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Blood pressure-lowering treatment for preventing recurrent stroke, major vascular events, and dementia in patients with a history of stroke or transient ischaemic attack (Review)

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[Intervention Review]

Blood pressure-lowering treatment for preventing recurrent stroke, major vascular events, and dementia in patients with a history of stroke or transient ischaemic attack

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ABSTRACT

Background

Stroke is an important cause of death and disability worldwide. Since high blood pressure is an important risk factor for stroke and stroke recurrence, drugs that lower blood pressure might play an important role in secondary stroke prevention.

Objectives

To investigate whether blood pressure-lowering drugs (BPLDs) started at least 48 hours after the index event are effective for the prevention of recurrent stroke, major vascular events, and dementia in people with stroke or transient ischaemic attack (TIA). Secondary objectives were to identify subgroups of people in which BPLDs are effective, and to investigate the optimum systolic blood pressure target after stroke or TIA for preventing recurrent stroke, major vascular events, and dementia.

Search methods

In August 2017, we searched the Trials Registers of the Cochrane Stroke Group and the Cochrane Hypertension Group, the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 8), MEDLINE Ovid (1946 to August 2017), Embase Ovid (1974 to August 2017), ClinicalTrials.gov, the ISRCTN Registry, Stroke Trials Registry, Trials Central, and the World Health Organization (WHO) International Clinical Trials Registry Platform Portal.

Selection criteria

Randomised controlled trials (RCTs) of BPLDs started at least 48 hours after stroke or TIA.

Data collection and analysis

Two review authors independently screened all titles and abstracts, selected eligible trials, extracted the data, assessed risk of bias, and used GRADE to assess the quality of the evidence. If necessary, we contacted the principal investigators or corresponding authors for additional data.

Main results

We included 11 studies involving a total of 38,742 participants: eight studies compared BPLDs versus placebo or no treatment (35,110 participants), and three studies compared different systolic blood pressure targets (3632 participants). The risk of bias varied greatly between included studies. The pooled risk ratio (RR) of BPLDs for recurrent stroke was 0.81 (95% confidence interval (CI) 0.70 to 0.93; 8 RCTs; 35,110 participants; moderate-quality evidence), for major vascular event 0.90 (95% CI 0.78 to 1.04; 4 RCTs; 28,630 participants; high-quality evidence), and for dementia 0.88 (95% CI 0.73 to 1.06; 2 RCTs; 6671 participants; high-quality evidence). We mainly observed a reduced risk of recurrent stroke in the subgroup of participants using an angiotensin-converting enzyme (ACE) inhibitor or a diuretic (I^2 statistic for subgroup differences 72.1%; P = 0.006). The pooled RR of intensive blood pressure-lowering for recurrent stroke was 0.80 (95% CI 0.63 to 1.00), and for major vascular event 0.58 (95% CI 0.23 to 1.46).

Authors' conclusions

Our results support the use of BPLDs in people with stroke or TIA for reducing the risk of recurrent stroke. Current evidence is primarily derived from trials studying an ACE inhibitor or a diuretic. No definite conclusions can be drawn from current evidence regarding an optimal systolic blood pressure target after stroke or TIA.

PLAIN LANGUAGE SUMMARY

Blood pressure drugs for preventing stroke and cardiovascular diseases in patients with a stroke or transient ischaemic attack (TIA)

Questions

Do blood pressure drugs prevent stroke, other blood vessel diseases, and dementia, in people with a stroke or transient ischaemic attack (TIA)? What blood pressure target is best for preventing stroke, other blood vessel diseases, and dementia, in people with a stroke or TIA?

Background

Stroke, due to blocked or bleeding blood vessels in the brain affects about 14 million people worldwide each year. Stroke survivors are at increased risk of recurrent stroke, other blood vessel diseases, and dementia. High blood pressure is an important risk factor that can increase this risk. Blood pressure-lowering drugs are known to prevent first ever stroke. However, in stroke survivors lowering the blood pressure too far (using blood pressure drugs) may be harmful especially early after the stroke. Therefore, we reviewed trials that tested blood pressure-lowering drugs started at least 48 hours after the stroke or TIA.

Study characteristics: this review is up-to-date to August 2017. We included 11 trials involving 38,742 participants: eight trials assessed the effect of blood pressure drugs, and three trials compared different blood pressure targets. Ten studies were hospital-based and one trial was performed in a general practitioner setting. Not all trials contributed information to all outcomes.

Key results: blood pressure drugs lowered the risk of recurrent stroke in patients with a stroke or TIA, whereas there is insufficient evidence to conclude whether they reduce the risk of other blood vessel diseases and dementia. There is also insufficient evidence to conclude which blood pressure target is best for patients with a stroke or TIA.

Quality of the evidence: overall, the quality of the trials in this review was moderate. However, we found similar results in an analysis using only high-quality trials. More research is needed to investigate whether blood pressure drugs also prevent dementia, and what blood pressure targets are best for patients with a stroke or TIA.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Blood pressure-lowering drugs (BPLDs) compared to placebo or no treatment for preventing recurrent stroke, major vascular events, and dementia in patients with a history of TIA or stroke

Blood pressure-lowering drugs (BPLDs) compared to placebo or no treatment for preventing recurrent stroke, major vascular events, and dementia in patients with a history of TIA or stroke

Patient or population: patients with a history of TIA or stroke

Settings: in hospital or community

Intervention: BPLDs

Comparison: placebo or no treatment

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo or no treatment	Risk difference with BPLDs
Recurrent stroke of any type	35,110 (8 RCTs)	⊕⊕⊕⊖ Moderate[a]	RR 0.81 (0.70 to 0.93)	Study population	
				101 per 1000	19 fewer per 1000 (30 fewer to 7 fewer)
Time to recurrent stroke	26,889 (3 RCTs)	⊕⊕⊕⊕ High	HR 0.82 (0.65 to 1.03)	Study population	
				Not available	Not available
Major vascular event (composite of non-fatal stroke, non-fatal myocardial infarction, or death from any vascular cause)	28,630 (4 RCTs)	⊕⊕⊕⊕ High	RR 0.90 (0.78 to 1.04)	Study population	
				151 per 1000	15 fewer per 1000 (33 fewer to 6 more)
Myocardial infarction	34,747 (6 RCTs)	⊕⊕⊕⊕ High	RR 0.90 (0.72 to 1.11)	Study population	
				21 per 1000	2 fewer per 1000 (6 fewer to 2 more)
Vascular death	34,747 (6 RCTs)	⊕⊕⊕⊕ High	RR 0.85 (0.76 to 0.95)	Study population	
				47 per 1.000	7 fewer per 1000

					(11 fewer to 2 fewer)
Death by any cause	35,110 (8 RCTs)	⊕⊕⊕⊖ Moderate[a]	RR 0.98 (0.91 to 1.05)	Study population	
				79 per 1000	2 fewer per 1000 (7 fewer to 4 more)
Dementia	6671 (2 RCTs)	⊕⊕⊕⊕ High	RR 0.88 (0.73 to 1.06)	Study population	
				67 per 1000	8 fewer per 1000 (18 fewer to 4 more)

*__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).

BPLDs: blood pressure-lowering drugs; **CI:** confidence interval; **HR**: hazard ratio; **RCT**: randomised 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.

[a]We downgraded the quality of evidence for the outcomes 'recurrent stroke of any type', and 'death by any cause' because multiple studies with a high or unclear risk of bias were included for these outcomes.

BACKGROUND

Description of the condition

Stroke is the second most common cause of death and the second leading cause of disability-adjusted life-years (DALYs) lost worldwide (GBD 2016). Despite improved prevention and management of stroke in high-income countries, the numbers of worldwide incident strokes, prevalent stroke survivors, DALYs lost due to stroke, and stroke-related deaths are still increasing. In 2016, an estimated 13.7 million incident strokes and 5.5 million stroke-related deaths occurred, and 116 million DALYs were lost due to stroke (GBD 2016). Stroke patients are at high risk of stroke recurrence, with cumulative risks increasing from 3% at 30 days to 40% at 10 years after their first stroke (Mohan 2011). Patients with a transient ischaemic attack (TIA) are also at high risk for stroke recurrence, with reviews reporting a cumulative stroke risk of 3% at 30 days (Valls 2016), and 18% at 10 years (van Wijk 2005). In addition, TIA patients have a cumulative 10-year mortality risk of 34% and a cumulative 10-year risk of major vascular event of 36% (van Wijk 2005).

Description of the intervention

Elevated blood pressure is a well-known and modifiable risk factor for ischaemic and haemorrhagic stroke, as well as for myocardial infarction, major vascular events, and dementia (Lewington 2002; Qiu 2005). There is overwhelming evidence that treatment with blood pressure-lowering drugs (BPLDs) is effective for the primary prevention of strokes and major vascular events in patients with elevated blood pressure (BPLTTC 2003; Lackland 2014). However, there is still considerable debate on the effectiveness of BPLDs in secondary prevention of stroke (Feldstein 2014). One reason why the effect of BPLDs after a first stroke is doubted, is the possible existence of a J- or U-shaped curve representing the association between blood pressure levels and recurrent stroke (Irie 1993). If such an association indeed exists, lowering blood pressure below certain thresholds could increase the risk of recurrent stroke. Furthermore, there are concerns about a harmful decrease in cerebral perfusion as a result of decreased or disrupted autoregulation in patients with a history of stroke, especially in elderly patients (Birns 2005), which might be associated with an increased risk of dementia.

How the intervention might work

All BPLDs reduce blood pressure, which in turn decreases endothelial dysfunction and thereby the risk of atherosclerosis and small vessel disease. In addition, different BPLD classes have different sites and mechanisms of action, and therefore class-specific effects.

Why it is important to do this review

Patients with a TIA or stroke are at risk for recurrence, major vascular events, and dementia. High blood pressure is a known and modifiable risk factor for these events.

OBJECTIVES

To investigate whether blood pressure-lowering drugs (BPLDs) started at least 48 hours after the index event are effective for the prevention of recurrent stroke, major vascular events, and dementia in people with stroke or transient ischaemic attack (TIA).

Secondary objectives were to identify subgroups of people in which BPLDs are effective, and to investigate the optimum systolic blood pressure target after stroke or TIA for preventing recurrent stroke, major vascular events, and dementia.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) only. We did not limit trials by any concomitant disease, baseline cardiovascular risk, or language. The effect must be estimated either in the main analysis or in a subgroup analysis. The effect must be estimated in an intention-to-treat analysis. We did not use individual participant data.

Types of participants

Adult patients with an ischaemic stroke, haemorrhagic stroke or TIA, regardless of presence of elevated blood pressure. We defined haemorrhagic stroke as intracerebral haemorrhage, thus excluding subarachnoid haemorrhage.

Types of interventions

We included trials comparing BPLDs (regardless of type, dosage or administration route) versus placebo or no treatment. We also included trials comparing intensive blood pressure lowering (defined as a blood pressure target < 130/85 mmHg) with standard blood pressure lowering (defined as a blood pressure target < 140 to 160/90 to 100 mmHg). The intervention was started at least 48 hours after the index event. We did not define a maximum time period for treatment initiation. We included trials with a factorial design if the investigators accounted for a possible interaction between the different interventions.

Types of outcome measures

We included trials if they reported any of our outcome measures. All outcome measures are expressed as risk ratios (RRs), except for the secondary outcome measure 'time to recurrent stroke', which is time-to-event data. We only took into account composite endpoints (major vascular event and any stroke or death) if they were reported identically.

Primary outcomes

- Recurrent stroke of any type (fatal and non-fatal).

Secondary outcomes

- Time to recurrent stroke
- Major vascular event (composite of non-fatal stroke, non-fatal myocardial infarction, or death from any vascular cause)
- Myocardial infarction
- Vascular death
- Death by any cause
- Dementia
- Ischaemic stroke
- Haemorrhagic stroke

Search methods for identification of studies

See the 'Specialized register' section in the Cochrane Stroke Group module. We did not impose any language restrictions and we arranged for the translation of articles where necessary.

Electronic searches

On 29 August 2017, we searched the Trials Registers of the Cochrane Stroke Group, the Cochrane Hypertension Group, the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 8) in the Cochrane Library (Appendix 1), MEDLINE Ovid (from 1946 to 29 August 2017) (Appendix 2), and Embase Ovid (from 1974 to 29 August 2017) (Appendix 3).

We developed the MEDLINE search strategy with the help of the Cochrane Stroke Group Information Specialists Brenda Thomas and Joshua Cheyne (Appendix 2), and they adapted it for the other databases.

In August 2017, we searched for ongoing and unpublished trials in ClinicalTrials.gov (clinicaltrials.gov/), the ISRCTN Registry (www.isrctn.com), Stroke Trials Registry (www.strokecenter.org/trials), Trials Central (www.trialscentral.org), and WHO International Clinical Trials Registry Platform (ICTRP) Portal (Appendix 4).

Searching other resources

We checked the reference lists of all relevant articles reporting studies selected for inclusion in this review retrieved from the above-mentioned searches. When clarification was needed, we contacted the principal investigators or corresponding authors, or both, of the relevant studies.

Data collection and analysis

Selection of studies

Two review authors (TPZ and either NDK or ER) independently screened all titles, abstracts and keywords of publications identified by the searches to assess their eligibility. We obtained full-texts of all possibly eligible manuscripts, and two review authors (TPZ and NDK) selected trials based on our inclusion criteria. Disagreements were resolved by discussion and, if necessary, by a third review author (ER). We included a PRISMA flowchart of our study selection (Moher 2009).

Data extraction and management

Two review authors (TPZ and NDK) independently extracted the data. They resolved disagreements by discussion and, if necessary, by involving a third review author (ER). We used data reported in the published sources for analysis in this review. If reported data conflicted between two reports of the same study, we used the data of the most recent report. Where we needed additional data, we attempted to contact the principal investigator(s) or the corresponding author of the study or report. On a standardised data extraction form we recorded:

- general information: published/unpublished, title, authors, reference, country, language of publication, year of publication, duplicate publications, sponsor, setting;
- trial characteristics/methodology: design, inclusion and exclusion criteria, method of randomisation, sequence generation, allocation concealment, blinding (participants/personnel and outcome assessors) and analysis (intention-to-treat, per protocol), duration of follow-up, presence of selective reporting, other types of bias;
- participant characteristics: number of participants randomised to each arm, age, sex, ethnicity, type of index event, presence of elevated blood pressure, level of blood pressure, compliance, duration of follow-up;
- intervention characteristics: type, class and dose of BPLD, timing of treatment initiation, duration of treatment, additional interventions;
- outcomes: all specified primary and secondary outcomes, other reported outcomes, number of participants with complete follow-up and reasons for loss to follow-up.

Assessment of risk of bias in included studies

To assess risk of bias in each included study, two review authors (TPZ and NDK) independently assessed the methodological quality using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We created a 'Risk of bias' table per study, including a description and a judgement (low, high, or unclear risk of bias) for each of the seven types of possible bias. We considered studies with three or more entries of high or unclear risk of bias as being of low methodological quality. We summarised the risk of bias in a 'Risk of bias' graph and summary.

Measures of treatment effect

We expressed the size of the treatment effect on the dichotomous outcome measures as pooled risk ratios (RRs) with 95% confidence intervals (CIs). We expressed the outcome 'time to recurrent stroke' as pooled log hazard ratio estimate with 95% CIs.

Unit of analysis issues

For each study we considered whether participants were randomised individually or as a group and whether there were multiple observations for the same outcome.

Dealing with missing data

We attempted to collect missing data by contacting (through multiple e-mails) the principal investigators and corresponding authors of the studies in question.

Assessment of heterogeneity

We calculated Tau^2, Chi^2, and I^2 to explore the between-study variance. We considered I^2 statistic percentages greater than 50% as an indicator of substantial heterogeneity.

Assessment of reporting biases

We did not create funnel plots to assess reporting biases, as the number of included studies per comparison (BPLD versus placebo or no treatment; intensive blood pressure-lowering versus mild or standard blood pressure-lowering) was lower than 10.

Data synthesis

We processed data and performed quantitative analyses using Review Manager 5 (Review Manager 2014). We used random-effects models for all analyses, regardless of the statistical amount of heterogeneity, to take heterogeneous designs and participants into account.

Subgroup analysis and investigation of heterogeneity

We defined the following subgroup analyses to investigate heterogeneous results for the primary outcome 'recurrent stroke of any type' and the secondary outcomes 'major vascular event' and 'dementia'.

