both.
- Proportion of participants reaching the target blood pressure level.
- Number of antihypertensive drugs that each participant needed at the end of the study.

We considered participant withdrawals due to adverse effects to be an important outcome and included these data in the 'Summary of findings' table.

Search methods for identification of studies

Electronic searches

The Cochrane Hypertension Information Specialist conducted systematic searches of the following databases for RCTs without language, publication year, or publication status restrictions.

- Cochrane Hypertension Specialised Register via the Cochrane Register of Studies (CRS-Web) (searched 6 November 2019).
- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies (CRS-Web) (searched 6 November 2019).
- MEDLINE Ovid (from 1946 onwards), MEDLINE Ovid Epub Ahead of Print, and MEDLINE Ovid In-Process & Other Non-Indexed Citations (searched 6 November 2019).
- Embase Ovid (from 1974 onwards) (searched 6 November 2019).
- Latin American and Caribbean Health Sciences Literature (LILACS) Bireme (from 1982 onwards) (searched 6 November 2019).
- ClinicalTrials.gov (www.clinicaltrials.gov) (searched 6 November 2019).
- World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch) (searched 6 November 2019).

The Information Specialist modelled subject strategies for databases on the search strategy designed for MEDLINE. When appropriate, subject strategies were combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying RCTs (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.b. (Higgins 2011)). We have provided search strategies for databases in [Appendix 1](#). We did not apply a language restriction to the database searches.

Searching other resources

The Cochrane Hypertension Information Specialist searched the Hypertension Specialised Register segment (which includes searches of MEDLINE, Embase, and Epistemonikos for systematic reviews) to retrieve existing systematic reviews relevant to this systematic review, so that we could scan their reference lists for additional trials. The Specialised Register also includes searches of CAB Abstracts & Global Health, Cumulative Index to Nursing and Allied Health Literature (CINAHL), ProQuest Dissertations & Theses, and Web of Science.

We checked the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant trials.

When necessary, we contacted the authors of key papers and abstracts to request additional information about their trials.

We searched Trip Database (www.tripdatabase.com/), updated to March 2020.

We attempted to identify additional trials by searching the reference lists of included trials and (systematic) reviews, meta-analyses, and health technology assessment reports ([Appendix 2](#)). We contacted authors of trials reporting incomplete information to request the missing information.

Duplicate publications

When we identified more than one publication of an original trial, we assessed these articles together to maximize data collection. We collated multiple reports of the same study, so that each study rather than each report was the unit of interest in the review. In the case of substantial disagreements between articles, we contacted study authors.

References from published studies

We examined the references of included and excluded studies to identify further references linked to potentially eligible RCTs.

Language

We applied no language restrictions. Any study not published in English, French, or Spanish was translated.

Correspondence

We contacted trial investigators to request data from subgroups of participants with cardiovascular disease or missing data, or to clarify study details.

Data collection and analysis

Review authors worked in pairs to assess search results independently. One review author (LCS) reviewed all results. We used Early Review Organizing Software version 2.0 (www.eros-systematic-review.org) and Covidence (www.covidence.org) when screening and classifying references.

Selection of studies

Two review authors independently carried out the selection of papers, excluding records when title, keywords, and abstract showed that they were not RCTs, groups had fewer than 50 participants, follow-up was less than six months, no review primary outcomes were addressed, participants did not match prespecified criteria, blood pressure targets were not the only intervention, or specific targets were different from those prespecified. We obtained the full text of all remaining articles considered for inclusion and excluded these if inclusion criteria were not met. We obtained the full text of papers that could not be assessed by information presented in the abstract. We provisionally included studies that were likely to include subgroups of participants who met our criteria, and we contacted study authors to request data for those subgroups.

We resolved discrepancies by discussion or by consultation with a third review author, if necessary. When we considered an issue to be a highly significant point, we scheduled a plenary discussion.

We constructed a PRISMA flow diagram depicting the study selection process ([Figure 1](#)).

Figure 1. Results of the search. RCT: randomized controlled trial.

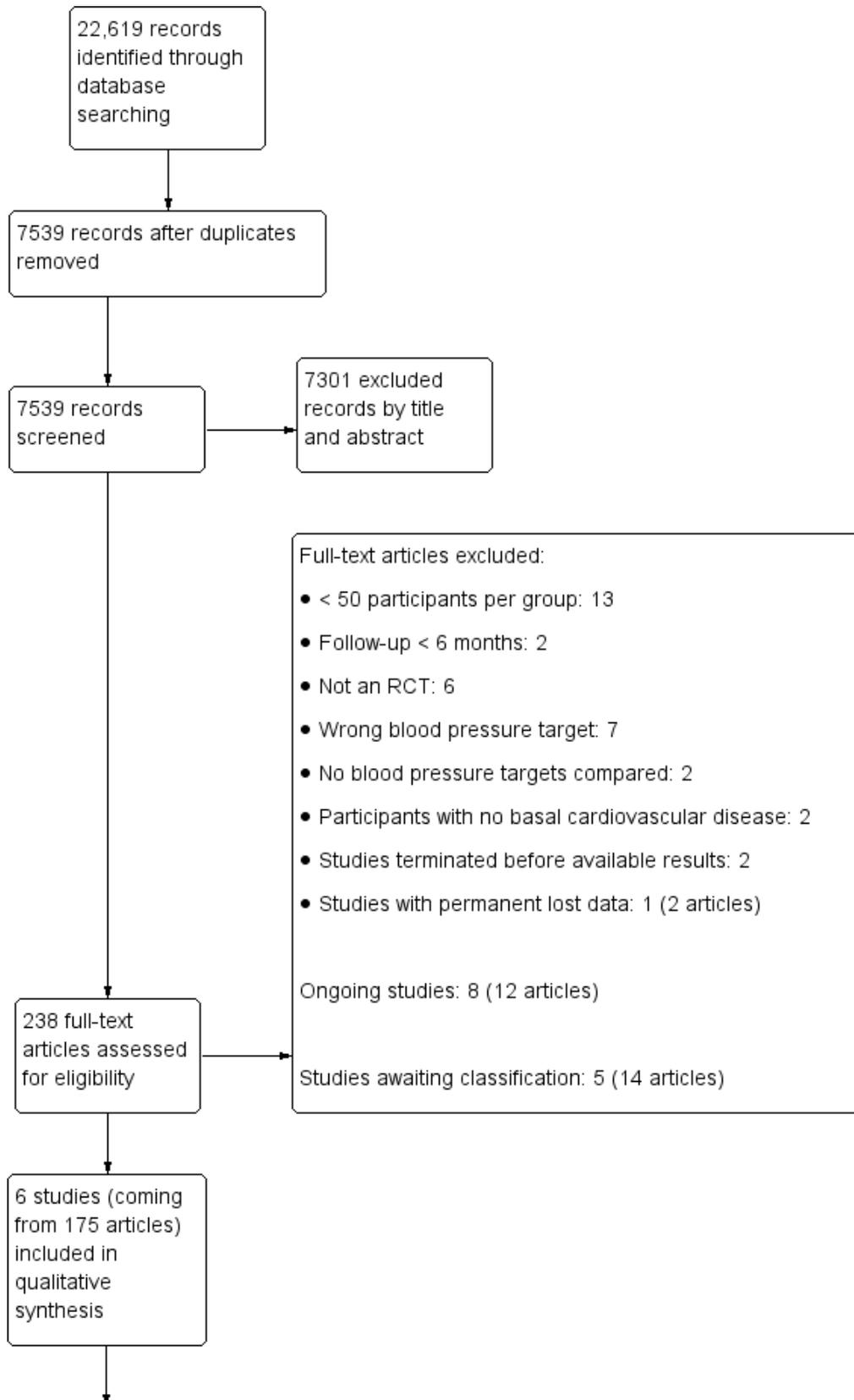
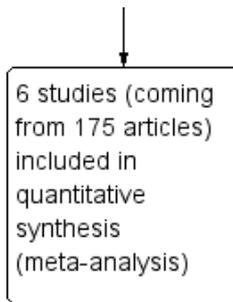


Figure 1. (Continued)



Data extraction and management

Two review authors independently extracted data from included trials using a previously prepared data extraction form, including basic information, verification of study eligibility, assessment of risk of bias, baseline study characteristics, results in outcomes, and subgroup analyses. Another review author cross-checked extracted data.

We resolved differences between review authors by discussion and by involvement of a third review author, when necessary. We used [Review Manager 2014](#) for data analyses. We based quantitative analyses of outcomes on the intention-to-treat principle.

We used Microsoft Access and Microsoft Excel when organizing and analyzing individual participant data.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias of each study using the six domains of the Cochrane 'Risk of bias' tool, according to the method described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We resolved any differences in opinion by discussion among all review authors.

We tried to find study protocols for comparison with published study reports.

Review authors reported the overall risk of bias for all included studies according to the following.

- Low risk of bias (plausible bias unlikely to seriously alter the results) if all criteria were met.
- Unclear risk of bias (plausible bias that raised some doubt about the results) if we assessed one or more criteria as unclear.
- High risk of bias (plausible bias that seriously weakened confidence in the results) if one or more criteria were not met.

We performed sensitivity analyses excluding trials with high or unclear risk of bias.

Measures of treatment effect

We used [Review Manager 2014](#) for analyses. We based quantitative analyses of outcomes on intention-to-treat results. We used risk ratios (RRs) and a fixed-effect model, if appropriate, to combine dichotomous outcomes across trials. We calculated absolute risk reduction (ARR) or absolute risk increase (ARI) and number needed to treat for an additional beneficial outcome (NNTB) or number needed to treat for an additional harmful outcome (NNTH) for total mortality, total serious adverse events, and total cardiovascular

events. We estimated 95% confidence intervals (CIs). We recorded combined outcomes and analyzed participants with at least one event in the outcome.

We combined data for blood pressure reached and the difference from baseline using mean difference (MD). This combines weight based on the number of participants in the trial and within-study variance. If the trial did not report within-study variance for decrease in blood pressure, we imputed the standard deviation (SD) from the mean SD provided by other trials. This imputation is a limitation, and to overcome it, we reported the 99% CI instead of the standard 95% CI as reported for all other data. We carried out sensitivity analyses to assess the impact of changing the assumptions made.

Unit of analysis issues

We based the analysis of outcomes on randomized participants, but if cluster-randomized trials were included, we planned to conduct appropriate analyses. We have taken special care to identify if data presented signified the total number of events or the total number of participants with a first event. We contacted study authors for clarification when necessary.

We selected data for the longest follow-up of the trial.

Dealing with missing data

We contacted study authors to obtain additional information not provided in published articles.

Assessment of heterogeneity

We used Chi² and I² statistics to test for heterogeneity of treatment effect among trials. We consider a Chi² P < 0.05 or I² > 50% as indicative of heterogeneity. We used a random-effects model to test for statistical significance when significant heterogeneity existed and 'random' distribution of intervention effects could be justified.

We planned to investigate reasons for data showing more than moderate heterogeneity (I² > 60%). If we could not identify sources of heterogeneity, we excluded studies from meta-analysis.

Assessment of reporting biases

We planned to construct a funnel plot to test for asymmetry if we included 10 or more studies in the meta-analysis.

Data synthesis

Two review authors analyzed data using [Review Manager 2014](#) and reported data in accordance with guidance provided in the

Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). If meta-analysis was not appropriate, we planned to provide a narrative description of the results.

Subgroup analysis and investigation of heterogeneity

If possible, we planned subgroup analysis for:

- participants with diabetes;
- male and female participants; and
- people aged 75 years or older.

We aimed to investigate clinical heterogeneity by examining differences in achieved blood pressure among trials, trial duration, different interventions used for hypertension, and history of stroke or CHD as inclusion criteria.

Sensitivity analysis

We tested the robustness of results using several sensitivity analyses including:

- risk of bias of trials; and
- industry-sponsored versus non-industry-sponsored trials.

We also tested the robustness of results by repeating the analysis using different measures of effect size (e.g. odds ratio) and different statistical models.

RESULTS

Description of studies

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

Results of the search

The search identified 22,619 records. After removal of duplicates and partial screening, 7539 records remained; we assessed them on the basis of title and abstract and excluded 7301 records. We obtained the full text of 238 study reports; after exclusions, 19 reports remained. When needed, we contacted the authors of these studies for further information and subsequently labelled eight studies as ongoing projects and five reports as awaiting classification studies.

Six studies in this update met the review inclusion criteria (Figure 1).

Included studies

We included six studies (AASK 2002; ACCORD BP 2010; HOT 1998; PAST BP 2016; SPRINT 2015; SPS3 2013).

Four trials compared two different SBP targets that met our inclusion criteria (SPS3 2013; and subgroups of participants with basal cardiovascular disease in ACCORD BP 2010; PAST BP 2016 and SPRINT 2015). One trial compared two different DBP targets within our criteria for lower and standard targets in a subgroup of participants with secondary cardiovascular prevention (HOT 1998). One trial compared two MBP targets in a subgroup of participants who met our predefined inclusion criteria (AASK 2002). We described comparative basal characteristics of these six studies in Table 1.

Methods

All included trials were randomized and open with blinded endpoint design. In AASK 2002, participants were also randomly assigned (in a 3 × 2 factorial design) to metoprolol, ramipril, or amlodipine treatment. In ACCORD BP 2010, participants were randomized to intensive or standard glycaemic control according to a 2 × 2 factorial design. HOT 1998 used a 3 × 2 factorial design and randomized participants to receive aspirin (acetylsalicylic acid) or placebo. SPS3 2013 had a 2 × 2 factorial design with additional randomization to aspirin plus placebo or aspirin plus clopidogrel.

Mean follow-up duration was 3.7 years (range 1.0 years to 4.7 years).

Participants

The total number of participants included in the review was 9484 (lower target, 5301; standard target, 4183). AASK 2002 included 155 participants (14% of total AASK (African American Study of Kidney Disease and Hypertension) study); ACCORD BP 2010 1531 participants (32% of total ACCORD (Action to Control Cardiovascular Risk in Diabetes) study); HOT 1998 3232 participants (17% of total HOT (Hypertension Optimal Treatment) study); PAST BP 2016 295 participants (56% of total PAST BP (Prevention After Stroke – Blood Pressure) trial); SPRINT 2015 1562 participants (17% of total SPRINT study); and SPS3 2013 2709 participants (90% of total SPS3 (Secondary Prevention of Small Subcortical Strokes) study).

AASK 2002 and SPRINT 2015 were conducted in the USA; ACCORD BP 2010 in the USA and Canada; PAST BP 2016 in the UK; SPS3 2013 in eight countries in the Americas and Europe; and HOT 1998 in over 20 countries in Asia, the Americas, and Europe.

Basal participant characteristics differed among trials (Table 1).

For participants' basal cardiovascular condition, we accepted the following participant profiles as valid secondary prevention.

- AASK 2002: participants with IHD, stroke, or PVD.
- ACCORD BP 2010: participants with myocardial infarction, stroke, or angina.
- HOT 1998: participants with myocardial infarction, stroke, or angina.
- PAST BP 2016: participants had stroke or, less frequently, IHD.
- SPRINT 2015: participants all had IHD or PVD.
- SPS3 2013: some participants had IHD, but all had recent lacunar stroke.

We considered myocardial infarction and angina identified by electrocardiogram (ECG) or coronary revascularization, and silent events, as meeting the inclusion criteria. In general, stroke was the prevalent condition in AASK 2002, PAST BP 2016, and SPS3 2013, whereas ischaemic myocardial infarction was the most prevalent condition in ACCORD BP 2010, HOT 1998, and SPRINT 2015.

AASK 2002 and SPRINT 2015 excluded people with history of diabetes, but HOT 1998, PAST BP 2016, and SPS3 2013 included some people with diabetes; all ACCORD BP 2010 participants had this cardiovascular risk factor.

All studies included more men than women with mean age from 57 years to 71 years.

Ethnicity varied from all or mostly Caucasian (assumed to be white people) ([HOT 1998](#); [PAST BP 2016](#)), to mixed populations ([ACCORD BP 2010](#); [SPRINT 2015](#); [SPS3 2013](#)), to African American people ([AASK 2002](#)).

Trials included people with reduced kidney function ([AASK 2002](#)), additional cardiovascular risk factors ([ACCORD BP 2010](#); [SPRINT 2015](#)), previous stroke ([PAST BP 2016](#); [SPS3 2013](#)), or general hypertension ([HOT 1998](#)).

The baseline blood pressure required for inclusion varied. [AASK 2002](#) required DBP 95 mmHg or greater and [HOT 1998](#) required DBP 100 mmHg to 115 mmHg. [ACCORD BP 2010](#) and [SPRINT 2015](#) required SBP 130 mmHg to 180 mmHg, [PAST BP 2016](#) sought SBP 125 mmHg, and [SPS3 2013](#) had SBP 130 mmHg or greater or DBP 85 mmHg or greater (or both) or a history of hypertension with blood pressure-lowering medication at randomization.

[HOT 1998](#) was fully industry funded, and [AASK 2002](#) was partially industry funded. [ACCORD BP 2010](#), [PAST BP 2016](#), [SPRINT 2015](#), and [SPS3 2013](#) were fully publicly funded. [ACCORD BP 2010](#), [SPRINT 2015](#), and [SPS3 2013](#) were supported by the National Institutes of Health in the USA. [PAST BP 2016](#) was funded by the National Institute for Health Research (NIHR) in the UK.

Interventions

Participants in [AASK 2002](#) were randomized to MBP 102 mmHg to 107 mmHg (standard target) or MBP less than 92 mmHg (lower target). [ACCORD BP 2010](#) and [SPRINT 2015](#) randomized participants to SBP less than 140 mmHg (standard target) or SBP less than 120 mmHg (lower target). Participants in [PAST BP 2016](#) were randomized to SBP less than 140 mmHg (standard target) or less than 130 mmHg (lower target); participants in [SPS3 2013](#) to SBP 130 mmHg to 149 mmHg (standard target) or SBP less than 130 mmHg (lower target); and participants in [HOT 1998](#) to DBP 90 mmHg or less (standard target) or to DBP 85 mmHg or less or 80 mmHg or less (lower target).

In [AASK 2002](#), if the blood pressure goal could not be achieved by the drug initially randomized (metoprolol, ramipril, or amlodipine), researchers added open-labelled antihypertensives sequentially (furosemide, doxazosin, clonidine, hydralazine, or minoxidil). Felodipine was proposed as basal therapy in [HOT 1998](#), with other drugs added according to a five-step regimen. In [SPRINT 2015](#), the protocol encouraged the use of drug classes with strongest evidence for reduction in cardiovascular outcomes, including thiazide-type diuretics (chlorthalidone encouraged as the first-line agent), loop diuretics (for participants with advanced chronic kidney disease), and beta-adrenergic blockers (for people with coronary artery disease). [ACCORD BP 2010](#), [PAST BP 2016](#), and [SPS3 2013](#) provided no specific drug instructions.

Outcomes

The primary analysis in [AASK 2002](#) focused on change in glomerular filtration rate, with relevant cardiovascular events measured as secondary outcomes. In [ACCORD BP 2010](#), [HOT 1998](#), and [SPRINT 2015](#), the main outcome was occurrence of several types of cardiovascular events. The primary outcome in [PAST BP 2016](#) was change in SBP between baseline and one year. Time to recurrent stroke was the main analysis in [SPS3 2013](#).

