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Bath PMW, Krishnan K

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[Intervention Review]

Interventions for deliberately altering blood pressure in acute stroke

Philip MW Bath[1], Kailash Krishnan[1]

[1]Stroke, Division of Clinical Neuroscience, University of Nottingham, Nottingham, UK

Contact address: Philip MW Bath, Stroke, Division of Clinical Neuroscience, University of Nottingham, City Hospital Campus, Nottingham, NG5 1PB, UK. philip.bath@nottingham.ac.uk.

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ABSTRACT

Background

It is unclear whether blood pressure should be altered actively during the acute phase of stroke. This is an update of a Cochrane review first published in 1997, and previously updated in 2001 and 2008.

Objectives

To assess the clinical effectiveness of altering blood pressure in people with acute stroke, and the effect of different vasoactive drugs on blood pressure in acute stroke.

Search methods

We searched the Cochrane Stroke Group Trials Register (last searched in February 2014), the Cochrane Database of Systematic reviews (CDSR) and the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2014, Issue 2), MEDLINE (Ovid) (1966 to May 2014), EMBASE (Ovid) (1974 to May 2014), Science Citation Index (ISI, Web of Science, 1981 to May 2014) and the Stroke Trials Registry (searched May 2014).

Selection criteria

Randomised controlled trials of interventions that aimed to alter blood pressure compared with control in participants within one week of acute ischaemic or haemorrhagic stroke.

Data collection and analysis

Two review authors independently applied the inclusion criteria, assessed trial quality and extracted data. The review authors cross-checked data and resolved discrepancies by discussion to reach consensus. We obtained published and unpublished data where available.

Main results

We included 26 trials involving 17,011 participants (8497 participants were assigned active therapy and 8514 participants received placebo/control). Not all trials contributed to each outcome. Most data came from trials that had a wide time window for recruitment; four trials gave treatment within six hours and one trial within eight hours. The trials tested alpha-2 adrenergic agonists (A2AA), angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor antagonists (ARA), calcium channel blockers (CCBs), nitric oxide (NO) donors, thiazide-like diuretics, and target-driven blood pressure lowering. One trial tested phenylephrine.

At 24 hours after randomisation oral ACEIs reduced systolic blood pressure (SBP, mean difference (MD) -8 mmHg, 95% confidence interval (CI) -17 to 1) and diastolic blood pressure (DBP, MD -3 mmHg, 95% CI -9 to 2), sublingual ACEIs reduced SBP (MD -12.00 mm Hg, 95% CI -26 to 2) and DBP (MD -2, 95%CI -10 to 6), oral ARA reduced SBP (MD -1 mm Hg, 95% CI -3 to 2) and DBP (MD -1 mm Hg, 95% CI -3 to 1), oral beta blockers reduced SBP (MD -14 mm Hg; 95% CI -27 to -1) and DBP (MD -1 mm Hg, 95% CI -9 to 7), intravenous (iv) beta blockers reduced SBP (MD -5 mm Hg, 95% CI -18 to 8) and DBP (-5 mm Hg, 95% CI -13 to 3), oral CCBs reduced SBP (MD -13 mmHg, 95% CI -43 to 17) and DBP (MD -6 mmHg, 95% CI -14 to 2), iv CCBs reduced SBP (MD -32 mmHg, 95% CI -65 to 1) and DBP (MD -13, 95% CI -31 to 6), NO donors reduced SBP (MD -12 mmHg, 95% CI -19 to -5) and DBP (MD -3, 95% CI -4 to -2) while phenylephrine, non-significantly increased SBP (MD 21 mmHg, 95% CI -13 to 55) and DBP (MD 1 mmHg, 95% CI -15 to 16).

Blood pressure lowering did not reduce death or dependency either by drug class (OR 0.98, 95% CI 0.92 to 1.05), stroke type (OR 0.98, 95% CI 0.92 to 1.05) or time to treatment (OR 0.98, 95% CI 0.92 to 1.05). Treatment within six hours of stroke appeared effective in reducing death or dependency (OR 0.86, 95% CI 0.76 to 0.99) but not death (OR 0.70, 95% CI 0.38 to 1.26) at the end of the trial. Although death or dependency did not differ between people who continued pre-stroke antihypertensive treatment versus those who stopped it temporarily (worse outcome with continuing treatment, OR 1.06, 95% CI 0.91 to 1.24), disability scores at the end of the trial were worse in participants randomised to continue treatment (Barthel Index, MD -3.2, 95% CI -5.8, -0.6).

Authors' conclusions

There is insufficient evidence that lowering blood pressure during the acute phase of stroke improves functional outcome. It is reasonable to withhold blood pressure-lowering drugs until patients are medically and neurologically stable, and have suitable oral or enteral access, after which drugs can than be reintroduced. In people with acute stroke, CCBs, ACEI, ARA, beta blockers and NO donors each lower blood pressure while phenylephrine probably increases blood pressure. Further trials are needed to identify which people are most likely to benefit from early treatment, in particular whether treatment started very early is beneficial.

PLAIN LANGUAGE SUMMARY

Drug interventions for deliberately altering blood pressure in acute stroke

Background: In people who have just had a stroke (a sudden brain attack due to either blockage or rupture of an artery in the brain), very high and very low blood pressures may be harmful. Therefore, drugs that raise low blood pressure or lower high blood pressure might be beneficial. Up to 50% of people admitted with acute stroke are taking blood pressure tablets on hospital admission and it is not clear whether these medications should be continued or discontinued in the acute situation. This review looked at those trials that deliberately altered blood pressure or compared continuing or stopping blood pressure-lowering tablets taken before stroke.

Study characteristics: This review is up-to-date to May 2014. We included 26 trials involving 17,011 participants: 24 trials assessed lowering blood pressure, one trial tested raising blood pressure, and two trials assessed what to do with drugs taken before stroke. All studies took place in hospitals that were used to treating people with stroke. Not all trials contributed information to all outcomes, and we have used data that were available in publications.

Key results: There is insufficient evidence to say that lowering blood pressure saves lives or reduces disability in people with acute stroke. Immediately restarting blood pressure-lowering drugs taken before the stroke may increase disability.

Conclusion: More research is needed to identify those people who are most likely to benefit from altering blood pressure in acute stroke, the time window in which the treatment is likely to be of benefit, what types of stroke are likely to respond favourably, and the environment in which such treatment may be best given in routine practice.

BACKGROUND

Description of the condition

Stroke is the third most common cause of death and the most

common cause of disability in the western world. Acute stroke, whether due to infarction or haemorrhage, is associated with high blood pressure in 75% of patients, of whom 50% have a previous history of high blood pressure (Britton 1986; Oppenheimer 1992). After a stroke, blood pressure falls in most patients over a week although a third of patients remain hypertensive (Wallace 1981; Britton 1986; Harper 1994). A number of small studies have assessed the relationship between blood pressure (Marshall 1959; Adams 1965; Droller 1965; Bourestom 1967; Marquarsden 1969; Carlberg 1993) and outcome. A meta-analysis of these studies found that elevated blood pressure was associated with a poor outcome (Willmot 2004). Data from 17,398 participants in the International Stroke Trial identified a U-shaped relationship such that both low and high blood pressure were associated independently with increased early death and later death or dependency (Leonardi-Bee 2002), a finding that has been replicated by others (Castillo 2004; Vemmos 2004). High blood pressure is also associated with an increased early recurrence of stroke (Leonardi-Bee 2002; Sprigg 2006).

The mechanisms underlying high blood pressure in stroke are complex but pre-existing hypertension, hospitalisation stress, activation of the sympathetic renin-angiotensin-aldosterone, cortisol and natriuretic peptide neuroendocrine systems, and the Cushing reflex (raised blood pressure secondary to raised intracranial pressure) all contribute (Myers 1982). In ischaemic stroke, high blood pressure also appears to adversely affect outcome through increasing the risk of cerebral oedema, but not haemorrhagic transformation (Leonardi-Bee 2002). Haematoma expansion is related to high blood pressure in people with intracerebral haemorrhage (ICH) although this relationship may be confounded by stroke severity and time to presentation (Fujii 1994; Kazui 1997; Fujii 1998; Bath 2003).

Description of the intervention

Although debated more than 29 years ago, it still remains unclear whether high blood pressure should (Spence 1985) or should not (Yatsu 1985) be treated acutely following stroke. Recent guidelines recommend that acute lowering of blood pressure should be delayed for several days or even weeks unless blood pressure is greater than 220/120 mmHg, blood pressure is greater than 200/100 mmHg with end organ involvement (hypertensive encephalopathy, aortic dissection, cardiac ischaemia, pulmonary oedema, acute renal failure), or blood pressure is greater than 200/120 mmHg with primary ICH, are present (O'Connell 1994; EUSI 2004; AHA-HS 2010; RCP 2012; AHA-IS 2013). Though the evidence is weaker, guidelines now recommend that patients who have elevated blood pressure and are otherwise eligible for treatment with recombinant tissue plasminogen activator may have their blood pressure lowered so that systolic blood pressure (SBP) is less than or equal to 185 mmHg and diastolic blood pressure (DBP) is less than or equal to 110 mmHg before thrombolysis using intravenous labetalol, nitroprusside or nicardipine and it should be maintained below 180/105 mmHg for at least the first 24 hours after therapy (AHA-IS 2013). Unfortunately, such guidelines are inconsistent and are based on theoretical arguments and individual case reports, and not on the results of systematic overviews or large intervention trials of blood pressure manipulation in acute stroke. Nevertheless, a number of case reports and series have suggested that active lowering of blood pressure in people with primary intracranial haemorrhage and ischaemic stroke may improve (Dandapani 1995; Chamorro 1998) or worsen (Graham 1975; Britton 1980; Fischberg 2000) outcome.

Low blood pressure is not common in acute stroke but it, like high blood pressure, is associated with a poor outcome (Leonardi-Bee 2002). Possible reasons for low blood pressure include potentially reversible conditions such as hypovolaemia, sepsis, impaired cardiac output secondary to cardiac failure, arrhythmias or cardiac ischaemia, and aortic dissection (Sprigg 2005). Guidelines recommend that causes of hypotension in the setting of acute stroke should be sought with the view to correcting reversible causes such as hypovolaemia and cardiac arrhythmias (AHA-IS 2013). Since cerebral autoregulation is lost following stroke (Strandgaard 1973; Burke 1986; Paulson 1990), such that cerebral blood flow becomes dependent on systemic blood pressure, some researchers have hypothesised that blood pressure should be increased to improve cerebral perfusion (Sandercock 1992) and a case series (Rordorf 1997) and a pilot randomised trial of phenylephrine (Hillis 2003) reporting this approach have been published.

How the intervention might work

Although the different drugs assessed work in a variety of ways, all lower (or elevate - phenylephrine) blood pressure.

Why it is important to do this review

We are reviewing this topic in three parts (Bath 1997).

Part 1: this review

Assessment of trials in which the primary aim of the intervention was to alter blood pressure in people with acute stroke with the aim of improving clinical outcome.

A Cochrane review of blood pressure intervention in stroke published in 2001 (BASC 2001) updated the original review published in 1997. It was again updated in 2008 to include more information from 13 trials published between 2003 and 2008 including a total of 1153 participants (BASC 2009). With a relatively small amount of data, there was insufficient evidence to evaluate the effect of altering blood pressure during the acute phase of stroke. The present review includes all new trials completed and published since 2008. The total number of participants is now 17,011,

a 14-fold increase since the review in 1997 and 2008. Although many of the data are from trials testing blood pressure alteration in the acute phase (≤ 48 hours), some recent trials have examined specific questions such as lowering blood pressure in ICH (INTERACT pilot 2008; INTERACT-2 2013), with angiotensin receptor antagonists (SCAST 2011), or glyceryl nitrate (ENOS 2014) or in the pre-hospital setting (PIL-FAST 2013; RIGHT 2013). Furthermore, two trials (COSSACS 2010; ENOS 2014) have investigated whether to continue or stop temporarily pre-stroke antihypertensive therapy. This systematic review includes these data and provides up-to-date evidence.