- Subgroups based on baseline blood pressure, according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) classification (Chobanian 2003) (normal blood pressure, defined as a systolic blood pressure < 120 mmHg and a diastolic blood pressure < 80 mmHg; prehypertension, defined as a systolic blood pressure 120 to 139 mmHg or a diastolic blood pressure 80 to 89 mmHg; stage 1 hypertension, defined as a systolic blood pressure 140 to 159 mmHg or a diastolic blood pressure 90 to 99 mmHg; stage 2 hypertension, defined as a systolic blood pressure ≥ 160 mmHg or a diastolic blood pressure ≥ 100 mmHg).
- Subgroups based on class of BPLD (diuretics, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, angiotensin II type 1 receptor blockers, adrenergic beta-antagonists, other).
- Subgroups based on self-reported ethnicity (Blacks, Whites, Hispanics, Asians, others).
- Subgroups based on prior history of hypertension (yes versus no).
- Subgroups based on age (< 60 years, 60 to 79 years, 80 years or older).
- Subgroups based on index stroke event (TIA, ischaemic stroke, haemorrhagic stroke).
- Subgroups based on sex (men versus women).

Sensitivity analysis

We planned the following sensitivity analyses.

- Methodological quality (0 to 2 entries of unclear or high risk versus 3 or more entries of unclear or high risk).
- Time of treatment initiation (within 2 weeks after stroke or TIA versus after 2 weeks following stroke or TIA).
- Duration of treatment and follow-up (shorter versus longer than 1 year).
- Level of achieved systolic blood pressure-lowering in comparison with baseline (> 5 mmHg versus ≤ 5 mmHg).
- Level of achieved diastolic blood pressure-lowering in comparison with baseline (> 3 mmHg versus ≤ 3 mmHg).
- Contrast in achieved systolic blood pressure-lowering between intervention and control group (> 3 mmHg versus ≤ 3 mmHg).

GRADE assessment and 'Summary of findings' table

We used the GRADEpro Gudeline Development Tool to create a 'Summary of findings' table for the comparison of BPLDs versus placebo or no treatment (GRADEpro GDT; Summary of findings for the main comparison). This table presents the results and the quality of the evidence of the main outcomes, using the GRADE system, which classifies the quality of evidence as high, moderate, low, and very low. The outcomes included are: recurrent stroke of any type, time to recurrent stroke, major vascular event (composite of non-fatal stroke, non-fatal myocardial infarction, or death from any vascular cause), myocardial infarction, vascular death, death by any cause, and dementia. The GRADE approach appraises the quality of the body of evidence according to the extent to which one can be confident that an estimate of effect or association reflects the item assessed. The quality of a body of evidence is based on within-study risk of bias (methodological quality), directness of the evidence, heterogeneity of the data, precision of effect estimates, and risk of publication bias (Schünemann 2011).

RESULTS

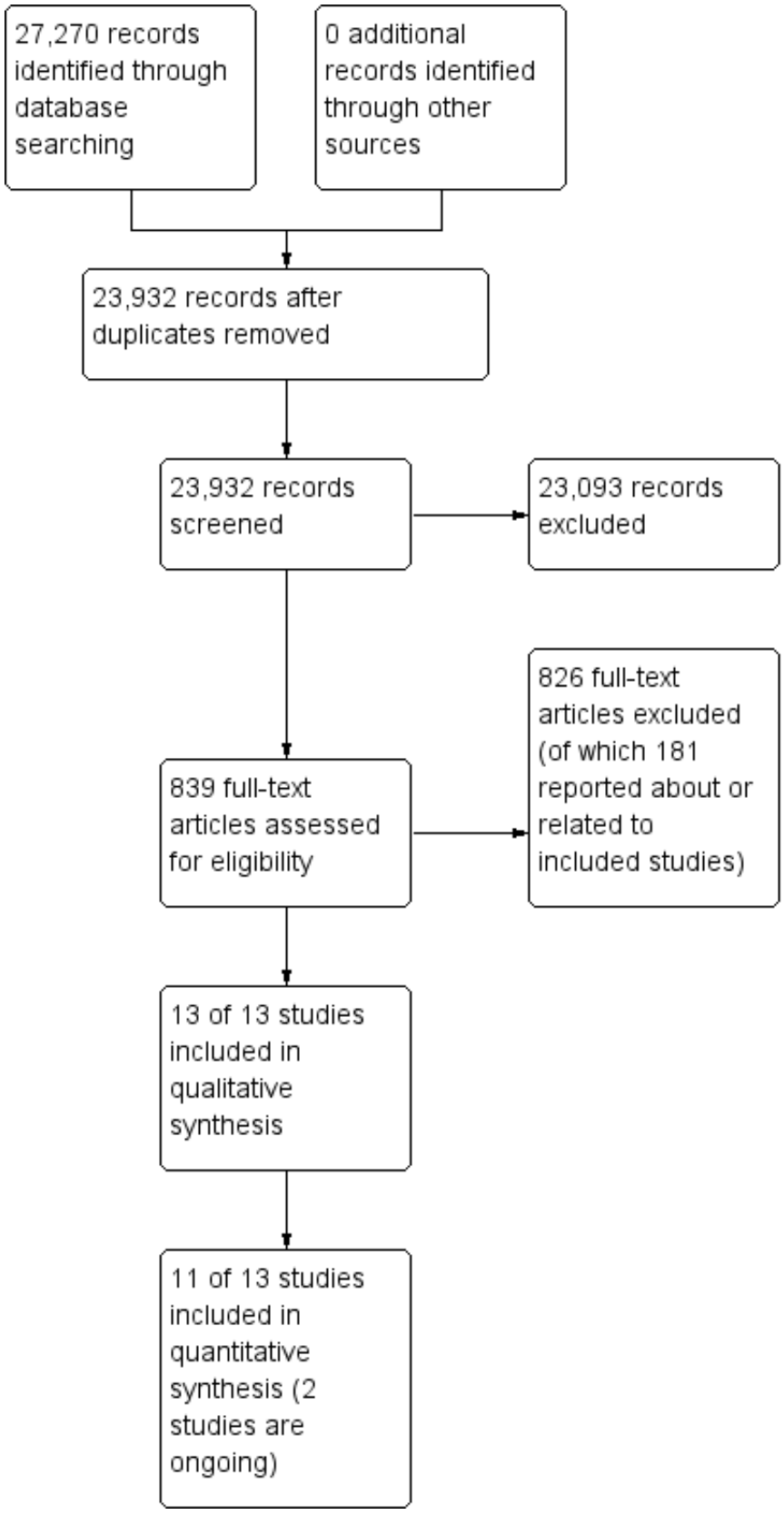
Description of studies

See Characteristics of included studies and Characteristics of excluded studies.

Results of the search

The search strategy yielded 23,932 unique results, of which we excluded 23,093 after reading titles and abstracts (Figure 1). We retrieved the remaining 839 records for detailed evaluation. Among these, we identified 13 randomised controlled trials (RCTs) eligible for inclusion.

Figure 1. Study flow diagram.



Two of the 13 trials that met our inclusion criteria are ongoing: The NCT01220622 is investigating the effect of nimodipine started within seven days after ischaemic stroke on mortality at six months; the NCT01563731 trial studies the effect of three different systolic blood pressure targets (< 145 to 135, < 135 to 125, and < 125 mmHg) on stroke and cardiovascular events in people with a transient ischaemic attack (TIA) or stroke (Characteristics of ongoing studies).

Included studies

In total, we included 11 studies involving 38,742 participants (Characteristics of included studies); eight studies in the BPLD versus placebo or no treatment comparison, and three studies in the intensive blood pressure-lowering versus mild or standard blood pressure-lowering comparison.

Blood pressure-lowering drugs (BPLDs) versus placebo or no treatment

Eight studies (35,110 participants) met the inclusion criteria for our primary and secondary objectives (Carter 1970; Co-operative Study 1975; Marti Masso 1990; Dutch TIA Trial 1993; PATS 1995; PROGRESS 2001; PRoFESS 2008; TEST 1995), the largest of which included 20,332 participants (PRoFESS 2008).

Type of intervention

Five studies (28,454 participants) compared a single BPLD with placebo (Dutch TIA Trial 1993; PATS 1995; PRoFESS 2008; TEST 1995), or with no treatment (Marti Masso 1990), two trials investigated individually tailored regimens consisting of either one or two BPLDs versus placebo or no treatment (Carter 1970; PROGRESS 2001), and one trial investigated a combined blood pressure-lowering intervention versus placebo (Co-operative Study 1975).

Five classes of BPLDs were evaluated; angiotensin-converting enzyme (ACE) inhibitors (with individually tailored addition of diuretics, PROGRESS 2001), beta-blockers (Dutch TIA Trial 1993; TEST 1995), angiotensin II receptor antagonists (PRoFESS 2008), diuretics (Co-operative Study 1975: a combination of two diuretic drugs; PATS 1995), calcium channel blockers (Marti Masso 1990), and an individually tailored regimen of diuretics and centrally acting BPLDs (Carter 1970). Two trials had a 2x2 factorial design (Dutch TIA Trial 1993; PRoFESS 2008), both also comparing different antithrombotic regimens.

Index event

In four studies, the qualifying event could either be a TIA, ischaemic stroke, or haemorrhagic stroke (Co-operative Study 1975; PATS 1995; PROGRESS 2001; TEST 1995). One of these studies also included people with a subarachnoid haemorrhage (112 of 5665 participants (2.0%), PATS 1995), and one study did not require a specific qualifying event but a prior history of TIA or stroke (PROGRESS 2001). Three studies included people with a TIA or ischaemic stroke (Dutch TIA Trial 1993; Marti Masso 1990; PRoFESS 2008). One study only included people with an ischaemic stroke (Carter 1970). However, this diagnosis was based on a lumbar puncture negative for blood, as computerised tomography (CT) scanners were not yet available to reliably distinguish between ischaemic and haemorrhagic stroke. Six out of the seven studies, including TIA participants, based inclusion on the clinical syndrome only, whereas one study required confirmatory brain imaging (CT or magnetic resonance imaging (MRI), PRoFESS 2008).

Time window for inclusion

Five trials included participants within a limited period after the index event: three weeks (TEST 1995), three months (Dutch TIA Trial 1993; PRoFESS 2008), one year (Co-operative Study 1975), and five years (PROGRESS 2001). One of these studies recommended participants to be stable two weeks after the index event (PROGRESS 2001), and one used a six-week run-in period before participants were randomised (Co-operative Study 1975). Median time from index event to randomisation was reported in two of these trials; 15 days (PRoFESS 2008), and eight months (PROGRESS 2001). One study reported that 22% of participants were randomised within one week from index event (Dutch TIA Trial 1993). One study did not report data on time between index event and start of treatment (TEST 1995).

Three trials included participants after a minimum time period after the index event; two weeks (Carter 1970), four weeks (PATS 1995), and one year (Marti Masso 1990). Two of these studies did not report median time from index event to intervention, whereas one study reported a median of 31 months (PATS 1995).

Blood pressure at baseline

Increased blood pressure at baseline was not part of our inclusion criteria. Overall mean blood pressure at baseline was not different between participants randomised to blood pressure-lowering or to placebo or no treatment (Analysis 1.10; Analysis 1.11).

Follow-up

Median overall follow-up duration was reported in six studies, and ranged from 12 to 47 months. Seven trials reported (recurrent) stroke as the primary outcome measure (Carter 1970; Co-operative Study 1975; Marti Masso 1990; PATS 1995; PRoFESS 2008; PROGRESS 2001; TEST 1995), whereas one trial primarily reported a composite endpoint of major vascular events (Dutch TIA Trial 1993).

Intensive versus standard blood pressure-lowering

Three trials (3632 participants) met the inclusion criteria for our second comparison, intensive blood pressure-lowering versus mild or standard blood pressure-lowering (PAST-BP 2016; PODCAST 2017; SPS3 2013). All three trials compared a lower versus a higher systolic blood pressure target, although with slightly different targets (< 130 mmHg versus 130 to 149 mmHg (SPS3 2013); < 130 mmHg or a reduction of 10 mmHg if systolic blood pressure was between 125 mmHg and 140 mmHg at randomisation versus < 140 mmHg (PAST-BP 2016), < 125 mmHg versus < 140 mmHg (PODCAST 2017). The qualifying event was TIA or stroke in one trial (PAST-BP 2016), stroke in one trial (PODCAST 2017), and lacunar stroke only in one trial (SPS3 2013). Participants were randomised between two weeks and seven months after the qualifying event, with a median 62 days in one trial (SPS3 2013), a median 4.5 months in one trial (PODCAST 2017), and unknown median time in one trial (PAST-BP 2016). Median overall follow-up was 12 months (PAST-BP 2016), 24 months (PODCAST 2017), and 44 months (SPS3 2013). One trial had a 2x2 factorial design, also comparing different antithrombotic regimens (SPS3 2013). One trial primarily reported recurrent stroke (SPS3 2013), whereas the other trials primarily reported change in systolic blood pressure (PAST-BP 2016), and Addenbrooke's Cognitive Examination-Revised score (PODCAST 2017).

Excluded studies

We excluded three studies after discussing their eligibility with the third review author. We excluded two trials because of the large proportion of participants in the control group in whom BPLDs were started during follow-up, resulting in a lack of contrast between the two treatment arms (Lithell 2003; Schrader 2003). One trial did not report baseline characteristics for the intention-to-treat population, and a small subset of participants did not have an index TIA or stroke (Lee 2015).

Risk of bias in included studies

In all included studies, we assessed the risk of selection bias, performance bias, attrition bias, detection bias and reporting bias. We used the 'Risk of bias' tool in the *Cochrane Handbook for Systematic Reviews of Interventions* to classify the seven described domains as 'low risk', 'high risk' or 'unclear risk' (Higgins 2011). An overview is given in the 'Risk of bias summary' (Figure 2), and the 'Risk of bias graph' (Figure 3).

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

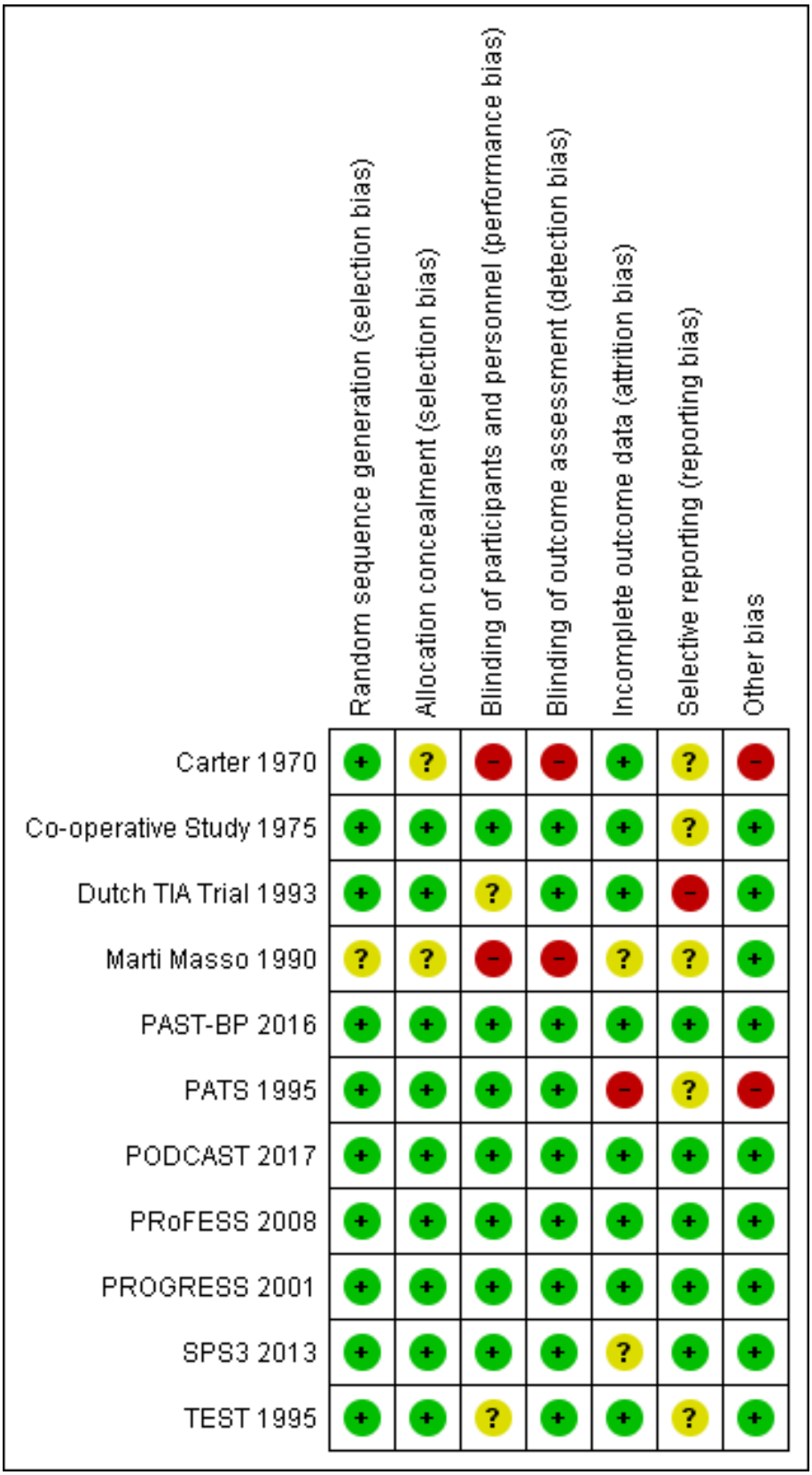
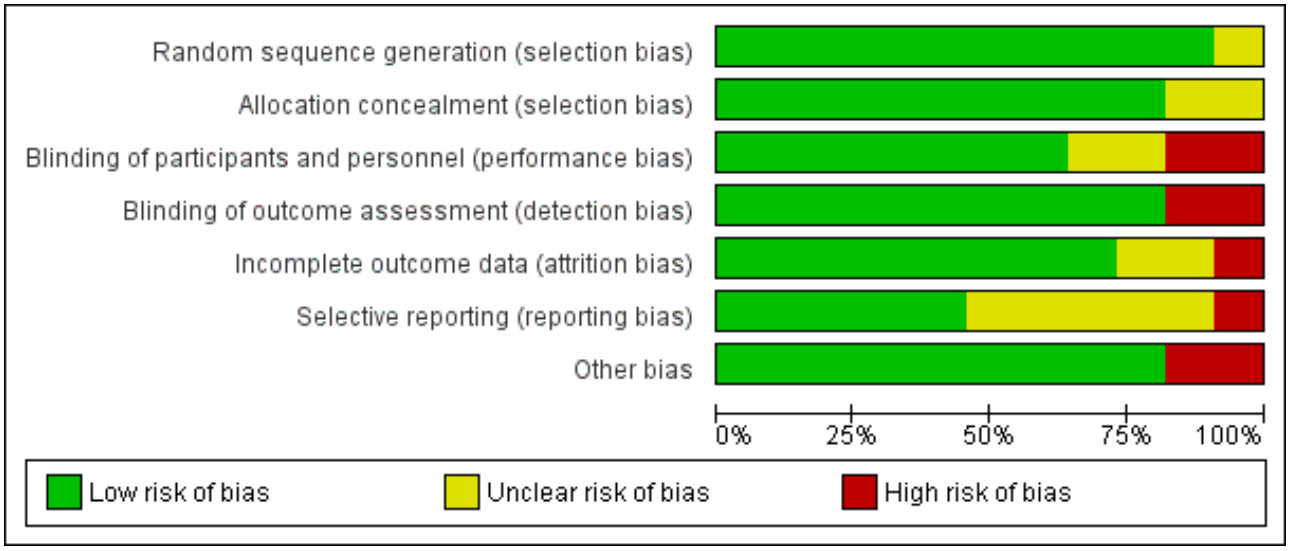