Additional notes

[AASK 2002](#) was conducted between February 1995 and September 2001; [ACCORD BP 2010](#) between January 2001 and June 2009; [HOT 1998](#) between October 1992 and August 1997; [PAST BP 2016](#) between July 2008 and July 2012; [SPRINT 2015](#) between November 2010 and March 2013; and [SPS3 2013](#) between February 2003 and April 2012.

Excluded studies

We excluded 36 records following assessment of full-text reports ([Figure 1](#)). Among them, we considered it useful to provide more detailed information about nine excluded studies ([BBB 1994](#); [HOSP 2006](#); [INFINITY 2019](#); [MDRD 1994](#); [NCT01230216](#); [PODCAST 2013](#); [PRESERVE 2018](#); [REIN-2 2005](#); [RESTART-AP 2013](#)).

[BBB 1994](#) was a multicentre, prospective, randomized and open trial conducted in Sweden with blinded endpoint (PROBE; Prospective, Randomized, Open-label, Blinded Endpoint) design. Adults aged 47 to 67 years were included if their treated DBP was in the range 90 mmHg to 100 mmHg on at least three consecutive visits. Specific exclusion criteria were: history of IHD or pathological ECG or both, somatic disorders expected to cause a significant deterioration in health within the next few years, or inability to participate. Two interventions were compared: standard (unchanged) target: DBP 90 mmHg to 100 mmHg versus intensive target: DBP 80 mmHg or less. Study data were lost. The principal author (Professor Lennart Hansson) is deceased; Dr Bjorn Dahlöf confirmed that data were not retained. Bayer was also contacted but confirmed the company does not have any data available for the BBB (Behandla Blodtryck Bättre) study. The journal *Blood Pressure*, in which BBB results were published, confirmed the manuscript received was essentially as published, and the documentation was destroyed about 10 years before (following Professor Hansson's death). The Swedish Council on Health Technology Assessment assessed the study in a report (No. 170/2) but did not have access to the original data. We also approached the Östra Hospital, where Professor Hansson was working at during the time the study was conducted. No records were found, and we were told that the legal requirement to keep records safe expired after 15 years.

[HOSP 2006](#) randomized participants up to five years and intended to assess two home blood pressure target strategies. The number of recruited participants was much smaller than intended and was not sufficient for analysis of the effects of different levels of target home blood pressure.

[INFINITY 2019](#) was a prospective, randomized, open-label trial with blinded endpoints. It was designed to compare a standard target (24-hour SBP less than 145 mmHg) versus an intensive target (24-hour SBP less than 130 mmHg) in people older than 74 years with SBP greater than 150 mmHg and at risk for cerebrovascular disease. Participants had visible white matter hyperintensity lesions on cerebral magnetic resonance imaging (MRI) screening. It was confirmed that the trial included fewer than 50 participants per group (39 participants per group).

[MDRD 1994](#) focused mainly on effects of dietary protein restriction and blood pressure control on progression of chronic kidney disease. The National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK, USA) provided individual participant data. However, after a first analysis, we excluded this study because

researchers included fewer than 50 participants per group (an inclusion criterion) (lower target: 56 participants, eight total deaths; standard target: 47 participants, three total deaths).

[NCT01230216](#) was designed to assess whether an intensive blood pressure target could reduce the per cent of atheroma volume measured by intravascular ultrasound in people with hypertension and coronary artery disease. This study was terminated early owing to slow patient enrolment.

The primary outcome for [PODCAST 2013](#) was Addenbrooke's Cognitive Examination. Secondary outcomes included vascular events, quality of life, functional outcome, depression, and death. The trial recruited 83 participants during the pilot phase. Low recruitment meant that the trial did not proceed and did not meet the 50 participants per group inclusion criterion of this review.

[PRESERVE 2018](#) was designed to assess potential differences between two strategies for lowering blood pressure in terms of a composite cognitive score and other secondary outcomes. Only 62 analyzable participants were recruited, and this did not meet the 50 participants per group inclusion criterion.

[REIN-2 2005](#) was designed to establish whether further blood pressure-lowering therapy in addition to angiotensin-converting enzyme inhibitors (ACEIs) could benefit people with chronic kidney disease. Accordingly, the primary objective assessed the effect of intensified versus conventional blood pressure control on progression to end-stage kidney disease. The Istituto di Ricerche Farmacologiche Mario Negri (Bergamo, Italy) provided individual participant data. It was confirmed that the trial included fewer than 50 participants per group, so this study did not meet this

review inclusion criterion (lower target: 34 participants, two deaths; standard target: 39 participants, two deaths).

[RESTART-AP 2013](#) was designed to determine whether restarting antithrombotic agents had an impact on the number of new-onset cerebral microbleeds, and if intensive blood pressure lowering reduced their numbers. Study authors confirmed that insufficient funding was available, and the study was terminated early.

Studies awaiting classification

Five studies await classification ([ABCD-H 1998](#); [Cardio-Sis 2014](#); [RESPECT 2019](#); [STABLE-ICAS 2018](#); [Zeng 2016](#)). Four studies did not report data for participants with cardiovascular disease at baseline ([ABCD-H 1998](#); [Cardio-Sis 2014](#); [RESPECT 2019](#); [Zeng 2016](#)). We have repeatedly requested these data from study authors but have not received them before publication of this review. [STABLE-ICAS 2018](#) showed severe inconsistencies when presenting outcomes. Despite our efforts, to date, we have been unable to reach an adequate clarification from the authors.

Ongoing studies

We identified eight ongoing studies ([BROAD 2019](#); [ESH-CHL-SHOT 2014](#); [ESPRIT 2019](#); [IBIS 2019](#); [OPTIMAL-DIABETES 2019](#); [OPTIMAL Stroke 2019](#); [NCT03015311](#); [NCT03666351](#)). We will evaluate these studies when complete for possible inclusion in updates of this review.

Risk of bias in included studies

The summary of the risk of bias assessment of each trial is shown in [Figure 2](#). Assessment of risk of bias was based on both published and unpublished data.

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): All outcomes	Blinding of outcome assessment (detection bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias
AASK 2002							
ACCORD BP 2010							
HOT 1998							
PAST BP 2016							
SPRINT 2015							
SPS3 2013							

Allocation

SPRINT 2015 did not report any specific random sequence generation in its protocol. However, the study authors confirmed via e-mail that they used a permuted block randomization scheme with random block lengths, stratified by clinic ([Reboussin 2020 \[pers comm\]](#)). All other included studies specified a computerized system for randomization (random permuted blocks, minimization or Pocock-Simon method). Thus, we judged methods used for allocation at low risk of bias for all six studies ([AASK 2002](#); [ACCORD BP 2010](#); [HOT 1998](#); [PAST BP 2016](#); [SPRINT 2015](#); [SPS3 2013](#)). The allocation concealment domain was at low risk of bias for all included trials.

Blinding

None of the included studies was blinded to participants or clinicians because of the need to titrate antihypertensive drugs to reach a specific blood pressure goal. However, an independent committee blinded to group allocation assessed clinical events in all trials. Hence, we assessed all trials at high risk of performance bias and low risk of detection bias.

Incomplete outcome data

Available information (both published and unpublished) for five trials did not suggest a significant imbalance between groups for withdrawals or dropouts ([AASK 2002](#); [ACCORD BP 2010](#); [PAST BP 2016](#); [SPRINT 2015](#); [SPS3 2013](#)); we assessed these trials at low risk of attrition bias.

In [HOT 1998](#), 14% of total ECGs could not be obtained, leading to some uncertainty on silent myocardial infarctions. We decided to assume a conservative perspective and consider this trial to have unclear risk of bias.

Selective reporting

We assessed protocols and published articles for [AASK 2002](#), [ACCORD BP 2010](#), [HOT 1998](#), [PAST BP 2016](#), and [SPRINT 2015](#) and confirmed no sign of reporting bias. We assessed these trials at low risk of reporting bias.

Serious adverse effects reporting in [SPS3 2013](#) was related to hypotension and blood pressure management only. We contacted

study authors for clarification but received no response. Finally, the National Institute of Neurological Disorders and Stroke (NINDS) provided individual participant data. After reviewing all data, we assessed this study at low risk of selective reporting bias.

Other potential sources of bias

All data used in this Cochrane Review came from subgroups of participants not predefined in the original study protocols, and this constitutes a potential source of bias.

Some studies were partially (e.g. [AASK 2002](#)) or fully (e.g. [HOT 1998](#)) funded by pharmaceutical industry sources, which constitutes another potential source of bias.

We also considered early termination of [SPRINT 2015](#) as a potential source of bias.

Effects of interventions

See: [Summary of findings 1 Lower blood pressure targets compared with standard blood pressure targets for mortality and morbidity](#)

Lower versus standard blood pressure targets

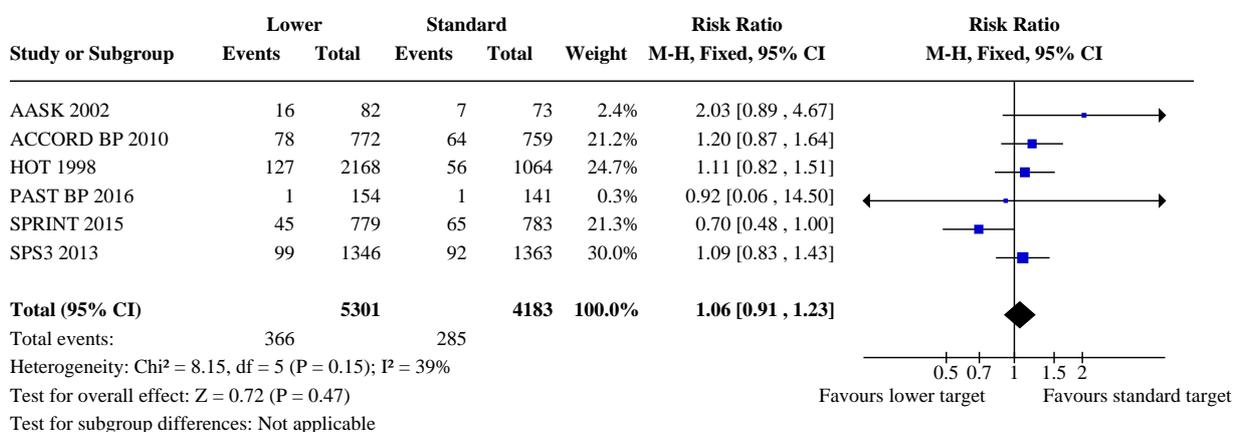
Six RCTs met the inclusion criteria ([AASK 2002](#); [ACCORD BP 2010](#); [HOT 1998](#); [PAST BP 2016](#); [SPRINT 2015](#); [SPS3 2013](#)). We obtained data from published and unpublished sources. We assumed that silent myocardial infarction complied with the definition of cardiovascular event when provided.

Primary outcomes

Total mortality

There was no evidence of a difference in total mortality between lower and standard blood pressure target groups (RR 1.06, 95% CI 0.91 to 1.23; 6 studies; P = 0.47; [Analysis 1.1](#)). When the absolute effect was measured, results showed four additional total deaths per 1000 participants identified in the lower target (95% CI 6 fewer to 16 more total deaths per 1000 participants). Researchers reported a total of 366 deaths (of 5301 participants) in the lower target group and 285 deaths (of 4183 participants) in the standard target group ([Figure 3](#)).

Figure 3. Forest plot of comparison: 1 Lower versus standard, outcome: 1.1 Total mortality.

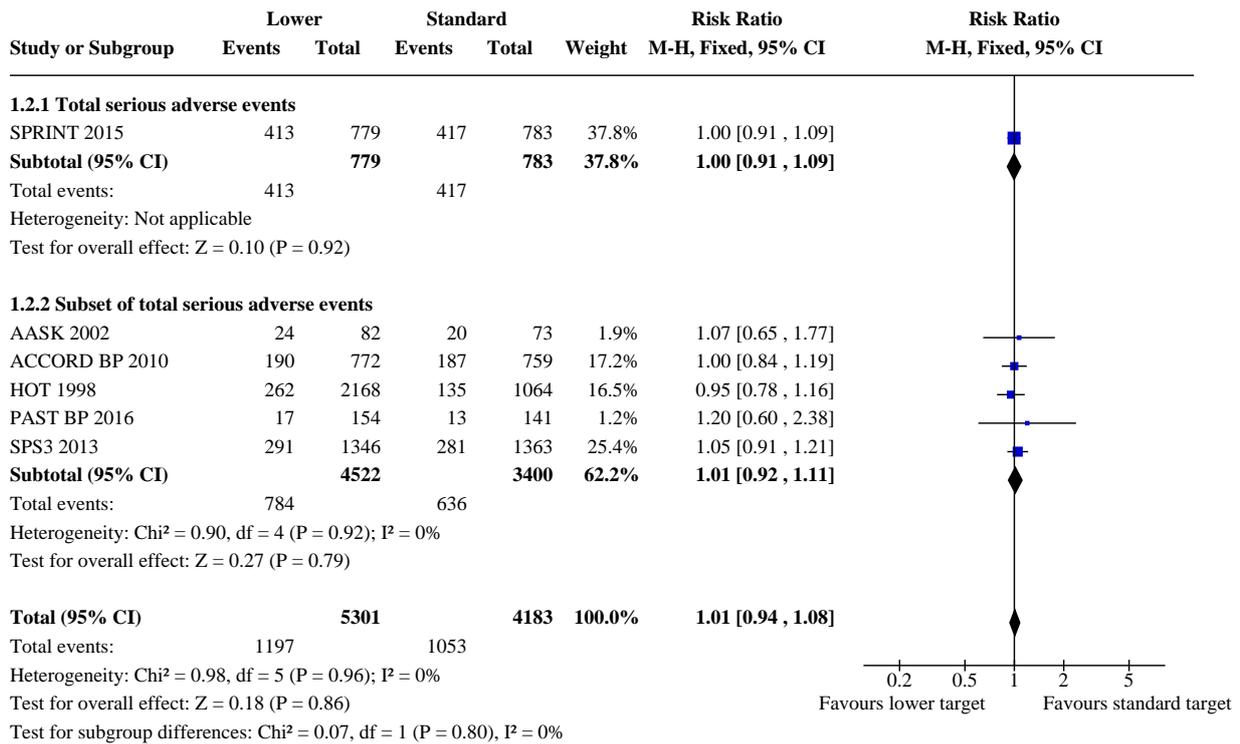


Total serious adverse events

All included studies provided data for analysis of serious adverse events. We adopted a broad definition of serious adverse event, according to [ICH 1995](#). We included participants with any cause of death, any cardiovascular event (as predefined in our protocol), or any other serious adverse event as defined by trial authors, while avoiding double-counting of participants. When all data were pooled, there was no evidence of a difference in serious adverse events between lower and standard blood pressure target groups (RR 1.01, 95% CI 0.94 to 1.08; P = 0.86; [Analysis 1.2](#)). When measuring

the absolute effect, researchers identified three additional serious adverse events per 1000 participants in the lower target group (95% CI 15 fewer to 20 more serious adverse events per 1000 participants). Results showed 1197 (of 5301 participants) with at least one serious adverse event in the lower target group and 1053 (of 4183 participants) in the standard target group ([Figure 4](#)). We considered [SPRINT 2015](#) to report the full range of serious adverse events ([Analysis 1.2.1](#)), and five studies reported subsets of events ([AASK 2002](#); [ACCORD BP 2010](#); [HOT 1998](#); [PAST BP 2016](#); [SPS3 2013](#); [Analysis 1.2.2](#)).

Figure 4. Forest plot of comparison: 1 Lower versus standard, outcome: 1.2 Serious adverse events.



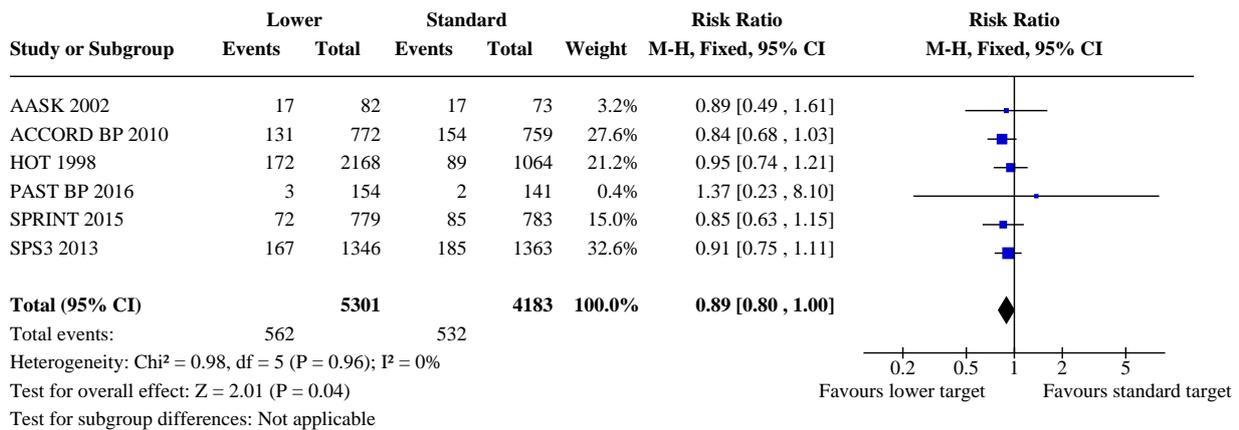
Total cardiovascular events

[AASK 2002](#) analyzed data from 27 participants in relation to individual cardiovascular events for myocardial infarction, stroke, and heart failure hospitalization; as well as data from seven further participants from a direct cardiovascular mortality diagnosis.

Five included studies provided data using well-defined categories. The total number of cardiovascular events was not significantly reduced in the lower blood pressure target group compared with

the standard group (RR 0.89, 95% CI 0.80 to 1.00; 6 studies; P = 0.044; [Analysis 1.3](#)). When measuring the absolute effect, researchers in these studies identified 14 fewer cardiovascular events per 1000 participants in the lower blood pressure target group (95% CI 0 to 25 fewer cardiovascular events per 1000 participants). Results showed 562 (of 5301 participants) with cardiovascular events in the lower target group and 532 (of 4183 participants) with cardiovascular events in the standard target group ([Figure 5](#)).

Figure 5. Forest plot of comparison: 1 Lower versus standard, outcome: 1.3 Cardiovascular events.