Part 2: vasoactive drugs for acute stroke

Assessment of trials where vasoactive drugs were administered to people with acute stroke and where clinical outcome was measured. Drugs include: alpha receptor antagonists, angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor inhibitors (ARA), beta receptor antagonists, calcium channel blockers (CCB), diuretics, magnesium, naftidrofuryl, nitric oxide donors (nitrates), papaverine, pentoxifylline, prostacyclin, serotonin receptor antagonists, sympathomimetics, theophylline (and mimetics), thromboxane A2 antagonists, vinpocetine, and their derivatives. Aggregated patient data are analysed separately for drugs which lower and elevate blood pressure (BASC 2000). Work on this analysis is ongoing.

Part 3: analysis of individual patient data from the trials identified in parts 1 and 2

Work on this analysis is ongoing through the international Blood pressure in Acute Stroke Collaboration. In brief, individual patient data from the trials included in Part 1 and Part 2 are being collated with the intention of extending analyses, particularly in subgroups of participants and interventions.

OBJECTIVES

To assess the clinical effectiveness of altering blood pressure in people with acute stroke, and the effect of different vasoactive drugs on blood pressure in acute stroke.

METHODS

Criteria for considering studies for this review

Types of studies

Published and unpublished randomised controlled trials (RCTs) of vasoactive drugs in acute ischaemic stroke or acute intracerebral haemorrhage (ICH) where the aim of the trial was to alter blood pressure, and drug therapy was initiated within one week of stroke onset. We excluded uncontrolled studies, confounded controlled studies where two or more active interventions were compared, and studies of people with subarachnoid haemorrhage.

Types of participants

Adults (age 18 or older) of either sex with acute ischaemic stroke or ICH who were eligible for randomisation to either active treatment, or placebo or open control.

Types of interventions

We sought RCTs evaluating single or multiple agents of deliberate blood pressure lowering or elevation in acute stroke, regardless of dosage or route of treatment, compared against placebo or open control. We also included trials with two groups receiving different doses of the same BP lowering agent, and studies assessing effects of continuing or stopping pre-existing antihypertensive treatment.

Types of outcome measures

Primary outcomes

- Combined death or disability/dependency at end of trial (≥ one month after stroke). We defined death or dependency as the modified Rankin Scale (mRS) > 2 (or > 3 as available).

Secondary outcomes

- Blood pressure when first measured after randomisation.
- Early case fatality (< one month).
- Late case fatality (≥ one month).
- Early neurological deterioration (< one month). As there is no consensus on how early neurological deterioration should be standardised, we used the trial-specific definition as a decrease in the Scandinavian Stroke Scale (SSS) of > 5 points or a decrease in consciousness part of the SSS by > 2 points (ENOS 2014), increase in the National Institutes of Health Stroke Scale (NIHSS) of 2 (Koch 2008) or more (CHHIPS 2009; COSSACS 2010; INTERACT-2 2013) or decline of 2 or more points in Glasgow Coma Scale (GCS) (INTERACT-2 2013).
- Late disability or dependency (Barthel Index ≥ one month).
- Baseline and on-treatment blood pressure and heart rate.

Search methods for identification of studies

See the 'Specialized register' section in the Cochrane Stroke Group module. Our methods comprised electronic searches and assessment of studies referenced in published systematic and non-systematic reviews. We applied no language restrictions.

Electronic searches

We searched the Cochrane Stroke Group Trials Register, (last searched by the Managing Editor in February 2014), the Cochrane Database of Systematic reviews (CDSR) and the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2014, Issue 2), MEDLINE (Ovid) (1966 to May 2014) (Appendix 1), EMBASE (Ovid) (1974 to May 2014) (Appendix 2), Science Citation Index (ISI, Web of Science, 1981 to May 2014) (Appendix 3) and the Stroke Trials Registry (www.strokecenter.org/trials/) (searched May 2014).

Searching other resources

We searched reviews of acute stroke relating to drugs that may alter blood pressure, including: calcium channel blockers (CCBs) (Horn 2001), nitric oxide (Bath 2002), pentoxifylline (Bath 2004a) and prostacyclin (Bath 2004b). In addition, we searched reference lists of included trials and relevant papers. We contacted principal investigators and researchers when we required additional information. For a previous version of this review (BASC 2001), we contacted the following pharmaceutical companies: Bayer (nimodipine), Napp (pentoxifylline), Novartis (isradipine), Lipha Sante (naftidrofuryl), Hoffmann la Roche (N-methyl-D-aspartate), Hoechst (flunarizine) and UCB Pharma (piracetam).

Data collection and analysis

We extracted data using a standard proforma; KK entered data into Review Manager (RevMan 2012) and PB checked the data.

Selection of studies

For this update, one review author (KK) screened the records obtained from the electronic searches and excluded obviously irrelevant studies. We obtained the full paper copy of the remaining studies and both review authors (KK and PB) selected trials for inclusion criteria detailed previously. We resolved any disagreements by discussion.

Data extraction and management

We extracted data from published and unpublished material where available. We recorded information on the method of randomisation, concealment of allocation, blinding of treatment administration, analysis (intention-to-treat, efficacy analysis), stroke type (ischaemia, haemorrhage, or mixed), drug dose, route of administration (oral, sublingual, intravenous, transdermal) and timing, blood pressure and heart rate before and during treatment, numbers of deaths, functional disability, quality of life, and length of stay.

Assessment of risk of bias in included studies

We assessed the methodological quality of the trials using the following criteria.

- Method of randomisation.
- Balance of prognostic factors.
- Allocation concealment.
- Blinding of treatment administration.
- Intention-to-treat analysis.
- Blinding of outcome assessment.
- Follow-up.

We used the quality criteria to derive an overall assessment bias score as 'low risk' (all criteria met), moderate risk (one or more criteria unclear) and high risk (one or more criteria absent) (Higgins 2011).

Measures of treatment effect

We calculated the weighted estimate of the typical treatment effect across trials using RevMan 5 (RevMan 2012), odds ratios (OR) using the Mantel-Haenszel random-effects model for binary data, and mean difference (MD) using the inverse variance method for continuous data, each with 95% confidence intervals (CI).

Unit of analysis issues

The primary outcome was based on the modified Rankin Scale (mRS 0 to 6, where death = 6) assessed using the binary outcome of combined death or dependency (mRS > 1 or > 2 depending on trial definition). The Barthel Index (BI) (disability measure of activities of daily living) was also assessed (BI 100 to -5, where death = -5). Where functional outcome was not assessed, we excluded the trial from analysis of functional outcome.

Dealing with missing data

We attempted to collect missing data from trial investigators. In instances where on-treatment blood pressure data were not provided or could not be obtained from study authors, we obtained data (mean, SD) from graphs in the trial publication; where the SD was not presented graphically, we used baseline data, a conservative strategy. We excluded trials from individual analyses when summary data were omitted in the trial publication.

Assessment of heterogeneity

We assessed heterogeneity between RCTs' results using the I^2 statistic based on the DerSimonian-Laird formula.

Assessment of reporting biases

We examined reporting bias using funnel plots (Figure 1; Figure 2).

Figure 1. Funnel plot of comparison: 1 Blood pressure lowering therapy in acute stroke, outcome: 1.1 Death or dependency, end of trial by intervention.

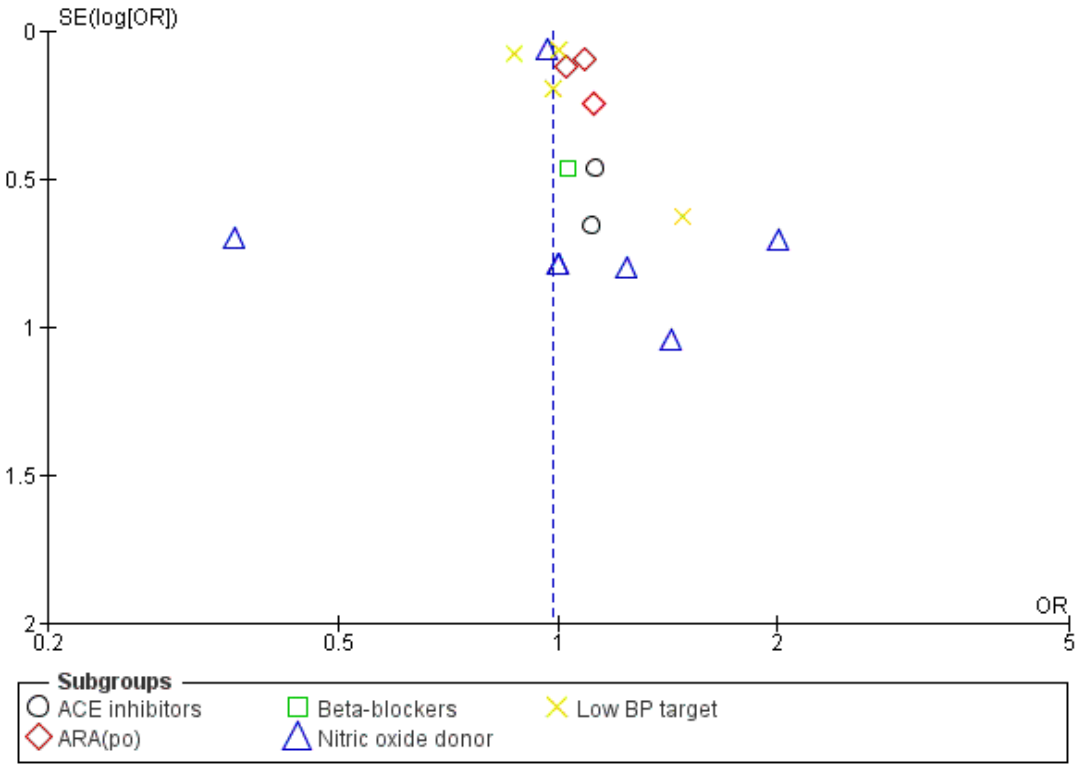
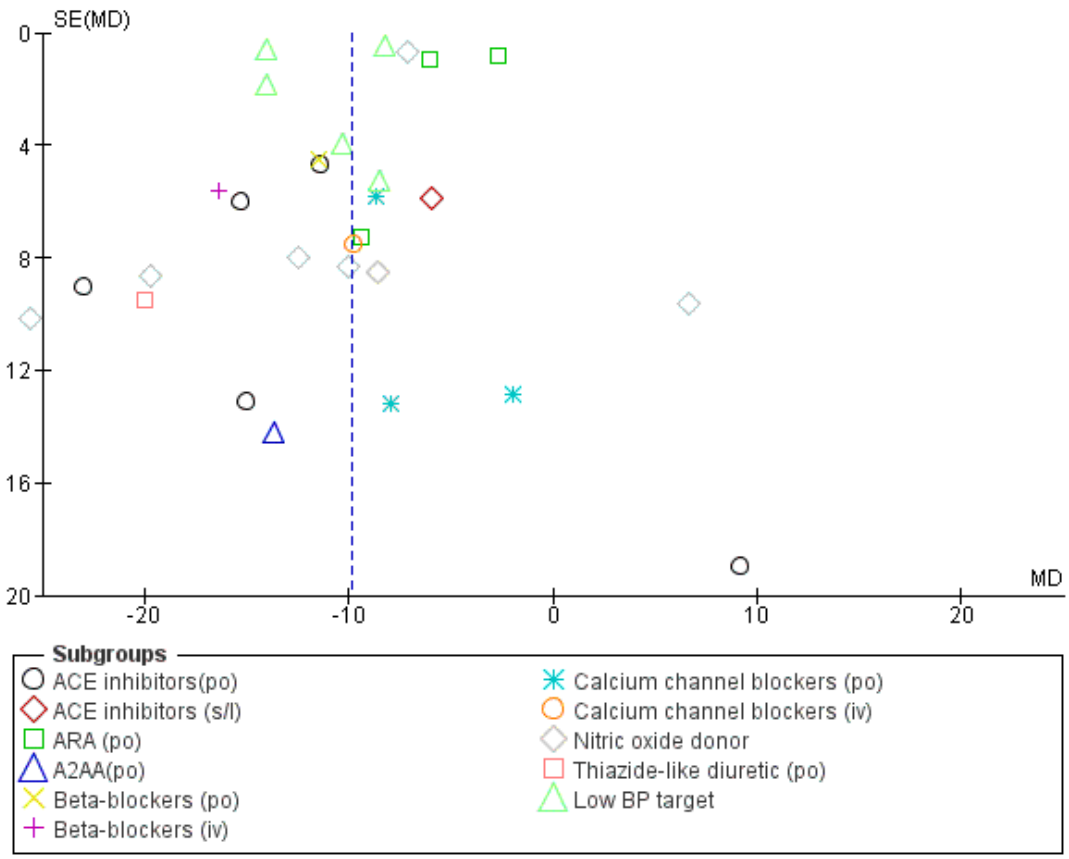