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Two studies did not describe their methods of allocation concealment (Carter 1970; Marti Masso 1990); we assessed these to have an unclear risk of bias. One study did not describe their method of sequence generation (Marti Masso 1990); we assessed this as an unclear risk of bias. We assessed the remaining studies as having a low risk of selection bias.

Blinding

Two studies did not describe their methods of blinding (Carter 1970; Marti Masso 1990); we assessed these to have a high risk of bias. Two studies only reported their blinding of participants and personnel as being "double-blind" (Dutch TIA Trial 1993; TEST 1995); we assessed these to have an unclear risk of bias. We assessed the remaining studies as having a low risk of performance bias and detection bias.

Incomplete outcome data

All trials were analysed according to the intention-to-treat principle. One study used a per protocol analysis for their primary outcome measure (blood pressure reduction), and intention-to-treat analyses for the clinical outcome events (PAST-BP 2016); as we did not use their primary outcome measure, we assessed this study as having a low risk of bias. One study did not address loss to follow-up (Marti Masso 1990), and one study only reported overall (reasons for) loss to follow-up (SPS3 2013); we assessed these studies as having an unclear risk of bias. One study reported 28% loss to follow-up without further explanation (PATS 1995); we assessed this study to be at high risk of bias. We assessed the remaining studies as having low risk of attrition bias.

Selective reporting

One study was designed to report functional outcome at three months, but primarily reported major vascular events instead (Dutch TIA Trial 1993); we assessed this study as having a high risk of bias. Because there was no study protocol available or published, we assessed five studies as having an unclear risk of bias (Carter 1970; Co-operative Study 1975; Marti Masso 1990; PATS 1995; TEST 1995), whereas the remaining studies were assessed as having a low risk of reporting bias (PAST-BP 2016; PODCAST 2017; PRoFESS 2008; PROGRESS 2001; SPS3 2013).

Other potential sources of bias

One study was performed by a single-investigator, and did not report a definition of the primary endpoint (Carter 1970). In another study, both the number of participants per treatment group and the number of outcome events differed between subsequent reports (PATS 1995); based on these findings we assessed these studies as having a high risk of bias. We did not identify any potential sources of bias in the remaining studies.

Effects of interventions

See: **Summary of findings for the main comparison** Blood pressure-lowering drugs (BPLDs) compared to placebo or no treatment for preventing recurrent stroke, major vascular events, and dementia in patients with a history of TIA or stroke

See Data and analyses.

Blood pressure-lowering drugs (BPLDs) versus placebo or no treatment

See Summary of findings for the main comparison

Recurrent stroke of any type

Data from eight trials (35,110 participants) were available for our primary analysis (Carter 1970; Co-operative Study 1975; Dutch TIA Trial 1993; Marti Masso 1990; PATS 1995; PROGRESS 2001; PRoFESS 2008; TEST 1995). The pooled risk ratio (RR) of BPLDs for recurrent stroke was 0.81 (95% confidence interval (CI) 0.70 to 0.93; moderate-quality evidence; Analysis 1.1). To explore the substantial heterogeneity (I^2 = 61%), we performed subgroup analyses.

Subgroup analyses

Recurrent stroke of any type by baseline systolic blood pressure

Data from three trials (6656 participants) were available (Carter 1970; Co-operative Study 1975; PROGRESS 2001). The pooled RRs of BPLDs for recurrent stroke were 0.65 (95% CI 0.51 to 0.83) in participants with a baseline systolic blood pressure of 160 mmHg or above, and 0.71 (95% CI 0.57 to 0.89) in those with a baseline systolic blood pressure between 140 and 160 mmHg. The RRs of BPLDs for recurrent stroke were 0.86 (95% CI 0.67 to 1.12) in participants with a baseline systolic blood pressure between 120 and 140 mmHg, and 1.01 (95% CI 0.47 to 2.19) in those with a baseline systolic blood pressure below 120 mmHg (Analysis 2.1). The I^2 statistic for subgroup differences was 5.3% (P = 0.37).

Recurrent stroke of any type by intervention

Data from eight trials (35,110 participants) were available (Carter 1970; Co-operative Study 1975; Marti Masso 1990; Dutch TIA Trial 1993; PATS 1995; PROGRESS 2001; PRoFESS 2008; TEST 1995). The pooled RRs of BPLDs for recurrent stroke were 0.73 (95% CI 0.64 to 0.84) in participants using ACE inhibitors, 0.72 (95% CI 0.59 to 0.87) in those using diuretics, and 0.94 (95% CI 0.75 to 1.18) in those using beta-blockers. The RRs of BPLDs for recurrent stroke were 0.95 (95% CI 0.87 to 1.03) in participants using angiotensin receptor blockers, and 0.55 (95% CI 0.18 to 1.67) in those using calcium channel blockers (Analysis 2.2). The I^2 statistic for subgroup differences was 72.1% (P = 0.006).

Recurrent stroke of any type by type of index event

Data from one trial (5854 participants) were available (PROGRESS 2001). The RRs of BPLDs for recurrent stroke were 0.76 (95% CI 0.64 to 0.89) in participants with an ischaemic index stroke, 0.59 (95% CI 0.39 to 0.89) in those with an haemorrhagic index stroke, and 0.77 (95% CI 0.50 to 1.18) in those with an index TIA (Analysis 2.3). The I^2 statistic for subgroup differences was 0% (P = 0.53).

Sensitivity analyses

Recurrent stroke of any type, methodological quality

Five trials (29,082 participants) were of high methodological quality (Co-operative Study 1975; Dutch TIA Trial 1993; PROGRESS 2001; PRoFESS 2008; TEST 1995). The pooled RR of BPLDs for recurrent stroke was 0.86 (95% CI 0.75 to 1.00; Analysis 3.1).

Recurrent stroke of any type, minimum 5 mmHg systolic blood pressure reduction

Four trials (33,575 participants) achieved a minimum systolic blood pressure reduction of 5 mmHg at the end of the observation period (Dutch TIA Trial 1993; PATS 1995; PROGRESS 2001; PRoFESS 2008). The pooled RR of BPLDs for recurrent stroke was 0.81 (95% CI 0.68 to 0.96; Analysis 3.2).

Recurrent stroke of any type, minimum 3 mmHg diastolic blood pressure reduction

Five trials (34,295 participants) achieved a minimum systolic blood pressure reduction of 3 mmHg at the end of the observation period (Dutch TIA Trial 1993; PATS 1995; PROGRESS 2001; PRoFESS 2008; TEST 1995). The pooled RR of BPLDs for recurrent stroke was 0.84 (95% CI 0.72 to 0.97; Analysis 3.3).

Recurrent stroke of any type, excluding patients with subarachnoid haemorrhage as possible index event

One trial not only included participants with an ischaemic of haemorrhagic stroke, but also with subarachnoid haemorrhage (PATS 1995). Recurrent stroke was reported separately for participants with an ischaemic stroke as index event and a haemorrhagic stroke as index event (comprising both intracerebral and subarachnoid haemorrhage). Therefore, we performed this additional sensitivity analysis, excluding the participants from this trial with a haemorrhagic stroke as index event.

Data from eight trials (33,690 participants) were available (Carter 1970; Co-operative Study 1975; Dutch TIA Trial 1993; Marti Masso 1990; PATS 1995; PROGRESS 2001; PRoFESS 2008; TEST 1995). The pooled RR of BPLDs for recurrent stroke was 0.81 (95% CI 0.70 to 0.93; Analysis 3.4).

We did not perform subgroup analyses based on self-reported ethnicity, prior history of hypertension, age, and sex because of insufficient studies reporting estimates for these subgroups. We did not perform sensitivity analyses based on time of treatment initiation, duration of treatment and follow-up, or the achieved contrast in systolic blood pressure-lowering between intervention and control. All studies treated and followed participants for at least one year, and studies did not uniformly report time of treatment initiation or the contrast in systolic blood pressure-lowering at the end of the observation period.

Time to recurrent stroke

We transformed tabular data for the Co-operative Study 1975 into a hazard ratio using spreadsheets developed by Tierney et al (Tierney 2007; Wang 2013).

Data from three trials (26,889 participants) were available (Co-operative Study 1975; PROGRESS 2001; PRoFESS 2008). The pooled hazard ratio of BPLDs for time to recurrent stroke was 0.82 (95% CI 0.65 to 1.03; high-quality evidence; Analysis 1.2).

Major vascular event (composite of non-fatal stroke, non-fatal myocardial infarction, or death from any vascular cause)

Data from four trials (28,630 participants) were available (Dutch TIA Trial 1993; PROGRESS 2001; PRoFESS 2008; TEST 1995). The pooled RR of BPLDs for major vascular event was 0.90 (95% CI 0.78 to 1.04; high-quality evidence; Analysis 1.3). To explore the substantial heterogeneity (I^2 = 75%), we performed a subgroup analysis.

Subgroup analyses

Major vascular event by intervention

Data from four trials (28,630 participants) were available (Dutch TIA Trial 1993; PROGRESS 2001; PRoFESS 2008; TEST 1995). The RRs of BPLDs for major vascular event were 0.76 (95% CI 0.68 to 0.85) in participants using ACE inhibitors, and 0.94 (95% CI 0.88 to 1.01) in those using angiotensin receptor blockers. The pooled RR of BPLDs for major vascular event was 1.01 (95% CI 0.84 to 1.21) in participants using beta-blockers (Analysis 2.4).

We did not perform subgroup analyses based on baseline blood pressure, self-reported ethnicity, prior history of hypertension, age, index stroke event and sex because of insufficient studies reporting estimates for these subgroups.

Ischaemic stroke

Data from three trials (26,701 participants) were available (Marti Masso 1990; PROGRESS 2001; PRoFESS 2008). The pooled RR of BPLDs for ischaemic stroke was 0.86 (95% CI 0.70 to 1.05; Analysis 1.4).

Haemorrhagic stroke

Data from two trials (26,437 participants) were available (PROGRESS 2001; PRoFESS 2008). The pooled RR of BPLDs for haemorrhagic stroke was 0.66 (95% CI 0.39 to 1.12; Analysis 1.5).

Myocardial infarction

Data from six trials (34,747 participants) were available (Co-operative Study 1975; Dutch TIA Trial 1993; PATS 1995; PROGRESS 2001; PRoFESS 2008; TEST 1995). The pooled RR of BPLDs for myocardial infarction was 0.90 (95% CI 0.72 to 1.11; high-quality evidence; Analysis 1.6).

Vascular death

Data from six trials (34,747 participants) were available (Co-operative Study 1975; Dutch TIA Trial 1993; PATS 1995; PROGRESS 2001; PRoFESS 2008; TEST 1995). The pooled RR of BPLDs for vascular death was 0.85 (95% CI 0.76 to 0.95; high-quality evidence; Analysis 1.7).

Death by any cause

Data from eight trials (35,110 participants) were available (Carter 1970; Co-operative Study 1975; Marti Masso 1990; Dutch TIA Trial 1993; PATS 1995; PROGRESS 2001; PRoFESS 2008; TEST 1995). The pooled RR of BPLDs for death by any cause was 0.98 (95% CI 0.91 to 1.05; moderate-quality evidence; Analysis 1.8).

Dementia

Data from two trials (6671 participants) were available (PROGRESS 2001; PRoFESS 2008). The pooled RR of BPLDs for dementia was 0.88 (95% CI 0.73 to 1.06; high-quality evidence; Analysis 1.9).

We did not perform subgroup analyses based on baseline blood pressure, self-reported ethnicity, prior history of hypertension, age, index stroke event, and sex, because of insufficient studies reporting estimates for these subgroups.

Intensive versus standard blood pressure-lowering

One trial classified their outcome event 'intracranial haemorrhage' as either 'intracerebral', 'subdural or epidural' or 'other' (SPS3 2013). We did not count 'subdural or epidural' and 'other' as 'stroke of any type' or 'haemorrhagic stroke'. However, we included these outcome events in the 'time to recurrent stroke' analyses, as only summary estimates (hazard ratio and 95% CI) were reported for these time-to-event data.

Data from three trials (3632 participants) were available for recurrent stroke of any type, major vascular event, myocardial infarction, and death by any cause (PAST-BP 2016; PODCAST 2017; SPS3 2013). The pooled RRs of intensive blood pressure-lowering were 0.80 (95% CI 0.63 to 1.00) for recurrent stroke (Analysis 4.1), 0.58 (95% CI 0.23 to 1.46) for major vascular event (Analysis 4.3), 0.90 (95% CI 0.58 to 1.38) for myocardial infarction (Analysis 4.6), and 1.08 (95% CI 0.83 to 1.39) for death by any cause (Analysis 4.8).

Data from two trials (3549 participants) were available for vascular death (PAST-BP 2016; SPS3 2013). The pooled RR of intensive blood pressure-lowering was 0.87 (95% CI 0.56 to 1.35) (Analysis 4.7).

Data from two trials (3103 participants) were available for ischaemic and haemorrhagic stroke (PODCAST 2017; SPS3 2013). The pooled RR of intensive blood pressure-lowering was 0.86 (95% CI 0.67 to 1.09) for ischaemic stroke (Analysis 4.4), and 0.42 (95% CI 0.17 to 1.02) for haemorrhagic stroke (Analysis 4.5).

Data from one trial (3020 participants) were available for time to recurrent stroke (SPS3 2013). The hazard ratio of intensive blood pressure-lowering for time to recurrent stroke was 0.81 (95% CI 0.64 to 1.03; Analysis 4.2).

Data from one trial (83 participants) were available for dementia (PODCAST 2017). The RR of intensive blood pressure-lowering for dementia was 5.12 (95% CI 0.25 to 103.48; Analysis 4.9).

DISCUSSION

Summary of main results

Blood pressure-lowering drugs (BPLDs) versus placebo or no treatment

Blood pressure-lowering drugs (BPLDs) initiated at least 48 hours after stroke or transient ischaemic attack (TIA) reduced the risk of recurrent stroke. We observed substantial heterogeneity, and predefined subgroup analyses were hampered by lack of trials assessing these specific subgroups.