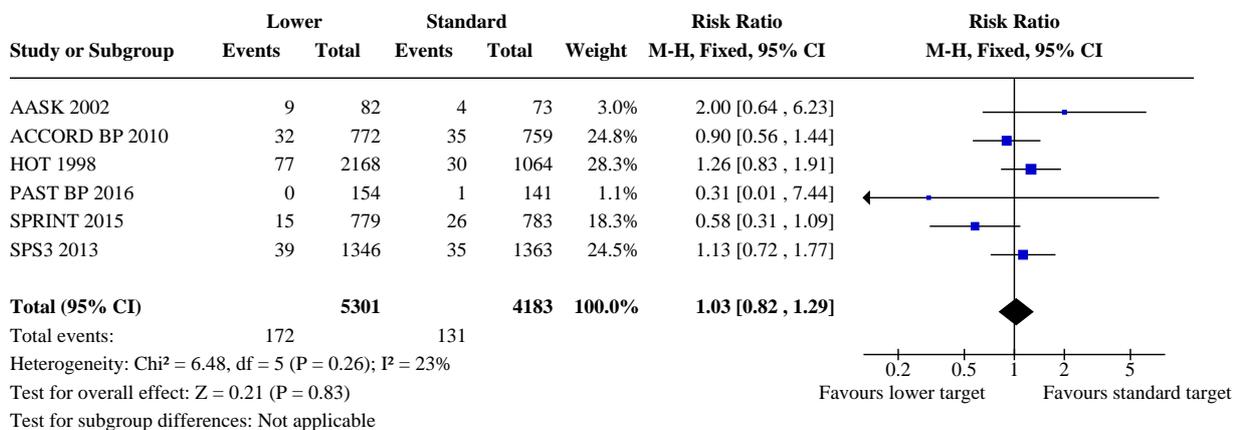
Cardiovascular mortality

We need to make some comments related to AASK 2002 before we report analysis results. AASK 2002 researchers used two different documents to register causes of death (CARDIO_REVV Form #38 and CC_DEATH Form #48). We noted no complete overlap between forms. After discussion, we considered there to be valid cardiovascular mortality when the researcher answered 'yes' to question 4 on Form #38: "Was there a cardiovascular death?" This indicated 11 deaths. Two clinicians (a cardiologist and a general practitioner) analyzed data from Form #48 case-by-case

and identified two additional deaths after completing a careful validation process.

Five trials provided data using well-defined categories. Results showed no difference in cardiovascular mortality between lower and standard blood pressure target groups (RR 1.03, 95% CI 0.82 to 1.29; P = 0.83; Analysis 1.4). Researchers reported 172 cardiovascular deaths (of 5301 participants) in the lower target group and 131 (of 4183 participants) in the standard target group (Figure 6).

Figure 6. Forest plot of comparison: 1 Lower versus standard, outcome: 1.4 Cardiovascular mortality.



Secondary outcomes

Participant withdrawals due to adverse effects

Four trials provided no information about withdrawals due to adverse effects among participants with basal cardiovascular disease (AASK 2002; ACCORD BP 2010; SPRINT 2015; SPS3 2013).

Review authors extracted data from free-text notes only for HOT 1998; PAST BP 2016 provided data of better quality. Despite limited information, results showed a difference in withdrawals due to adverse effects between lower and standard blood pressure target groups (RR 8.16, 95% CI 2.06 to 32.28; P = 0.003; Analysis 1.5). Researchers reported 22 withdrawals due to adverse effects

(among 420 participants) in the lower target group and only two (among 270 participants) in the standard target group.

Systolic blood pressure change from baseline at one year

After the first year of therapy, the mean SBP achieved was significantly lower in the lower blood pressure target group (MD -8.90 mmHg, 95% CI -4.56 mmHg to -13.24 mmHg; 6 trials; P = 0.000058; Analysis 1.7). Heterogeneity among trials was high, so we preferred a random-effects model for this analysis. We considered the different targets and specific basal characteristics for each trial as the most likely causes of this heterogeneity.

Diastolic blood pressure change from baseline at one year

After the first year of therapy, the mean DBP achieved was significantly lower in the lower blood pressure target group (MD -4.50 mmHg, 95% CI -2.65 mmHg to -6.35 mmHg; 6 trials; $P < 0.00001$; [Analysis 1.8](#)). Heterogeneity between trials for this outcome was high, so we chose a random-effects model for this analysis. We considered the different targets and specific basal characteristics for each trial as the most likely causes of this heterogeneity.

Proportion of participants reaching the target blood pressure level

Results showed that 3073 of 4820 (64%) participants reached the target in the lower target group and 2817 of 3768 (75%) in the standard target group (six trials; [Analysis 1.6](#)). Therefore, more people in the standard group achieved particular blood pressure targets.

Number of antihypertensive drugs that each participant needed at the end of the study

At the end of the study, the number of antihypertensive drugs needed was significantly lower in the standard blood pressure target group (mean 1.9 drugs) than in the lower blood pressure target group (mean 2.4 drugs) (MD 0.56, 95% CI 0.16 to 0.96; 5 trials; $P = 0.0066$; [Analysis 1.9](#)). Heterogeneity between trials for this outcome was high, so we chose a random-effects model for this analysis. We considered the different targets and specific basal characteristics for each trial as the most likely causes of this heterogeneity.

DISCUSSION

Pharmacological treatment of high blood pressure aims to reduce morbidity and mortality. Specific blood pressure targets have been proposed in guidelines for people with hypertension who have established cardiovascular disease, but optimal thresholds remain uncertain because the benefit-to-harm ratio of more intensive treatment has not been established.

This Cochrane Review explored current evidence from RCTs and assessed relevant outcomes linked to two alternative strategies: standard blood pressure target (140 to 160/90 to 100 mmHg or less) and lower blood pressure target (135/85 mmHg or less).

We included six RCTs with 9484 participants and a mean follow-up of 3.7 years (range 1.0 years to 4.7 years) ([AASK 2002](#); [ACCORD BP 2010](#); [HOT 1998](#); [PAST BP 2016](#); [SPRINT 2015](#); [SPS3 2013](#)). Four studies compared SBP targets, one compared DBP targets, and one compared MBP targets. Individual participant data were available for all six trials.

Two previous Cochrane Reviews adopted different strategies for analysis. [Arguedas 2009](#) pooled trial data for the main analysis, but [Arguedas 2013](#) considered each target (SBP or DBP) separately. Both approaches are suitable and relevant, and our Cochrane protocol did not specify any particular strategy ([Gorricho 2013](#)). For this Cochrane Review, we decided to use pooled data as the main analysis, but we also tested whether results were consistent when blood pressure targets were considered separately. To avoid misclassification problems, we added a third category (MBP) to SBP/DBP.

Summary of main results

Evidence from the six included trials indicates that blood pressure targets were more frequently achieved in the standard blood pressure target group (2817/3768 (75%) participants) than in the lower target group (3073/4820 (64%) participants).

Researchers used more antihypertensive drugs in the lower blood pressure target group (mean 2.4 drugs) than in the standard group (mean 1.9 drugs).

Results show broad differences for systolic (-8.9 mmHg) and diastolic (-4.5 mmHg) blood pressure changes from baseline in the lower target group.

We detected no benefits for total mortality (RR 1.06, 95% CI 0.91 to 1.23) or cardiovascular mortality (RR 1.03, 95% CI 0.82 to 1.29). Subsequent analyses separating trials by SBP, DBP, or MBP targets did not change these results. We also found no difference with regard to total cardiovascular events (including myocardial infarction, stroke, sudden death, hospitalization, or death from congestive heart failure) (RR 0.89, 95% CI 0.80 to 1.00) and total serious adverse events (RR 1.01, 95% CI 0.94 to 1.08) in favour of the lower blood pressure target. When we considered SBP target trials separately, we identified no significant changes in the main results.

Most withdrawals due to adverse effects occurred in the lower target group (RR 8.16, 95% CI 2.06 to 32.28). However, little evidence was available, making establishment of a trustworthy global assessment of benefits and harms very challenging.

It is important to note that we detected no significant heterogeneity for any primary outcome. Therefore, at present, there does not seem to be sufficient sound evidence to justify more strict blood pressure targets (135/85 mmHg or less) than the standard range (140 to 160/90 to 100 mmHg or less) for people with hypertension and established cardiovascular disease.

We detected significant heterogeneity for two outcomes – blood pressure difference from baseline at one year and number of antihypertensive drugs that each participant needed at the end of study. We considered the different targets and the specific basal characteristics for each trial as the most likely causes for this heterogeneity. Subgroup analysis indicated significant heterogeneity in the male subgroup for cardiovascular mortality. The source of heterogeneity could be linked to a decrease in the numbers of participants and events and differences in trial design between [HOT 1998](#) and [ACCORD BP 2010/SPRINT 2015](#).

The minimum 5-mmHg difference in SBP or DBP targets predefined as clinically significant in our protocol is consistent with previous guideline decisions ([NICE 2019](#)). Nonetheless, as [Arguedas 2009](#) and [Arguedas 2013](#) reported, it could be argued that this difference is not large enough to show significant changes in relevant outcomes. To test this hypothesis, we conducted an additional sensitivity analysis of participants with diabetes, while excluding the intermediate less than 85 mmHg target in [HOT 1998](#); results were very similar between the main analysis in participants with cardiovascular disease and the subgroup analysis in participants with diabetes and showed large differences in targets ([Table 2](#)).

We specified in our Cochrane protocol three subgroup analyses (people with diabetes, participants by sex, and people aged ≥ 75 years) designed to explore potential differences in specific

populations (Gorricho 2013). Despite the large amount of information retrieved from individual participant data for this review, data available for people aged 75 years or older were too few to permit any definitive conclusions. When participant data were split according to sex, and when only participants with diabetes were considered, we found magnitudes of effect similar to those described in the main analysis. People with diabetes and established cardiovascular disease could be seen at first as being in a higher risk category than people who do not have diabetes (Mancia 2011). However, estimates for people with diabetes were similar to estimates for the general population with basal cardiovascular disease: no differences in total mortality, cardiovascular mortality, or total cardiovascular events associated with lower target; and no differences in both target strategies for serious adverse events. Evidence was insufficient to reveal greater effect from a lower blood pressure target in these subgroups, although sample sizes were not large enough to exclude a significant effect.

We planned two sensitivity analyses to test the robustness of results: risk of bias of the included trials and industry-sponsored versus non-industry-sponsored trials.

Because we rated overall risk of bias as high, we could not perform sensitivity analyses. We found no difference in any main outcome favouring the lower blood pressure target in industry-sponsored or non-industry-sponsored trials (ACCORD BP 2010; PAST BP 2016; SPRINT 2015; SPS3 2013).

Overall completeness and applicability of evidence

Cardiovascular diseases are prevalent, and high blood pressure is an added risk factor commonly treated in this population. Evidence-based guidelines focused on this issue are needed. However, data derived from RCTs designed to clarify this uncertainty remain insufficient.

All six studies contributed individual participant data for subgroups of participants (AASK 2002, 155 participants; ACCORD BP 2010, 1531 participants; HOT 1998, 3232 participants; PAST BP 2016, 295 participants; SPRINT 2015, 1562 participants; SPS3 2013, 2709 participants).

Although this review analyzed a significant body of evidence and results are considered to be robust, we cannot state these results as conclusive. Three ongoing trials have been designed to explicitly answer relevant questions for people with established cardiovascular disease (ESH-CHL-SHOT 2014; IBIS 2019; OPTIMAL Stroke 2019); it is anticipated that these studies will yield additional evidence.

Over 6000 participants provided data on SBP targets, and over 3000 on DBP targets. Neither subanalysis substantially changed overall results in primary outcomes when all target strategies were considered together. From this perspective, results of this review can be generalized for physicians prescribing antihypertensive drugs, no matter the specific target strategy (SBP, DBP, or both) chosen.

As identified by Arguedas 2009, and probably fuelled by the intention-to-treat approach, this review did not find real differences as wide as expected between groups in achieved SBPs and DBPs, according to the predefined targets for each study. All six included trials achieved the standard target, but only ACCORD BP 2010, PAST

BP 2016, and SPS3 2013 achieved the required blood pressure in the lower target group (in HOT 1998, the 80 mmHg or less target was not achieved). This underlines the difficulty of putting the intervention into practice, as often happens in real life. Accordingly, this aspect could be seen as both a limitation and a strength.

Quality of the evidence

We downgraded the quality of the evidence for total mortality and cardiovascular mortality to moderate owing to imprecision and lack of data. In our opinion, other potential limitations (e.g. cardiovascular disease subgroups were not predefined in several studies) are unlikely to lower confidence in the estimate, given the large sample sizes, the design of SPS3 2013 (29% of total participants), the sensitivity analysis performed about potential risk of bias, and the strength of the individual participant data analysis.

We also downgraded the quality of the evidence for other outcomes: we assessed total cardiovascular events and serious adverse events as providing low-quality evidence, and withdrawals due to adverse effects as providing very low-quality evidence. Total cardiovascular events, serious adverse events and withdrawals due to adverse events data were affected by high risk of bias. As for withdrawals, imprecision was especially marked, leading to further downgrading of evidence quality. (See Summary of findings 1.)

Potential biases in the review process

Because of study requirements, none of the included studies were blinded to participants or clinical researchers. However, all studies implemented mechanisms for assessment of outcomes by independent blinded committees. Consequently, we considered potential performance bias as high and detection bias as low.

Another potential source of bias came from the fact that all included participants were also included in subgroup studies. In addition, to adapt study interventions to those defined in our review, HOT 1998 participants in two different target groups (less than 85 mmHg and less than 80 mmHg) were pooled only for the lower blood pressure target.

Additionally, primary outcomes in AASK 2002 were not aligned with the interests of our review. It must be stressed that most subgroups included a large number of participants, and all findings were analyzed as individual participant data.

Differences between trials in types and definitions of outcomes could also be a source of bias (see Outcomes in Characteristics of included studies table). For example, not all studies provided adequate information about the ways silent myocardial infarctions were dealt with, revealing differences among studies that included heart failure hospitalization as an outcome.

We observed no homogeneous information among trials for serious adverse events – the most comprehensive outcome on safety. Only SPRINT 2015 was deemed to report the total number of serious adverse events according to its international standardized definition (ICH 1995). Other included trials provided an unreliably low number of serious adverse events (HOT 1998); reported only events judged by researchers as probably related to the interventions (ACCORD BP 2010); considered serious adverse events from an extremely narrow perspective (PAST BP 2016); or did not offer any specific information on this outcome (AASK

2002). Deaths, major cardiovascular events, and serious adverse effects reported by trialists were included as serious adverse events in analyses when only partial or disaggregated information was available, as in [SPS3 2013](#). Because of these concerns, we strongly suspect reporting bias for certain outcomes such as serious adverse events and withdrawals due to adverse effects, for which few data were reported.

Agreements and disagreements with other studies or reviews

To our knowledge, this is the first systematic review with meta-analysis that assessed blood pressure targets in people with established cardiovascular disease from RCTs that directly compared different target strategies.

We found no evidence of additional benefit from a lower blood pressure target compared to a standard blood pressure target in terms of total mortality, cardiovascular mortality, total cardiovascular events, or total serious adverse events.

Some prominent hypertension guidelines have not issued direct recommendations on blood pressure targets for people with previous cardiovascular disease ([JNC-8 2014](#); [NICE 2019](#)). Those reviews or guidelines that include explicit recommendations obtained them from observational data or post hoc analyses of achieved blood pressure in trials designed for various purposes ([Bangalore 2013](#)). This perspective could easily lead to selection bias, favouring lower risk of experiencing a cardiovascular event in participants with lower achieved blood pressure. Only one study directly compared clinical outcomes in people who had stroke and were treated to different blood pressure targets ([SPS3 2013](#)); no studies have been conducted in people with cardiovascular disease.

Our results do not seem to support widespread implementation of an intensive target strategy (135/85 mmHg or less) for cardiovascular secondary prevention. A similar systematic review on chronic kidney disease did not show that a blood pressure target less than 125/75 to 130/80 mmHg is more beneficial than a target less than 140/90 mmHg ([Upadhyay 2011](#)).

However, based on [SPRINT 2015](#) data, [Hypertension CANADA 2018](#) recommends consideration of lower targets in some people at high cardiovascular risk. Similarly, [ACC-AHA 2017](#) and [ESH-ESC 2018](#) suggests lower goals for people with established cardiovascular disease, according to [SPRINT 2015](#) data and the conclusions of several meta-analyses. However, no specific analysis was performed on this population. Other guidelines, such as [Joint ESC 2016](#), [Rosendorff 2015](#), and [Kernan 2014](#), only partially agree with our view. [Joint ESC 2016](#) recommends a 130 mmHg to 139 mmHg SBP target but supports a more intensive effort (80 mmHg to 85 mmHg) as the DBP goal. No specific supportive evidence was provided on this statement. Two American guidelines focusing on coronary and stroke patients are available. [Rosendorff 2015](#) suggests less than 140/90 mmHg as a reasonable target for secondary prevention of cardiovascular events in coronary patients but considers a lower target (less than 130/80 mmHg) as useful for some people; researchers admit that this is not supported by evidence and offer no additional details of potential benefit profiles. [Kernan 2014](#) recommends a less than 140/90 mmHg target strategy as a general rule for people with stroke but points out that 130/80 mmHg could be reasonable for people with a recent

lacunar stroke, based mainly on [SPS3 2013](#) results. However, the [SPS3 2013](#) study did not achieve a statistically significant difference between lower and standard targets for any of the primary or secondary outcomes measured. In [SPS3 2013](#), the difference detected in intracerebral haemorrhages (a subtype of intracranial haemorrhages not preplanned even as a secondary outcome) could well have been due to chance. It is surprising that despite no evidence of substantial benefit confirmed with the lower target, the [SPS3 2013](#) authors concluded that, based on their results, use of a SBP target less than 130 mmHg was likely to be beneficial in people with recent lacunar stroke.

[Ettehad 2016](#), a systematic review, identified large-scale blood pressure-lowering trials to quantify the effects of reducing SBP by 10 mmHg in terms of mortality and cardiovascular outcomes. This analysis was conducted for the main comparison and for several subgroups, one of them including people with established cardiovascular disease. Results showed benefit for this subgroup in terms of mortality and cardiovascular events when blood pressure was reduced but inconsistent results for safety outcomes. The review authors concluded that lowering current normotensive levels is supported by their review, provided there is a relevant absolute risk. In this regard, relevant limitations must be taken into account. First, heterogeneity was extremely high in [Ettehad 2016](#), including large differences among populations, basal comorbidities, and comparisons between treatment groups. In fact, some included studies compared the effects of different blood pressure targets, the effects of different drugs, or even the effects of drugs versus placebo. Second, the review did not consider individual participant data, leading to particularly low accuracy when conclusions are assumed about participants with or without basal cardiovascular disease. Finally, among the included studies comparing different blood pressure targets, researchers mixed strategies that were too diverse, from less than 120 mmHg to less than 150 mmHg SBP targets. Certainly, this review gathered a large amount of information, but, at the same time, a careful approach should be demanded to avoid misleading conclusions.

Another systematic review included clinical trials comparing only blood pressure targets ([Xie 2016](#)). Although this design seems to be more appropriate than that used in the previous case, review authors established inclusion criteria with high laxity. Limits were not well defined with regard to what was considered an intensive or standard target. Because of this, two studies could share the same target while simultaneously assigning treatment to different groups – standard and intensive ([Brunström 2016](#)). Participants with a wide range of blood pressure targets were mixed, leading to few informative results, even when data from a large number of participants were collected. The review authors declared that, with high cardiovascular risk, benefits from intensive treatment clearly overcome potential harms, even in people with targets less than 140 mmHg, calling for changes to current guidelines.