Figure 2. Funnel plot of comparison: 1 Blood pressure lowering therapy in acute stroke, outcome: 1.23 SBP, first after randomisation, by intervention.



Data synthesis

We performed statistical analysis using RevMan (RevMan 2012). We reported outcomes as ORs with 95% CIs for dichotomous data, and MD with 95% CI for continuous data. We used a random-effects model to analyse individual results regardless of whether there was heterogeneity or not; this is a conservative strategy and takes account that the trials had heterogenous designs and participant populations.

Subgroup analysis and investigation of heterogeneity

We assessed the primary outcomes in the following pre-specified subgroups.

- Class or type of intervention.
- Type of stroke: ischaemic stroke or ICH.
- Stroke location: cortical or subcortical ischaemic stroke; deep or superficial ICH. (The definition of deep haemorrhage was not defined in all the trials and we therefore used the data as given in the trials.)
- Timing of intervention: ultra-acute (≤ four hours) and pre-hospital, hyper-acute (≤ six hours) and in hospital, acute (≤ 48 hours), sub-acute (≤ 168 hours).

We considered an I^2 greater than 50% to infer significant heterogeneity. If significant heterogeneity was present, we looked for potential causes, e.g. differences in trial design and study participants.

Sensitivity analysis

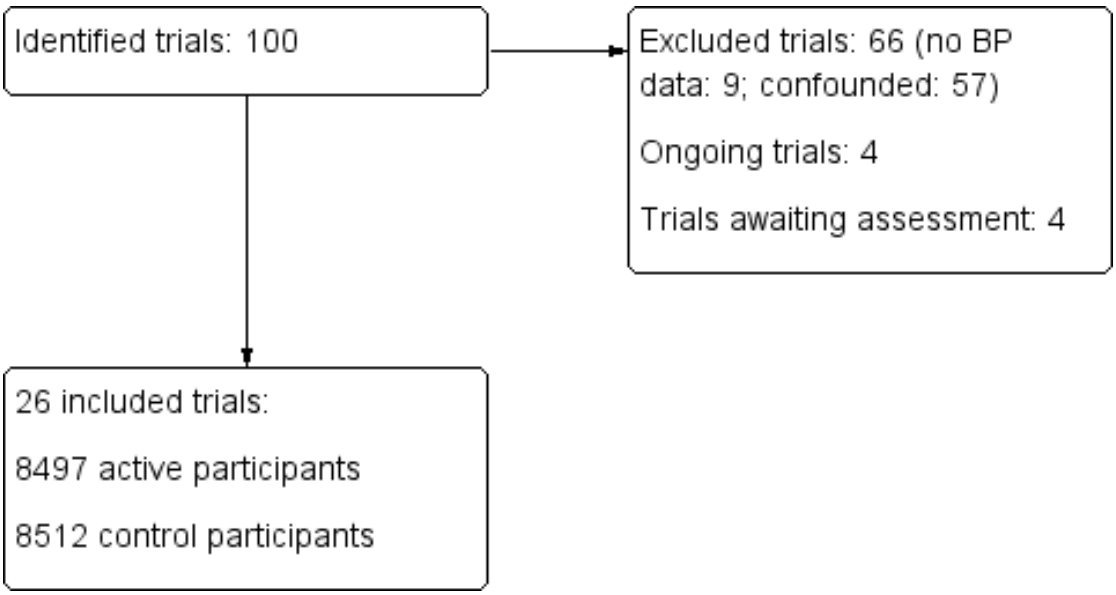
We based the analyses on all trials. We did not perform any sensitivity analyses.

RESULTS

Description of studies

The 26 included trials are summarised in Characteristics of included studies, including details on baseline characteristics (Figure 3).

Figure 3. Results of database search



Results of the search

The quantity of outcome data varied between studies:

- outcomes not universally collected;
- some data still to be published.;
- 'raw data' available by personal communication.

If a trial used more than one dose of a particular drug then the trial identifier is written as author followed by year and dose of the drug. Referencing the whole trial was given by author and year. For example the Fagan 1988 trial comprises: (Fagan 1988 120 mg; Fagan 1988 240 mg).

Included studies

We identified 26 trials that fulfilled the inclusion criteria (Fagan 1988 120 mg/Fagan 1988 240 mg; Lisk 1993; Uzuner 1995; Dyker 1997; Bath 2000; ACCESS 2003; Hillis 2003; Rashid 2003 5 mg/Rashid 2003 5/10 mg/Rashid 2003 10 mg; Eames 2005; ACCOST 2006; Willmot 2006; Eveson 2007; INTERACT pilot 2008; Koch 2008; CHHIPS 2009; PRoFESS 2009; COSSACS 2010; SCAST 2011; CATIS 2013; PIL-FAST 2013; RIGHT 2013; ICH-ADAPT 2013; INTERACT-2 2013; TAST 2013; VENTURE 2013; ENOS 2014). Three trials compared more than one drug against the control group (Lisk 1993; CHHIPS 2009; ICH-ADAPT 2013) and two studies compared different doses (Fagan 1988 120 mg/Fagan 1988 240 mg; Rashid 2003 5 mg/Rashid 2003 5/10 mg/Rashid 2003 10 mg).

We obtained trial protocols and group data from published material for the following studies (Fagan 1988 120 mg/Fagan 1988 240 mg; Lisk 1993; Hillis 2003; ACCESS 2003; Eames 2005; Eveson 2007; INTERACT pilot 2008; Koch 2008; CHHIPS 2009; PRoFESS 2009; COSSACS 2010; SCAST 2011; CATIS 2013; ICH-ADAPT 2013; INTERACT-2 2013; PIL-FAST 2013; RIGHT 2013; TAST 2013; ENOS 2014), whilst individual patient data were provided by seven sets of authors (Lisk 1993; Uzuner 1995; Dyker 1997; Bath 2000; Rashid 2003 5 mg/Rashid

2003 5/10 mg/Rashid 2003 10 mg; Willmot 2006; ENOS 2014). We obtained unpublished SBP, DBP and heart rate data for active and control groups by contacting the authors for three trials (Hillis 2003; Eveson 2007; COSSACS 2010).

A variety of strategies and drug classes were used to lower blood pressure.

- Alpha-2-adrenoceptor agonist, oral centrally-acting (clonidine: two participants): one trial (Lisk 1993).
- Angiotensin converting enzyme-inhibitor (ACE-I) (captopril, perindopril or lisinopril: 152 participants): five trials (Lisk 1993; Dyker 1997; Eveson 2007; CHHIPS 2009; PIL-FAST 2013).
- Angiotensin receptor antagonist (ARA), oral (candesartan or telmisartan: 4190 participants): six trials (ACCESS 2003; ACCOST 2006; PRoFESS 2009; SCAST 2011; TAST 2013; VENTURE 2013).
- Beta-receptor antagonist (ß-RA) (labetalol: 56 participants): one trial (CHHIPS 2009).
- Calcium channel blocker (CCB) (nimodipine or nicardipine: 75 participants): three trials (Fagan 1988 120 mg/ Fagan 1988 240 mg; Lisk 1993; Uzuner 1995).
- Diuretic, oral thiazide-like (bendrofluazide: 18 participants): one trial (Eames 2005).
- Nitric oxide (NO) donor (transdermal glyceryl trinitrate (GTN): 4197 participants): five trials (Bath 2000; Rashid 2003 5 mg/Rashid 2003 5/10 mg/Rashid 2003 10 mg; Willmot 2006; RIGHT 2013; ENOS 2014).
- Intensive versus guideline blood pressure targets (7421 participants): five trials (INTERACT pilot 2008; Koch 2008; CATIS 2013; ICH-ADAPT 2013; INTERACT-2 2013).
- Continue versus stop pre-stroke antihypertensive drugs (2860 participants): two trials (COSSACS 2010; ENOS 2014).

One strategy was used to raise blood pressure.

- Sympathomimetic, intravenous (phenylephrine: nine participants): one trial (Hillis 2003).

The trials recruited participants with only ischaemic stroke, mixed stroke (ischaemic stroke and ICH), or only ICH.

- Ischaemic stroke: 12 trials (Fagan 1988 120 mg; Fagan 1988 240 mg; Lisk 1993; Dyker 1997; ACCESS 2003; Hillis 2003; Eames 2005; ACCOST 2006; Eveson 2007; PRoFESS 2009; CATIS 2013; TAST 2013; VENTURE 2013). In the Fagan study (Fagan 1988 120 mg; Fagan 1988 240 mg) participants were recruited with presumed ischaemic stroke based on history and neurological examination.
- Mixed stroke: 10 trials (Uzuner 1995; Bath 2000; Rashid 2003 5 mg/Rashid 2003 5/10 mg/Rashid 2003 10 mg; Willmot 2006; CHHIPS 2009; COSSACS 2010; SCAST 2011; PIL-FAST 2013; RIGHT 2013; ENOS 2014).
- ICH: four trials (INTERACT pilot 2008; Koch 2008; ICH-ADAPT 2013; INTERACT-2 2013).

Trials recruited participants at different time frames after stroke:

- Ulta-acute (< four hours of onset)/pre-hospital: two trials (PIL-FAST 2013; RIGHT 2013).
- Hyper-acute (< six hours)/hospital: two trials (INTERACT pilot 2008; INTERACT-2 2013).
- Acute (< 48 hours): 11 trials (Uzuner 1995; ACCESS 2003; CHHIPS 2009; COSSACS 2010; SCAST 2011; Eveson 2007; Koch 2008; CATIS 2013; ICH-ADAPT 2013; VENTURE 2013; ENOS 2014).
- Sub-acute (< 168 hours): 10 trials (Lisk 1993; Dyker 1997; Bath 2000; Hillis 2003; Rashid 2003 5 mg/Rashid 2003 5/10 mg/Rashid 2003 10 mg; Eames 2005; ACCOST 2006; Willmot 2006; PRoFESS 2009; TAST 2013).
- Timing unclear: one trial (Fagan 1988 120 mg/Fagan 1988 240 mg).

Trials variously defined enrolment blood pressure levels.