BPLDs also reduced the risk of vascular death but did not reduce time to recurrent stroke, and risk of major vascular event, ischaemic stroke, haemorrhagic stroke, myocardial infarction, death by any cause, or dementia. However, point estimates for all secondary outcome measures were in favour of treatment with BPLDs.

Intensive versus standard blood pressure-lowering

Intensive blood pressure-lowering did not reduce the risk of recurrent stroke, time to recurrent stroke, risk of major vascular event, ischaemic stroke, myocardial infarction, vascular death, death by any cause, and dementia, whereas it did reduce the risk of haemorrhagic stroke. However, we observed a favourable trend for intensive blood pressure-lowering in the outcomes recurrent stroke, time to recurrent stroke, and major vascular events.

Overall completeness and applicability of evidence

Our primary analysis is based on 35,110 participants, and we assessed secondary outcome measures in a large subset of these participants, except for dementia, which was only assessed in a relatively small number of participants (n = 6671).

We included only three studies (3632 participants) comparing different blood pressure targets, and the largest of these studies only included participants with a lacunar stroke as index event. Therefore, many questions regarding the optimal blood pressure target after TIA or stroke remain unanswered.

Quality of the evidence

Overall, the trials included in our main analyses ranged from low to substantial risk of bias. In a sensitivity analysis based on high risk of bias, we excluded three trials. Two of these trials

mainly suffered from insufficient blinding and lack of description of their randomisation procedures, whereas the third suffered from significant numbers of loss to follow-up and differing numbers of outcome events between different reports.

The resulting quality of the evidence, as assessed in the GRADE format, was moderate for our primary outcome measure, 'recurrent stroke of any type'. The quality of evidence was high for most of our secondary outcome measures, except for 'death by any cause', which we also downgraded to moderate.

Potential biases in the review process

We conducted an extensive literature search according to current Cochrane standards, without language restrictions. Therefore, we consider it unlikely that we missed potentially relevant studies.

We did not use individual participant data. Therefore, we did not include participants from trials that investigated BPLDs in a more general population, as none of these trials reported a subgroup analysis of people with a history of TIA or stroke.

We included one trial that also included 2.0% of participants with subarachnoid haemorrhage (PATS 1995). Therefore, we performed an additional sensitivity analysis, in which we excluded patients with subarachnoid haemorrhage as possible index event.

Agreements and disagreements with other studies or reviews

Two similar meta-analyses on the effect of BPLDs in the secondary prevention of stroke were performed previously (Lakhan 2009; Liu 2009), which also found a positive effect of BPLDs on reducing recurrent stroke (pooled odds ratios 0.71 (95% confidence interval (CI) 0.59 to 0.86) and 0.78 (95% CI 0.68 to 0.90) respectively). Due to differences in inclusion criteria, the previous meta-analyses included three and two additional studies (respectively) in comparison with our meta-analysis, which resulted in the slight differences in effect estimates and CIs between all meta-analyses.

AUTHORS' CONCLUSIONS

Implications for practice

Our results support the use of blood pressure-lowering drugs (BPLDs) in secondary prevention after transient ischaemic attack (TIA) or stroke. Current evidence is primarily derived from trials of treatment with an angiotensin-converting enzyme (ACE) inhibitor or diuretic. BPLDs appeared to be most effective in people with high baseline blood pressure (> 140 mmHg); however, differences between these subgroups were not statistically significant.

Only limited data comparing different systolic blood pressure targets were available. Therefore, no conclusions can be drawn from current evidence regarding an optimal systolic blood pressure target after TIA or stroke.

Implications for research

An individual participant data meta-analysis could further identify specific subgroups of people who are likely to benefit from BPLDs after TIA or stroke. We recommend that future studies assess whether BPLDs lower the risk of dementia in TIA and stroke patients.

Additional large randomised controlled trials (RCTs) are needed to investigate the optimal blood pressure target after TIA or stroke.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Carter 1970

Methods	RCT
Participants	Total number of participants randomised: 99 Setting: hospital Participants: hypertensive survivors below the age of 80 of ischaemic type major strokes Mean age: 64 years Sex: 57% men Country: UK
Interventions	Tailored individually • thiazide diuretics (and restricted salt intake) • methyldopa (1-2 gram once a day) • guanethidine, bethanidine or debrisoquine (10 mg three/four times a day, up to 200 mg)
Outcomes	Recurrent stroke of any type Death by any cause
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were placed at random into treated or control groups."
Allocation concealment (selection bias)	Unclear risk	Comment: method of allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no blinding described, and outcome possibly influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: no blinding described, and outcome possibly influenced by lack of blinding
Incomplete outcome data (attrition bias)	Low risk	Quote: "Of the 99 patients in the trial, 2 have been lost to follow-up."

Carter 1970 *(Continued)*

All outcomes		Comment: missing outcome data balanced, and the proportion of missing outcomes compared with the observed event risk is unlikely to induce a clinically relevant impact on the effect estimate
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol published
Other bias	High risk	Comment: no endpoint definition given, single investigator study

Co-operative Study 1975

Methods	RCT
Participants	Total number of participants randomised: 452 Setting: hospital Participants: hypertensive patients with a stroke or TIA in the previous year Mean age: 59 years Sex: 59% men Country: USA
Interventions	Deserdipine (0.5 mg once a day) and methyclothiazide (5 mg twice a day)
Outcomes	Recurrent stroke of any type Time to recurrent stroke Myocardial infarction Vascular death Death by any cause
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The biostatistical section was responsible for assignment of patients to drug or placebo regimens."
Allocation concealment (selection bias)	Low risk	Quote: "The biostatistical section was responsible for (...), distribution of medication by mail to the individual clinics." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Neither the doctor nor the patient was aware of whether placebo or drug had been supplied."

Co-operative Study 1975 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "A stroke endpoint (...) also was confirmed by a majority of a committee consisting of two members outside of the study and the Central Registry neurologist."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: although the number of participants lost to follow-up was high, it was balanced between the groups in numbers and reasons
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol published
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

Dutch TIA Trial 1993

Methods	RCT
Participants	Total number of participants randomised: 1473 Setting: hospital Participants: patients with a TIA or non-disabling stroke less than 3 months before Mean age: unknown (52% of participants > 65 years) Sex: 64% men Country: the Netherlands
Interventions	Atenolol (50 mg once a day)
Outcomes	Recurrent stroke of any type Major vascular event (composite of non-fatal stroke, non-fatal myocardial infarction, or death from any vascular cause) Vascular death Death by any cause
Notes	Also compared two antithrombotic regimens in a 2x2 factorial design

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "... use of random permuted blocks"
Allocation concealment (selection bias)	Low risk	Quote: "Blinded randomization codes were distributed by telephone."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: method of blinding not described other than being double-blind

Dutch TIA Trial 1993 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All outcome events were independently classified by at least three members of the Auditing Committee for Outcome Events, without knowledge of treatment allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "No patient was lost to follow-up."
Selective reporting (reporting bias)	High risk	Comment: in the protocol manuscript, the primary outcome was defined as the modified Rankin Scale, but this outcome is not reported
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

Marti Masso 1990

Methods	RCT
Participants	Total number of participants randomised: 264 Setting: hospital Participants: patients with TIA or minor stroke in the previous 12 months Mean age: 61 years Sex: 71% men Country: Spain
Interventions	Nicardipine (20 mg three times a day)
Outcomes	Recurrent stroke of any type Ischaemic stroke Death by any cause
Notes	Distribution between intervention and control suggests a randomisation ratio of 2:1, which remains unexplained

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Comment: method of allocation concealment not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no blinding described, and outcome possibly influenced by lack of blinding
Blinding of outcome assessment (detection bias)	High risk	Quote: "At three, six and 12 months the patients were asked about new symptoms of ischaemic episodes."

Marti Masso 1990 *(Continued)*

All outcomes		Comment: no blinding described, and outcome possibly influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: the study did not address this outcome
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol published
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

PAST-BP 2016

Methods	Primary care-based, pragmatic RCT
Participants	Total number of participants randomised: 529 Setting: general practitioner Participants: patients with a past history of stroke or TIA Mean age: 72 years Sex: 59% men Country: UK
Interventions	Intensive versus guideline blood pressure-lowering (target systolic blood pressure < 130 mmHg or a target reduction of 10 mmHg if blood pressure was between 125-140 versus target systolic blood pressure < 140 mmHg)
Outcomes	Recurrent stroke of any type Major vascular event (composite of non-fatal stroke, non-fatal myocardial infarction, or death from any vascular cause) Myocardial infarction Death by any cause
Notes	The time period between prior stroke or TIA and enrolment or intervention is unknown

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Comment: not specifically mentioned, but probably adequately done because of the use of minimisation
Allocation concealment (selection bias)	Low risk	Quote: "The central study team at the University of Birmingham randomized patients (...). The research nurse ascertained treatment allocation either by telephone or online"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: no blinding of participants and personnel, but outcomes are not likely to be influenced by lack of blinding

PAST-BP 2016 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Key secondary events (stroke; myocardial infarction; fatal coronary heart disease and other cardiovascular death) will be reviewed by independent clinicians blinded to treatment to ensure unbiased coding of these events."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All patients were followed up for clinical events and deaths."
Selective reporting (reporting bias)	Low risk	Comment: study protocol published; all prespecified outcomes reported
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

PATS 1995

Methods	RCT
Participants	Total number of participants randomised: 5665 Setting: hospital Participants: patients with a history of TIA or stroke Mean age: 60 years Sex: 72% men Country: China
Interventions	Indapamide (2.5 mg once a day)
Outcomes	Recurrent stroke of any type Myocardial infarction Vascular death Death by any cause
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The Coordinating Center at the Fu Wai hospital generated a randomization list for each center."
Allocation concealment (selection bias)	Low risk	Quote: "The sealed envelope system was used to randomize the participants."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "(...) or a pill of matching placebo" Comment: probably adequately done

PATS 1995 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An Endpoint Committee, blinded to the randomization of patients, reviewed the clinical records and adjudicated all primary and secondary end points."
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: high proportion of incomplete outcome data, such that it could have influenced effect estimates
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol published
Other bias	High risk	Comment: multiple reports with different numbers of participants and outcome events

PODCAST 2017

Methods	Prospective, open-label blinded endpoint, phase IV RCT
Participants	Total number of participants randomised: 83 Setting: hospital Participants: patients with ischaemic stroke or intracerebral haemorrhage in the past 3 to 7 months Mean age: 74 years Sex: 77% men Country: UK
Interventions	Intensive versus guideline blood pressure-lowering (target systolic blood pressure < 125 mmHg versus < 140 mmHg)
Outcomes	Recurrent stroke of any type Major vascular event (composite of non-fatal stroke, non-fatal myocardial infarction, or death from any vascular cause) Ischaemic stroke Haemorrhagic stroke Myocardial infarction Death by any cause Dementia
Notes	Stopped early because of slow recruitment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "All participants (...) will be randomized centrally using a secure Internet site in real-time."

PODCAST 2017 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "This approach ensures concealment of allocation, (...)"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: no blinding of participants and personnel, but outcomes are not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "(...) outcome assessment will be assessed blinded to treatment assignment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no loss to follow-up
Selective reporting (reporting bias)	Low risk	Comment: study protocol published; all outcomes relevant to our review were reported
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

PRoFESS 2008

Methods	RCT
Participants	Total number of participants randomised: 20,332 Setting: hospital Participants: patients with ischaemic stroke in the previous 90 days Mean age: 66 years Sex: 64% men Country: 35 countries (all major continents)
Interventions	Telmisartan (80 mg once a day)
Outcomes	Recurrent stroke of any type Time to recurrent stroke Major vascular event (composite of non-fatal stroke, non-fatal myocardial infarction, or death from any vascular cause) Ischaemic stroke Haemorrhagic stroke Myocardial infarction Vascular death Death by any cause
Notes	Also compared two antithrombotic regimens in a 2x2 factorial design
Risk of bias	

PRoFESS 2008 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Comment: not specifically mentioned, but probably adequately done because of use of stratification
Allocation concealment (selection bias)	Low risk	Quote: "(...) with the use of a central telephone system."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The medication was 'double dummy' meaning that each patient received each medication, either active or matching placebo, so that all patients received identically appearing medication kits."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An Adjudication and Assessment Committee independent of the Steering Committee and sponsor verifies all primary and key secondary outcomes blinded to treatment allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "A total of 125 patients (51 in the telmisartan group and 74 in the placebo group) (0.6%) were lost to follow up." Comment: proportion of missing outcome not likely to induce clinically relevant bias in intervention effect estimate
Selective reporting (reporting bias)	Low risk	Comment: study protocol published; all prespecified outcomes reported
Other bias	Low risk	Comment: industry sponsored, but no concerns

PROGRESS 2001

Methods	RCT
Participants	Total number of participants randomised: 6105 Setting: hospital Participants: patients with TIA or stroke in the previous 5 years Mean age: 64 years Sex: 70% men Country: Australia, Belgium, China, France, Japan, Italy, New Zealand, Sweden and UK
Interventions	Perindopril (4 mg once a day) ± indapamide (2.5 mg once a day, Japan: 2 mg once a day)
Outcomes	Recurrent stroke of any type Time to recurrent stroke Major vascular event Ischaemic stroke Haemorrhagic stroke Myocardial infarction (composite of non-fatal myocardial infarction and fatal coronary) Vascular death

PROGRESS 2001 *(Continued)*

	Death by any cause Dementia
Notes	Index event was prior history of stroke or TIA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A minimization algorithm stratifies treatment allocation..."
Allocation concealment (selection bias)	Low risk	Quote: "Allocation to active treatment or to placebo was performed by fax from the collaborating clinical centres to the study randomization centre in Auckland."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients assigned placebo received placebo tablets identical in appearance to perindopril."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An endpoint adjudication committee reviewed source documentation for all individuals (...)" Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: missing outcome data balanced, and the proportion not enough to have a clinically relevant impact on the intervention effect estimate
Selective reporting (reporting bias)	Low risk	Comment: study protocol published; all prespecified outcomes reported
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

SPS3 2013

Methods	RCT
Participants	Total number of participants randomised: 3020 Setting: hospital Participants: patients with a lacunar stroke in the previous 180 days Mean age: 63 years Sex: 63% men Country: North America, Latin America, and Spain
Interventions	Systolic blood pressure target < 130 mmHg versus target 130-149 mmHg
Outcomes	Recurrent stroke of any type Time to recurrent stroke

SPS3 2013 *(Continued)*

	Major vascular event (composite of non-fatal stroke, non-fatal myocardial infarction, or death from any vascular cause) Ischaemic stroke Haemorrhagic stroke Myocardial infarction Vascular death Death by any cause Dementia
Notes	Also compared two antithrombotic regimens in a 2x2 factorial design

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The schedule was computer generated with a permuted-block design (variable block size)."
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation assignments (...) are stored in each clinical centre's electronic data entry system, and are protected from preview."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: no blinding of participants and personnel, but outcomes are not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All possible outcome and safety events are reviewed by the blinded Events Adjudication Committee (...) who are not otherwise involved in SPS3."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: number and reasons of loss to follow-up reported, but not per treatment group
Selective reporting (reporting bias)	Low risk	Comment: study protocol published; all prespecified outcomes reported
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

TEST 1995

Methods	RCT
Participants	Total number of participants randomised: 720 Setting: hospital Participants: patients with TIA or stroke in previous 3 weeks Mean age: 70 years Sex: 60% men Country: Sweden

TEST 1995 *(Continued)*

Interventions	Atenolol (50 mg once a day)
Outcomes	Recurrent stroke of any type Major vascular event (composite of non-fatal stroke, non-fatal myocardial infarction, or death from any vascular cause) Myocardial infarction Vascular death Death by any cause
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A computer-generated random scheme using a random permuted block design (...)"
Allocation concealment (selection bias)	Low risk	Quote: "A computer-generated random scheme using a random permuted block design (...)"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: method of blinding not described other than being double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An independent End Point Committee reviewed the fatal end-points..." Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no loss to follow-up
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol published
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

RCT: randomised controlled trial
TIA: transient ischaemic attack

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

Study	Reason for exclusion
Lee 2015	Not all participants had a TIA or stroke as index event
Lithell 2003	No comparison with placebo or no BPLDs (as BPLDs were started in a large proportion of participants in the control group during follow-up)

Study	Reason for exclusion
Schrader 2003	No comparison with placebo or no BPLDs (as BPLDs were started in a large proportion of participants in the control group during follow-up)