In contrast, our systematic review does not support this view. We have not identified any advantages after taking into account more appropriate inclusion criteria, all individual participant data, and informative outcomes such as serious adverse events. Furthermore, even if [SPRINT 2015](#) mortality results show a trend favouring the lower target strategy, we detected no overall benefits for these outcomes and noted that adverse events were poorly informed by all concerned clinical trials. In our opinion, whereas the scientific community is dealing with this key lack of information,

recommendations on blood pressure targets for people with hypertension with cardiovascular disease should give priority to caution.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence identified in this review from randomized controlled trials does not support lower blood pressure targets (less than 135/85 mmHg) as compared to standard blood pressure targets (less than 140 to 160/90 to 100 mmHg) in people with hypertension and established cardiovascular disease (myocardial infarction, stroke, chronic peripheral vascular occlusive disease, or angina pectoris).

We analyzed systolic, diastolic, or mean blood pressure goals as a whole and separately and obtained similar findings of little or no difference. In addition to lack of benefit for the lower blood pressure target in total or cardiovascular mortality, total cardiovascular events, and serious adverse events, the numerical increase in total mortality shown should lead to additional caution. Some uncertainties remain as the evidence was very low quality for withdrawals due to adverse effects.

Predefined subgroup analyses in older people, in people with diabetes, or based on participant sex did not suggest any differences in these conclusions.

According to the best available evidence, lower targets for people with hypertension and established cardiovascular disease provide minimal or no net health benefit.

Implications for research

Well-designed randomized controlled trials assessing lower blood pressure targets in people with hypertension and established cardiovascular disease are needed to ascertain the benefits and harms derived from intensive and more conservative strategies.

We have identified eight ongoing studies in people with stroke and coronary disease ([BROAD 2019](#); [ESH-CHL-SHOT 2014](#); [ESPRIT 2019](#); [IBIS 2019](#); [OPTIMAL-DIABETES 2019](#); [OPTIMAL Stroke 2019](#); [NCT03015311](#); [NCT03666351](#)), but additional studies exploring other types of basal cardiovascular disease (e.g. peripheral vascular disease, haemorrhagic stroke) are required. Future research should aim to report mortality rates and all serious adverse event outcomes.

Having access to individual participant data and other relevant documents (protocols, clinical study reports, raw data) becomes a major strength of systematic reviews with meta-analysis. Thus, the authors of past or future trials are highly encouraged to share their databases.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

AASK 2002

Study characteristics

Methods	<p>Multicentre, 3 × 2 factorial design, ITT strategy. Participants randomized equally to a usual mean arterial pressure goal of 102–107 mmHg or to a lower mean arterial pressure goal of ≤ 92 mmHg, and to treatment with metoprolol, ramipril, or amlodipine. When the blood pressure goal was not achieved using the randomized drug, other open-labelled antihypertensive agents were added to participants' treatment. Participants and investigators were not masked to the blood pressure goal.</p> <p>Follow-up: 3–6.4 years (mean 3.8 years)</p>
Participants	<p>African-American men and women, aged 18–70 years, with hypertension defined as sitting DBP ≥ 95 mmHg and reduced kidney function, defined as GFR 20–65 mL/min/1.73 m².</p> <p>Exclusion criteria: DBP < 95 mmHg, history of diabetes mellitus, urinary protein-to-creatinine ratio > 2.5, accelerated or malignant hypertension within 6 months, secondary hypertension, evidence of non-blood pressure-related causes of CKD, serious systemic disease, or clinical CHF.</p> <p>Baseline characteristics of 155 participants (% or mean): men/women: 68%/32%; age: 57 (SD 9) years; SBP: 149 (SD 28) mmHg; DBP: 93 (SD 16) mmHg; MBP: 112 (SD 19) mmHg; current smoker: 31%; types of drugs at 1 year: no information available. Previous cardiovascular condition: IHD: 25%; stroke: 69%; PVD: 23%.</p> <p>Country: USA</p>
Interventions	<p>Standard (usual) target: MBP 102–107 mmHg</p> <p>Lower target: MBP < 92 mmHg</p>
Outcomes	<p>Primary outcome: change in GFR (GFR slope).</p> <p>Key secondary outcomes: all cardiovascular events including cardiovascular deaths and hospitalizations for MI, stroke, heart failure, revascularization procedures, and other hospitalized cardiovascular events were reviewed and classified by a blinded endpoints committee according to a prespecified protocol.</p>
Funding sources	<p>NIDDK</p> <p>Also partially funded by other NIH grants, Office of Research in Minority Health, Pfizer, AstraZeneca, and King Pharmaceuticals.</p>
Declarations of interest	<p>Quote: "Dr Wright has no stock ownership but has received research grants, honoraria, and consult fees from Astra, Bayer, Bristol-Myers Squibb, Eli Lilly and Co, Merck & Co, Novartis Pharma AG, Pharmacia, Pfizer, Sankyo Inc, GlaxoSmithKline, and Solvay/Unimed. Dr Appel has received honoraria from Astra and Novartis Pharma AG. Dr Cheek is a speaker for Wyeth, Novartis, and Sanofi-Synthelabo, and investigator for Abbott Laboratories. Dr Middleton is a speaker for Merck and a consultant for King Pharmaceuticals."</p>

AASK 2002 (Continued)

Notes	<p>Among the three drug arms planned in the factorial design, the amlodipine group was halted in September 2000.</p> <p>Blood pressure achieved at the end of the trial was as follows: standard target: MBP 104 (SD 7) mmHg; lower target: MBP 95 (SD 8) mmHg.</p> <p>A public repository provided individual participant data from people with hypertension with established CVD for use in this systematic review.</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The computer screen displayed the blood pressure group to which the patient had been randomized (usual or low). Random permuted blocks with randomly varying block sizes were utilized" (p. S157).
Allocation concealment (selection bias)	Low risk	Quote: "The computer screen displayed the blood pressure group to which the patient had been randomized (usual or low)" (p. S157).
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study design was not compatible with blinding of participants and personnel.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All cardiovascular events including cardiovascular deaths and hospitalizations for MIs, strokes, heart failure, revascularization procedures, and other hospitalised cardiovascular events were reviewed and classified by a blinded endpoints committee according to a prespecified protocol" (p. S161).
Incomplete outcome data (attrition bias) All outcomes	Low risk	There did not seem to be a significant imbalance in follow-up flow diagram, according to Figure 1 (pp. 2421–31).
Selective reporting (reporting bias)	Low risk	Protocol checked against cardiovascular outcomes.
Other bias	Unclear risk	Subgroup of participants with basal CVD not predefined.

ACCORD BP 2010
Study characteristics

Methods	<p>Multicentre, 2 × 2 factorial design, ITT strategy. Participants and investigators were not masked to blood pressure goals. All participants in the ACCORD BP trial were randomly assigned to intensive or standard glycaemic control, and were also randomly assigned to intensive or standard blood pressure control.</p> <p>Follow-up: 4–8 years (mean 4.7 years)</p>
Participants	<p>Men and women with type 2 diabetes mellitus and a glycated haemoglobin level ≥ 7.5%, aged 40–79 years with CVD, or 55–79 years with anatomical evidence of a substantial amount of atherosclerosis, albuminuria, or LVH, or ≥ 2 additional risk factors for CVD (dyslipidaemia, hypertension, smoking, or obesity). Participants with SBP of 130–180 mmHg who were taking ≤ 3 antihypertensive medications and who had the equivalent of a 24-hour protein excretion rate < 1.0 g were also eligible for the blood pressure trial.</p>

ACCORD BP 2010 (Continued)

Exclusion criteria: BMI > 45, sCR level > 1.5 mg/dL, and other serious illness.

Baseline characteristics of 1531 participants (% or mean): men/women: 63%/37%; age: 62 (SD 8) years; age ≥ 75 years: 7%; SBP: 138 (SD 16) mmHg; DBP: 74 (SD 11) mmHg; current smoker: 13%; ethnic group: white: 62%, non-white: 38%. Types of drugs at 1 year: thiazides: 51%; ACEIs/ARBs: 84%; CCB: 26%; BB: 57%; other: 28%. Previous cardiovascular condition: IHD: 86%; stroke: 20%.

Countries: USA, Canada

Interventions	Standard target: SBP < 140 mmHg Lower (intensive) target: SBP < 120 mmHg
Outcomes	Primary outcome: first occurrence of a major cardiovascular event, defined as the composite of non-fatal MI, non-fatal stroke, or cardiovascular death. Secondary outcomes included: combination of the primary outcome plus revascularization or hospitalization for CHF; combination of a fatal coronary event, non-fatal MI, or unstable angina; non-fatal MI; fatal or non-fatal stroke; non-fatal stroke; death from any cause; death from cardiovascular causes; and hospitalization or death due to heart failure.
Funding sources	Supported by contracts from the NHLBI. The NIDDK, the National Institute on Aging, the National Eye Institute, and the Centers for Disease Control and Prevention also contributed funding. General Clinical Research Centers provided support at many sites. Several companies provided study medications.
Declarations of interest	Drs Bigger, Buse, Byington, Corson, Cushman, Cutler, Evans, Friedewald, Gerstein, Goff, Grimm, Ismail-Beigi, Katz, Peterson, and Probstfield declared different types of relationships with NIH institutions and pharmaceutical companies (consultancy, grants, honoraria).
Notes	The glycaemia ACCORD trial was stopped on 6 February 2008 Blood pressures achieved at the end of the trial were as follows: standard target: SBP 133.5 (SD 0.4) mmHg; lower target: SBP 119.3 (SD) 0.4 mmHg. A public repository provided individual participant data from people with hypertension with established CVD for use in this systematic review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed centrally on the study's Web site with the use of permuted blocks to maintain concealment of future study-group assignments" (pp. 1575–85).
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was performed centrally on the study's Web site with the use of permuted blocks to maintain concealment of future study-group assignments" (pp. 1575–85).
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study design was not compatible with blinding of participants and personnel.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "ACCORD utilized a centralized adjudication process for all deaths, and hospitalizations for myocardial infarction and strokes. Upon identification of a potential outcome, clinical site staff obtained medical records or details regarding the case. Personal identifiers and information that may have alerted adjudicators to treatment assignment (e.g. A1C values) were masked by

ACCORD BP 2010 (Continued)

		the clinical site and the medical records sent to the Coordinating Center" (pp. 1575–85; Appendix 1).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Consort diagram (section 2) (pp. 1575–85; Appendix 1).
Selective reporting (reporting bias)	Low risk	No reporting bias (protocol was checked).
Other bias	Unclear risk	Subgroup of participants with basal CVD not predefined.

HOT 1998
Study characteristics

Methods	<p>Multicentre, 3 × 2 factorial design, ITT strategy. Prospective Randomized Open with Blinded Endpoint (PROBE) trial. All participants in the HOT trial were randomly assigned to achieve 3 therapeutic goals (DBP ≤ 90 mmHg, ≤ 85 mmHg, or ≤ 80 mmHg) and to receive aspirin (acetylsalicylic acid) 75 mg daily or placebo under double-blind conditions. Participants were randomized on the basis of the following baseline variables: age, sex, previous antihypertensive therapy, smoking, previous MI, previous other CHD, previous stroke, and diabetes mellitus.</p> <p>Follow-up: 3.3–4.9 years (mean 3.8 years)</p>
Participants	<p>3232 men and women aged 50–80 years (mean 62 years) with essential hypertension. Required DBP ≥ 100 mmHg and ≤ 115 mmHg on 2 occasions, at least 1 week apart.</p> <p>Exclusion criteria included: malignant or secondary hypertension; stroke or MI within 12 months before randomization; decompensated CHF; serious disease affecting survival during the next 2–3 years; requirement for BB, ACEI, or diuretic treatment for reasons other than hypertension; requirement for antiplatelet or anticoagulant treatment; and diabetes requiring insulin.</p> <p>Baseline characteristics of 3232 participants (% or mean): men/women: 53%/47%; age: 62 years; SBP: 174 (SD 15) mmHg; DBP: 106 (SD 3) mmHg; diabetes: 12%; current smoker: 16%; and ethnic group: white: 92%, non-white: 8%. Previous cardiovascular condition: IHD: 95%; stroke: 7%.</p> <p>Countries: Argentina, Austria, Belgium, Canada, Denmark, East Asia, Finland, France, Germany, Great Britain, Greece, Hungary, Israel, Italy, Mexico, Norway, South East Asia, Spain, Sweden, Switzerland, Netherlands, and the USA.</p>
Interventions	<p>Standard target: DBP ≤ 90 mmHg</p> <p>Lower target: DBP ≤ 85 mmHg or ≤ 80 mmHg</p>
Outcomes	<p>Primary outcomes: pooled major cardiovascular events (non-fatal MI, non-fatal stroke, or cardiovascular death) and target blood pressures or DBP achieved during treatment.</p> <p>Secondary outcomes: target DBP and specific outcomes, such as total or cardiovascular mortality, fatal and non-fatal CHD, and stroke and hospitalization.</p>
Funding sources	Astra AB (Sweden), Astra Merck Inc. (USA), Teva (Israel), Hoechst (Argentina)
Declarations of interest	Not reported
Notes	Silent MIs were documented by ECG at randomization and final visit.

HOT 1998 (Continued)

Blood pressures achieved at end of the trial: standard target: DBP 85 (SD 5) mmHg; lower target: DBP 82 (SD 5) mmHg.

A private repository provided individual participant data from people with hypertension with established CVD that were used in this Cochrane Review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization was computer-generated based on communications by fax between investigators and the Study Coordinating Centre" (pp. 1755–62). Comment: the randomization procedure was a version of the Pocock-Simon randomization (Pocock SJ, 1975) Protocol, section 7.3.
Allocation concealment (selection bias)	Low risk	Quote: "The randomization was computer-generated based on communications by fax between investigators and the Study Coordinating Centre" (pp. 1755–62; and protocol, section 7.3).
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study design was not compatible with blinding of participants and personnel.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An Independent Clinical Event Committee evaluated all events (masked)" (pp. 1755–62; and protocol, section 7.2).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "14% of the ECG could not be obtained leading to uncertainty on silent myocardial infarctions. On the other hand, no significant differences among targets have been detected" (Clinical Study Report, p. 23, pp. 1755–62, Figure 1).
Selective reporting (reporting bias)	Low risk	The database showed all required results (study protocol, sections 3.1 and 3.2).
Other bias	Unclear risk	Subgroup of participants with basal CVD not predefined.

PAST BP 2016
Study characteristics

Methods	Multicentre, primary care-based, pragmatic RCT Randomization method used minimization to balance groups on the basis of age (< 80 years, ≥ 80 years), sex, diabetes mellitus, atrial fibrillation, baseline SBP, and practice. Follow-up: 1 year
Participants	Men and women with stroke/TIA diagnosis obtained through review of medical records and participant interview. Exclusion criteria: SBP < 125 mmHg at baseline, already taking ≥ 3 antihypertensive agents, orthostatic hypotension, treatment target of 130 mmHg SBP specified, or insufficient corroborative evidence of stroke/TIA from medical record and participant interview.

PAST BP 2016 (Continued)

Baseline characteristics of 295 participants (% or mean): men/women: 64%/36%; age: 71 (SD 9) years; SBP: 143 (SD 14) mmHg; DBP: 80 (SD 10) mmHg; current smoker: 13%; ethnic group: Caucasian: 98%. Types of drugs at 1 year: thiazides: 35%; ACEIs/ARBs: 65%; CCB: 43%; BB: 20%; other: 11%. Previous cardiovascular condition: IHD: 22%; stroke: 85%; PVD 7%.

Interventions	Standard target: SBP \leq 140 mmHg Intensive target: SBP \leq 130 mmHg, or 10 mmHg reduction if baseline SBP 125–140 mmHg
Outcomes	Primary outcome: change in SBP between baseline and 12 months. Key secondary outcomes: adverse effects, tolerability and adverse events; clinical outcomes (including major cardiovascular events (composite of fatal and non-fatal stroke, MI or fatal CHD, and other cardiovascular death), all-cause mortality and hospital admissions). Key secondary events (stroke, MI, fatal CHD, and other cardiovascular death) were reviewed by independent clinicians blinded to treatment to ensure unbiased coding of these events.
Funding sources	Financial support from the NIHR Programme Grants for Applied Research funding scheme.
Declarations of interest	Quote: "JM has received grants from Ferrer and the NIHR; RJMcM has received grants from Ferrer during the conduct of the study and grants and personal fees from Omron, grants from Lloyds Pharmacy, personal fees from the Japanese Society of Hypertension, and personal fees from the American Society of Nephrology outside the submitted work; AR has received grants from the University of Birmingham during the conduct of the study; FDRH has received grants from the NIHR and non-financial support from Omron and Microlife during the conduct of the study; no other relationships or activities that could appear to have influenced the submitted work."
Notes	This study has been concluded and published. Agreement was made with study authors to include data from people with hypertension with established CVD.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The central study team at the University of Birmingham randomized patients, with minimisation based on age, sex, diabetes mellitus, atrial fibrillation, baseline systolic blood pressure, and general practice. The research nurse ascertained treatment allocation either by telephone or online" (p. i708) "If the patient is eligible and willing to take part, the nurse will also gain written informed consent prior to randomization, and will telephone the randomization service to obtain treatment group allocation" (p. 37).
Allocation concealment (selection bias)	Low risk	Quote: "The randomization will use minimisation to balance the randomized groups on the basis of age (< 80 , ≥ 80), sex, diabetes mellitus, atrial fibrillation (because of the difficulties of obtaining accurate BP measurements in this group), baseline systolic BP and practice" (p. 37).
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study design was not compatible with blinding of participants and personnel.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The outcome measure was not blinded, but a nurse not directly involved in the participant's care obtained it by using an automated sphygmomanometer, so systematic recording bias is unlikely" (p. i708). Quote: "Key secondary events (stroke; myocardial infarction; fatal coronary heart disease and other cardiovascular death) will be reviewed by indepen-

PAST BP 2016 (Continued)

		dent clinicians blinded to treatment to ensure unbiased coding of these events" (p. 37).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Primary outcome data were available for 379 participants at one year follow-up (182 (68%) in the intensive target arm and 197 (75%) in the standard target arm). All patients were followed up for clinical events and deaths" (p. i708, Figure 1).
Selective reporting (reporting bias)	Low risk	No reporting bias (the protocol publication was checked).
Other bias	Unclear risk	Only half of the total number of study participants met the review inclusion criteria (participants with previous stroke).

SPRINT 2015
Study characteristics

Methods	Multicentre, randomized, parallel, controlled trial. Blinded to outcomes assessor. Intervention was stopped early after a median follow-up of 3.26 years.
Participants	Men and women aged ≥ 50 years with SBP 130–180 mmHg (on 0 or 1 medication), 130–170 mmHg (on up to 2 medications), 130–160 mmHg (on up to 3 medications), or 130–150 mmHg (on up to 4 medications). Participants also had ≥ 1 of the following risk factors: <ul style="list-style-type: none"> • presence of clinical or subclinical CVD other than stroke; • CKD; • Framingham risk score for 10-year CVD risk of 15%; • aged ≥ 75 years. 2 major exclusion criteria: diabetes mellitus and stroke. Other exclusion criteria were secondary hypertension, proteinuria, recent cardiovascular event or procedure, and symptomatic heart failure within the past 6 months. Baseline characteristics of 1562 participants (% or mean): men/women: 76%/24%; age: 70 (SD 9) years; SBP: 138 (SD 16) mmHg; DBP: 74 (SD 12) mmHg; current smoker: 14%; ethnic group: white: 71%.
Interventions	Standard target: SBP < 140 mmHg Intensive target: SBP < 120 mmHg
Outcomes	Primary outcome: composite of non-fatal MI, acute coronary syndrome not resulting in MI, non-fatal stroke, non-fatal acute decompensated heart failure, and death from CVD. 3 subgroups were of particular interest: participants with and without CKD, black or non-black participants, and participants aged < or ≥ 75 years. SPRINT prespecified secondary outcomes included components of the primary outcome, total mortality, and a composite of the primary outcome (i.e. \CVD-free survival). Additional secondary CVD outcomes included peripheral arterial disease, coronary revascularization, TIA, LVH on ECG, and atrial fibrillation or flutter. Peripheral arterial disease included carotid and peripheral revascularization, abdominal aortic aneurysm repair, and other objectively defined peripheral arterial disease events.
Funding sources	Federal funds from the NHLBI, NIDDK, the National Institute on Aging, and the National Institute of Neurological Disorders and Stroke.
Declarations of interest	Study authors declared no conflicts of interest (In Clinical Trials 2014;11(5):532–46).