- Hypertension (SBP > 120 to 170 and ≤ 220 mm Hg): 21 trials (Lisk 1993; Dyker 1997; Bath 2000; ACCESS 2003; Rashid 2003 5 mg/Rashid 2003 5/10 mg/Rashid 2003 10 mg; Eames 2005; Willmot 2006; Eveson 2007; INTERACT pilot 2008; CHHIPS 2009; PRoFESS 2009; SCAST 2011; ICH-ADAPT 2013; INTERACT-2 2013; PIL-FAST 2013; TAST 2013; VENTURE 2013; ENOS 2014).
- Normotension (systolic BP < 140 mmHg): two trials (Hillis 2003; ACCOST 2006).
- No BP criteria: three trials (Fagan 1988 120 mg/Fagan 1988 240 mg; Uzuner 1995; COSSACS 2010).

Trials treated participants for varying lengths of time.

- For one day: one trial (ICH-ADAPT 2013).
- For up to two days: three trials (Uzuner 1995; Hillis 2003; Koch 2008).
- For up to three days: one trial (Lisk 1993).
- For seven to 12 days: 13 trials (Bath 2000; Rashid 2003 5 mg/Rashid 2003 5/10 mg/Rashid 2003 10 mg; ACCESS 2003; Eames 2005; Willmot 2006; INTERACT pilot 2008; SCAST 2011; ICH-ADAPT 2013; INTERACT-2 2013; PIL-FAST 2013; RIGHT 2013; VENTURE 2013; ENOS 2014).
- For 14 days: five trials (Dyker 1997; Eveson 2007; CHHIPS 2009; COSSACS 2010; CATIS 2013).
- For 21 days: one trial (Fagan 1988 120 mg/Fagan 1988 240 mg).
- For 28 days: one trial (ACCOST 2006).
- For three months: one trial (TAST 2013).
- For up to 2.5 years: one trial (PRoFESS 2009); outcomes at one to three months are used and longer-term follow-up data are ignored.

The trials recruited from one or more centres.

- Single centre: 14 trials (Lisk 1993; Uzuner 1995; Dyker 1997; Bath 2000; Hillis 2003; Rashid 2003 5 mg/Rashid 2003 5/10 mg/Rashid 2003 10 mg; Eames 2005; ACCOST 2006; Willmot 2006; Eveson 2007; Koch 2008; PIL-FAST 2013; RIGHT 2013; TAST 2013).

- Multicentre: 12 trials (Fagan 1988 120 mg; Fagan 1988 240 mg; ACCESS 2003; INTERACT pilot 2008; CHHIPS 2009; COSSACS 2010; PRoFESS 2009; SCAST 2011; ICH-ADAPT 2013; CATIS 2013; INTERACT-2 2013; VENTURE 2013; ENOS 2014).

A total of 17,011 participants received placebo or control treatment across the studies. Several trials compared two or more active treatment groups (8497 participants) with one control group (8512 participants) (Fagan 1988 120 mg/Fagan 1988 240 mg; Lisk 1993; Rashid 2003 5 mg/Rashid 2003 5/10 mg/Rashid 2003 10 mg).

One study reported on 19 participants from a larger RCT (Fagan 1988 120 mg/Fagan 1988 240 mg); further information on the main study is not available.

One trial was performed in two stages: this review includes the first phase, a double-blind comparison of candesartan versus placebo (ACCOST 2006), and excludes the second open-label comparison of candesartan and an ACE-I.

One study expressly included patients with either ICH, who were given intravenous nimodipine (treatment: eight participants; placebo: three participants), or ischaemic stroke, who were given oral nimodipine (treatment: 38 participants; placebo: 39 participants) (Uzuner 1995); 10 participants (treatment: two participants; placebo: eight participants) treated with antihypertensive agents for malignant hypertension, and two participants treated with intravenous nimodipine for subarachnoid haemorrhage were excluded.

Data from two trials were only available from published abstracts (ACCOST 2006; VENTURE 2013).

Blood pressure measurements

Sixteen studies reported the method by which blood pressure was measured, including equipment (manufacturer, model) and patient posture (Lisk 1993; Dyker 1997; Bath 2000; Rashid 2003 5 mg/Rashid 2003 5/10 mg/Rashid 2003 10 mg; Eames 2005; Willmot 2006; Eveson 2007; Koch 2008; CHHIPS 2009; PRoFESS 2009; COSSACS 2010; SCAST 2011; CATIS 2013; RIGHT 2013; TAST 2013; ENOS 2014). The Fagan trial only reported the average blood pressure measurements at, and for one hour after, morning dosing over seven days of treatment (Fagan 1988 120 mg/Fagan 1988 240 mg); in the absence of individual patient data, it is not possible to determine the blood pressure at selected time points during treatment. Furthermore, this trial co-administered beta blockers to some participants, although these were always given at least two hours before or after nimodipine. In ACCESS 2003, during the first three days blood pressure measurements were performed by nurses as part of routine clinical care; on day seven, automatic 24-hour blood pressure recording was performed. The other nine trials (Fagan 1988 120 mg/Fagan 1988 240 mg; Uzuner 1995; Hillis 2003; ACCOST 2006; INTERACT pilot 2008; INTERACT-2 2013; ICH-ADAPT 2013; PIL-FAST 2013; VENTURE 2013) made no mention of patient posture or how blood pressure was measured.

Three trials recorded systolic but not diastolic BP after the first intervention: (Koch 2008; ICH-ADAPT 2013; INTERACT-2 2013).

Outcomes

The trials reported a variety of outcomes.

- mRS or BI or both at ≥ one month: 15 trials (Bath 2000; ACCESS 2003; Rashid 2003 5 mg/Rashid 2003 5/10 mg/Rashid 2003 10 mg; Eames 2005; Willmot 2006; Eveson 2007; INTERACT pilot 2008; CHHIPS 2009; PRoFESS 2009; COSSACS 2010; SCAST 2011; CATIS 2013; INTERACT-2 2013; RIGHT 2013; ENOS 2014). Historically, trials dichotomised outcome as death or dependency, defined as mRS > 2, or mRS > 3, or BI < 60. Ordinal analysis of ordered categorical data is statistically more efficient and provides information on severity of outcome (Bath 2012) and recent trials have used ordinal analysis of mRS data (INTERACT pilot 2008; CHHIPS 2009; PRoFESS 2009; SCAST 2011; CATIS 2013; INTERACT-2 2013; TAST 2013; ENOS 2014).
- Case fatality at ≥ one month: 15 trials (Bath 2000; ACCESS 2003; Rashid 2003 5 mg/Rashid 2003 5/10 mg/Rashid 2003 10 mg; Eames 2005; Willmot 2006; Eveson 2007; INTERACT pilot 2008; CHHIPS 2009; PRoFESS 2009; COSSACS 2010; SCAST 2011; CATIS 2013; INTERACT-2 2013; RIGHT 2013; ENOS 2014).
- Early neurological impairment (e.g. NIHSS, SSS) at < one month: 11 trials (Lisk 1993; Dyker 1997; Hillis 2003; Eames 2005; Eveson 2007; INTERACT pilot 2008; CHHIPS 2009; COSSACS 2010; CATIS 2013; ICH-ADAPT 2013; INTERACT-2 2013).
- Hospital length of stay: four trials (CHHIPS 2009; CATIS 2013; RIGHT 2013; ENOS 2014).

Excluded studies

We excluded 66 studies because they lacked randomisation, were irrelevant to the questions addressed in the current review, or failed to provide blood pressure or outcome assessments (see Characteristics of excluded studies).

Other studies

Eight studies are either awaiting assessment (MAPAS 2009; ATTACI 2010; STABLE-ICAS 2010; ESH-CHL-SHOT 2013) or are ongoing (ATACH-2 2011; ENCHANTED 2011; SETIN-HYPERTENSION 2012; FAST-BP 2013) (Figure 3).

Risk of bias in included studies

Computed tomography was used prior to entry in 10 trials to identify people with ICH (Uzuner 1995; INTERACT pilot 2008; Koch 2008; ICH-ADAPT 2013; INTERACT-2 2013) or to exclude people with ICH (Lisk 1993; Dyker 1997; ACCESS 2003; Hillis 2003; Eames 2005). Another study attempted to exclude ICH through information from the history and neurological examination (Fagan 1988 120 mg/Fagan 1988 240 mg); it may therefore have inadvertently included some participants with ICH.

Statistical analysis

Four trials compared more than one treatment against a common control group (Fagan 1988 120 mg/Fagan 1988 240 mg; Lisk 1993; Rashid 2003 5 mg/Rashid 2003 5/10 mg/Rashid 2003 10 mg; CHHIPS 2009). The most appropriate analysis in this situation involves dividing the control group participants equally between treatment groups to prevent control participants being counted more than once and thereby artificially narrowing the confidence intervals.

Allocation

We classified allocation concealment as 'low risk', 'high risk' or 'unclear risk' according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Blinding

The method of randomisation was given for 23 trials (Dyker 1997; Bath 2000; ACCESS 2003; Rashid 2003 5 mg/Rashid 2003 5/10 mg/Rashid 2003 10 mg; Hillis 2003; Eames 2005; ACCOST 2006; Willmot 2006; Eveson 2007; INTERACT pilot 2008; Koch 2008; CHHIPS 2009; PRoFESS 2009; COSSACS 2010; SCAST 2011; ICH-ADAPT 2013; INTERACT-2 2013; PIL-FAST 2013; CATIS 2013; RIGHT 2013; TAST 2013; VENTURE 2013; ENOS 2014). Two authors were unable to describe the method of randomisation (Lisk 1993; Uzuner 1995) and one did not respond to our communication (Fagan 1988 120 mg/Fagan 1988 240 mg).

Participants and investigators were blinded to treatment as follows.

- Double-blind (participant and investigator blinded): 13 trials (Fagan 1988 120 mg; Lisk 1993; Dyker 1997; Bath 2000; ACCESS 2003; CHHIPS 2009; Eames 2005; SCAST 2011; ACCOST 2006; Eveson 2007; PRoFESS 2009; PIL-FAST 2013; TAST 2013).
- Single-blind (participant blinded): four trials (Rashid 2003 5 mg/Rashid 2003 5/10 mg/Rashid 2003 10 mg; Willmot 2006; RIGHT 2013; ENOS 2014).
- Open-label: six trials (Rashid 2003 5 mg; Rashid 2003 5/10 mg; Rashid 2003 10 mg; Koch 2008; COSSACS 2010; ICH-ADAPT 2013; INTERACT-2 2013; VENTURE 2013).

Incomplete outcome data

Sixteen trials were analysed by intention-to-treat (ITT) (Fagan 1988 120 mg/Fagan 1988 240 mg; Lisk 1993; Dyker 1997; Bath 2000; Rashid 2003 5 mg /Rashid 2003 5/10 mg/Rashid 2003 10 mg; Willmot 2006; INTERACT pilot 2008; Koch 2008; CHHIPS 2009; PRoFESS 2009; COSSACS 2010; SCAST 2011 CATIS 2013; INTERACT-2 2013; RIGHT 2013; ENOS 2014). One study excluded 10 participants from the analysis because they had been treated with antihypertensive agents for concurrent accelerated (malignant) hypertension (Uzuner 1995).

Cardiovascular data were analysed on a per-protocol basis and outcome data by intention-to-treat in one trial of lisinopril (Eveson 2007).

Selective reporting

We assessed selective reporting as low risk, high risk or unclear risk according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We did not see evidence of selective reporting in any of the trials.

Other potential sources of bias

One trial randomised participants before neuroimaging and those having a non-ischaemic stroke were subsequently withdrawn from the study (Eveson 2007). Two trials did not state the method of analysis (Hillis 2003; Eames 2005). We did not find any other potential risks to the validity of the included studies.