BPLDs: blood pressure-lowering drugs
TIA: transient ischaemic attack

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

NCT01220622

Trial name or title	Efficacy and safety study of nimodipine to prevent mild cognitive impairment after acute ischemic strokes (NICE)
Methods	Double-blind, placebo-controlled, phase IV randomised controlled trial
Participants	Participants aged 30–80 with ischaemic stroke ≤ 7 days
Interventions	Nimodipine (90 mg/day) or placebo (90 mg/day)
Outcomes	Death by any cause Dementia
Starting date	November 2010
Contact information	yongjunwang111@yahoo.com.cn; happyft@sina.com; minnie_wxm@hotmail.com
Notes	Status: unknown, results expected 2013 Size: 656 participants (23 Chinese centres)

NCT01563731

Trial name or title	Optimal blood pressure and cholesterol targets for preventing recurrent stroke in hypertensives (ESH-CHL-SHOT)
Methods	Prospective randomised open-label blinded endpoint trial, with a 3x2 factorial design
Participants	Participants aged > 65 years with stroke or TIA 1-6 months prior to randomisation
Interventions	• 3 different systolic blood pressure targets (< 145–135, < 135–125, and < 125 mmHg) • 2 different low-density lipoprotein cholesterol targets (2.8–1.8, < 1.8 mmol/L)
Outcomes	Stroke Time to recurrent stroke Major vascular event Ischaemic stroke Haemorrhagic stroke Vascular death Death by any cause

NCT01563731 *(Continued)*	
	Dementia
Starting date	April 2013
Contact information	alberto.zanchetti@auxologico.it; g.bilo@auxologico.it
Notes	Status: recruiting Size: 7500 planned

mg: milligram
mmHg: millimetres of mercury
mmol/L: millimoles per litre
TIA: transient ischaemic attack

DATA AND ANALYSES

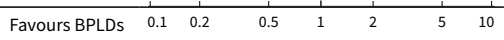
Comparison 1. Blood pressure-lowering drugs (BPLDs) versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrent stroke of any type	8	35110	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.70, 0.93]
2 Time to recurrent stroke	3	26889	Hazard Ratio (Random, 95% CI)	0.82 [0.65, 1.03]
3 Major vascular event (composite of non-fatal stroke, non-fatal myocardial infarction, or death from any vascular cause	4	28630	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.78, 1.04]
4 Ischaemic stroke	3	26701	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.70, 1.05]
5 Haemorrhagic stroke	2	26437	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.39, 1.12]
6 Myocardial infarction	6	34747	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.72, 1.11]
7 Vascular death	6	34747	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.76, 0.95]
8 Death by any cause	8	35110	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.91, 1.05]
9 Dementia	2	6671	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.73, 1.06]
10 Blood pressure baseline (systolic)	5	34295	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.39, 0.37]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11 Blood pressure baseline (diastolic)	5	34295	Mean Difference (IV, Random, 95% CI)	0.01 [-0.22, 0.24]

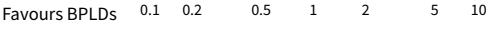
Analysis 1.1. Comparison 1 Blood pressure-lowering drugs (BPLDs) versus placebo or no treatment, Outcome 1 Recurrent stroke of any type.

Study or subgroup	BPLDs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Carter 1970	10/50	21/49		4.07%	0.47[0.25,0.89]
Co-operative Study 1975	37/233	42/219		8.43%	0.83[0.55,1.24]
Marti Masso 1990	6/170	6/94		1.53%	0.55[0.18,1.67]
Dutch TIA Trial 1993	52/732	62/741		9.96%	0.85[0.6,1.21]
PATS 1995	159/2840	219/2825		17.65%	0.72[0.59,0.88]
TEST 1995	74/372	69/348		12.41%	1[0.75,1.35]
PROGRESS 2001	307/3051	420/3054		21.46%	0.73[0.64,0.84]
PRoFESS 2008	880/10146	934/10186		24.5%	0.95[0.87,1.03]
Total (95% CI)	**17594**	**17516**		**100%**	**0.81[0.7,0.93]**
Total events: 1525 (BPLDs), 1773 (Control)					
Heterogeneity: Tau^2=0.02; Chi^2=17.94, df=7(P=0.01); I^2=60.97%					
Test for overall effect: Z=2.93(P=0)					



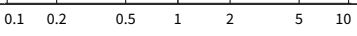
Analysis 1.2. Comparison 1 Blood pressure-lowering drugs (BPLDs) versus placebo or no treatment, Outcome 2 Time to recurrent stroke.

Study or subgroup	BPLDs N	Control N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
Co-operative Study 1975	233	219	-0.3 (0.24)		15.93%	0.76[0.47,1.21]
PROGRESS 2001	3051	3054	-0.3 (0.074)		40%	0.72[0.62,0.83]
PRoFESS 2008	10146	10186	-0.1 (0.049)		44.07%	0.95[0.86,1.04]
Total (95% CI)					**100%**	**0.82[0.65,1.03]**
Heterogeneity: Tau^2=0.03; Chi^2=10.1, df=2(P=0.01); I^2=80.2%						
Test for overall effect: Z=1.69(P=0.09)						



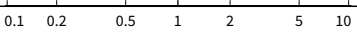
Analysis 1.3. Comparison 1 Blood pressure-lowering drugs (BPLDs) versus placebo or no treatment, Outcome 3 Major vascular event (composite of non-fatal stroke, non-fatal myocardial infarction, or death from any vascular cause.

Study or subgroup	BPLDs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Dutch TIA Trial 1993	97/732	95/741		16.74%	1.03[0.79,1.35]
TEST 1995	97/372	92/348		18.12%	0.99[0.77,1.26]
PROGRESS 2001	458/3051	604/3054		30.76%	0.76[0.68,0.85]
PRoFESS 2008	1289/10146	1377/10186		34.38%	0.94[0.88,1.01]
Total (95% CI)	**14301**	**14329**		**100%**	**0.9[0.78,1.04]**
Total events: 1941 (BPLDs), 2168 (Control)					
Heterogeneity: Tau²=0.01; Chi²=12.11, df=3(P=0.01); I²=75.22%					
Test for overall effect: Z=1.39(P=0.16)					



Analysis 1.4. Comparison 1 Blood pressure-lowering drugs (BPLDs) versus placebo or no treatment, Outcome 4 Ischaemic stroke.

Study or subgroup	BPLDs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Marti Masso 1990	6/170	6/94		3.14%	0.55[0.18,1.67]
PROGRESS 2001	246/3051	319/3054		43.77%	0.77[0.66,0.9]
PRoFESS 2008	774/10146	811/10186		53.09%	0.96[0.87,1.05]
Total (95% CI)	**13367**	**13334**		**100%**	**0.86[0.7,1.05]**
Total events: 1026 (BPLDs), 1136 (Control)					
Heterogeneity: Tau²=0.02; Chi²=6.03, df=2(P=0.05); I²=66.82%					
Test for overall effect: Z=1.51(P=0.13)					



Analysis 1.5. Comparison 1 Blood pressure-lowering drugs (BPLDs) versus placebo or no treatment, Outcome 5 Haemorrhagic stroke.

Study or subgroup	BPLDs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
PROGRESS 2001	37/3051	74/3054		48.52%	0.5[0.34,0.74]
PRoFESS 2008	59/10146	69/10186		51.48%	0.86[0.61,1.21]
Total (95% CI)	**13197**	**13240**		**100%**	**0.66[0.39,1.12]**
Total events: 96 (BPLDs), 143 (Control)					
Heterogeneity: Tau²=0.11; Chi²=4.09, df=1(P=0.04); I²=75.58%					
Test for overall effect: Z=1.54(P=0.12)					

Analysis 1.6. Comparison 1 Blood pressure-lowering drugs (BPLDs) versus placebo or no treatment, Outcome 6 Myocardial infarction.

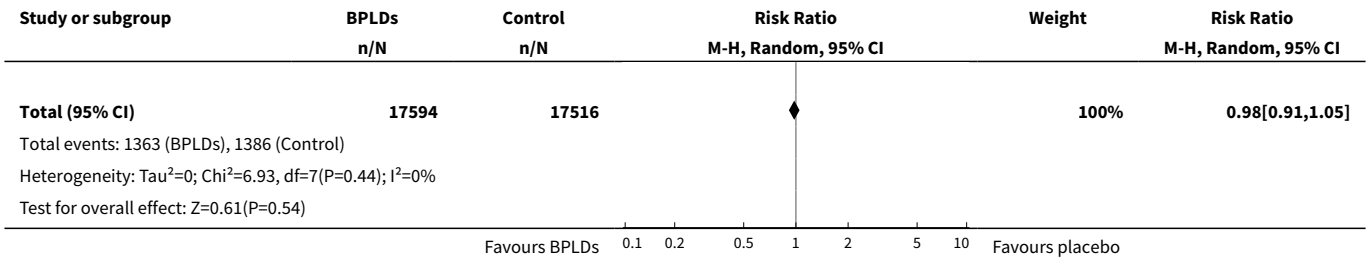
Study or subgroup	BPLDs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Co-operative Study 1975	5/233	7/219		3.34%	0.67[0.22,2.08]
Dutch TIA Trial 1993	45/732	40/741		17.14%	1.14[0.75,1.72]
PATS 1995	26/2840	23/2825		11.24%	1.12[0.64,1.97]
TEST 1995	26/372	29/348		12.92%	0.84[0.5,1.39]
PROGRESS 2001	60/3051	96/3054		23.1%	0.63[0.45,0.86]
PRoFESS 2008	168/10146	169/10186		32.26%	1[0.81,1.23]
Total (95% CI)	**17374**	**17373**		**100%**	**0.9[0.72,1.11]**
Total events: 330 (BPLDs), 364 (Control)					
Heterogeneity: Tau^2=0.03; Chi^2=8.1, df=5(P=0.15); I^2=38.26%					
Test for overall effect: Z=1(P=0.32)					

Analysis 1.7. Comparison 1 Blood pressure-lowering drugs (BPLDs) versus placebo or no treatment, Outcome 7 Vascular death.

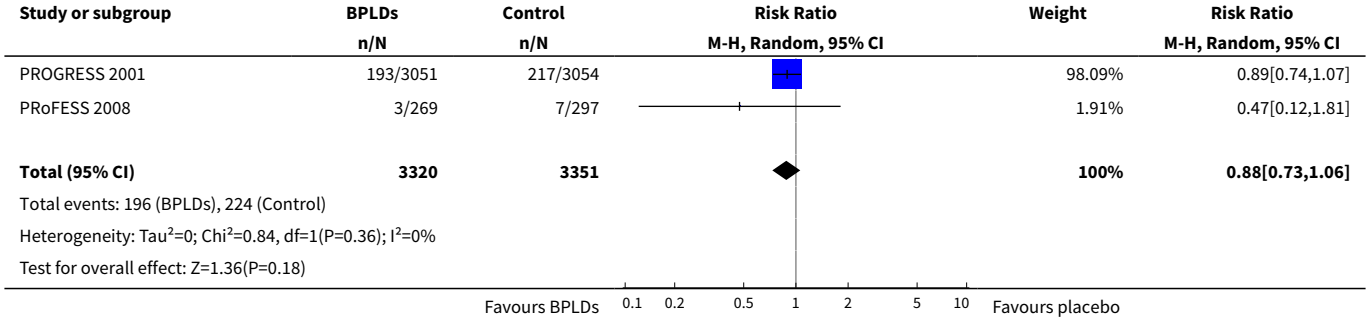
Study or subgroup	BPLDs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Co-operative Study 1975	12/233	19/219		2.52%	0.59[0.3,1.19]
Dutch TIA Trial 1993	41/732	33/741		5.98%	1.26[0.8,1.97]
PATS 1995	199/2840	258/2825		29.65%	0.77[0.64,0.92]
TEST 1995	34/372	39/348		6.26%	0.82[0.53,1.26]
PROGRESS 2001	181/3051	198/3054		25.65%	0.92[0.75,1.11]
PRoFESS 2008	223/10146	263/10186		29.94%	0.85[0.71,1.02]
Total (95% CI)	**17374**	**17373**		**100%**	**0.85[0.76,0.95]**
Total events: 690 (BPLDs), 810 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.83, df=5(P=0.32); I^2=14.21%					
Test for overall effect: Z=2.82(P=0)					

Analysis 1.8. Comparison 1 Blood pressure-lowering drugs (BPLDs) versus placebo or no treatment, Outcome 8 Death by any cause.

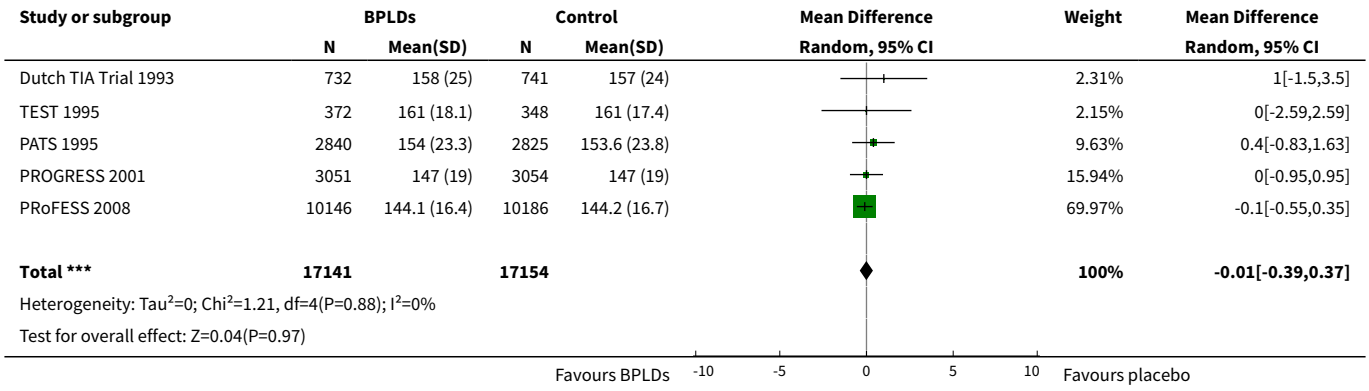
Study or subgroup	BPLDs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Carter 1970	13/50	22/49		1.62%	0.58[0.33,1.01]
Co-operative Study 1975	26/233	24/219		1.87%	1.02[0.6,1.72]
Marti Masso 1990	3/170	2/94		0.16%	0.83[0.14,4.88]
Dutch TIA Trial 1993	64/732	58/741		4.42%	1.12[0.79,1.57]
TEST 1995	51/372	60/348		4.33%	0.8[0.56,1.12]
PATS 1995	145/2840	161/2825		10.73%	0.9[0.72,1.11]
PROGRESS 2001	306/3051	319/3054		23.16%	0.96[0.83,1.11]
PRoFESS 2008	755/10146	740/10186		53.7%	1.02[0.93,1.13]



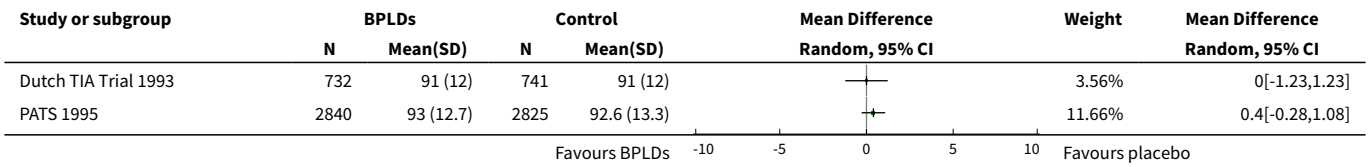
Analysis 1.9. Comparison 1 Blood pressure-lowering drugs (BPLDs) versus placebo or no treatment, Outcome 9 Dementia.

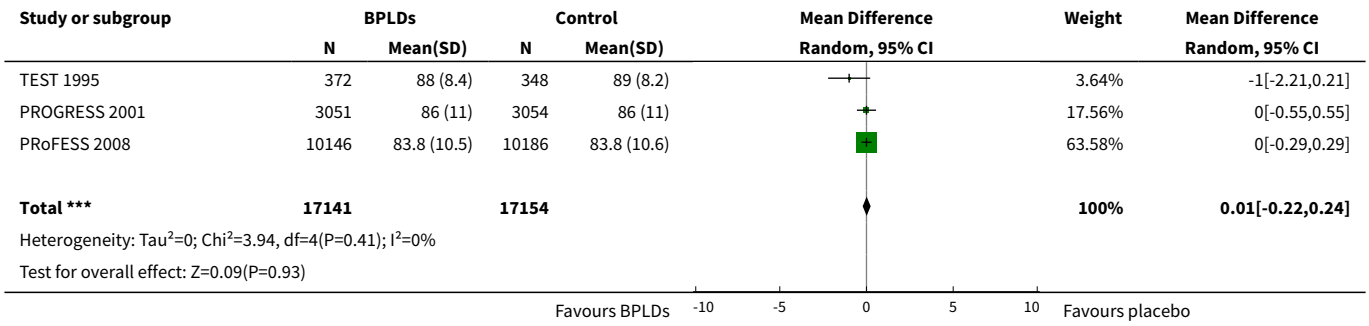


Analysis 1.10. Comparison 1 Blood pressure-lowering drugs (BPLDs) versus placebo or no treatment, Outcome 10 Blood pressure baseline (systolic).