SPRINT 2015 (Continued)

In *New England Journal of Medicine* 2015;26;373(22):2103–16, Dr Ambrosius, Dr Johnson, Dr Rahman, Dr Reboussin, Dr Rocco, Dr Sink, Dr Williamson, and Dr Wright, Jr, reported grant support from NIH/NHLBI and non-financial support from Takeda Pharmaceuticals International, Inc, and Arbor Pharmaceuticals, LLC, during the conduct of the study. Dr Cheung and Dr Goff reported grant support from the NIH during the conduct of the study. Dr Cushman reported grant support from the NIH and non-financial support from Takeda Pharmaceuticals International, Inc, and Arbor Pharmaceuticals, LLC, during the conduct of the study; and personal fees from Takeda and Novartis outside the submitted work. Dr Cutler reported non-financial support from Takeda International Pharmaceuticals Inc, and Arbor Pharmaceuticals, Inc, during the conduct of the study, and personal fees from the NHLBI outside the submitted work. Dr Fine, Ms Snyder, and Dr Whelton reported non-financial support from Takeda Pharmaceuticals International, Inc, and Arbor Pharmaceuticals, LLC, during the conduct of the study. Dr Kimmel reported personal fees from Academic Press outside the submitted work. Dr Lewis reported grant support from the NIH and non-financial support from Takeda Pharmaceuticals International and Arbor Pharmaceuticals during the conduct of the study; and grant support from Novo Nordisk outside the submitted work. Dr Oparil reported grant support from the NIH/NHLBI during the conduct of the study; grant support from Merck and Co, the NIH/NHLBI, Novartis, and Arbor Pharmaceuticals, LLC; grant support and personal fees from AstraZeneca and Bayer; grant support, personal fees, and non-financial support from Medtronic; and personal fees from Forest Laboratories, Inc, Amgen (Onyx – Subsidiary), Boehringer Ingelheim, and GlaxoSmithKline outside the submitted work. In addition, Dr Oparil was co-chair (JNC 8): quote: "Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report from the Panel Members Appointed to the Eighth Joint National Committee (JNC 8), and Co-Chair, 2007–2013" (*JAMA* 2014;311(5):507–20).

Notes

4 institutes of the NIH cosponsored SPRINT. Study authors declared no conflicts of interest.

A public repository provided individual participant data on people with hypertension with established CVD for use in this Cochrane Review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	No detailed information provided on the randomization system used in the trial. Contacted study authors who confirmed via e-mail that they used a permuted block randomization scheme with random block lengths, stratified by clinic.
Allocation concealment (selection bias)	Low risk	Quote: "Participant randomization: SPRINT will use an internet-based, web browser randomization procedure. Clinical Sites access the randomization application through the study web site. Access to this application is password protected and its communications are encrypted. Once security requirements are satisfied, a series of questions identify and verify the eligibility of the participant. When the session is complete, an e-mail is sent to the Clinic Coordinator, the appropriate CCN, and the CC indicating that the participant has been properly randomized and appended to the database" (pp. 2103–16).
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study design was not compatible with blinding of participants and personnel.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Participants and study personnel were aware of the study-group assignments, but outcome adjudicators were not" (pp. 2103–16).
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition bias detected (pp. 2103–16, Figure 1).

SPRINT 2015 (Continued)

Selective reporting (reporting bias)	Low risk	No reporting bias detected (protocol checked).
Other bias	High risk	Only about 17% of total participants met review inclusion criteria (participants with established CVD). Trial was assessed as biased because it was stopped early for benefit.

SPS3 2013
Study characteristics

Methods	Multicentre open-label, clinical trial, ITT strategy, 2 × 2 factorial design with randomization to both an antiplatelet intervention and a target level of SBP control. Follow-up: 0–8.6 years (mean 3.7 years)
Participants	Participants were aged ≥ 30 years; normotensive or hypertensive; had a recent (within 180 days), symptomatic, MRI-confirmed lacunar stroke; and were without surgically amenable ipsilateral carotid artery stenosis or high-risk cardio-embolic sources. Main exclusion criteria: disabling stroke (modified Rankin score ≥ 4), previous intracranial haemorrhage from non-traumatic causes, or cortical ischaemic stroke. Baseline characteristics of 2709 participants (% or mean): men/women: 62%/38%; age: 63 (SD 11) years; SBP: 146 (SD 18) mmHg; DBP: 79 (SD 11) mmHg; diabetes: 36%; current smoker: 20%; ethnic groups: white: 53%, non-white: 49%. Types of drugs at 1 year: thiazides: 35%; ACEIs/ARBs: 71%; CCBs: 28%; BBs: 27%; other: 8%. Previous cardiovascular condition: IHD: 11%; stroke: 99%. Countries: USA, Canada, Mexico, Ecuador, Peru, Chile, Argentina, and Spain.
Interventions	Standard (higher) target: SBP 130–149 mmHg Lower target: SBP < 130 mmHg
Outcomes	Primary outcome: time to recurrent stroke (first of fatal or non-fatal ischaemic stroke or central nervous system haemorrhage). All possible clinical stroke events were assessed at the clinical site by both the local neurology investigator and a neurologist blinded to assigned treatment groups. Secondary outcomes included acute MI and death, classified as vascular or non-vascular. Safety events were major cognitive decline, major extracranial (systemic) haemorrhage, serious complication of hypotension, and other SPS3-related serious adverse events. Serious adverse events were major vascular events and severe adverse events related to hypotension. No information about non-vascular deaths or severe adverse events other than hypotension-related events was provided.
Funding sources	National Institute of Neurological Disorders and Stroke (USA)
Declarations of interest	Study authors declared no conflicts of interest.
Notes	The antiplatelet component of the trial was terminated at the recommendation of the data and safety monitoring committee because of lack of efficacy combined with evidence of harm. Blood pressures achieved at the end of the trial were: standard target SBP 138 (SD 1) mmHg; lower target SBP 127 (SD 1) mmHg.

Risk of bias

SPS3 2013 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization assignments were generated using a permuted-block design (variable block size), stored in each clinical centre's electronic data entry system, and protected from preview" (pp. 164–75).
Allocation concealment (selection bias)	Low risk	Quote: "Randomization assignments were generated using a permuted-block design (variable block size), stored in each clinical centre's electronic data entry system, and protected from preview" (pp. 164–75).
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study design was not compatible with blinding of participants and personnel.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The Prospective, Randomized, Open-label, Blinded Endpoint (PROBE) study design, a standard for international blood pressure trials, was utilised" (pp. 164–75).
Incomplete outcome data (attrition bias) All outcomes	Low risk	After review of individual participant data, no imbalance was found between interventions in relation to reasons for end of SPS3 participation
Selective reporting (reporting bias)	Low risk	Only serious adverse events related to hypotension and blood pressure management were reported. Despite repeated attempts to obtain clarification from the study authors, no response was received. At a later stage, all data were reviewed thanks to the National Institute of Neurologic Diseases and Stroke, which provided full access to individual participant data.
Other bias	Low risk	All participants met the base CVD criteria.

ACEI: angiotensin-converting enzyme inhibitor; ACCORD: Action to Control Cardiovascular Risk in Diabetes; ARB: angiotensin II receptor blocker; BB: beta-blocker; BMI: body mass index; CCB: calcium channel blocker; CHF: congestive heart failure; CKD: chronic kidney disease; CVD: cardiovascular disease; DBP: diastolic blood pressure; ECG: electrocardiography/electrocardiogram; GFR: glomerular filtration rate; HOT: Hypertension Optimal Treatment; IHD: ischaemic heart disease; ITT: intention-to-treat; LVH: left ventricular hypertrophy; MBP: mean blood pressure; MI: myocardial infarction; min: minute; MRI: magnetic resonance imaging; NHLBI: National Heart, Lung and Blood Institute; NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases; NIH: National Institutes of Health; NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases; NIH: National Institutes of Health; NIHR: National Institute for Health Research; PROBE: Prospective, Randomized, Open-label, Blinded Endpoint; PVD: peripheral vascular disease; RCT: randomized controlled trial; SBP: systolic blood pressure; sCR: serum creatinine; SD: standard deviation; SPRINT: Systolic Blood Pressure Intervention Trial; SPS3: Secondary Prevention of Small Subcortical Strokes; TIA: transient ischaemic attack.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
BBB 1994	Study data have been lost. The principal author (Professor Lennart Hansson) is deceased; Dr Bjorn Dahlöf confirmed that data have not been retained. Bayer was also contacted but confirmed the company does not have any data available for the BBB (Behandla Blodtryck Bättre) study. The journal <i>Blood Pressure</i> , in which BBB results were published, confirmed the manuscript received was essentially as the published version, and the documentation was destroyed about 10 years before (following Professor Hansson's death). The Swedish Council on Health Technology Assessment assessed the study in a report (No. 170/2) but did not have access to the original data. We also approached the Östra Hospital, where Professor Hansson was working at the time the study was conducted. No records were found, and we were told that the legal requirement to keep records safe expired after 15 years.

Study	Reason for exclusion
HOSP 2006	Number of recruited participants much smaller than intended and not enough for analysis of the effects of different levels of target home blood pressure.
INFINITY 2019	Fewer than 50 participants in each group with cardiovascular disease at baseline.
MDRD 1994	Fewer than 50 participants in each group with cardiovascular disease at baseline.
NCT01230216	Study not completed owing to slow participant enrolment.
PODCAST 2013	Fewer than 50 participants in each group with cardiovascular disease at baseline. Study is in progress, but the recruitment phase has closed.
PRESERVE 2018	Fewer than 50 participants in each group with cardiovascular disease at baseline.
REIN-2 2005	Fewer than 50 participants in each group with cardiovascular disease at baseline.
RESTART-AP 2013	Study not completed owing to lack of funding, according to information provided by study authors.

Characteristics of studies awaiting classification [ordered by study ID]

ABCD-H 1998

Methods	<p>Multicentre, controlled, randomized, 2 × 2 factorial design. The ABCD-H trial included hypertensive (DBP ≥ 90.0 mmHg) NIDDM. Participants were randomized to 1 of 4 groups: intensive treatment with nisoldipine, intensive treatment with enalapril, moderate treatment with nisoldipine, or moderate treatment with enalapril. Participants and investigators were not masked to blood pressure goals.</p> <p>Follow-up: 5 years</p>
Participants	<p>Adults with NIDDM aged 40–74 years with minimum DBP ≥ 90.0 mmHg.</p> <p>Exclusion criteria: MI, unstable angina or CVA within the previous 6 months, CABG surgery within the previous 3 months, Class III or IV NYHA CHF, absolute need for therapy with ACEI or CCB, haemodialysis or peritoneal dialysis, or serum creatinine concentration > 3 mg/dL (265 mmol/L).</p> <p>Country: USA</p>
Interventions	<p>Standard (moderate) target: DBP 80–89 mmHg</p> <p>Intensive target: DBP ≤ 75 mmHg</p>
Outcomes	<p>Primary endpoint: effect of intensive or moderate blood pressure control on the change in 24-hour creatinine clearance assessed every 6 months.</p> <p>Secondary endpoints: effects of intensive as compared with moderate blood pressure control on the incidence of cardiovascular events, retinopathy, clinical neuropathy, urinary albumin excretion, and LVH.</p> <p>All cardiovascular events were reviewed by an independent endpoints committee blinded to participants' assigned treatment groups. Cardiovascular outcomes were defined as death due to cardiovascular events (sudden death, progressive heart failure, fatal MI, fatal arrhythmias, CVAs, or ruptured aortic aneurysm); non-fatal MI; non-fatal CVA; heart failure requiring hospital admission; or pulmonary infarction.</p>

ABCD-H 1998 (Continued)

Notes	<p>Trial included a number of unspecified participants with basal angina as reported in the published article. Study authors were contacted to clarify this issue, but no definitive answer was received before publication of this review.</p> <p>After 67 months of study, the committee recommended discontinuation of nisoldipine therapy among participants with hypertension.</p>
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Cardio-Sis 2014

Methods	<p>Prospective, multicentre, randomized study with 2 parallel groups, ITT strategy, open-label design.</p> <p>Follow-up: 2 years</p>
Participants	<p>Adults aged > 55 years with uncontrolled SBP (≥ 150 mmHg) and ≥ 1 additional cardiovascular risk factor (cigarette smoking, total cholesterol ≥ 5.2 mmol/L, HDL cholesterol < 1.0 mmol/L, LDL cholesterol ≥ 3.4 mmol/L, family history of premature CVD in a first-degree relative (aged < 65 years in women and < 55 years in men), previous TIA or stroke, or established coronary or peripheral arterial disease).</p> <p>Exclusion criteria: diabetes, kidney failure, chronic atrial fibrillation or flutter, clinically significant hepatic or haematological disorders, alcoholism, or drug addiction, with causes precluding ECG interpretation for LVH, significant valvular heart disease, or any disease causing reduced life expectancy.</p> <p>Baseline characteristics (% or mean): men/women: 52%/48%; age: 71 (SD 7) years; SBP: 159 (SD 9) mmHg; DBP: 85 (SD 9) mmHg; current smoker: 7%; ethnic group: white: 100%.</p> <p>Country: Italy</p>
Interventions	<p>Standard (conventional) target: SBP < 140 mmHg</p> <p>Lower (aggressive) target: SBP < 130 mmHg</p>
Outcomes	<p>Primary outcome: prevalence of ECG LV hypertrophy at the final 2-year visit.</p> <p>Main secondary outcome: composite of all-cause mortality, non-fatal MI, non-fatal stroke, TIA, CHF NYHA stage III or IV requiring hospitalization, angina pectoris with objective evidence of myocardial ischemia, new-onset atrial fibrillation, coronary revascularization, aortic dissection, occlusive peripheral arterial disease, and kidney failure requiring dialysis.</p> <p>For participants with > 1 event, survival time up to the first event was used in the analysis. The comparison between groups in serial changes in SBP and DBP was another secondary endpoint of the study.</p>
Notes	<p>216 participants (115 in standard group, 101 in lower group) met the inclusion criteria for the review, but additional information on outcomes is needed to obtain useful data. Study authors were contacted, and they forwarded our questions to the Steering Committee. An answer had not been received from the committee before review publication</p> <p>Blood pressures achieved at the end of the trial were: standard target: SBP 139 (SD 14) mmHg; lower target: SBP 134 (SD 14) mmHg.</p>

RESPECT 2019

Methods	<p>Prospective, multicentre, open, masked endpoint, randomized clinical trial that included 140 hospitals in Japan between 20 October 2010 and 7 December 2016.</p>
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RESPECT 2019 (Continued)

Follow-up: 3.9 years

Participants	<p>Aged 50–85 years, independent ambulation, SBP 130–180 mmHg or DBP 80–110 mmHg on a regimen of 0–3 antihypertensive medications, and a history of stroke within the previous 3 years (evidence of an acute disturbance of focal neurological functions, with symptoms lasting > 24 hours, and symptomatic ischaemic stroke or intracerebral haemorrhage confirmed by MRI or computed tomography). Participation required written informed consent, and approval was provided by all local ethics committees for human research.</p> <p>Exclusion criteria: people in whom stroke onset occurred within previous month.</p>
Interventions	<p>Standard target: SBP < 140/90 mmHg or < 130/80 mmHg for people with diabetes, chronic kidney disease or history of MI</p> <p>Lower target: SBP < 120/80 mmHg</p>
Outcomes	<p>Primary endpoint: recurrent stroke, including ischaemic stroke and intracerebral haemorrhage. Recurrent stroke was clinically defined as a focal neurological deficit persisting for > 24 hours, as confirmed by MRI or computed tomography. Stroke was deemed fatal if death occurred within 30 days.</p> <p>Secondary endpoints: reductions in ischaemic stroke, subtype of ischaemic stroke (including atherothrombotic infarction, cardioembolic infarction, lacunar infarction, or infarction due to other and unknown aetiology), intracerebral haemorrhage, subarachnoid haemorrhage, TIA, acute MI defined by standard criteria (compatible clinical history with changes on ECG or in cardiac enzyme concentration), composite cardiovascular events (cardiovascular death, non-fatal stroke, and non-fatal MI), all-cause death, and the composite of all-cause death, non-fatal stroke, and non-fatal MI. Cardiovascular death was defined as sudden death, fatal stroke, fatal MI, fatal CHF, or death attributed to other CVD. All reported efficacy outcomes were confirmed by a central adjudication committee that was masked to treatment assignment. Serious adverse events were defined as those that were fatal or life-threatening, that resulted in clinically significant or persistent disability, that required hospitalization, or that were judged as a significant hazard or harm that required medical or surgical interventions.</p>
Notes	<p>Participants assigned to a standard target < 130/80 mmHg should be excluded from our database because they overlap with our lower target criteria ($\leq 135/85$ mmHg). To date, we have been unable to obtain information from the study authors to solve this issue.</p>

STABLE-ICAS 2018

Methods	<p>Prospective, randomized, open, blinded endpoint trial conducted at 10 centres in South Korea</p> <p>Follow-up: 6 months</p>
Participants	<p>People aged ≥ 40 years with symptomatic ICAS from 7 to 42 days after index ischaemic stroke. Symptomatic ICAS was defined as from the previous trials. Index ischaemic stroke lesions were elucidated on DWIs with a significant stenosis (> 50%) or occlusion at the corresponding middle cerebral artery (M1 portion) or distal ICA documented by MRI or computed tomography angiogram. Among them, those with a mean SBP ≥ 140 mmHg or who were taking antihypertensive medication were enrolled. After 5 minutes of stabilization, blood pressure was measured 3 times at 1-minute intervals from a sitting position. The participants whose mean SBP of the second and third measurements exceeded 140 mmHg were eligible.</p> <p>Key exclusion criteria: intractable hypertension on screening SBP 150 mmHg with > 3 antihypertensive medications), thrombolytic therapy for index ischaemic stroke without residual steno-occlusion, orthostatic hypotension, presumed cardioembolic stroke, planned cerebrovascular surgery or intervention within 7 months, absent baseline FLAIR image, severe stroke (National Institute of Health Stroke Scale 16), severe hypertension (mean SBP > 200 mmHg) during screening period and</p>

STABLE-ICAS 2018 *(Continued)*

	severe heart failure (NYHA class III or IV). The protocol was approved by the ethics committees of all participating centres.
Interventions	Standard (modest) target: SBP 130–140 mmHg Lower (intensive) target: SBP 110–120 mmHg
Outcomes	Primary endpoint: WML volume change in the whole forebrain on FLAIR image between baseline and 24 weeks. Secondary radiological endpoints: ischaemic lesion volume change in the ipsilateral hemisphere to the symptomatic ICAS between baseline and 24 weeks and NIL on 24-weeks FLAIR image. Secondary clinical endpoints were recurrent stroke, MI, and vascular death at 24 weeks.
Notes	We were interested in clarifying what type of cardiovascular events were included in the study because information in the article and clinicaltrials.gov was not coherent. Other controversial issues were the real number of total serious adverse events and ischaemic strokes reported. We made several attempts to contact the study authors but received no response. ClinicalTrials.gov: NCT01104311

Zeng 2016

Methods	Prospective, controlled, open-label study Follow-up: 10 years
Participants	People with hypertension aged > 65 years with chronic renal disease III to IV stage and macroproteinuria. Before randomization, all participants had been treated for 1 year with ACEI or ARBs and other antihypertensive drugs, but their SBP > 140 mmHg and < 150 mmHg.
Interventions	Standard target: SBP ≤ 150 mmHg Lower target: SBP ≤ 120 mmHg
Outcomes	Progress of renal disease and risk of development of CVD.
Notes	Complete information for this study is lacking. To date, only an abstract has been published in spite of the fact that the current follow-up is 10 years. For this reason, the study has been considered as a finished project awaiting classification.