Effects of interventions

The Results section is split into three parts.

- Comparisons of BP lowering with control.
- Comparisons of continuing versus stopping temporarily pre-stroke antihypertensive drugs.
- Comparisons of BP elevation with control.

Blood pressure lowering

Clinical outcomes

Twenty-one trials provided data on one or more outcomes relating to treatment with:

- ACE-I (lisinopril): (Eveson 2007; CHHIPS 2009; PIL-FAST 2013);
- ARA (candesartan, telmisartan): (ACCESS 2003; PRoFESS 2009; SCAST 2011; TAST 2013; VENTURE 2013);
- ß-RA (labetalol): (CHHIPS 2009);
- CCB (nimodipine): (Uzuner 1995);

- NO donor (glyceryl trinitrate): (Bath 2000; Rashid 2003 5 mg/Rashid 2003 5/10 mg/Rashid 2003 10 mg; Willmot 2006; RIGHT 2013; ENOS 2014);
- intensive blood pressure lowering: (INTERACT pilot 2008; Koch 2008; CHHIPS 2009; CATIS 2013; ICH-ADAPT 2013; INTERACT-2 2013);
- blood pressure elevation (phenylephrine): (Hillis 2003).

Death or dependency, end of trial

Drug class

Combined death or dependency was assessed using the mRS at the end of follow-up. Data were available for 15,489 participants recruited into 14 trials (Analysis 1.1). We observed no significant difference between blood pressure lowering and control (OR 0.98; 95% CI 0.92 to 1.05), and heterogeneity was minimal. No individual comparison within drug classes or BP lowering strategies was significant (Analysis 1.1).

Stroke type

The effect of lowering blood pressure did not vary by stroke subtype (ischaemic stroke, mixed stroke, ICH) across 14 trials (Analysis 1.2).

Stroke location

The effect of lowering blood pressure did not vary by stroke location (ICH deep or not, ischaemic stroke cortical or subcortical) across six trials with 11951 participants (Analysis 1.2). Although there was insufficient evidence to assess heterogeneity, blood pressure lowering in deep ICH almost reached significance (OR 0.86; 95% CI 0.73 to 1.00, P value = 0.06) (Analysis 1.3).

Time to treatment

Data from 15 trials involving 15,520 participants were available. There was significant reduction in death or dependency if treatment was administered during the hyperacute period and in hospital (OR 0.87; 95% CI 0.76 to 0.99, P value = 0.03). Recruitment of participants later than this was associated with no benefit (Analysis 1.4).

Death, early and end of trial

There was no overall effect of treatment on early death or death at end of trial (Analysis 1.5; Analysis 1.8). When considering subgroups, no differences existed when analysed by drug class (Analysis 1.5; Analysis 1.8), stroke type (Analysis 1.6; Analysis 1.9), or time to treatment (Analysis 1.7; Analysis 1.10).

Barthel Index (disability), end of trial

We assessed the BI at the end of follow-up in two trials with 4350 participants (Analysis 1.11). Although we observed no significant difference between blood pressure lowering and control (OR 0.63; 95% CI -3.28 to -4.54) (Analysis 1.11) and did not vary with stroke type (Analysis 1.12), BI scores were lower if treatment was started within six hours of stroke onset (Analysis 1.13).

Neurological deterioration, early

There was no overall difference in the rate of early neurological deterioration across seven trials (Analysis 1.14). Subgroup differences were not present when analysed by drug class or intensity (Analysis 1.14), or stroke type (Analysis 1.15). However, subgroup differences were apparent when assessed by time to treatment (Analysis 1.16); specifically, an increase in neurological deterioration was seen in participants with acute stroke ($\leq$ 48 hours post stroke) (OR 1.39; 95% CI 1.07 to 1.81, P value = 0.01) but not when trials specifically treated earlier during the ultra-acute and hyperacute periods.

Quality of life

Quality of life, assessed using the EQ-5D and transformed into a Health Utility Status, was assessed in three trials (Analysis 1.17; Analysis 1.18). Health Utility scores were higher/better with blood pressure lowering (MD 0.02; 95% CI 0.01 to 0.04). However, heterogeneity was apparent between studies (I^2 = 76.0%) with a significant result in INTERACT-2 2013, but not ENOS 2014. When broken down into stroke types, participants with ICH in INTERACT-2 2013 treated with blood pressure lowering tended to report a better quality of life (Analysis 1.18). When assessed by time to treatment, Health Utility Status scores were higher in participants treated $\leq$ six hours (MD 0.06; 95% CI 0.03 to 0.08), but not when treated later (Analysis 1.19).

Length of stay

Length of stay was not influenced by lowering blood pressure and there were no subgroup differences by type of intervention, stroke type or time to treatment (Analysis 1.20; Analysis 1.21; Analysis 1.22).

Haemodynamic measures

Blood pressure

The effect of different blood pressure-lowering strategies on blood pressure after the first dose are summarised in Analysis 1.23 and Analysis 1.29, and in Table 1. Altogether, 24 trials studied 15,432 participants; most participants received an ARA, a NO donor or intensive blood pressure lowering. The focus for the following comments are on systolic rather than diastolic blood pressure. The magnitude of blood pressure reduction varied between -4.6/-2.5 mmHg for oral ARA (primarily candesartan and telmisartan) and -13.7/-7.9 mmHg for ACE-Is. When assessed by stroke type, heterogeneity was present; slightly larger reductions in blood pressure were seen in participants with ICH (-11.8/-5.1 mmHg) with mixed stroke intermediate (-7.9/-3.0 mmHg) and ischaemic stroke least (-7.0/-3.1 mmHg) (Analysis 1.22; Analysis 1.30). Similarly, the magnitude of reduction varied by time to randomisation or treatment (I^2 = 89%); a graded decrease was seen by time with the largest reduction occurring in participants treated during the ultra-acute/pre-hospital (-16.0/-15.0 mmHg), hyper-acute/hospital (-13.4/-7.5 mmHg), acute (-8.2/-2.8 mmHg) and sub-acute (-7.3/-4.9 mmHg) periods.

The effect of the various types of intervention over the first week are summarised in Table 2.

Heart rate

Thirteen trials reported heart rate measurements (Lisk 1993; Uzuner 1995; Dyker 1997; Bath 2000; Rashid 2003 5 mg/Rashid 2003 5/10 mg/Rashid 2003 10 mg; Eames 2005; Willmot 2006; Eveson 2007; PRoFESS 2009; ICH-ADAPT 2013; RIGHT 2013; TAST 2013; ENOS 2014). The heart rate for glyceryl trinitrate increased at day one (MD 4.5 bpm; 95% CI 2 to 8) (Analysis 1.37) (Table 3). Intravenous CCBs reduced heart rate at day one (Uzuner 1995) (Analysis 1.37).

Continuing versus stopping pre-stroke antihypertensive drugs

Two trials tested whether pre-stroke antihypertensives should be continued in the immediate post-stroke period, or stopped temporarily (COSSACS 2010; ENOS 2014). The total number of participants numbered 2860.

Clinical outcomes

Death or dependency, end of trial

There was no significant difference in mRS at day 90 between those participants assigned to continue or stop antihypertensives (OR 1.06; 95% CI 0.91 to 1.24) (Analysis 2.1). Within subgroups, the effect of continuing versus stopping antihypertensives did not differ by stroke types or time to treatment across both trials (Analysis 2.2 and Analysis 2.3).

Death, early and at the end of trial

The rates of death at the end of treatment, and at the end of trial, did not differ between the treatment groups (Analysis 2.4 and Analysis 2.7). No significant differences were observed by stroke types or time to treatment (Analysis 2.5; Analysis 2.6; Analysis 2.8; Analysis 2.9).

Barthel Index

Barthel Index scores were lower in participants assigned to continue treatment (MD -3.18; 95% CI -0.55 to -5.80, P value = 0.02) (Analysis 2.10).

Neurological deterioration, early

The rate of death at the end of treatment did not differ between the treatment groups (Analysis 2.11).

Quality of life

Quality of life, assessed using the EQ-5D and transformed into a Health Utility Status, was lower (i.e. worse) in participants randomised to continue pre-stroke antihypertensive drugs (MD -0.03; 95% CI -0.05 to -0.01, P value = 0.008) (Analysis 2.12).

Haemodynamic measures

Blood pressure

Blood pressure was lower by -7.9/-1.2 mmHg at the first measurement after randomisation in participants randomised to continue treatment with the reduction in systolic BP much greater in COSSACS 2010 than in ENOS 2014 (Analysis 2.14). By the end of treatment, blood pressure was lower by -11.3/-6.4 mmHg in the continue group.

Heart rate

Data were only available for ENOS 2014. Heart rate was significantly lower by 3.2 bpm by end of treatment in those who were randomised to continue treatment (Analysis 2.21).

Blood pressure elevation therapy in acute stroke

Phenylephrine

Phenylephrine non-significantly increased systolic blood pressure at 24 hours (MD 21 mmHg; 95% CI -13 to 55 mmHg), but had no significant effect on diastolic blood pressure (Hillis 2003) (Analysis 3.4). Insufficient data were available on clinical outcomes.

DISCUSSION

Twenty-six trials, involving 17,011 participants with stroke, assessed the effects of deliberate blood pressure alteration.

Blood pressure lowering

The results come from 24 trials that studied 15,432 participants.

Clinical outcomes

Overall, lowering blood pressure did not improve outcome, whether assessed as death, combined death or dependency, neurological deterioration or quality of life. These findings were maintained irrespective of type of intervention (drug class, intensity of lowering) or type of stroke. However, when assessed by time to treatment, very early blood pressure lowering (before hospital presentation or within six hours of stroke onset) was associated with reduced death or dependency, and improved quality of life (INTERACT-2 2013; RIGHT 2013).

Haemodynamic effects

All the studied antihypertensive drug classes lowered blood pressure during the period of treatment. Reductions in blood pressure after the first treatment varied between -4.6/-2.5 mmHg for oral ARA and -21.0/-7.9 mmHg for ACE-I. Slightly larger reductions in blood pressure were seen in participants with ICH (-11.8/-5.1 mmHg) than in those with ischaemic stroke (-7.0/-3.1 mmHg). The largest reductions were seen if treatment was started very early before hospital presentation (-16.0/-15.0 mmHg); smaller reductions occurred if treatment was started beyond 48 hours after stroke onset (-7.3/-4.9 mmHg).

Discussion

A variety of hypotheses can be postulated for why functional outcome was better if blood pressure lowering was started very early after stroke. First, the magnitude of blood pressure lowering may be important since the greatest improvement in outcome occurred when treatment was started early. Second, the type of intervention may be important since improved outcome was seen with early intensive blood pressure lowering (INTERACT-2 2013), and early nitrate administration (RIGHT 2013; ENOS 2014). Conversely, apparent hazard was seen with ARA drugs (SCAST 2011; Jusufovic 2014).

Perhaps surprisingly, stroke type may not be particularly relevant since differential effects on outcome were not seen for ischaemic stroke versus ICH.

In summary, very early treatment with an appropriate agent or target blood pressure may be the most important strategy to test in the future, irrespective of stroke type. Importantly, systolic blood pressure should not be lowered excessively (> 20%), at least in ischaemic stroke, since trials of intravenous CCBs found that these worsened outcome (Bridgers 1991; Wahlgren 1994).

Continue versus stop pre-stroke antihypertensive drugs

The results come from two trials that studied 2860 participants (COSSACS 2010; ENOS 2014).