Analysis 1.11. Comparison 1 Blood pressure-lowering drugs (BPLDs) versus placebo or no treatment, Outcome 11 Blood pressure baseline (diastolic).





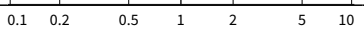
Comparison 2. Blood pressure-lowering drugs (BPLDs) versus placebo or no treatment (subgroups)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrent stroke of any type by baseline systolic blood pressure (SBP)	3	6656	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.64, 0.83]
1.1 SBP < 120 mmHg	1	350	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.47, 2.19]
1.2 SBP 120 - 139 mmHg	1	1787	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.67, 1.12]
1.3 SBP 140 - 159 mmHg	2	2565	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.57, 0.89]
1.4 SBP > 160 mmHg	3	1954	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.51, 0.83]
2 Recurrent stroke of any type by intervention	8	35110	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.70, 0.93]
2.1 ACE inhibitors	1	6105	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.64, 0.84]
2.2 Angiotensin receptor antagonists	1	20332	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.87, 1.03]
2.3 Beta-blockers	2	2193	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.75, 1.18]
2.4 Calcium channel blockers	1	264	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.18, 1.67]
2.5 Diuretics	3	6216	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.59, 0.87]
3 Recurrent stroke of any type by type of index event	1	5854	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.64, 0.85]
3.1 TIA	1	981	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.50, 1.18]
3.2 Ischaemic stroke	1	4262	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.64, 0.89]
3.3 Intracerebral haemorrhage	1	611	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.39, 0.89]
3.4 Combined Ischaemic stroke and Intracerebral haemorrhage	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Major vascular event by intervention	4	28630	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.78, 1.04]
4.1 ACE inhibitors	1	6105	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.68, 0.85]
4.2 Angiotensin receptor antagonists	1	20332	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.88, 1.01]
4.3 Beta-blockers	2	2193	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.84, 1.21]

Analysis 2.1. Comparison 2 Blood pressure-lowering drugs (BPLDs) versus placebo or no treatment (subgroups), Outcome 1 Recurrent stroke of any type by baseline systolic blood pressure (SBP).

Study or subgroup	BPLDs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 SBP < 120 mmHg					
PROGRESS 2001	12/174	12/176		2.76%	1.01[0.47,2.19]
Subtotal (95% CI)	**174**	**176**		**2.76%**	**1.01[0.47,2.19]**
Total events: 12 (BPLDs), 12 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.03(P=0.98)					
2.1.2 SBP 120 - 139 mmHg					
PROGRESS 2001	95/898	109/889		24.49%	0.86[0.67,1.12]
Subtotal (95% CI)	**898**	**889**		**24.49%**	**0.86[0.67,1.12]**
Total events: 95 (BPLDs), 109 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=1.12(P=0.26)					
2.1.3 SBP 140 - 159 mmHg					
Co-operative Study 1975	10/83	14/86		2.89%	0.74[0.35,1.57]
PROGRESS 2001	105/1192	150/1204		29.45%	0.71[0.56,0.9]
Subtotal (95% CI)	**1275**	**1290**		**32.35%**	**0.71[0.57,0.89]**
Total events: 115 (BPLDs), 164 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.91); I^2=0%					
Test for overall effect: Z=2.98(P=0)					
2.1.4 SBP > 160 mmHg					
Carter 1970	10/50	21/49		3.99%	0.47[0.25,0.89]
Co-operative Study 1975	27/150	28/133		7.3%	0.86[0.53,1.37]
PROGRESS 2001	95/787	149/785		29.11%	0.64[0.5,0.81]
Subtotal (95% CI)	**987**	**967**		**40.4%**	**0.65[0.51,0.83]**
Total events: 132 (BPLDs), 198 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=2.34, df=2(P=0.31); I^2=14.51%					
Test for overall effect: Z=3.5(P=0)					
Total (95% CI)	**3334**	**3322**		**100%**	**0.73[0.64,0.83]**
Total events: 354 (BPLDs), 483 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.94, df=6(P=0.43); I^2=0%					



Study or subgroup	BPLDs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=4.9(P<0.0001)					
Test for subgroup differences: Chi²=3.17, df=1 (P=0.37), I²=5.28%					

Favours BPLDs 0.1 0.2 0.5 1 2 5 10 Favours placebo

Analysis 2.2. Comparison 2 Blood pressure-lowering drugs (BPLDs) versus placebo or no treatment (subgroups), Outcome 2 Recurrent stroke of any type by intervention.

Study or subgroup	BPLD n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 ACE inhibitors					
PROGRESS 2001	307/3051	420/3054		21.46%	0.73[0.64,0.84]
Subtotal (95% CI)	**3051**	**3054**		**21.46%**	**0.73[0.64,0.84]**
Total events: 307 (BPLD), 420 (Control)					
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%					
Test for overall effect: Z=4.43(P<0.0001)					
2.2.2 Angiotensin receptor antagonists					
PRoFESS 2008	880/10146	934/10186		24.5%	0.95[0.87,1.03]
Subtotal (95% CI)	**10146**	**10186**		**24.5%**	**0.95[0.87,1.03]**
Total events: 880 (BPLD), 934 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.24(P=0.21)					
2.2.3 Beta-blockers					
Dutch TIA Trial 1993	52/732	62/741		9.96%	0.85[0.6,1.21]
TEST 1995	74/372	69/348		12.41%	1[0.75,1.35]
Subtotal (95% CI)	**1104**	**1089**		**22.36%**	**0.94[0.75,1.18]**
Total events: 126 (BPLD), 131 (Control)					
Heterogeneity: Tau²=0; Chi²=0.51, df=1(P=0.48); I²=0%					
Test for overall effect: Z=0.56(P=0.57)					
2.2.4 Calcium channel blockers					
Marti Masso 1990	6/170	6/94		1.53%	0.55[0.18,1.67]
Subtotal (95% CI)	**170**	**94**		**1.53%**	**0.55[0.18,1.67]**
Total events: 6 (BPLD), 6 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.05(P=0.29)					
2.2.5 Diuretics					
Carter 1970	10/50	21/49		4.07%	0.47[0.25,0.89]
Co-operative Study 1975	37/233	42/219		8.43%	0.83[0.55,1.24]
PATS 1995	159/2840	219/2825		17.65%	0.72[0.59,0.88]
Subtotal (95% CI)	**3123**	**3093**		**30.15%**	**0.72[0.59,0.87]**
Total events: 206 (BPLD), 282 (Control)					
Heterogeneity: Tau²=0; Chi²=2.22, df=2(P=0.33); I²=9.89%					
Test for overall effect: Z=3.36(P=0)					
Total (95% CI)	**17594**	**17516**		**100%**	**0.81[0.7,0.93]**
Total events: 1525 (BPLD), 1773 (Control)					

Favours BPLD 0.1 0.2 0.5 1 2 5 10 Favours placebo

Study or subgroup	BPLD n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0.02; Chi²=17.94, df=7(P=0.01); I²=60.97%					
Test for overall effect: Z=2.93(P=0)					
Test for subgroup differences: Chi²=14.33, df=1 (P=0.01), I²=72.09%					

Favours BPLD 0.1 0.2 0.5 1 2 5 10 Favours placebo

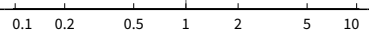
Analysis 2.3. Comparison 2 Blood pressure-lowering drugs (BPLDs) versus placebo or no treatment (subgroups), Outcome 3 Recurrent stroke of any type by type of index event.

Study or subgroup	BPLDs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 TIA					
PROGRESS 2001	33/491	43/490		10.54%	0.77[0.5,1.18]
Subtotal (95% CI)	**491**	**490**		**10.54%**	**0.77[0.5,1.18]**
Total events: 33 (BPLDs), 43 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.2(P=0.23)					
2.3.2 Ischaemic stroke					
PROGRESS 2001	229/2135	302/2127		77.39%	0.76[0.64,0.89]
Subtotal (95% CI)	**2135**	**2127**		**77.39%**	**0.76[0.64,0.89]**
Total events: 229 (BPLDs), 302 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.42(P=0)					
2.3.3 Intracerebral haemorrhage					
PROGRESS 2001	32/306	54/305		12.07%	0.59[0.39,0.89]
Subtotal (95% CI)	**306**	**305**		**12.07%**	**0.59[0.39,0.89]**
Total events: 32 (BPLDs), 54 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.53(P=0.01)					
2.3.4 Combined Ischaemic stroke and Intracerebral haemorrhage					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (BPLDs), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**2932**	**2922**		**100%**	**0.73[0.64,0.85]**
Total events: 294 (BPLDs), 399 (Control)					
Heterogeneity: Tau²=0; Chi²=1.25, df=2(P=0.53); I²=0%					
Test for overall effect: Z=4.27(P<0.0001)					
Test for subgroup differences: Chi²=1.25, df=1 (P=0.53), I²=0%					

Favours BPLDs 0.1 0.2 0.5 1 2 5 10 Favours placebo

Analysis 2.4. Comparison 2 Blood pressure-lowering drugs (BPLDs) versus placebo or no treatment (subgroups), Outcome 4 Major vascular event by intervention.

Study or subgroup	BPLD n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.4.1 ACE inhibitors					
PROGRESS 2001	458/3051	604/3054		30.76%	0.76[0.68,0.85]
Subtotal (95% CI)	**3051**	**3054**		**30.76%**	**0.76[0.68,0.85]**
Total events: 458 (BPLD), 604 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.89(P<0.0001)					
2.4.2 Angiotensin receptor antagonists					
PRoFESS 2008	1289/10146	1377/10186		34.38%	0.94[0.88,1.01]
Subtotal (95% CI)	**10146**	**10186**		**34.38%**	**0.94[0.88,1.01]**
Total events: 1289 (BPLD), 1377 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=1.72(P=0.09)					
2.4.3 Beta-blockers					
Dutch TIA Trial 1993	97/732	95/741		16.74%	1.03[0.79,1.35]
TEST 1995	97/372	92/348		18.12%	0.99[0.77,1.26]
Subtotal (95% CI)	**1104**	**1089**		**34.86%**	**1.01[0.84,1.21]**
Total events: 194 (BPLD), 187 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.07, df=1(P=0.8); I^2=0%					
Test for overall effect: Z=0.09(P=0.93)					
Total (95% CI)	**14301**	**14329**		**100%**	**0.9[0.78,1.04]**
Total events: 1941 (BPLD), 2168 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=12.11, df=3(P=0.01); I^2=75.22%					
Test for overall effect: Z=1.39(P=0.16)					
Test for subgroup differences: Chi^2=12.04, df=1 (P=0), I^2=83.39%					



Comparison 3. Blood pressure-lowering drugs (BPLDs) versus placebo or no treatment (sensitivity analyses)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrent stroke of any type, methodological quality	5	29082	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.75, 1.00]
2 Recurrent stroke of any type, minimum 5 mmHg systolic blood pressure (SBP) reduction	4	33575	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.68, 0.96]
3 Recurrent stroke of any type, minimum 3 mmHg diastolic blood pressure (DBP) reduction	5	34295	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.72, 0.97]
4 Recurrent stroke of any type, excluding patients with subarachnoid haemorrhage as possible index event	8	33690	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.70, 0.93]

Analysis 3.1. Comparison 3 Blood pressure-lowering drugs (BPLDs) versus placebo or no treatment (sensitivity analyses), Outcome 1 Recurrent stroke of any type, methodological quality.

Study or subgroup	BPLDs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Co-operative Study 1975	37/233	42/219		9.99%	0.83[0.55,1.24]
Dutch TIA Trial 1993	52/732	62/741		11.96%	0.85[0.6,1.21]
TEST 1995	74/372	69/348		15.25%	1[0.75,1.35]
PROGRESS 2001	307/3051	420/3054		28.83%	0.73[0.64,0.84]
PRoFESS 2008	880/10146	934/10186		33.97%	0.95[0.87,1.03]
Total (95% CI)	**14534**	**14548**		**100%**	**0.86[0.75,1]**
Total events: 1350 (BPLDs), 1527 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=10.32, df=4(P=0.04); I^2=61.24%					
Test for overall effect: Z=1.95(P=0.05)					

Favours BPLDs Favours placebo

Analysis 3.2. Comparison 3 Blood pressure-lowering drugs (BPLDs) versus placebo or no treatment (sensitivity analyses), Outcome 2 Recurrent stroke of any type, minimum 5 mmHg systolic blood pressure (SBP) reduction.

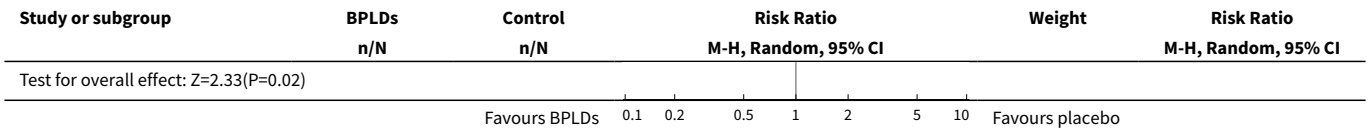
Study or subgroup	BPLDs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Dutch TIA Trial 1993	52/732	62/741		14.02%	0.85[0.6,1.21]
PATS 1995	159/2840	219/2825		24.18%	0.72[0.59,0.88]
PROGRESS 2001	307/3051	420/3054		29.01%	0.73[0.64,0.84]
PRoFESS 2008	880/10146	934/10186		32.78%	0.95[0.87,1.03]
Total (95% CI)	**16769**	**16806**		**100%**	**0.81[0.68,0.96]**
Total events: 1398 (BPLDs), 1635 (Control)					
Heterogeneity: Tau^2=0.02; Chi^2=12.75, df=3(P=0.01); I^2=76.47%					
Test for overall effect: Z=2.43(P=0.02)					

Favours BPLDs Favours placebo

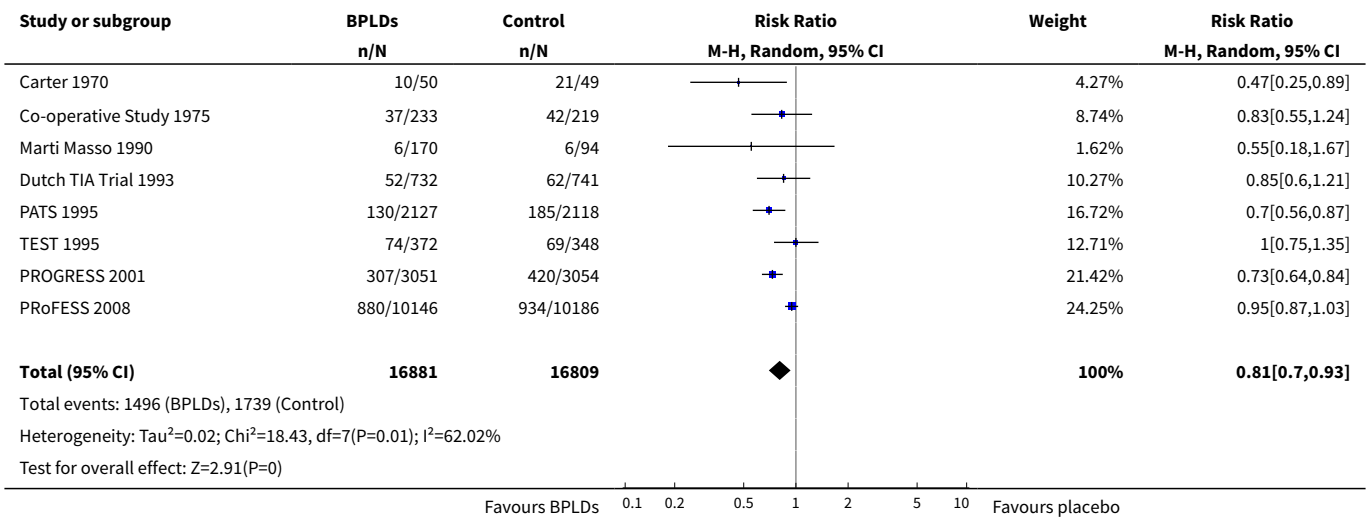
Analysis 3.3. Comparison 3 Blood pressure-lowering drugs (BPLDs) versus placebo or no treatment (sensitivity analyses), Outcome 3 Recurrent stroke of any type, minimum 3 mmHg diastolic blood pressure (DBP) reduction.