ABCD-H: Appropriate Blood Pressure Control in Diabetes – Hypertension; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin AT1 receptor blocker; CABG: coronary artery bypass graft; CCB: calcium channel blocker; CHF: congestive heart failure; CVA: cerebrovascular accident; CVD: cardiovascular disease; DBP: diastolic blood pressure; DWI: diffusion weighted image; ECG: electrocardiogram; FLAIR: fluid-attenuated inversion recovery; HDL: high-density lipoprotein; ICA: internal carotid artery; ICAS: intracranial atherosclerosis; IHD: ischaemic heart disease; ITT: intention-to-treat; LDL: low-density lipoprotein; LV: left ventricular; LVH: left ventricular hypertrophy; MI: myocardial infarction; MRI: magnetic resonance imaging; NIDDM: non-insulin-dependent diabetes mellitus; NIL: new ischaemic lesion; NYHA: New York Heart Association; SBP: systolic blood pressure; SD: standard deviation; TIA: transient ischaemic attack; WML: white matter lesion.

Characteristics of ongoing studies *[ordered by study ID]*
BPROAD 2019

Study name	BPROAD study
Methods	Multicentre, open-label, parallel-group, randomized controlled trial that will be conducted across mainland China.

Blood pressure targets for the treatment of people with hypertension and cardiovascular disease (Review)

BPROAD 2019 (Continued)

Expected follow-up: 5 years

Participants	<p>Inclusion criteria: men and women aged ≥ 50 years; diabetes defined as: a self-reported previous diagnosis by healthcare professionals and taking antidiabetic medications; fasting plasma glucose level ≥ 126 mg/dL (7.0 mmol/L); SBP ≥ 140 mmHg on 0 medication; 130–180 mmHg on 1 medication; 130–170 mmHg on up to 2 medications; 130–160 mmHg on up to 3 medications; or 130–150 mmHg on up to 4 medications; increased risk of CVD.</p> <p>Exclusion criteria: history consistent with type 1 diabetes; known secondary cause of hypertension; 1 minute standing SBP < 110 mmHg; arm circumference too large to allow accurate BP measurement with available devices; cardiovascular event or procedure or hospitalization for unstable angina within the past 3 months; symptomatic heart failure within the past 6 months or left ventricular ejection fraction (by any method) $< 35\%$ within the past 6 months; ALT or AST levels more than twice the upper limit of the normal range or active liver diseases; dialysis, kidney transplantation, eGFR < 30 mL/minute/1.73 m², or sCR > 2.0 mg/dL; proteinuria; previous diagnosis of polycystic kidney disease or glomerulonephritis; a medical condition likely to limit survival to < 5 years; any factors judged by the clinic team to be likely to limit adherence to interventions; failure to obtain informed consent from participant; currently participating in another intervention study; currently living with another BPROAD participant; pregnancy, currently trying to become pregnant, or of child-bearing potential and not using contraception.</p>
Interventions	<p>Standard target: SBP < 140 mmHg</p> <p>Lower target: SBP < 120 mmHg</p>
Outcomes	<p>Primary outcome: major cardiovascular events.</p> <p>Secondary outcomes: composite of the primary outcome and all-cause mortality; macrovascular outcomes; major coronary artery diseases; total stroke; heart failure; cardiovascular death; total mortality; cognitive function; health-related quality of life; kidney outcomes.</p>
Starting date	February 2019
Contact information	<p>Yu Xu, MD, PhD +86-15921811120 jane.yuxu@gmail.com</p> <p>Yufang Bi, MD, PhD +86-21-64370045 ext 663340 byf10784@rjh.com.cn</p>
Notes	Sponsor: Shanghai Jiao Tong University School of Medicine

ESH-CHL-SHOT 2014

Study name	ESH-CHL-SHOT study
Methods	<p>Prospective, multinational, randomized trial, with a 3×2 factorial design: 3 different SBP targets; 2 different LDL-C targets. The trial is designed as a Prospective, Randomized, Open-Blind Endpoint evaluation (PROBE) trial.</p> <p>Expected mean follow-up: 4 years</p>
Participants	<p>Men and women aged ≥ 65 years. Qualifying event is stroke or TIA 1–6 months before randomization. Untreated people should have SBP ≥ 140 mmHg, and those on antihypertensive treatment could be included irrespective of their BP. People not receiving statin treatment with LDL-C > 2.8 mmol/L, and those on statin treatment with any LDL-C value could be included. All participants should receive antiplatelet therapy (or anticoagulant whenever indicated) unless contraindicated.</p> <p>Exclusion criteria: people with unstable clinical conditions; clinical disturbances caused by non-stroke pathology; haemodynamically significant carotid stenosis or requiring carotid revascularization; secondary hypertension; SBP > 140 mmHg with 3 antihypertensive drugs at full doses and</p>

ESH-CHL-SHOT 2014 (Continued)

orthostatic hypotension; people with LDL-C > 2.8 mmol/L under full dose of a statin, LDL-C > 4.5 mmol/L with low dose of a statin or untreated, history of MI if baseline LDL-C < 1.8 mmol/L; dementia; severe disability (modified Rankin scale > 4); severe CKD defined as sCR > 250 mmol/L.

Interventions	Standard target: SBP < 135–145 mmHg Intensive target: SBP < 125–135 mmHg or < 125 mmHg
Outcomes	Primary endpoint: occurrence of (recurrent) stroke (fatal and non-fatal). Secondary cardiovascular endpoints are time to occurrence of: first major cardiovascular event: a composite of cardiovascular death, non-fatal stroke, non-fatal MI, vascular interventions, and hospitalized heart failure; CHD events: a composite of sudden death, fatal and non-fatal MI, unstable angina, and coronary interventions; all-cause death; cardiovascular death: a composite of fatal stroke, fatal MI, sudden death, any other death attributed to CVD; hospitalized heart failure; new-onset atrial fibrillation; ischaemic stroke; haemorrhagic stroke; composite of stroke and TIA.
Starting date	April 2013
Contact information	Alberto Zanchetti, Istituto Auxologico Italiano, Via L. Ariosto 13, 20145 Milan, Italy. Tel: +39 02 619112237; e-mail: alberto.zanchetti@auxologico.it
Notes	The published byline includes 53 co-authors; no reported conflicts of interest. The activity of the General Coordinating Centre in Milan is supported by institutional research funds of Fondazione Istituto Auxologico Italiano. It also collaborates the European Society of Hypertension and the Chinese Hypertension League.

ESPRIT 2019

Study name	ESPRIT study
Methods	Multicentre, open-label, randomized controlled trial Expected follow-up: 4 years
Participants	Participants aged ≥ 50 years with a mean baseline SBP ≥ 130 mmHg and history of CVDs or at high vascular risk.
Interventions	Standard target: SBP < 140 mmHg Intensive target: SBP < 120 mmHg
Outcomes	Primary outcome: number of participants with composite of major CVD events Secondary outcomes: number of participants with: MI; coronary revascularization; non-coronary revascularization; chronic or acute decompensated heart failure hospitalization or emergency department visit; stroke; cardiovascular death; all-cause death; composite outcome of the primary composite with all-cause death; ESKD, a sustained decline in eGFR to < 10 mL/minute/1.73 m ² , renal death, or a sustained decline of ≥ 40% in eGFR from randomization; all-cause dementia or mild cognitive impairment.
Starting date	August 2019
Contact information	Jing Li, MD, PhD +86 (10) 6086 6077 jing.li@fwoxford.org Xinghe Huang, PhD +86 18800120831 xinghe.huang@fwoxford.org

ESPRIT 2019 (Continued)

Notes

Sponsor: China National Center for Cardiovascular Diseases

IBIS 2019

Study name	IBIS study
Methods	Multicentre, randomized, controlled trial
Participants	<p>Inclusion criteria: men and women aged ≥ 40 years; history of symptomatic, MRI/CT-confirmed ischaemic stroke (3–12 months since last acute onset); SBP ≥ 140 mmHg on 0 medication; 135–180 mmHg on 1 medication; 135–170 mmHg on up to 2 medications; 135–160 mmHg on up to 3 medications; or 135–150 mmHg on up to 4 medications.</p> <p>Exclusion criteria: documented symptomatic intracranial or extracranial stenosis ($\geq 50\%$) (or both), or asymptomatic intracranial or extracranial stenosis ($\geq 70\%$) (or both); disabling stroke (modified Rankin score ≥ 4); previous intracranial haemorrhage from a non-traumatic cause; any symptoms of orthostatic hypotension during the standing BP measurement, or standing SBP < 110 mmHg; severe heart failure (NYHA class III and IV) within the past 6 months or left ventricular ejection fraction (by any method) $< 35\%$; any history of atrial fibrillation, ventricular aneurysm, or suspicion of cardioembolic pathology for stroke; other specific cause of stroke identified by routine clinical care (e.g. arteritis, dissection, migraine/vasospasm, drug abuse); dialysis, eGFR < 20 mL/minute/1.73 m², urine protein-to-creatinine ratio ≥ 1 g/g, or albumin-to-creatinine ratio ≥ 600 mg/g; planned or probable revascularization (any angioplasty or vascular surgery) within 3 months after screening; a medical condition likely to limit survival to < 3 years; a cancer diagnosed and treated within the past 2 years that, in the judgement of clinical study staff, would compromise a participant's ability to comply with the protocol and complete the trial (except non-melanoma skin cancer, early-stage prostate cancer, or localized breast cancer); any factors judged by the clinic team to be likely to limit adherence to the intervention; failure to obtain informed consent from a participant; currently participating in another intervention study; pregnant, currently trying to become pregnant, or of child-bearing potential and not using contraception.</p>
Interventions	<p>Standard target: SBP < 140 mmHg</p> <p>Intensive target: SBP < 120 mmHg</p>
Outcomes	<p>Primary outcome: stroke event</p> <p>Secondary outcomes: composite major CVD events; MI; non-MI acute coronary syndrome; heart failure; dementia; all-cause mortality</p>
Starting date	July 2020
Contact information	<p>Jiang He, MD, PhD 504-988-5165 jhe@tulane.edu</p> <p>Yilong Wang, MD, PhD 011-86-13911666571 yilong528@aliyun.com</p>
Notes	Sponsors: Tulane University and Beijing Tiantan Hospital

NCT03015311

Study name	STEP study
Methods	<p>Multicentre, prospective, randomized, open-label, blind endpoint trial</p> <p>Follow-up: 4 years</p>

NCT03015311 (Continued)

Participants	<p>Men and women aged 60–80 years, with SBP 140–190 mmHg in the 3 screening visits or currently under antihypertensive treatment and having signed the written informed content.</p> <p>Exclusion criteria: SBP \geq 190 mmHg or DBP $<$ 60 mmHg; known secondary cause of hypertension; history of large atherosclerotic cerebral infarction or haemorrhagic stroke (not lacunar infarction and TIA); hospitalization for MI or unstable angina within the previous 6 months; coronary revascularization (PCI or CABG) within the previous 12 months; planned to perform coronary revascularization (PCI or CABG) in the next 12 months; history of sustained atrial fibrillation or ventricular arrhythmias at entry influencing the measurement of electronic BP; NYHA class III or IV heart failure at entry or hospitalization for exacerbation of chronic heart failure within the previous 6 months; severe valvular disease or valvular disease likely to require surgery or percutaneous valve replacement during the trial; dilated or hypertrophic cardiomyopathy, rheumatic heart disease, or congenital heart disease; uncontrolled diabetes (serum fasting glucose \geq 200 mg/dL (11.1 mmol/L, HbA1c $>$ 8%); laboratory tests indicating abnormal liver or kidney function (ALT $>$ 3 times the upper limit of normal value, or ESKD on dialysis, or eGFR $<$ 30 mL/minute, or sCR $>$ 2.5 mg/dL ($>$ 221 μmol/L)); severe somatic disease such as cancer; severe cognitive impairment or mental disorders; participating in other clinical trials.</p>
Interventions	<p>Standard target: 130–149 mmHg</p> <p>Intensive target: 110–129 mmHg</p>
Outcomes	<p>Primary outcomes: a composite endpoint comprising MI, first occurrence of symptomatic stroke (ischaemic or haemorrhagic, fatal or non-fatal), hospitalization for unstable angina or acute decompensated heart failure, coronary revascularization (PCI, CABG), and death from cardiovascular causes.</p> <p>Secondary outcomes: major coronary events comprising MI, hospitalization for unstable angina or acute decompensated heart failure, coronary revascularization (PCI, CABG), and death from cardiovascular causes; first occurrence of symptomatic stroke (ischaemic or haemorrhagic, fatal or non-fatal); all-cause death; cardiovascular death; MI; hospitalization for unstable angina; hospitalization for acute decompensated heart failure; coronary revascularization (PCI, CABG); first occurrence of diabetes mellitus; decline in cognitive function; decline in renal function or development of ESKD; major artery function changes.</p>
Starting date	December 2016
Contact information	Weili Zhang, MD (zhangweili1747@yahoo.com); Guomei Wu (wuguomei513@163.com)
Notes	

NCT03666351

Study name	NCT03666351
Methods	A prospective, multicentre, randomized, open label, evaluator blind study
Participants	<p>Inclusion criteria: men or women aged \geq 19 years and $<$ 80 years; diagnosis of mild-moderate AS or mild-moderate AR; applicable to 2.0–3.9 m/second of aortic jet velocity for mild-moderate AS or to 0.2–0.6 cm of Vena contracta for mild-moderate AR; diagnosis of hypertension (SBP $>$ 130 mmHg if being treated or SBP $>$ 140 mmHg if being untreated); for women of childbearing potential; negative pregnancy test results during the screening period and prior to administration of the investigational product, and agreement on use of medically allowable contraceptive measures (condom, oral contraceptive pills, injectable or implantable contraceptives, intrauterine devices, birth control patches, etc.) during the study period; voluntary written consent to taking part in the clinical study and willingness to comply with requirements of the study.</p>

NCT03666351 (Continued)

	<p>Main exclusion criteria: history of a cardiac valve replacement surgery (replacement surgery of mitral valve, aortic valve or tricuspid valve); accompanied by severe mitral regurgitation; admitted to needing a surgery by the current treatment guidelines; accompanied by symptoms such as angina pectoris, exertional dyspnoea, syncope, etc.; < 50% of left ventricular ejection fraction.</p>
Interventions	<p>Standard target: SBP ≤ 140 mmHg</p> <p>Lower target: SBP ≤ 130 mmHg</p>
Outcomes	<p>Primary outcome: changes from baseline in left ventricular mass at 24 months</p> <p>Secondary outcomes: changes from baseline in left ventricular global longitudinal strain at 24 months; changes from baseline in E/E' (E: early diastolic LV inflow velocity, E': early diastolic mitral annulus velocity) at 24 months; changes from baseline in left ventricular volumes at 24 months; rate of disease progression; changes from baseline in SBP at 6 months, 12 months, 18 months, 24 months; cumulative incidence rate for each visit time point; changes from baseline in stroke volume index at 24 months; changes from baseline in left ventricular ejection fraction at 24 months</p>
Starting date	August 2018
Contact information	Jong-Hwan Jeon +821040984928 jonghwan06@hanmi.co.kr
Notes	Sponsor: Hanmi Pharmaceutical Company Limited

OPTIMAL Stroke 2019

Study name	OPTIMAL Stroke study
Methods	<p>2-group, multicentre, randomized clinical trial</p> <p>Expected follow-up: 3.5 years</p>
Participants	<p>Inclusion criteria: history of ischaemic stroke or TIA, considered clinically stable in the 2 weeks prior to inclusion in the study (they will be classified into a recent stroke < 120 days or chronic when > 120 days), AND SBP 130–180 mmHg, 130–180 mmHg and use of up to 1 antihypertensive drug, 130–170 mmHg and use of up to 2 drugs, 130–160 mmHg and use of up to 3 drugs, 130–150 mmHg and use of up to 4 drugs. AND to be considered as having a high cardiovascular risk.</p> <p>Main exclusion criteria: history of primary intracranial haemorrhage; severe disability after the event that qualified him for the study, defined as a modified Rankin (mRankin) scale ≥ 4; being part of another clinical trial involving interventions for cardiovascular prevention; mean SBP at the screening visit < 130 mmHg; body mass index > 45 kg/m²; pregnancy or breastfeeding; secondary hypertension; Class IV Canadian Cardiovascular Society (CCS) resting angina; severe renal disease (GFR, 20 mL/minute/1.73 m² calculated by the Modification of Diet in Renal Disease equation); refusal to consent.</p>
Interventions	<p>Standard target: SBP < 140 mmHg</p> <p>Intensive target: SBP < 120 mmHg</p>
Outcomes	<p>Primary outcome: time to non-fatal MI, non-fatal stroke, or cardiovascular death.</p> <p>Secondary outcomes: time to non-fatal MI, non-fatal stroke, or total death; time to death; time to cardiovascular death; time to stroke; time to haemorrhagic stroke; time to ischaemic stroke; time to unclassified stroke; time to MI; time to hospitalization due to heart failure; time to hospitalization due to unstable angina; time to renal outcome; time to mild cognitive impairment; time to a composite outcome of mild cognitive impairment or probable all-cause dementia; total brain volume; white matter lesions volume.</p>

OPTIMAL Stroke 2019 (Continued)

Starting date	August 2019
Contact information	Maria Julia Machline Carrion, MD, PhD 11 2151-5915 ext 75915 julia.carrion@einstein.br Gisele Sampaio Silva, MD, PhD 11 2151-5915 ext 75915
Notes	Sponsors: Hospital Israelita Albert Einstein and Ministry of Health, Brazil