Clinical outcomes

The findings were mixed with some comparisons, in particular dependency (mRS), death, and neurological deterioration, neutral for the comparison of continue versus stop pre-stroke antihypertensive drugs. In contrast, measures of disability (BI) and quality of life (EQ-5D, transformed into a Health Utility Status) were worse in participants randomised to continue treatment immediately.

Haemodynamic effects

Immediately continuing antihypertensive drugs taken before stroke was associated with a lower blood pressure by -7.9/-1.2 mmHg at the first measurement after randomisation, and -11.3/-6.4 mmHg by end-of-treatment.

Discussion

The discrepancy in findings for two measures of functional outcome, mRS and BI, is challenging to explain. First, it may represent chance such that no difference exists between the interventions. Second, it could reflect outcome bias since it is not possible to test this question in a double-blind placebo-controlled design. Nevertheless, both trials used blinded outcome assessment for both mRS and BI. Further, since a majority of stroke physicians tend to continue treatment in routine practice (Bath 2000b), the result seen across the two results is counter-intuitive. Last, the difference may be real in which case mRS, usually considered to be the optimal functional outcome in stroke trials (Lees 2012), failed to detect a difference in contrast to a comparison of BI scores.

If continuing drugs immediately is, indeed, hazardous, then the two trials do not identify the cause. Drugs that attenuate stress hormones, in particular that down-regulate the renin-angiotensin-aldosterone-system (RAAS) were commonly taken before stroke, e.g. ACE-I, ARA and ß-receptor antagonists. Initiating these drugs in the acute phase of stroke has been associated with harm (BEST 1988; SCAST 2011), so it can be postulated that continuing these

during the acute phase of stroke is potentially harmful. Alternatively, continuing drugs in people who are dysphagic and who do not have safe enteral access for feeding may be hazardous through aspiration of these drugs and then the development of pneumonia. The ENOS trial gives some support for this hypothesis (ENOS 2014).

The main implication for clinicians is that it is reasonable to withhold BP-lowering drugs until patients are medically and neurologically stable, and have suitable oral or enteral access, after which drugs can then be reintroduced.

General

An important problem with some of the trials was the absence of detailed information on how blood pressure was measured. Hence, the quality of blood pressure readings is unknown. It is essential that future trials describe in detail how blood pressure is measured by including the following information.

1. Equipment: manufacturer, model, measurement method (mercury, anaeroid or oscillometry, and manual or automatic), and whether the equipment has been independently validated, and if so by whom.
2. Measurer: who measured blood pressure, and how they were trained, assessed, re-trained and re-assessed.
3. Measurements: the number of readings at each time point, site of measurement (brachial, finger, etc) and what position the person was in (supine, sitting, standing).

Little is known about the effect of blood pressure altering in older people with acute stroke, who comprise the largest group of patients, including those with ischaemic stroke who need thrombolysis. Of the trials, only two had mean age over 75 years contributing to a total of 98 participants (CHHIPS 2009; RIGHT 2013). The number and proportion of older people is likely to increase with population ageing. As the variation in response by individuals to blood pressure modulating agents increases with age, e.g. related to concurrent isolated systolic hypertension or cardiac dysfunction, it may be inappropriate to assume that the effects of changing blood pressure seen in younger populations will necessarily be the same in older ones.

This review is Part 1 of the Blood pressure in Acute Stroke Collaboration and reports only those trials that specifically set out to alter blood pressure in people with acute stroke. Part 2 of the project assesses all RCTs in acute stroke where vasoactive drugs were administered and includes all those studies covered in Part 1. Although progress has been made in the number and quality of stroke trials in the last few years, a substantial number of questions remain. The number of participants included in this review is very small in comparison to the global burden of stroke (about 15,000,000 per year worldwide). At present, any benefit of treatment is small, and additional data are required to recommend changes to routine clinical practice. The centres that took part in the trials were interested and familiar with the management of acute stroke. To extrapolate these results in routine clinical practice to less specialist centres could result in greater hazard or completely negate any potential benefit. Therefore, there is a need for new centres to participate in trials. Further evidence is needed on:

- how to select participants;
- the influence of age, time of onset, stroke subtype, severity, choice of drug, dose, route of administration and blood pressure variability, on response to active changes in blood pressure.

Recent guidelines based on the non-systematic analysis of (largely) observational data recommend that hypertension should not be treated for up to two weeks after an ischaemic stroke unless severe hypertension, hypertensive encephalopathy, heart failure, cardiac ischaemia, aortic dissection, or continued intracerebral bleeding are present (O'Connell 1994; EUSI 2004; AHA-HS 2010; AHA-IS 2013). Persistent hypertension after two weeks should be treated since the risk of stroke in people with cerebrovascular disease is dependent on systolic and diastolic blood pressure (Rodgers 1996). In PROGRESS 2001, perindopril (with or without indapamide) reduced the risk of stroke among both hypertensive and non-hypertensive participants with a history of stroke or transient ischaemic attack. Further, evidence from the Heart Outcomes Prevention Evaluation (HOPE) trial suggests that an ACE-I may reduce stroke and other vascular events in people with prior cerebrovascular disease (HOPE 2000). Overall, lowering blood pressure in people with chronic stroke reduces the subsequent risk of recurrence (Rashid 2003).

Summary of main results

In this updated review, blood pressure lowering did not improve functional outcome. However, early initiation of treatment might be beneficial, and further studies are required to test this specific question. Immediately continuing pre-stroke antihypertensive drugs appears to be associated with a worse functional outcome and lower quality of life; hence, it is reasonable to delay treatment until patients are stable and have oral or enteral access to allow safe administration of drugs.

Overall completeness and applicability of evidence

The included trials are an excellent start to answering the question of optimal blood pressure management in acute stroke. The lack of a definitive result based on data from more than 16,000 participants confirms that the question is complex and future trials need to refine trial design, especially focusing on very early treatment.

Quality of the evidence

The quality of the included studies was variable. Methods of randomisation and allocation concealment were not always clear. Not all trials contributed to each outcome. Details of blood pressure recording including equipment, number of readings and patient positioning were not provided in some studies. Trials in the last decade were more standardised compared with earlier ones when reporting baseline stroke characteristics, primary and secondary outcomes. Outcome assessment was blinded in recent large RCTs and clearly reported in trial protocols. Trials were largely not representative of unselected stroke populations around the world - participants tended to be younger, have fewer comorbidities and be conscious, so that poor outcomes were less common than might be expected.

Potential biases in the review process

This review follows an extensive literature search by both the Cochrane Stroke Review Group, and the authors, and without any language restrictions. Hence the risk of study inclusion bias is low.

Agreements and disagreements with other studies or reviews

The limited data mean that we can draw no firm conclusions, as shown in other reviews.

AUTHORS' CONCLUSIONS

Implications for practice

The lack of definitive results for blood pressure lowering, and very limited data for raising blood pressure, mean that no firm recommendations can be made.

There is no evidence to support the routine policy of immediately continuing prestroke antihypertensive drugs; treatment may be restarted once patients have stabilised medically and neurologically, and once safe feeding or enteral access is available.

The very limited data related to blood pressure elevation mean that no recommendations can be made.

Implications for research

Large randomised controlled trials (RCTs) of blood pressure lowering are needed to:

- test the effect of ultra-acute/pre-hospital lowering of blood pressure in RCTs;
- test the effect of hyper-acute/hospital lowering of blood pressure in RCTs. Two trials are important examples of ongoing studies (ATACH-2 2011; ENCHANTED 2011);
- determine the effects on long-term survival (≥ one year);
- determine the effects on quality of life and cost-effectiveness.

An individual patient data (IPD) meta-analysis is required to:

- identify subgroups of patients who are likely to benefit or be harmed, e.g. by age, sex, race-ethnicity group, baseline blood pressure, history of hypertension, stroke type (ischaemic stroke, ICH);
- identify what type of treatment is required, e.g. drug class, route, dose of administration.

The ongoing 'Blood pressure in Acute Stroke Collaboration' is performing an IPD meta-analysis and includes many of the quoted trials.

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Data collation and analysis, and review writing for this version of the review: K Krishnan, PMW Bath.

Trialists:

- DR Lisk, JC Grotta: (summary and individual data) (Lisk 1993).
- N Uzuner: (summary and individual data) (Uzuner 1995).
- AG Dyker, K Lees: (summary and individual patient data) (Dyker 1997).
- PMW Bath: (summary and individual patient data) (Bath 2000; Rashid 2003 10 mg; Rashid 2003 5/10 mg; Rashid 2003 5 mg; Willmot 2006; RIGHT 2013; TAST 2013; ENOS 2014).
- AB Hillis: (summary data) (Hillis 2003).
- D Eveson: (summary data) (Eveson 2007).
- FJ Bath-Hextall was a co-author involved with the following aspects of the first version of the review: design, development of search strategies, carrying out searches, input of data, analysis, and writing.
- The late C Geeganage was a co-author involved with the following aspects of the second version of the review: development of search strategies, carrying out searches, input of data, analysis, and writing.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

ACCESS 2003

Methods	Double-blind, placebo-controlled Method of randomisation not known
Participants	Germany, multicentre 339 participants. T: 173, C: 166 Age T: 68 years, C: 67.8 years Male T: 50%, C: 52% Inclusion: IS 100% CT Enrolment within 24 to 36 hours after admission
Interventions	T: candesartan 4 mg po on day 1 and dose was increased to 8 or 16 mg if BP exceeded 160 mmHg SBP or 100 mmHg DBP C: matching placebo Rx: 7 days
Outcomes	BP measured by a nurse or automatically Case fatality and disability using BI 3 months
Notes	Exclusion: age > 85 years, > 70% stenosis of internal carotid artery, disorders in consciousness, cardiac failure, unstable angina, malignant hypertension, and high grade aortic or mitral stenosis

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear

ACCOST 2006

Methods	Double-blind, placebo-controlled Method of randomisation not known
Participants	UK, single centre 38 participants, T: 19, C: 19 Age: not given Inclusion: IS with BP > 120/70 Enrolment within 72 hours
Interventions	T: candesartan 4 mg once daily C: matching placebo Rx: 28 days Dose was increased to 8 mg or 2 placebo if BP criteria not met. Target BP not reported

ACCOST 2006 (*Continued*)

Outcomes	BP methodology not given All-cause mortality and mortality due to vascular causes 90 days: NIHSS, mRS, BI
Notes	Exclusion criteria: not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	This was an abstract only. The author reported the study as being prospective, double-blind and placebo-controlled
Allocation concealment (selection bias)	Unclear risk	No further information available
Blinding (performance bias and detection bias) All outcomes	Unclear risk	This was an abstract only. The authors described the study as being double-blind, although it was unclear who was blinded and how
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	This was an abstract only. The authors described the study as being double-blind, although it was unclear who was blinded and how
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was an abstract only. The authors described the study as being double-blind, although it was unclear who was blinded and how
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	This was an abstract only. 38 participants were enrolled into this trial, insufficient data to assess attrition
Selective reporting (reporting bias)	Unclear risk	This was an abstract only
Other bias	Unclear risk	This was an abstract only

Bath 2000

Methods	Double-blind, placebo-controlled Randomisation by computer (with minimisation on age and mean arterial BP, baseline SSS, hours from onset presence of a visible stroke lesion on CT)
Participants	UK, single centre 37 participants. T: 16, C: 21 Age T: 76 years, C: 72 years

Bath 2000 (*Continued*)

	Male T: 6, C: 12 Inclusion: IS or ICH 100% CT Enrolment within 5 days
Interventions	T: transdermal GTN (Schwarz Pharma) 5 mg once daily C: matching placebo Rx: 12 days
Outcomes	24-hour ambulatory BP (Spacelabs 90207, measured 3 times/hour during the day, hourly during the night) at days 0, 1 and 8 Rankin scale, BI and case fatality at 3 months
Notes	Exclusion: taking part in another trial