Study or subgroup	BPLDs n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Dutch TIA Trial 1993	52/732	62/741		11.5%	0.85[0.6,1.21]
PATS 1995	159/2840	219/2825		20.51%	0.72[0.59,0.88]
TEST 1995	74/372	69/348		14.36%	1[0.75,1.35]
PROGRESS 2001	307/3051	420/3054		25.01%	0.73[0.64,0.84]
PRoFESS 2008	880/10146	934/10186		28.62%	0.95[0.87,1.03]
Total (95% CI)	**17141**	**17154**		**100%**	**0.84[0.72,0.97]**
Total events: 1472 (BPLDs), 1704 (Control)					
Heterogeneity: Tau^2=0.02; Chi^2=13.8, df=4(P=0.01); I^2=71.01%					

Favours BPLDs Favours placebo



Analysis 3.4. Comparison 3 Blood pressure-lowering drugs (BPLDs) versus placebo or no treatment (sensitivity analyses), Outcome 4 Recurrent stroke of any type, excluding patients with subarachnoid haemorrhage as possible index event.



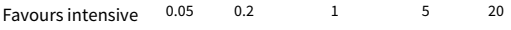
Comparison 4. Intensive versus standard blood pressure-lowering

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Stroke of any type (fatal and non-fatal)	3	3632	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.63, 1.00]
2 Time to recurrent stroke	1	3020	Hazard Ratio (Random, 95% CI)	0.81 [0.64, 1.03]
3 Major vascular event (composite of non-fatal stroke, non-fatal myocardial infarction, or death from any vascular cause	3	3632	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.23, 1.46]
4 Ischaemic stroke	2	3103	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.67, 1.09]
5 Haemorrhagic stroke	2	3103	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.17, 1.02]
6 Myocardial infarction	3	3632	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.58, 1.38]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Vascular death	2	3549	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.56, 1.35]
8 Death by any cause	3	3632	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.83, 1.39]
9 Dementia	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

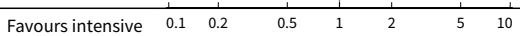
Analysis 4.1. Comparison 4 Intensive versus standard blood pressure-lowering, Outcome 1 Stroke of any type (fatal and non-fatal).

Study or subgroup	Lower SBP target n/N	Higher SBP target n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
SPS3 2013	118/1501	147/1519		98.33%	0.81[0.64,1.02]
PAST-BP 2016	0/266	3/263		0.6%	0.14[0.01,2.72]
PODCAST 2017	1/41	3/42		1.07%	0.34[0.04,3.15]
Total (95% CI)	**1808**	**1824**		**100%**	**0.8[0.63,1]**
Total events: 119 (Lower SBP target), 153 (Higher SBP target)					
Heterogeneity: Tau²=0; Chi²=1.91, df=2(P=0.39); I²=0%					
Test for overall effect: Z=1.94(P=0.05)					



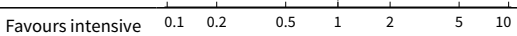
Analysis 4.2. Comparison 4 Intensive versus standard blood pressure-lowering, Outcome 2 Time to recurrent stroke.

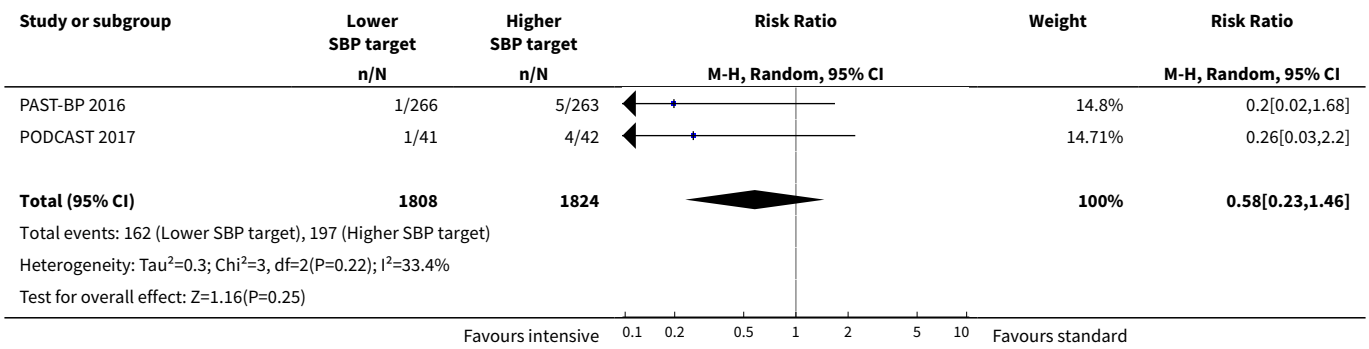
Study or subgroup	Lower SBP target N	Higher SBP target N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
SPS3 2013	1501	1519	-0.2 (0.121)		100%	0.81[0.64,1.03]
Total (95% CI)					**100%**	**0.81[0.64,1.03]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.74(P=0.08)						



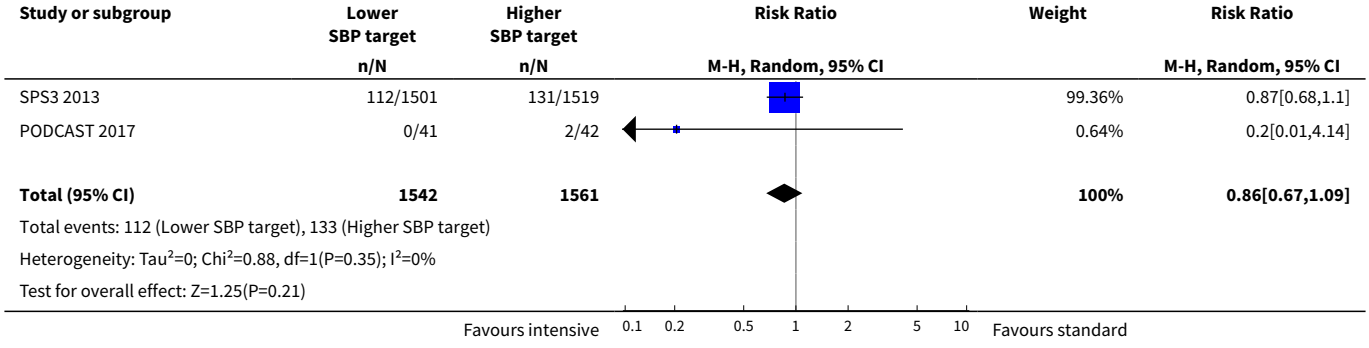
Analysis 4.3. Comparison 4 Intensive versus standard blood pressure-lowering, Outcome 3 Major vascular event (composite of non-fatal stroke, non-fatal myocardial infarction, or death from any vascular cause.

Study or subgroup	Lower SBP target n/N	Higher SBP target n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
SPS3 2013	160/1501	188/1519		70.48%	0.86[0.71,1.05]

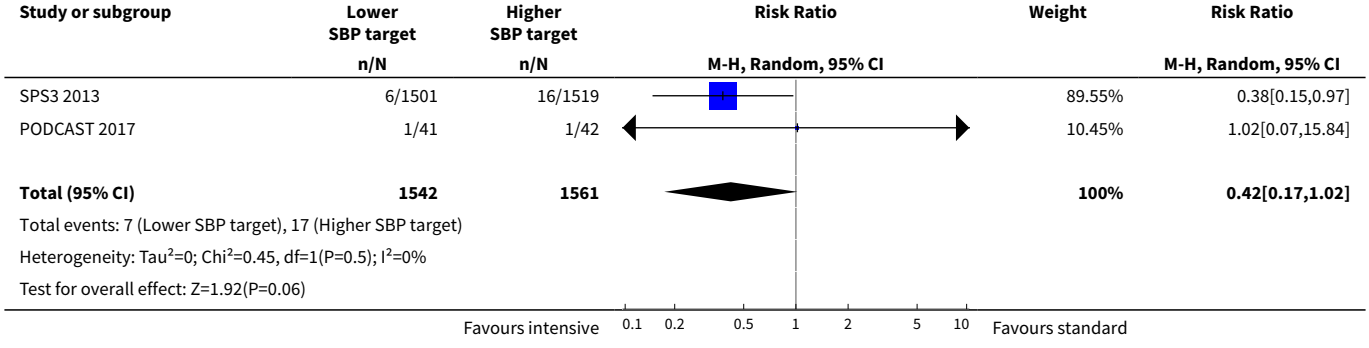




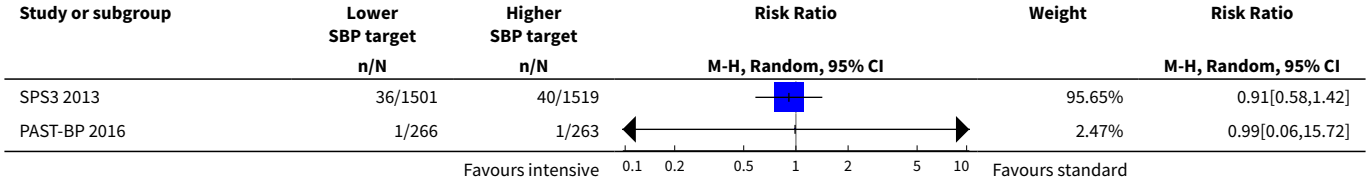
Analysis 4.4. Comparison 4 Intensive versus standard blood pressure-lowering, Outcome 4 Ischaemic stroke.

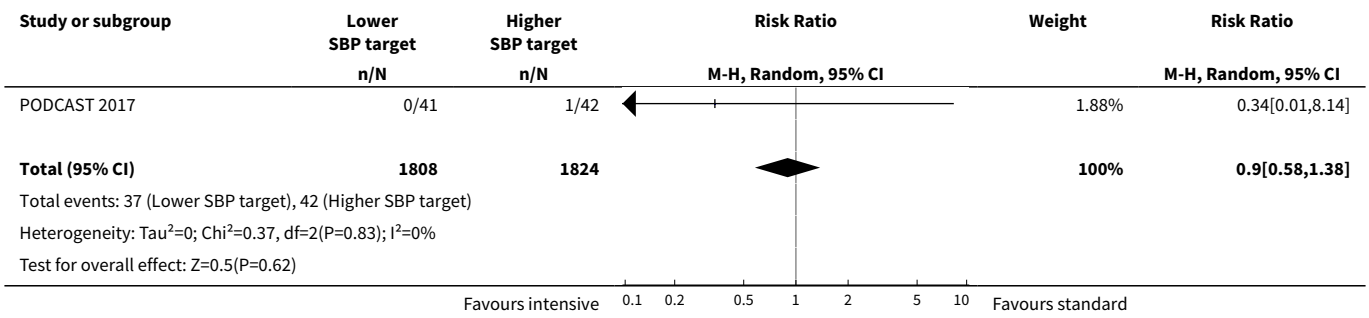


Analysis 4.5. Comparison 4 Intensive versus standard blood pressure-lowering, Outcome 5 Haemorrhagic stroke.

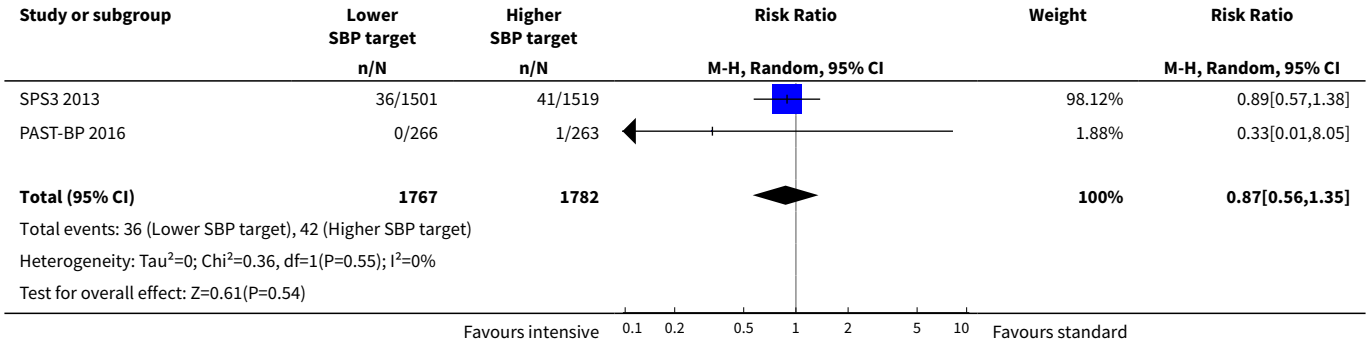


Analysis 4.6. Comparison 4 Intensive versus standard blood pressure-lowering, Outcome 6 Myocardial infarction.

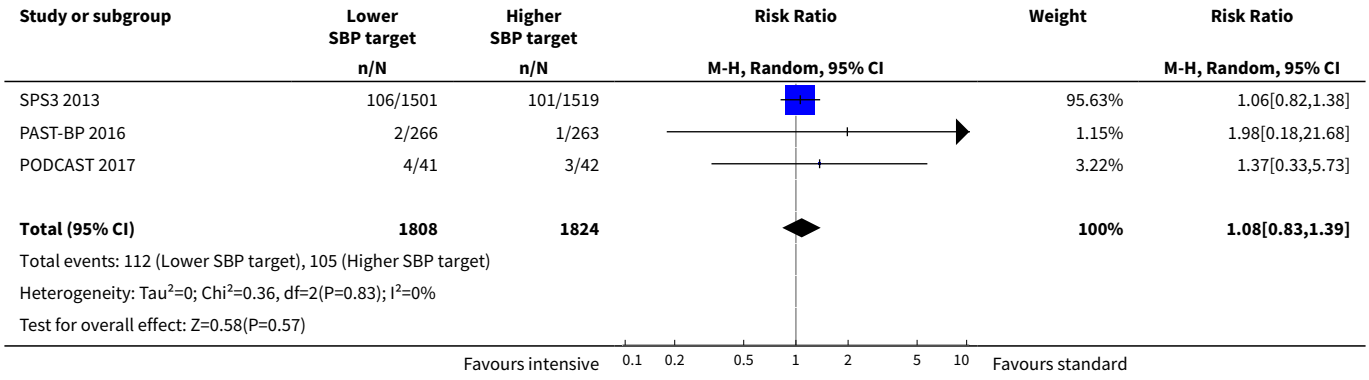




Analysis 4.7. Comparison 4 Intensive versus standard blood pressure-lowering, Outcome 7 Vascular death.



Analysis 4.8. Comparison 4 Intensive versus standard blood pressure-lowering, Outcome 8 Death by any cause.