OPTIMAL-DIABETES 2019

Study name	OPTIMAL-DIABETES study
Methods	2-group, multicentre, randomized clinical trial Expected follow-up: 3.5 years
Participants	Inclusion criteria: SBP 130–180 mmHg, 130–150 mmHg (if on 0–4 medications), 130–160 mmHg (if on 0–3 medications), 130–170 mmHg (if on 0–2 medications), 130–180 mmHg (if on 0–1 medications); type 2 diabetes; to be considered as having a high cardiovascular risk, including ≥ 1 of the following factors: established CVD; subclinical CVD, chronic kidney disease, additional cardiovascular risk factors. Main exclusion criteria: refusal to provide written informed consent; body mass index > 45 kg/m ² , known secondary cause of hypertension, severe renal dysfunction with GFR < 20 mL/minute/1.73 m ² calculated by the CKD-EPI equation; angina at rest Class IV Canadian Cardiovascular Society; acute coronary syndrome in the last 6 months; symptomatic heart failure Class IV NYHA or ejection fraction $< 35\%$ on Doppler echocardiography in the last 6 months.
Interventions	Standard target: SBP < 140 mmHg Intensive target: SBP < 120 mmHg
Outcomes	Primary outcome: time to cardiovascular death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, or hospitalization for heart failure. Secondary outcomes: time to cardiovascular death, non-fatal MI, or non-fatal stroke; time to total death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, or hospitalization for heart failure; time to death; time to cardiovascular death; time to renal death; time to MI; time to stroke; time to ischaemic stroke; time to haemorrhagic stroke; time to undetermined type of stroke; time to TIA; time to hospitalization for unstable angina; time to hospitalization for heart failure; time to renal outcome; time to mild cognitive impairment; time to mild cognitive impairment or all-cause probable dementia; time to all-cause probable dementia; total brain volume; white matter lesions volume.
Starting date	August 2019
Contact information	Karla Santo, MD, PhD +55 11 2151-5915 karla.santo@einstein.br Diogo Moia +55 11 2151-5915 diogo.moia@einstein.br
Notes	Sponsors: Hospital Israelita Albert Einstein and Ministry of Health, Brazil

ALT: alanine aminotransferase; AR: aortic regurgitation; AS: aortic stenosis; AST: aspartate aminotransferase; BP: blood pressure; BROAD: Blood Pressure Control Target in Diabetes; CABG: coronary artery bypass graft; CHD: coronary heart disease; CHF: congestive heart failure; CKD: chronic kidney disease; CT: computer tomography; CVD: cardiovascular disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; GFR: glomerular filtration rate; HbA1c: glycosylated haemoglobin; LDL-C:

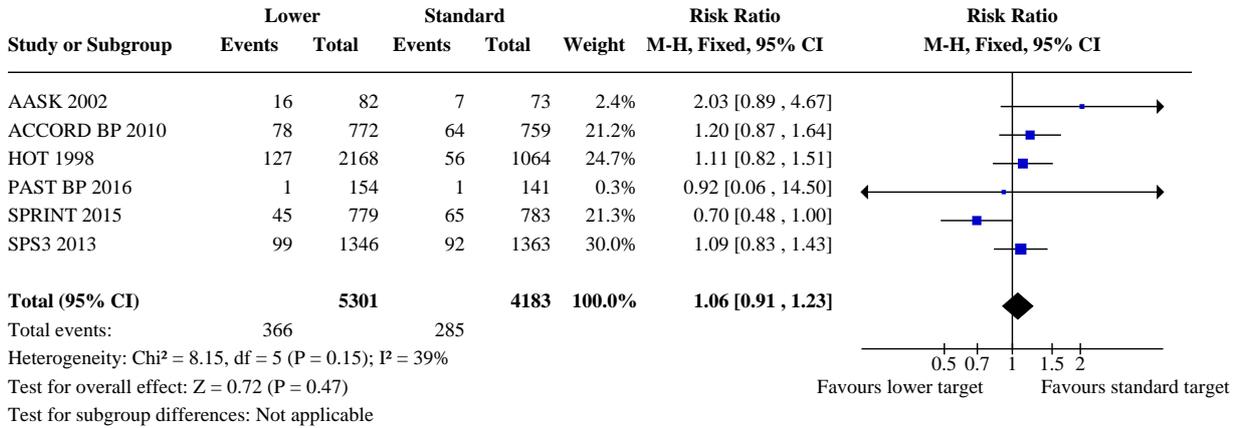
low-density lipoprotein cholesterol; MI: myocardial infarction; MRI: magnetic resonance imaging; DWI: diffusion weighted imaging; PCI: percutaneous coronary intervention; SBP: systolic blood pressure; sCR: serum creatinine; TIA: transient ischaemic attack.

DATA AND ANALYSES

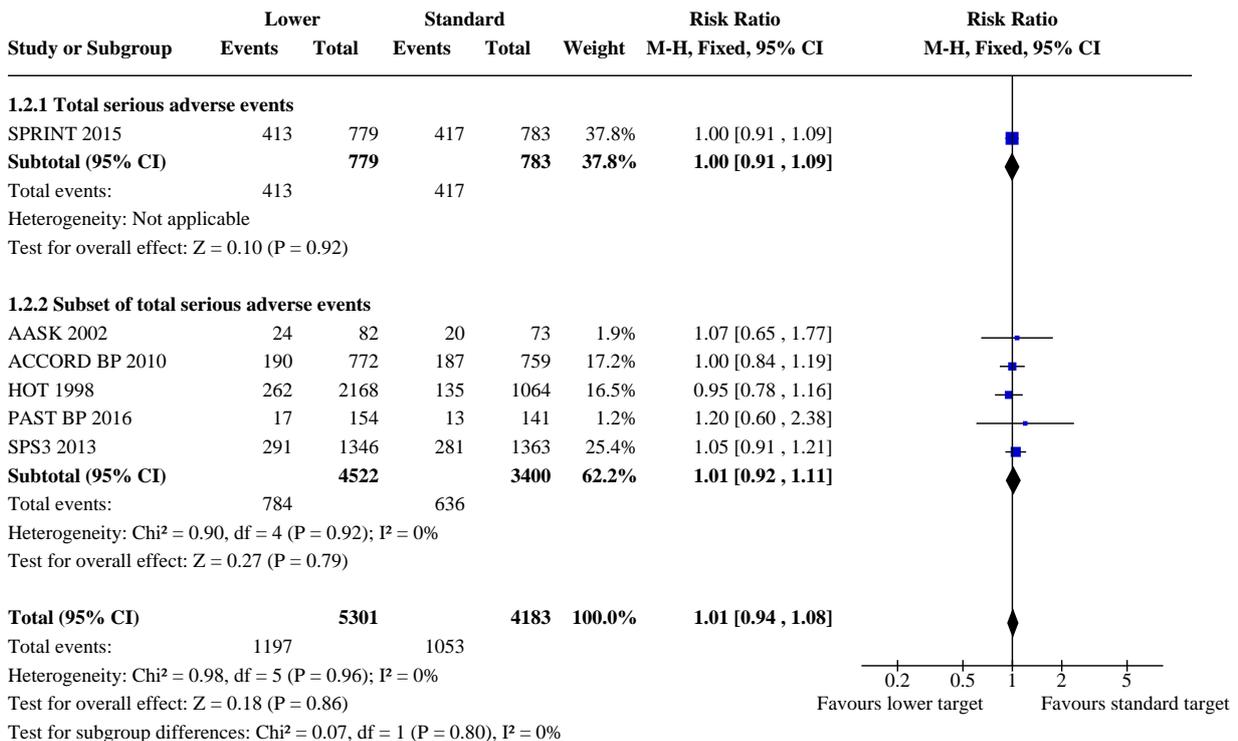
Comparison 1. Lower versus standard blood pressure targets for people with hypertension and history of cardiovascular disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Total mortality	6	9484	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.91, 1.23]
1.2 Total serious adverse events	6	9484	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.94, 1.08]
1.2.1 Total serious adverse events	1	1562	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.91, 1.09]
1.2.2 Subset of total serious adverse events	5	7922	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.92, 1.11]
1.3 Total cardiovascular events	6	9484	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.80, 1.00]
1.4 Cardiovascular mortality	6	9484	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.82, 1.29]
1.5 Participant withdrawals due to adverse effects	2	690	Risk Ratio (M-H, Fixed, 95% CI)	8.16 [2.06, 32.28]
1.6 Blood pressure target achieved at 1 year	6	8588	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [1.17, 1.24]
1.7 Systolic blood pressure change from baseline at 1 year	6	8546	Mean Difference (IV, Random, 95% CI)	-8.90 [-13.24, -4.56]
1.8 Diastolic blood pressure change from baseline at 1 year	6	8546	Mean Difference (IV, Random, 95% CI)	-4.50 [-6.35, -2.65]
1.9 Number of antihypertensive drugs needed that each participant at the end of study	5	7910	Mean Difference (IV, Random, 95% CI)	0.56 [0.16, 0.96]

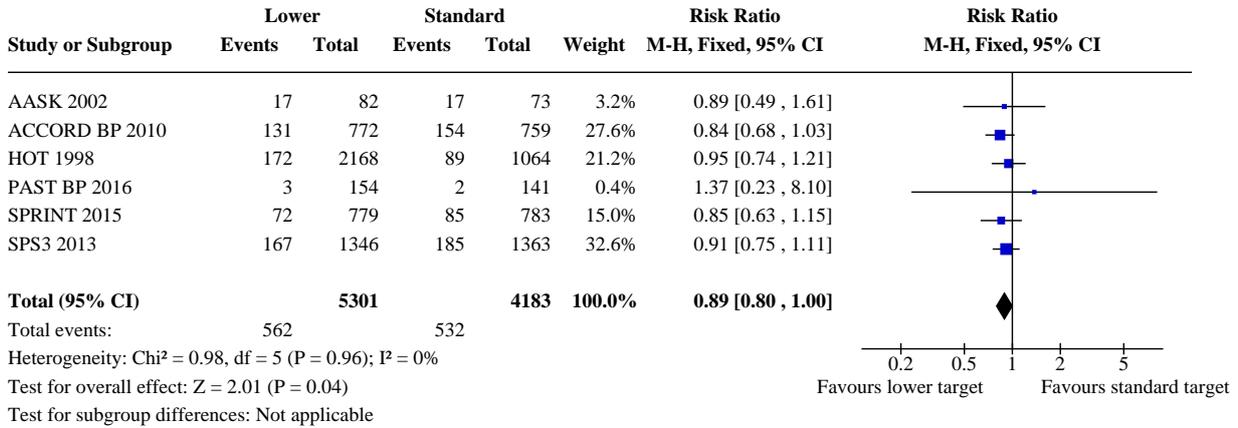
Analysis 1.1. Comparison 1: Lower versus standard blood pressure targets for people with hypertension and history of cardiovascular disease, Outcome 1: Total mortality



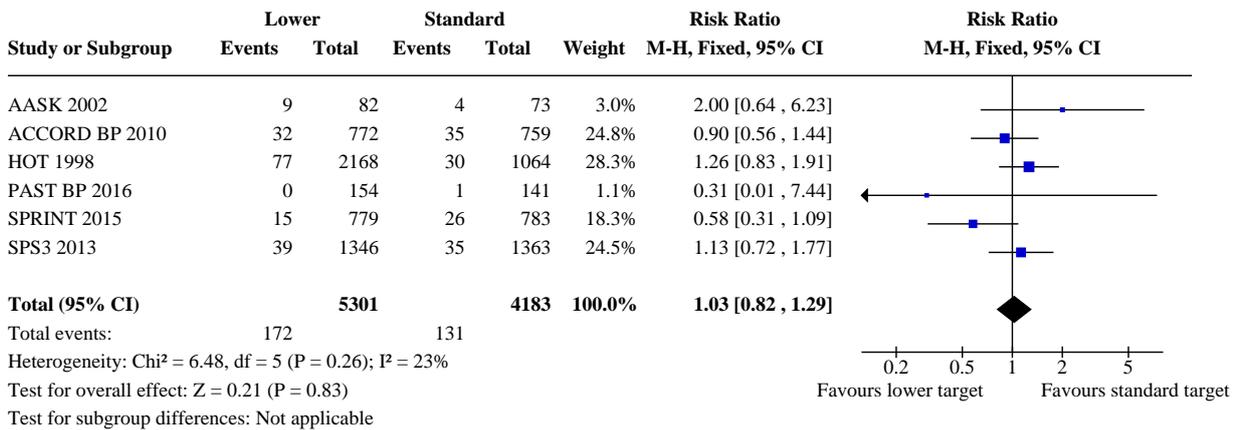
Analysis 1.2. Comparison 1: Lower versus standard blood pressure targets for people with hypertension and history of cardiovascular disease, Outcome 2: Total serious adverse events



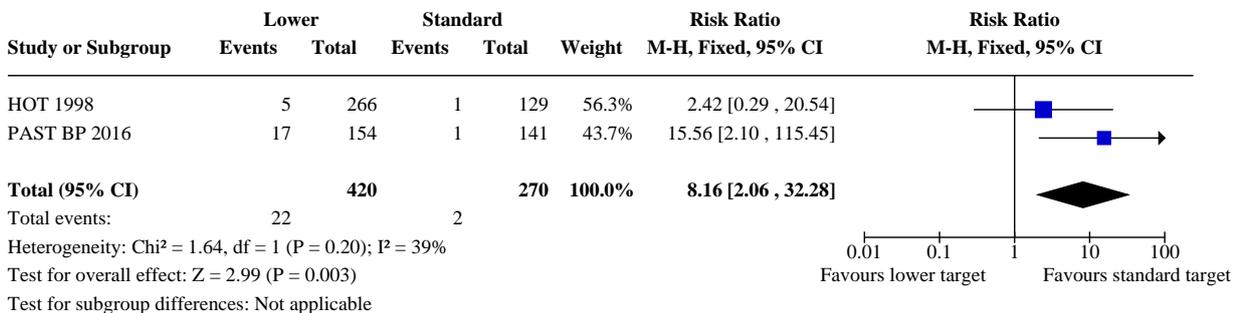
Analysis 1.3. Comparison 1: Lower versus standard blood pressure targets for people with hypertension and history of cardiovascular disease, Outcome 3: Total cardiovascular events



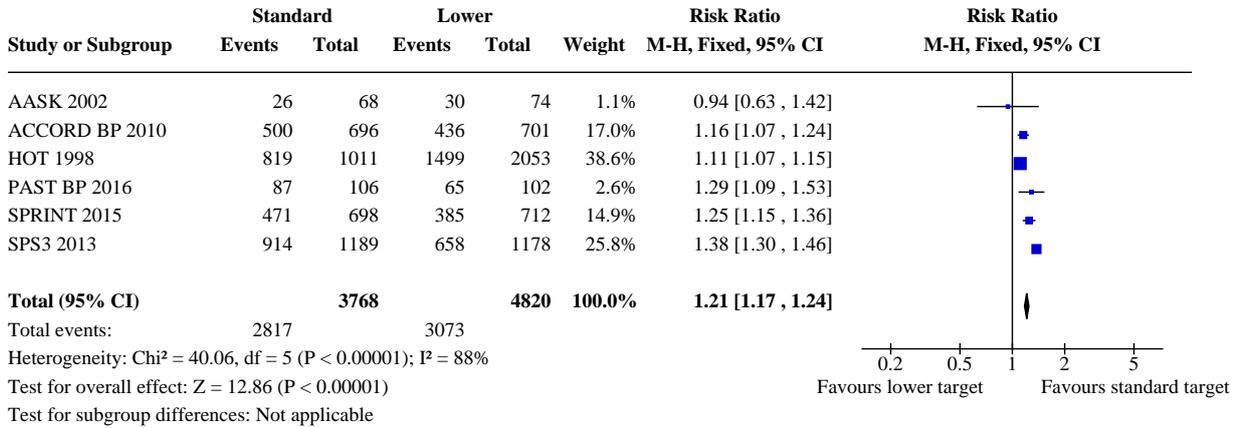
Analysis 1.4. Comparison 1: Lower versus standard blood pressure targets for people with hypertension and history of cardiovascular disease, Outcome 4: Cardiovascular mortality



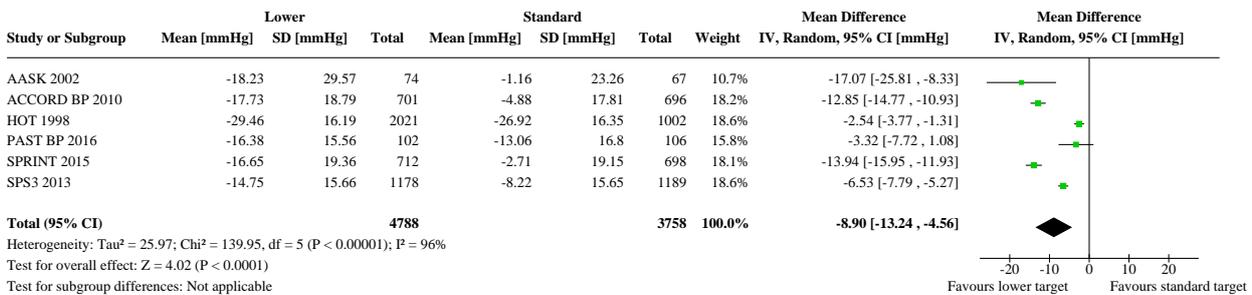
Analysis 1.5. Comparison 1: Lower versus standard blood pressure targets for people with hypertension and history of cardiovascular disease, Outcome 5: Participant withdrawals due to adverse effects



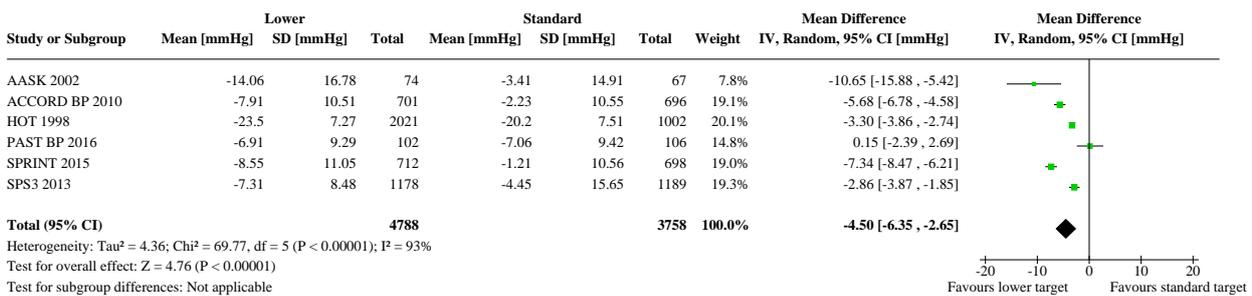
Analysis 1.6. Comparison 1: Lower versus standard blood pressure targets for people with hypertension and history of cardiovascular disease, Outcome 6: Blood pressure target achieved at 1 year