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Adequate

CATIS 2013

Methods	Single blind, blinded end-point Randomisation central and stratified by participating hospitals and use of antihypertensives. Randomisation schedules generated using SAS PROC PLAN in SAS and concealed until eligible participant was ready for enrolment
Participants	China, multicentre 4071 participants, T: 2038, C: 2033 Males T: 62.1 years, C: 61.8 years Male T: 1317, C: 1287 Inclusion: IS confirmed by CT or MRI with SBP between 140 to 220 mmHg Enrolment within 48 hours FU: losses - T: 50 participants, C: 46 participants
Interventions	T: early intensive lowering of BP (target BP 140/90 mmHg) C: stop pre-existing antihypertensive drugs Rx: 14 days
Outcomes	BP measured supine using a standard sphygmomanometer and using 1 of 4 cuff sizes (paediatric, regular, adult, large adult, or thigh) based on arm circumference. After randomisation, 3 BP measurements every 2 hours on day 1, every 4 hours on day 2 and 3 and three times a day until hospital discharge or death Primary outcomes: BP at days 1, 7, 14; death and major disability at day 14 Secondary outcomes: death and major disability at day 14 and 90

CATIS 2013 (*Continued*)

Notes	Exclusion: severe heart failure, myocardial infarction, unstable angina, atrial fibrillation, aortic dissection, cerebrovascular stenosis, or resistant hypertension, deep coma, treatment with iv rtPA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate
Allocation concealment (selection bias)	Low risk	Central randomisation ensured allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Treating clinicians and nurses were not blinded to treatment group assignment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Although participants were masked to treatment allocation, treating clinicians and nurses were not blinded to treatment group assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were assessed by investigators centrally masked to all clinical details
Incomplete outcome data (attrition bias) All outcomes	Low risk	Very few participants (96 among 4071) lost to follow up; no differences between trial groups
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported; no difference in reporting between groups
Other bias	Low risk	No other biases found

CHHIPS 2009

Methods	Double-blind, placebo-controlled Block randomisation (6 per block) by secure Internet centrally to receive either active treatment or placebo in 2:1 ratio
Participants	UK, multicentre 179 participants, T: 113, C: 59 Labetalol arm: 56 participants Mean age T: 74 years; C: 74 years Males T: 34 (61%), C: 31 (53%) Lisinopril arm: 57 participants

	Mean age: 75 years; C: 74 years Males T: 30 (53%), C: 31 (53%) Inclusion: neuroradiologically confirmed stroke patients 12 hours of stroke onset, hypertensive (SBP > 160), non dysphagic ischaemic and haemorrhagic stroke within 36 hours of stroke onset and hypertensive, dysphagic ischaemic and haemorrhagic stroke patients within 36 hours of stroke onset
Interventions	Non-dysphagic patients: T: oral labetalol 50 mg or lisinopril 5 mg orally; C: matching oral placebo Dysphagic patients: either of: T: iv labetalol 50 mg C: sublingual placebo T: 5 mg sl lisinopril C: intravenous placebo T: sublingual placebo C: intravenous placebo Rx: 14 days
Outcomes	BP changes at 24 hours and 2 weeks. BP measured in the brachial artery every 30 minutes for 8 hours post treatment using a validated A&D UA-767 blood pressure monitor and appropriate cuff Primary outcomes: death or dependency mRS and BI at 14 days following stroke onset Secondary outcomes: NIHSS at 72 hours, mRS and NIHSS day 14, stroke recurrence over 2 weeks, death, quality of life, discharge disposition at 3 months
Notes	Exclusion: hypertensive encephalopathy, co-existing cardiac or vascular emergency, SBP > 200 mm Hg and/or diastolic blood pressure > 120 mm Hg with ICH, pre-existing antihypertensive treatment in patients without dysphagia, NIHSS section 1a $\geq$ 2 points, premorbid mRS > 3, any coexisting life-threatening condition with a life expectancy of < 6 months

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Adequate
Allocation concealment (selection bias)	Low risk	Central randomisation ensured allocation concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	Treatment assignment was blinded. Both active and placebo tablets were identical in shape, size and colour. Similarly, the vials of labetalol and placebo were identical in size, shape and colour

CHHIPS 2009 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatment assignment was blinded. Both active and placebo tablets were identical in shape, size and colour. Similarly, the vials of labetalol and placebo were identical in size, shape and colour
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were assessed by investigators centrally masked to all clinical details
Incomplete outcome data (attrition bias) All outcomes	Low risk	No differences between trial groups
Selective reporting (reporting bias)	Low risk	All outcomes were reported; no differences between trial groups
Other bias	Low risk	No other biases found

COSSACS 2010

Methods	Prospective, open-label, blinded-endpoint Randomisation (1:1) with a block size of 4 centrally by secure Internet Allocation to continue or stop treatment was done by computer with stratification by age at entry (< 75 years and > 75 years)
Participants	UK, multicentre 763 participants. T: 379, C: 384 Mean age T: 74 years, C: 74 years Males T: 210, C: 216 Inclusion: non-dysphagic ischaemic or haemorrhagic stroke within 48 hours of last dose of antihypertensive drugs
Interventions	T: continue pre-existing antihypertensive medications C: stop pre-existing antihypertensive drugs Rx: 14 days
Outcomes	BP measured by use of a UA-767 BP monitor (A&D Medical, San Jose, CA, USA). BP calculated throughout the treatment period as mean of 2 sets of 3 supine readings taken 10 minutes apart Primary outcome: death or dependency at 2 weeks Secondary outcomes: BP changes at admission and 2 weeks; NIHSS, BI at 2 weeks; death, recurrent stroke, quality of life at 2 weeks Discharge disposition at 2 weeks and 6 months
Notes	Exclusion: hypertensive encephalopathy; coexisting cardiac or vascular urgency; SBP greater than 200 mm Hg or DBP greater than 120 mm Hg associated with known primary ICH; contraindications to stopping or indications for continuing antihypertensive treatment; dysphagia; impaired consciousness (NIHSS section 1a score $\geq$ 2 points)

	; women of childbearing potential; premorbid dependency (mRS > 3 points); any coexisting life-threatening condition with an estimated life expectancy of less than 6 months; and no evidence of stroke on neuroimaging

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were randomised using a computer and the method of random sequence generation was described
Allocation concealment (selection bias)	Low risk	Central web-based allocation ensured allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Treatment was open-label, therefore participants and clinicians knew whether treatment was either to stop or continue
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Treatment was open-label, therefore participants and clinicians knew whether treatment was either to stop or continue. However all participants were to receive best medical care and there was no difference in care between treatment groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were assessed by investigators centrally masked to all clinical details
Incomplete outcome data (attrition bias) All outcomes	Low risk	No differences between trial groups
Selective reporting (reporting bias)	Low risk	All outcomes were reported; no differences between trial groups
Other bias	Low risk	No other biases found

Dyker 1997

Methods	Double-blind, placebo-controlled Method of randomisation not known
Participants	UK, single centre 28 participants. T: 14, C: 14 Mean age 70 years Males T: 9, C: 8 Inclusion: ischaemic strokes with mild to moderate hypertension (170 to 250/95 to 120

Dyker 1997 (*Continued*)

	mmHg) 100% CT on entry Enrolment within 1 week Patients admitted on prescribed antihypertensive therapy had treatment discontinued for at least 48 hours before entry into the study
Interventions	T: perindopril 4 mg po once daily C: matching placebo Rx: 15 days
Outcomes	BP measured semi-automatically pre-treatment and hourly at 10 hours repeated at 24 hours and at 2 weeks Neurological impairment: NIHSS made at baseline and day 15
Notes	Exclusion: severe carotid disease

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Adequate

Eames 2005

Methods	Double-blind, placebo-controlled, parallel group study Block randomisation (4 per block)
Participants	UK, single centre 37 participants. T: 18, C: 19 Age: 68 years Male: 86% Inclusion: neuroradiologically diagnosed ischaemic stroke with 24 hour BP > 130/80 mmHg or daytime mean BP > 135/85 mmHg Enrolment within 96 hours of stroke onset
Interventions	T: bendrofluazide 2.5 mg po daily C: matching placebo Rx: 7 days
Outcomes	Casual and non-invasive beat-to-beat arterial BP level, cerebral blood flow velocity, ECG and transcutaneous carbon dioxide levels within 70 - 20 hours of cerebral infarction and 7 days later were measured. 24-hour BP monitoring with Spacelabs 90207 and brachial artery BP with validated semi-automatic BP monitor (Omron 711)
Notes	Exclusion: history of previous stroke, dysphagia, symptoms lasting < 24 hours, or presented > 76 hours after symptom onset (to allow for 24 hour BP monitoring to be performed prior to randomisation)

Eames 2005 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Adequate

ENOS 2014

Methods	Single-blind, parallel-group, partial factorial study Randomisation via password protected, data-encrypted website, with: stratification by prior antihypertensive treatment and country; minimisation by sex, age, stroke severity, time to treatment and total anterior circulation syndrome
Participants	International (23 countries), multicentre (173 sites) 4011 participants. T: 2000; C: 2011 Age T: 70 years, C: 70 years Male T: 1147 (57%), C:1150 (57%) Inclusion: haemorrhagic or ischaemic stroke; motor deficit in arm and/or leg; SBP between 140 to 220 mmHg Enrolment: < 48 hours of onset
Interventions	Factor 1: T: Transdermal GTN 5 mg C: No GTN Blinding with a gauze dressing applied over GTN patch or equivalent area of skin Factor 2 (in relevant participants): T: Continue pre-stroke antihypertensive therapy C: Stop pre-stroke antihypertensive therapy Rx: 7 days
Outcomes	Primary outcome: mRS at day 90 Secondary outcomes: • BP and HR measured with validated automated blood pressure monitor (Omron HEM-705CP or HEM-757, Illinois, USA) • Days 1 to 7: BP, HR • Day 7: Recurrent stroke • Discharge: Length of stay; disposition • Day 90: Death or dependency (mRS 3 to 6); BI; QoL (EQ-5D, EQ-VAS); MMSE; TICS; Animal naming; Zung depression
Notes	Exclusions: GCS < 8; pure sensory stroke; preceding dependency (mRS 3 to 5); confounding neurological or psychiatric disease; stroke mimic; severe liver or renal dysfunction; severe concomitant medical conditions: pregnant or breastfeeding; planned surgical intervention; previous participation in ENOS 2014; definite need for, or contradiction to, nitrates and/or prestroke antihypertensive therapy
Risk of bias	

ENOS 2014 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation
Allocation concealment (selection bias)	Low risk	Central web-based allocation ensured allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	GTN was given in a single-blind design as no manufacturer was able to supply placebo patches. Participants were blinded with placement of a gauze dressing over an area of skin out of view (e.g. back or shoulders) with or without GTN patch a underneath. The continue versus stop arm was open-label
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	GTN was given in a single-blind design as no manufacturer was able to supply placebo patches. Participants were blinded with placement of a gauze dressing over an area of skin out of view (e.g. back or shoulders) with or without GTN patch a underneath. The continue versus stop arm was open-label. All participants were to receive best medical care and there was no difference in care between treatment groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were assessed by investigators centrally masked to all clinical details
Incomplete outcome data (attrition bias) All outcomes	Low risk	No differences between trial groups
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported; no differences between trial groups
Other bias	Low risk	No other biases found

Eveson 2007

Methods	Double-blind, placebo-controlled, parallel-group study Randomisation by numbered identical study packs
Participants	UK, single centre 40 participants. T: 18, C: 22 Age T: 73 years, C: 75 years