APPENDICES

Appendix 1. CENTRAL search strategy

Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2016, Issue 6: searched July 2016);

1 [mh ^"cerebrovascular disorders"] or [mh "basal ganglia cerebrovascular disease"] or [mh "brain ischemia"] or [mh "carotid artery diseases"] or [mh "intracranial arterial diseases"] or [mh "intracranial embolism and thrombosis"] or [mh "intracranial hemorrhages"] or [mh ^stroke] or [mh "brain infarction"] or [mh ^"vasospasm, intracranial"] or [mh ^"vertebral artery dissection"]

#2 (stroke or cerebrovasc* or brain next vasc* or cerebral next vasc* or cva* or apoplex* or isch*emi* next attack* or tia or tias):ti,ab

#3 ((brain* or cerebr* or cerebell* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or MCA) near/5 (isch*emi* or infarct* or thrombo* or emboli* or occlus* or hypox* or vasospasm)):ti,ab

#4 ((brain* or cerebr* or cerebell* or intracerebral or intracran* or intraventricular or infratentorial or supratentorial or basal next gangli*) near/5 (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*)):ti,ab

#5 #1 or #2 or #3 or #4

#6 [mh "antihypertensive agents"] or [mh "vasodilator agents"] or [mh "adrenergic agonists"] or [mh diuretics] or [mh thiazides] or [mh "sodium chloride symporter inhibitors"] or [mh "sodium potassium chloride symporter inhibitors"]

#7 [mh "angiotensin-converting enzyme inhibitors"] or [mh "angiotensin II type 1 receptor blockers"] or [mh "calcium channel blockers"] or [mh "adrenergic beta-antagonists"] or [mh "adrenergic alpha antagonists"]

#8 [mh enalapril] or [mh ^losartan] or [mh hydralazine]

#9 [mh ^Hypertension/AE,DE,DT,PC] or [mh ^"Blood Pressure"/DE,PD]

#10 (antihypertens* or anti-hypertens*):ti,ab

#11 (("Blood pressure" or hypertens*) near/5 (lower* or reduc* or decreas*)):ti,ab

#12 (angiotensin near/3 convert* near/3 enzyme near/3 (inhibit* or antagonist* or block*)):ti,ab

#13 (((ace or renin) near/3 inhibit*) or ACEI):ti,ab

#14 (angiotensin near/3 receptor* near/3 (inhibit* or antagonist* or block*)):ti,ab

#15 (calcium near/2 (inhibit* or antagonist* or block*)):ti,ab

#16 (adrenergic near/3 beta* near/3 (inhibit* or antagonist* or block*)):ti,ab

#17 (adrenergic near/3 alpha* near/3 (inhibit* or antagonist* or block*)):ti,ab

#18 ((loop or ceiling) next diuretic*):ti,ab

#19 (amiloride or benzothiadiazine or bendroflumethiazide or bumetanide or chlorothiazide or cyclopenthiazide or furosemide or hydrochlorothiazide or hydroflumethiazide or methyclothiazide or metolazone or polythiazide or trichlormethiazide or veratide or thiazide*):ti,ab 5009

#20 (chlorthalidone or chlortalidone or phthalamudine or chlorphthalidolone or oxodoline or thalitone or hygroton or indapamide or metindamide or "s-1520" or s1520 or "se-1520" or se1520):ti,ab

#21 (alacepril or altiopril or benazepril or captopril or ceronapril or cilazapril or delapril or enalapril or fosinopril or idapril or imidapril or lisinopril or moexipril or moveltipril or pentopril or perindopril or quinapril or ramipril or spirapril or temocapril or trandolapril or zofenopril or aliskiren or remikiren):ti,ab

#22 ("KT3-671" or candesartan or eprosartan or irbesartan or losartan or olmesartan or tasosartan or telmisartan or valsartan):ti,ab

#23 (amlodipine or amrinone or bencyclane or bepridil or cinnarizine or conotoxins or diltiazem or felodipine or fendiline or flunarizine or gallopamil or isradipine or lidoflazine or "magnesium sulphate" or mibefradil or nicardipine or nifedipine or nimodipine or nisoldipine or nitrendipine or perhexiline or prenylamine or verapamil or "omega-agatoxin iva" or "omega-conotoxin gvia" or "omega-conotoxins"):ti,ab

#24 (methyldopa or alphamethyldopa or amodopa or dopamet or dopegyt or dopegit or dopegite or emdopa or hyperpax or hyperpaxa or "methylpropionic acid" or dopergit or meldopa or methyldopate or medopa or medomet or sembrina or aldomet or aldometil or aldomin or hydopa or methyldihydroxyphenylalanine or "methyl dopa" or mulfasin or presinol or presolisin or sedometil or sembrina or taquinil or dihydroxyphenylalanine or methylphenylalanine or methylalanine or "alpha methyl dopa"):ti,ab

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

#26 (clonidine or adesipress or arkamin or caprysin or catapres* or catasan or chlofazolin or chlophazolin or clinidine or clofelin* or clofenil or clomidine or clondine or clonistada or clonnirit or clophelin* or dichlorophenylaminoimidazoline or dixarit or duraclon or gemiton or haemiton or hemiton or imidazoline or isoglaucon or klofelin or klofenil or "m-5041t" or normopresan or paracefan or "st-155" or "st 155" or "tesno timelets"):ti,ab

#27 (hydralazin* or hydrallazin* or hydralizine or hydrazinophtalazine or hydrazinophthalazine or hydrazinophtalizine or dralzine or hydralacin or hydrolazine or hypophthalin or hypoftalin or hydrazinophthalazine or idralazina or "1-hydrazinophthalazine" or apressin or nepresol or apressoline or apresoline or apresolin or alphapress or alazine or idralazina or lopress or plethorit or praeparat):ti,ab

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

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

#30 {or #6-#29}

#31 #5 and #30

Appendix 2. MEDLINE search strategy

MEDLINE (1946 to July 2016) in Ovid;

1. cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp intracranial arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or stroke/ or exp brain infarction/ or vasospasm, intracranial/ or vertebral artery dissection/

2. (stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or isch?emi$ attack$ or tia$1).tw.

3. ((brain$ or cerebr$ or cerebell$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or MCA) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypox$ or vasospasm)).tw.

4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or intraventricular or infratentorial or supratentorial or basal gangli$) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.

5. 1 or 2 or 3 or 4

6. exp antihypertensive agents/ or exp vasodilator agents/ or exp adrenergic agonists/ or exp diuretics/ or exp thiazides/ or exp sodium chloride symporter inhibitors/ or exp sodium potassium chloride symporter inhibitors/

7. exp angiotensin-converting enzyme inhibitors/ or exp angiotensin II type 1 receptor blockers/ or exp calcium channel blockers/ or exp adrenergic beta-antagonists/ or exp adrenergic alpha antagonists/

8. exp enalapril/ or losartan/ or exp hydralazine/

9. Hypertension/ae, de, dt, pc or Blood Pressure/de, pd

10. (antihypertens$ or anti-hypertens$).tw.

11. ((Blood pressure or hypertens$) adj5 (lower$ or reduc$ or decreas$)).tw.

12. (angiotensin adj3 convert$ adj3 enzyme adj3 (inhibit$ or antagonist? or block$)).tw.

13. (((ace or renin) adj3 inhibit$) or ACEI).tw.

14. (angiotensin adj3 receptor? adj3 (inhibit$ or antagonist? or block$)).tw.

15. (calcium adj2 (inhibit$ or antagonist? or block$)).tw.

16. (adrenergic adj3 beta$ adj3 (inhibit$ or antagonist? or block$)).tw.

17. (adrenergic adj3 alpha$ adj3 (inhibit$ or antagonist? or block$)).tw.

18. ((loop or ceiling) adj diuretic?).tw.

19. (amiloride or benzothiadiazine or bendroflumethiazide or bumetanide or chlorothiazide or cyclopenthiazide or furosemide or hydrochlorothiazide or hydroflumethiazide or methyclothiazide or metolazone or polythiazide or trichlormethiazide or veratide or thiazide?).mp.

20. (chlorthalidone or chlortalidone or phthalamudine or chlorphthalidolone or oxodoline or thalitone or hygroton or indapamide or metindamide or s-1520 or s1520 or se-1520 or se1520).mp.

21. (alacepril or altiopril or benazepril or captopril or ceronapril or cilazapril or delapril or enalapril or fosinopril or idapril or imidapril or lisinopril or moexipril or moveltipril or pentopril or perindopril or quinapril or ramipril or spirapril or temocapril or trandolapril or zofenopril or aliskiren or remikiren).mp.

22. (KT3-671 or candesartan or eprosartan or irbesartan or losartan or olmesartan or tasosartan or telmisartan or valsartan).mp.

23. (amlodipine or amrinone or bencyclane or bepridil or cinnarizine or conotoxins or diltiazem or felodipine or fendiline or flunarizine or gallopamil or isradipine or lidoflazine or magnesium sulfate or mibefradil or nicardipine or nifedipine or nimodipine or nisoldipine or nitrendipine or perhexiline or prenylamine or verapamil or omega-agatoxin iva or omega-conotoxin gvia or omega-conotoxins).mp.

24. (methyldopa or alphamethyldopa or amodopa or dopamet or dopegyt or dopegit or dopegite or emdopa or hyperpax or hyperpaxa or methylpropionic acid or dopergit or meldopa or methyldopate or medopa or medomet or sembrina or aldomet or aldometil or aldomin or hydopa or methyldihydroxyphenylalanine or methyl dopa or mulfasin or presinol or presolisin or sedometil or sembrina or taquinil or dihydroxyphenylalanine or methylphenylalanine or methylalanine or alpha methyl dopa).mp.

25. (reserpine or serpentina or rauwolfia or serpasil).mp.

26. (clonidine or adesipress or arkamin or caprysin or catapres$ or catasan or chlofazolin or chlophazolin or clinidine or clofelin$ or clofenil or clomidine or clondine or clonistada or clonnirit or clophelin$ or dichlorophenylaminoimidazoline or dixarit or duraclon or gemiton or haemiton or hemiton or imidazoline or isoglaucon or klofelin or klofenil or m-5041t or normopresan or paracefan or st-155 or st 155 or tesno timelets).mp.

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

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

29. (alfuzosin or bunazosin or doxazosin or metazosin or neldazosin or prazosin or silodosin or tamsulosin or terazosin or tiodazosin or trimazosin).mp.

30. or/6-29

31. Randomized Controlled Trials as topic/

32. random allocation/

33. Controlled Clinical Trials as topic/

34. control groups/

35. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/

36. Clinical Trials Data Monitoring Committees/

37. double-blind method/

38. single-blind method/

39. Placebos/

40. placebo effect/

41. Therapies, Investigational/

42. Drug Evaluation/

43. Research Design/

44. randomized controlled trial.pt.

45. controlled clinical trial.pt.

46. clinical trial.pt.

47. random$.tw.

48. random$.tw.

49. (clinical$ adj5 trial$).tw.

50. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.

51. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.

52. placebo$.tw.

53. or/31-52

54. 5 and 30 and 53

55. exp animals/ not humans.sh.

56. 54 not 55

Appendix 3. Embase search strategy

Embase (1980 to July 2016) in Ovid;

1. cerebrovascular disease/ or basal ganglion hemorrhage/ or exp brain hematoma/ or exp brain hemorrhage/ or exp brain infarction/ or exp brain ischemia/ or exp carotid artery disease/ or cerebral artery disease/ or cerebrovascular accident/ or exp intracranial aneurysm/ or exp occlusive cerebrovascular disease/ or stroke/

2. stroke patient/ or stroke unit/

3. (stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or isch?emi$ attack$ or tia$1).tw.

4. ((brain$ or cerebr$ or cerebell$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or MCA) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypox$ or vasospasm)).tw.

5. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracran$ or intraventricular or infratentorial or supratentorial or basal gangli$) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.

6. 1 or 2 or 3 or 4 or 5

7. exp antihypertensive agent/ or antihypertensive activity/ or antihypertensive therapy/ or exp vasodilator agent/ or exp adrenergic receptor stimulating agent/ or exp diuretic agent/

8. exp dipeptidyl carboxypeptidase inhibitor/ or exp angiotensin receptor antagonist/ or exp calcium channel blocking agent/ or exp beta adrenergic receptor blocking agent/ or exp alpha adrenergic receptor blocking agent/

9. losartan/ or hydralazine/

10. hypertension/ae, dt, pc or exp blood pressure/pd

11. (antihypertens$ or anti-hypertens$).tw.

12. (hypotensive adj3 (agent$ or drug or drugs)).tw.

13. ((Blood pressure or hypertens$) adj5 (lower$ or reduc$ or decreas$)).tw.

14. (angiotensin adj3 convert$ adj3 enzyme adj3 (inhibit$ or antagonist? or block$)).tw.

15. (((ace or renin) adj3 inhibit$) or ACEI).tw.

16. (angiotensin adj3 receptor? adj3 (inhibit$ or antagonist? or block$)).tw.

17. (calcium adj2 (inhibit$ or antagonist? or block$)).tw.

18. (adrenergic adj3 beta$ adj3 (inhibit$ or antagonist? or block$)).tw.

19. (adrenergic adj3 alpha$ adj3 (inhibit$ or antagonist? or block$)).tw.

20. ((loop or ceiling) adj diuretic?).tw.

21. (amiloride or benzothiadiazine or bendroflumethiazide or bumetanide or chlorothiazide or cyclopenthiazide or furosemide or hydrochlorothiazide or hydroflumethiazide or methyclothiazide or metolazone or polythiazide or trichlormethiazide or veratide or thiazide?).mp.

22. (chlorthalidone or chlortalidone or phthalamudine or chlorphthalidolone or oxodoline or thalitone or hygroton or indapamide or metindamide or s-1520 or s1520 or se-1520 or se1520).mp.

23. (alacepril or altiopril or benazepril or captopril or ceronapril or cilazapril or delapril or enalapril or fosinopril or idapril or imidapril or lisinopril or moexipril or moveltipril or pentopril or perindopril or quinapril or ramipril or spirapril or temocapril or trandolapril or zofenopril or aliskiren or remikiren).mp.

24. (KT3-671 or candesartan or eprosartan or irbesartan or losartan or olmesartan or tasosartan or telmisartan or valsartan).mp.

25. (amlodipine or amrinone or bencyclane or bepridil or cinnarizine or conotoxins or diltiazem or felodipine or fendiline or flunarizine or gallopamil or isradipine or lidoflazine or magnesium sulfate or mibefradil or nicardipine or nifedipine or nimodipine or nisoldipine or nitrendipine or perhexiline or prenylamine or verapamil or omega-agatoxin iva or omega-conotoxin gvia or omega-conotoxins).mp.

26. (methyldopa or alphamethyldopa or amodopa or dopamet or dopegyt or dopegit or dopegite or emdopa or hyperpax or hyperpaxa or methylpropionic acid or dopergit or meldopa or methyldopate or medopa or medomet or sembrina or aldomet or aldometil or aldomin or hydopa or methyldihydroxyphenylalanine or methyl dopa or mulfasin or presinol or presolisin or sedometil or sembrina or taquinil or dihydroxyphenylalanine or methylphenylalanine or methylalanine or alpha methyl dopa).mp.

27. (reserpine or serpentina or rauwolfia or serpasil).mp.

28. (clonidine or adesipress or arkamin or caprysin or catapres$ or catasan or chlofazolin or chlophazolin or clinidine or clofelin$ or clofenil or clomidine or clondine or clonistada or clonnirit or clophelin$ or dichlorophenylaminoimidazoline or dixarit or duraclon or gemiton or haemiton or hemiton or imidazoline or isoglaucon or klofelin or klofenil or m-5041t or normopresan or paracefan or st-155 or st 155 or tesno timelets).mp.

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

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

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

32. or/7-31

33. Randomized Controlled Trial/

34. Randomization/

35. Controlled Study/

36. control group/

37. clinical trial/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or controlled clinical trial/

38. Double Blind Procedure/

39. Single Blind Procedure/ or triple blind procedure/

40. placebo/

41. trial.ti.

42. "types of study"/

43. random$.tw.

44. (controlled adj5 (trial$ or stud$)).tw.

45. (clinical$ adj5 trial$).tw.

46. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.

47. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.

48. placebo$.tw.

49. or/33-48

50. 6 and 32 and 49

51. (exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/) not (human/ or normal human/ or human cell/)

52. 50 not 51

Appendix 4. Trial registers search strategy

The basic search strategy we used for all trial registers was (cerebrovascular OR cerebral OR stroke OR transient ischemic attack OR TIA) AND (antihypertensive OR blood pressure), adapted for each trial register based on their specific search functionality.

WHAT'S NEW

Date	Event	Description
2 August 2018	Amended	Amendment to the 'Main results' section in the Abstract.

CONTRIBUTIONS OF AUTHORS

- Draft the protocol: MD Vergouwen, RJ de Haan, M Vermeulen, YB Roos
- Develop the search strategy: MD Vergouwen, TP Zonneveld, M Vermeulen, YB Roos, E Richard
- Search for trials: TP Zonneveld
- Obtain copies of trials: TP Zonneveld, ND Kruyt
- Select trials for inclusion: TP Zonneveld, ND Kruyt, E Richard
- Extract data: TP Zonneveld, ND Kruyt, E Richard
- Enter data into Review Manager: TP Zonneveld
- Carry out the analysis: TP Zonneveld, ND Kruyt, PJ Nederkoorn, YB Roos, E Richard

- Interpret the analysis: TP Zonneveld, ND Kruyt, PJ Nederkoorn, MD Vergouwen, RJ de Haan, YB Roos, E Richard
- Draft the final review: TP Zonneveld, ND Kruyt, PJ Nederkoorn, MD Vergouwen, RJ de Haan, YB Roos, E Richard
- Update the review: TP Zonneveld, ND Kruyt, E Richard

DECLARATIONS OF INTEREST

Thomas P Zonneveld: none known.
Edo Richard: none known.
Mervyn DI Vergouwen: none known.
Paul J Nederkoorn: none known.
Rob de Haan: none known.
Yvo BW Roos: none known.
Nyika D Kruyt: none known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Outcomes

We did not include the outcome 'heart failure' because of the difficulties in uniformly defining the condition, and a lack of studies assessing this outcome. Furthermore, we added 'death by any cause' as an outcome measure instead of 'any stroke or death', as total mortality was usually assessed, whereas a composite with stroke was not.

Publication bias

We did not produce a funnel plot to assess publication bias, as we included less than 10 studies per comparison.

INDEX TERMS

Medical Subject Headings (MeSH)

*Secondary Prevention; Angiotensin-Converting Enzyme Inhibitors [therapeutic use]; Antihypertensive Agents [*therapeutic use]; Blood Pressure [drug effects]; Cardiovascular Diseases [prevention & control]; Cause of Death; Dementia, Vascular [*prevention & control]; Diuretics [therapeutic use]; Hypertension [complications] [*drug therapy]; Ischemic Attack, Transient [*prevention & control]; Primary Prevention; Randomized Controlled Trials as Topic; Recurrence; Stroke [etiology] [*prevention & control]; Systole; Time Factors

MeSH check words

Humans