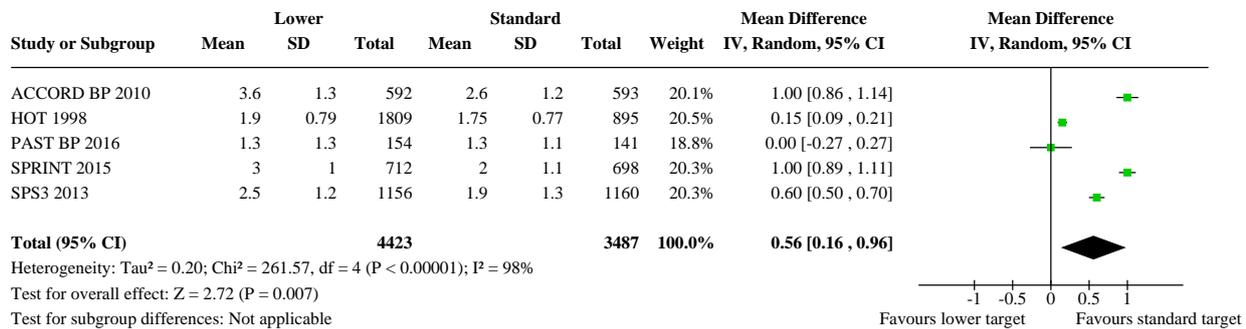
Analysis 1.7. Comparison 1: Lower versus standard blood pressure targets for people with hypertension and history of cardiovascular disease, Outcome 7: Systolic blood pressure change from baseline at 1 year



Analysis 1.8. Comparison 1: Lower versus standard blood pressure targets for people with hypertension and history of cardiovascular disease, Outcome 8: Diastolic blood pressure change from baseline at 1 year



Analysis 1.9. Comparison 1: Lower versus standard blood pressure targets for people with hypertension and history of cardiovascular disease, Outcome 9: Number of antihypertensive drugs needed that each participant at the end of study



ADDITIONAL TABLES

Table 1. Baseline characteristics of included study participants

Mean unless otherwise stated	AASK 2002	ACCORD BP 2010	HOT 1998	PAST BP 2016	SPRINT 2015	SPS3 2013
Number of participants	155	1531	3232	295	1562	2709
Sex (% male)	68%	63%	53%	64%	76%	62%
Age (years)	57 (SD 9)	62 (SD 8)	62 (-)	71 (SD 9)	70 (SD 9)	63 (SD 11)
Ethnic group (% Caucasian)	0%	62%	92%	98%	71%	53%
Diabetes	0%	100%	12%	10%	0%	36%
Current smoker	31%	13%	16%	13%	14%	20%
Systolic blood pressure	149 (SD 28)	138 (SD 16)	174 (SD 15)	143 (SD 14)	138 (SD 16)	146 (SD 18)
Diastolic blood pressure	93 (SD 16)	74 (SD 11)	106 (SD 3)	80 (SD 10)	74 (SD 12)	79 (SD 11)
Ischaemic heart disease	25%	86%	95%	22%	—	11%
Stroke	69%	20%	7%	85%	0%	99%
Peripheral vascular disease	23%	—	—	7%	—	—
Thiazides	—	51%	—	35%	—	35%
ACEI/ARB	—	84%	—	65%	—	71%
Calcium channel blocker	—	26%	—	43%	—	28%
Beta blocker	—	57%	—	20%	—	27%

Table 1. Baseline characteristics of included study participants (Continued)

Other antihypertensive drugs	—	28%	—	11%	—	8%
Number of antihypertensive drugs	—	3.0 (SD 1.4)	1.0 (-)	1.1 (SD 0.8)	2.1 (SD 1.0)	1.7 (SD 1.1)

(-) no information is available. Ischaemic heart disease, stroke, and peripheral vascular disease percentages are independent of each other because participants can have more than one cardiovascular event at the same time. A similar explanation can be offered with respect to percentages in the different classes of antihypertensive drugs.

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; SD: standard deviation.

Table 2. Lower versus standard blood pressure target; people with diabetes, difference in targets 10 mmHg or greater

Outcome	Studies	Participants	Statistical method	Effect estimate
Total mortality	ACCORD BP 2010 ; HOT 1998 ; SPS3 2013	2773	Risk ratio (M-H, fixed, 95% CI)	1.15 (0.91 to 1.45)
Cardiovascular mortality	ACCORD BP 2010 ; HOT 1998 ; SPS3 2013	2773	Risk ratio (M-H, fixed, 95% CI)	0.98 (0.69 to 1.39)
Cardiovascular events	ACCORD BP 2010 ; HOT 1998 ; SPS3 2013	2773	Risk ratio (M-H, fixed, 95% CI)	0.88 (0.74 to 1.03)
Serious adverse events	ACCORD BP 2010 ; HOT 1998 ; SPS3 2013	2773	Risk ratio (M-H, fixed, 95% CI)	1.01 (0.88 to 1.15)

APPENDICES

Appendix 1. Search strategies

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

Search Date: 6 November 2019

1 exp cardiovascular diseases/ (2316710)
 2 ((heart or myocardial) adj5 (attack\$ or disease\$ or infarc\$)).tw,kf. (375371)
 3 (coronary adj5 (disease\$ or syndrome\$)).tw,kf. (179550)
 4 ((cardiovascular or peripheral or vascular) adj5 disease\$).tw,kf. (258940)
 5 atrial fibril\$.tw,kf. (66863)
 6 ((cardiac or heart) adj failure).tw,kf. (174233)
 7 angina\$.tw,kf. (54772)
 8 exp ischemia/ (57462)
 9 (ischaemi\$ or ischemi\$).tw,kf. (368139)
 10 exp stroke/ (126849)
 11 (CVA or poststroke or post-stroke or stroke or strokes).tw,kf. (240455)
 12 apoplexy.tw,kf. (3030)
 13 cerebrovascul\$.tw,kf. (55617)
 14 cerebral vascular.tw,kf. (5788)
 15 ((brain\$ or cerebral\$ or lacunar) adj2 (accident\$ or infarct\$)).tw,kf. (27760)
 16 or/1-15 (2718485)
 17 ((goal? or intensive\$ or strict\$ or target\$ or tight\$) adj6 (antihypertensive? or anti-hypertensive? or bp or control or dbp or diastolic or pressure? or sbp or systolic or treat\$)).tw,kf. (190436)
 18 hypertension/ (229360)
 19 essential hypertension/ (2286)

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20 (antihypertens\$ or hypertens\$).tw,kf. (438936)
 21 exp blood pressure/ (285264)
 22 (blood pressure or bloodpressure).tw,kf. (295071)
 23 or/18-22 (766427)
 24 randomized controlled trial.pt. (493887)
 25 controlled clinical trial.pt. (93410)
 26 randomized.ab. (459969)
 27 placebo.ab. (202711)
 28 clinical trials as topic/ (189050)
 29 randomly.ab. (321220)
 30 trial.ti. (207652)
 31 or/24-30 (1249639)
 32 animals/ not (humans/ and animals/) (4607630)
 33 31 not 32 (1149583)
 34 16 and 17 and 23 and 33 (3277)
 35 34 and (2017\$ or 2018\$ or 2019\$).dt. (476)

 Database: Hypertension Group Specialised Register via Cochrane Register of Studies (CRS-Web)
 Search Date: 6 November 2019

#1 ((intensive* NEAR bp) OR (intensive* NEAR dbp) OR (intensive* NEAR pressure*) OR (intensive* NEAR sbp)) AND INSEGMENT
 #2 ((strict* NEAR bp) OR (strict* NEAR dbp) OR (strict* NEAR pressure*) OR (strict* NEAR sbp)) AND INSEGMENT
 #3 ((target* NEAR bp) OR (target* NEAR dbp) OR (target* NEAR pressure*) OR (target* NEAR sbp)) AND INSEGMENT
 #4 ((tight* NEAR bp) OR (tight* NEAR dbp) OR (tight* NEAR pressure*) OR (tight* NEAR sbp)) AND INSEGMENT
 #5 #1 OR #2 OR #3 OR #4 AND INSEGMENT
 #6 ((cardiovascular NEAR disease*) OR (heart NEAR attack*) OR (heart NEAR disease*) OR (heart NEAR infarct*)) AND INSEGMENT
 #7 ((peripheral NEAR disease*) OR (myocardial NEAR attack*) OR (myocardial NEAR disease*) OR (myocardial NEAR infarct*)) AND INSEGMENT
 #8 ((coronary NEAR disease*) OR (coronary NEAR syndrome*) OR (vascular NEAR disease*) OR (atrial fibril*)) AND INSEGMENT
 #9 ((cardiac failure) OR (heart failure) OR (angina*) OR (ischemi*)) AND INSEGMENT
 #10 (stroke OR (strokes) OR (ischaemi*) OR (CVA)) AND INSEGMENT
 #11 (apoplexy OR (cerebrovascul*) OR (cerebral vascular) OR (brain accident*)) AND INSEGMENT
 #12 ((brain infarct*) OR (cerebral NEAR accident*) OR (lacunar NEAR accident*) OR (lacunar NEAR infarct*)) AND INSEGMENT
 #13 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 AND INSEGMENT
 #14 RCT:DE AND INSEGMENT
 #15 Review:ODE AND INSEGMENT
 #16 #14 OR #15 AND INSEGMENT
 #17 #5 AND #13 AND #16 AND INSEGMENT
 #18 #17 AND 01/02/2018_TO_06/11/2019:CRSCREATED AND INSEGMENT

 Database: Cochrane Central Register of Controlled Trials via Cochrane Register of Studies (CRS-Web)
 Search Date: 6 November 2019

#1 ((intensive* NEAR bp) OR (intensive* NEAR dbp) OR (intensive* NEAR pressure*) OR (intensive* NEAR sbp)) AND CENTRAL:TARGET
 #2 ((strict* NEAR bp) OR (strict* NEAR dbp) OR (strict* NEAR pressure*) OR (strict* NEAR sbp)) AND CENTRAL:TARGET
 #3 ((target* NEAR bp) OR (target* NEAR dbp) OR (target* NEAR pressure*) OR (target* NEAR sbp)) AND CENTRAL:TARGET
 #4 ((tight* NEAR bp) OR (tight* NEAR dbp) OR (tight* NEAR pressure*) OR (tight* NEAR sbp)) AND CENTRAL:TARGET
 #5 #1 OR #2 OR #3 OR #4 AND CENTRAL:TARGET
 #6 ((cardiovascular NEAR disease*) OR (heart NEAR attack*) OR (heart NEAR disease*) OR (heart NEAR infarct*)) AND CENTRAL:TARGET
 #7 ((peripheral NEAR disease*) OR (myocardial NEAR attack*) OR (myocardial NEAR disease*) OR (myocardial NEAR infarct*)) AND CENTRAL:TARGET
 #8 ((coronary NEAR disease*) OR (coronary NEAR syndrome*) OR (vascular NEAR disease*) OR (atrial fibril*)) AND CENTRAL:TARGET
 #9 ((cardiac failure) OR (heart failure) OR (angina*) OR (ischemi*)) AND CENTRAL:TARGET
 #10 (stroke OR (strokes) OR (ischaemi*) OR (CVA)) AND CENTRAL:TARGET
 #11 (apoplexy OR (cerebrovascul*) OR (cerebral vascular) OR (brain accident*)) AND CENTRAL:TARGET
 #12 ((brain infarct*) OR (cerebral NEAR accident*) OR (lacunar NEAR accident*) OR (lacunar NEAR infarct*)) AND CENTRAL:TARGET
 #13 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 AND CENTRAL:TARGET
 #14 #5 AND #13 AND CENTRAL:TARGET
 #15 #14 AND 01/02/2018_TO_06/11/2019:CRSCREATED AND CENTRAL:TARGET

 Database: Embase <1974 to 2018 February 12>
 Search Date: 6 November 2019

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1 exp cardiovascular disease/ (3890678)
 2 ((heart or myocardial) adj5 (attack\$ or disease\$ or infarc\$)).tw. (500208)
 3 (coronary adj5 (disease\$ or syndrome\$)).tw. (256179)
 4 ((cardiovascular or peripheral or vascular) adj5 disease\$).tw. (352982)
 5 atrial fibril\$.tw. (117350)
 6 ((cardiac or heart) adj failure).tw. (273710)
 7 angina\$.tw. (73097)
 8 exp ischemia/ (765529)
 9 (ischaemi\$ or ischemi\$).tw. (532587)
 10 exp stroke/ (198172)
 11 (CVA or poststroke or post-stroke or stroke or strokes).tw. (378233)
 12 apoplexy.tw. (2905)
 13 cerebrovascul\$.tw. (74652)
 14 cerebral vascular.tw. (7653)
 15 ((brain\$ or cerebral\$ or lacunar) adj2 (accident\$ or infarct\$)).tw. (38724)
 16 or/1-15 (4179352)
 17 ((goal? or intensive\$ or strict\$ or target\$ or tight\$) adj6 (antihypertensive? or anti-hypertensive? or bp or control or dbp or diastolic or pressure? or sbp or systolic or treat\$)).tw. (286275)
 18 exp hypertension/ (696425)
 19 (antihypertens\$ or hypertens\$).tw. (636651)
 20 exp blood pressure/ (533808)
 21 (blood pressure or bloodpressure).mp. (579388)
 22 or/18-21 (1299540)
 23 randomized controlled trial/ (577823)
 24 crossover procedure/ (61220)
 25 double-blind procedure/ (167039)
 26 (randomi?ed or randomly).tw. (1189663)
 27 (crossover\$ or cross-over\$).tw. (102763)
 28 placebo.ab. (289455)
 29 (doubl\$ adj blind\$).tw. (204019)
 30 assign\$.ab. (372013)
 31 allocat\$.ab. (142284)
 32 or/23-31 (1731802)
 33 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.) (6253638)
 34 32 not 33 (1510600)
 35 16 and 17 and 22 and 34 (5712)
 36 remove duplicates from 35 (5596)
 37 limit 36 to dc=20170204-20191106 (1211)

Database: LILACS

Search date: 6 November 2019

((cardiovascular disease?) or (heart attack\$) or (myocardial infarct\$) or (heart disease\$) or (myocardial disease\$) or (coronary disease\$) or (coronary syndrome\$) or (cardiovascular disease\$) or (peripheral disease\$) or (vascular disease\$) or (atrial fibril\$) or (cardiac failure) or (heart failure) or (angina\$) or (ischaemi\$) or (ischemi\$) or (stroke\$) or (CVA) or (poststroke) or (post-stroke) or (apoplexy) or (cerebrovascul \$) or (cerebral vascular) or (brain\$ accident\$) or (brain infarct\$) or (cerebral\$ accident\$) or (cerebral\$ infarct\$) or (lacunar accident\$) or (lacunar infarct\$)) and ((intensive\$ bp) or (intensive\$ dbp) or (intensive\$ blood pressure?) or (intensive\$ sbp) or (strict\$ bp) or (strict\$ dbp) or (strict\$ blood pressure?) or (strict\$ sbp) or (target\$ bp) or (target\$ dbp) or (target\$ blood pressure?) or (target\$ sbp) or (tight\$ bp) or (tight\$ dbp) or (tight\$ blood pressure?) or (tight\$ sbp)) and ((hypertension) or (hypertens\$) or (blood pressure) or (bloodpressure)) and (((PT:"randomised controlled trial" or (PT:"controlled clinical trial" or (AB:"randomi?ed" or (AB:"placebo" or (clinical trials) or (AB:"randomly" or (TI:"trial" and not ((animals) and not (humans and animals))))))

Database: ClinicalTrials.gov

Search Date: 6 November 2019

Condition or disease: (hypertension) AND (angina OR cardiovascular OR myocardial infarction OR peripheral vascular OR stroke)

Other terms: (intensive OR strict OR target OR tight) AND (randomized)

Study type: Interventional Studies

Outcome Measure: blood pressure or BP

First Posted: From 02/04/2017 To 11/06/2019

Database: WHO International Clinical Trials Registry Platform
 Search Date: 6 November 2019

 #1 intensive AND blood pressure AND randomized
 #2 strict AND blood pressure AND randomized
 #3 target* AND blood pressure AND randomized
 #4 tight AND blood pressure AND randomized
 #5 #1 OR #2 OR #3 OR #4

Database: TRIP Database
 Search date: 22 March 2020

 (blood) AND (pressure) AND (targets) AND (intensive) AND (standard)

Appendix 2. Reviews and guidelines checked

ACC-AHA 2017; Arguedas 2009; Arguedas 2013; Bangalore 2011; Bangalore 2013; Bangalore 2017; BPLTTC 2013; BPLTTC 2014; Hypertension CANADA 2018; Drozda 2011; ESH-ESC 2013; ESH-ESC 2018; Ettehad 2016; Feldstein 2014; Lim 2019; Lv 2012; Lv 2013; McBrien 2012; NICE 2019; Rosendorff 2009; Rosendorff 2015; Roy 2010; SBU 2007; Verdecchia 2016; Vidal-Petiot 2018; Xie 2016.

WHAT'S NEW

Date	Event	Description
24 March 2020	New citation required but conclusions have not changed	The main conclusions remain unchanged after this update.
24 March 2020	New search has been performed	This systematic review has been updated with a new bibliographic search on 6 November 2019. Two promising studies have been labelled as 'awaiting classification' after failing in getting enough information to include or exclude them from the review. Random sequence generation in SPRINT 2015 has been considered as low risk of bias, after authors confirmation that they used a permuted block randomization scheme with random block lengths, stratified by clinic.

HISTORY

Protocol first published: Issue 1, 2013
 Review first published: Issue 10, 2017

Date	Event	Description
24 August 2018	Amended	The Risk of Bias figure and table have been amended to correct an error affecting the SPRINT study. As the main text correctly explained, this trial must be rated as 'unclear' in the random sequence generation domain. The 'allocation concealment' domain must be rated as 'low' risk of bias.
27 April 2018	New citation required and conclusions have changed	Four review authors included in the original version of the review (Muruz $\text{£} \text{b} \text{a} \text{l}$ L, Mal#n MDM, Montoya R, L#pez A) have not participated in this update, and two new contributors (Erвити J, Leache L) have now been included as review authors

CONTRIBUTIONS OF AUTHORS

LCS is the lead author. He co-ordinated the review, entered the text of the review into Review Manager 5, conducted external correspondence, appraised inclusion criteria and quality, and extracted and analyzed study data.

JGo led the protocol, appraised inclusion criteria and quality of studies, extracted study data, and drafted the final review.

JGa appraised inclusion criteria and quality of studies, extracted study data, and drafted the final review.

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

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

LL appraised inclusion criteria and quality of studies, extracted study data, and drafted the final review.

All review authors participated in writing of the Discussion and Conclusions.

DECLARATIONS OF INTEREST

LCS: none.

JGo: none.

JGa: none.

MCC: none.

JE: none.

LL: none.

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- Navarre Health Service and Health Department of the Government of Navarre, Spain

Working time of authors (employees of the Government of Navarre).

Facilities.

External sources

- European Social Fund Operational Programme 2007-2013, Other

50% of the full research project, as salary from September 2012 to December 2015 for the Pharmacotherapy Research Coordinator in the Navarre Health Service (LCS).

- University of British Columbia, Vancouver, Canada

Bibliographic searches. Methodological support.

INDEX TERMS

Medical Subject Headings (MeSH)

Antihypertensive Agents [adverse effects] [*therapeutic use]; Blood Pressure [*drug effects] [physiology]; Cardiovascular Diseases [*drug therapy] [mortality]; Diastole; Hypertension [complications] [*drug therapy] [mortality]; Patient Dropouts [statistics & numerical data]; Randomized Controlled Trials as Topic; Reference Values; Systole

MeSH check words

Humans