Eveson 2007 (*Continued*)

	Male: 63% Inclusion: acute IS within previous 24 hours with mean SBP level ≥ 140 mmHg or DBP level ≥ 90 mmHg Randomisation done before neuroimaging; participants with non-IS were withdrawn from the study
Interventions	T: lisinopril 5 mg po once daily C: matching placebo Rx: 14 days Dose was increased to 10 mg or 2 placebo on day 7 if SBP ≥ 140 mmHg or DBP ≥ 90mmHg
Outcomes	Casual brachial artery BP monitoring at 5-minute intervals during a 30-minute period with a validated monitor (A&D UA 767) NIHSS score at day 14, BI and mRS at day 14 and day 90
Notes	Exclusion: severe carotid stenosis, significant aortic stenosis, cardiac failure, MI within past 6 months, dysphagia, dehydration, adverse reactions to ACEI, and pre-stroke mRS score > 2

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Adequate
Blinding (performance bias and detection bias) All outcomes	Low risk	

Fagan 1988 120 mg

Methods	Double-blind, placebo-controlled Randomisation technique not stated Intention-to-treat analysis FU: no losses
Participants	USA, multicentre 19 participants, T: 10, C: 9 Age > 45 years, no genders given IS diagnosed on history and neurological examination Enrolment times not given
Interventions	T: nimodipine (Miles Pharmaceuticals, USA) 120 mg/day (20 mg 4 hourly) po C: matching placebo Rx for 21 days

Fagan 1988 120 mg (*Continued*)

Outcomes	Brachial BP before and 30 and 60 minutes after each morning dose for 7 days BP methodology not stated	
Notes	Exclusion: concurrent calcium channel antagonists, antihypertensive agents (other than beta blockers) Part of a larger unpublished trial to evaluate the safety and efficacy of nimodipine	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	Inadequate

Fagan 1988 240 mg

Methods	Double-blind, placebo-controlled Randomisation technique not stated Intention-to-treat analysis FU: no losses	
Participants	USA, multicentre 19 participants, T: 10, C: 9 Age > 45 years, no genders given IS diagnosed on history and neurological examination Enrolment times not given	
Interventions	T: nimodipine (Miles Pharmaceuticals, USA) 240 mg/day (40 mg 4 hourly) po C: matching placebo Rx: for 21 days	
Outcomes	Brachial BP before and 30 and 60 minutes after each morning dose for 7 days BP methodology not stated	
Notes	Exclusion: concurrent calcium channel antagonists,antihypertensive agents (other than beta blockers) Part of a larger unpublished trial to evaluate the safety and efficacy of nimodipine	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	Inadequate

Hillis 2003

Methods	Pilot randomised controlled trial Method of randomisation: 2:1 to BP elevation or conventional management FU: no losses
Participants	USA, single centre 15 participants T: 9, C: 6 Age T: 59 years, C: 68 years Male T: 2, C: 2 Inclusion: IS > 20% diffusion perfusion mismatch; quantifiable, stable or worsening aphasia; hemispatial neglect or hemiparesis Enrolment: up to 7 days from the onset of stroke symptoms Prior antihypertensive medication was discontinued prior to initiation
Interventions	T: intravenous phenylephrine was titrated to reach 10% to 20% increase MAP and continued for maximum of 72 hours. After 24 hours the participants were started on midodrine (up to 10 mg), fludrocortisone(up to 0.2 mg) and sodium chloride tablets with simultaneous weaning of intravenous phenylephrine. By 4 weeks, midodrine, fludrocortisone and sodium chloride were tapered providing no clinical deterioration C: conventional management
Outcomes	BP measurement method not given NIHSS and cognitive tests on day 1, day 3 and 6 to 8 weeks
Notes	Exclusion: CI or inability to tolerate MRI, cardiac ejection fraction < 25%, recent congestive heart failure, myocardial ischaemia, unstable angina, bradycardia, allergy to gadolinium, haemorrhage seen on initial CT, agitation requiring ongoing sedation, or MAP > 140 with no intervention

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

ICH-ADAPT 2013

Methods	Open-label, blinded-endpoint randomised trial Block randomisation (6 per block), stratified by onset to treatment time (≤ 6 and 6 to 24 hours) Treatment allocation using a random number generator before trial commencement Treatment assignment in sealed, opaque envelopes at the site
Participants	Canada, multicentre 75 participants, T: 39, C: 36 Mean age T: 70.7 years, C: 68.7 years Male T: 26, C: 28 Inclusion: spontaneous ICH confirmed by CT and elevated BP ≥ 150 mm Hg (≥ 2 readings, ≥ 5 minutes apart) Enrolment: within 24 hours of symptom onset

ICH-ADAPT 2013 (*Continued*)

	Rx: 1 day FU: no losses
Interventions	T: early intensive BP lowering of BP (SBP target < 150 mm Hg) with iv Labetalol/ hydralazine/enalapril C: guideline based management of BP (target SBP 180 mm Hg) At 24 hours, both groups received perindopril 4 mg daily and or previous antihypertensives po or ng as per investigators discretion
Outcomes	Primary: perihaematoma relative CBF, as measured with CT perfusion 2 hours after initiation of antihypertensive therapy Secondary: continuous non-invasive BP and HR monitoring for minimum 24 hours (BP methodology not stated); NIHSS at 2 hours; mRS, NIHSS at 24 hours, day 30 and 90; BI at day 30 and 90
Notes	Exclusion: secondary ICH, planned surgical resection, or CIs to CT perfusion e.g. contrast allergy or renal impairment

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Adequate
Allocation concealment (selection bias)	Low risk	Randomisation by sequential numbered packs (allocation have been generated randomly)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Treatment was open-label, therefore participants and clinicians knew whether treatment was either to stop or continue
Blinding of participants and personnel (performance bias) All outcomes	High risk	Treatment was open-label, therefore participants and clinicians knew whether the assigned treatment was intensive or guideline-recommended management of BP
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Images were measured centrally by readers blinded to treatment and clinical outcomes Clinical assessment were performed by investigators masked to image analysis
Incomplete outcome data (attrition bias) All outcomes	Low risk	No differences between treatment groups
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported; no differences between trial groups

ICH-ADAPT 2013 (*Continued*)

Other bias	Low risk	No other biases found

INTERACT pilot 2008

Methods	Open, blinded outcome, randomised trial Randomisation done with minimisation through a password protected Internet-based system Intention-to-treat analysis
Participants	International, multicentre 404 participants, T: 203, C: 201 Age 63 years Male 65% Inclusion: spontaneous ICH confirmed by CT and elevated SBP ($\geq$ 2 measurements of 150 to 220 mmHg, recorded $\geq$ 2 minutes apart) 100% CT Enrolment: within 6 hours of ICH onset FU: no losses
Interventions	T: early intensive lowering of BP (target SBP 140 mmHg) C: standard guideline based management of BP (target SBP 180 mmHg) Both groups received oral as well as intravenous agents for lowering BP Rx: for 7 days
Outcomes	Proportional change in haematoma volume at 24 hours BP methodology not stated
Notes	Exclusion: indication for intensive lowering of BP, CI to intensive lowering of BP, ICH secondary to structural cerebral abnormality or use of thrombolytic agent, IS within 30 days, deep coma (3 to 5 on the GCS), pre-stroke disability or medical illness, and early planned decompressive neurosurgical intervention

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Adequate

INTERACT-2 2013

Methods	Open, blinded outcome, randomised trial Randomisation done with minimisation through a password protected Internet based system
Participants	International, multicentre 2839 participants, T: 1382, C: 1412 Mean age T: 63 years, C:64.1 years

INTERACT-2 2013 (*Continued*)

	Male T: 64.2%, C: 61.7% Inclusion: spontaneous ICH confirmed by CT and elevated SBP (≥ 2 measurements of 150 to 220 mmHg, recorded ≥ 2 minutes apart) 100% CT Enrolment: within 6 hours of ICH onset FU: no losses
Interventions	T: intensive lowering of BP (target SBP 140 mmHg) C: standard guideline based management of BP (target SBP 180 mmHg) Both groups received oral as well as intravenous agents for lowering BP Rx: for 7 days
Outcomes	Primary: mRS at day 90 Secondary: combined death and dependency at day 90 in participants treated < 4 hours of ICH onset; recurrent stroke; haematoma expansion and cerebral oedema at 24 and 72 hours; BP during 7 days of treatment (BP methodology not stated); length of stay; discharge disposition; BI, QoL (EuroQoL), MMSE, Zung depression at day 90 (BP methodology not stated)
Notes	Exclusion: indication for intensive lowering of BP, CI to intensive lowering of BP, ICH secondary to structural cerebral abnormality or use of thrombolytic agent, IS within 30 days, deep coma (3 to 5 on the GCS), pre-stroke disability or medical illness, and early planned decompressive neurosurgical intervention

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation by secure Internet system
Allocation concealment (selection bias)	Low risk	Central web-based allocation ensured allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Treatment was open-label, therefore participants and clinicians knew whether the assigned treatment was intensive or guideline-recommended management of BP
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Treatment was open-label, therefore participants and clinicians knew whether the assigned treatment was intensive or guideline-recommended management of BP. All participants were to receive best medical care and there was no differences in care between the 2 treatment groups

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were assessed by investigators centrally masked to all clinical details
Incomplete outcome data (attrition bias) All outcomes	Low risk	No difference between trial groups
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported; no differences between trial groups
Other bias	Low risk	No other biases found

Koch 2008

Methods	Open-label, blinded outcome, randomised trial Allocation concealment by numbered envelopes in random sequence
Participants	USA, single centre 42 participants: T: 21, C: 21 Mean age T: 61 years, C: 60 years Male T: 9, C: 14 Inclusion: CT confirmed spontaneous supratentorial ICH Enrolment: within 8 hours of ICH onset Rx: 2 days
Interventions	T: intensive lowering of BP (target MAP < 110 mm Hg) C: guideline based management of BP (target MAP 110 to 130 mm Hg)
Outcomes	BP; monitored every 15 minutes for the first 3 hours, every 30 minutes from 3 to 6 hours, and hourly from 6 to 48 hours. BP measured with automated cuff sphygmomanometry NIHSS, GCS at 24 and 48 hours Haematoma and oedema growth between baseline and 24 hours mRS day 90
Notes	Exclusion: inability to consent, head injury, comatose, coagulopathy (platelet count < 50, 000 or INR $\geq$ 1.8), MAP < 110 mm Hg, ICH secondary to other causes (arteriovenous malformations, trauma, aneurysm) or needing surgical evacuation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation has been stratified by centre, but method of random sequence generation was not described
Allocation concealment (selection bias)	Low risk	Allocation have been done randomly

Koch 2008 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Treatment was open-label, therefore participants and clinicians knew whether the assigned treatment was intensive or guideline-recommended management of BP
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Treatment was open-label, therefore participants and clinicians knew whether the assigned treatment was intensive or guideline-recommended management of BP
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were assessed by investigators centrally masked to all clinical details
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for; no differences between trial groups
Selective reporting (reporting bias)	Low risk	All outcomes reported; no difference between treatment groups
Other bias	Low risk	No other biases found

Lisk 1993

Methods	Double-blind, placebo-controlled Randomisation technique not stated Intention-to-treat analysis FU: no losses
Participants	USA, single centre Mean age 66 years, range 46 to 83 years, 4 male, 12 female IS, 14 participants had MCA territory infarct 100% CT pre-entry Enrolment within 72 hours Baseline SBP 170 to 220 mmHg and DBP 95 to 120 mmHg, or mean BP 120 to 140 mmHg History of previous hypertension (current treatment or clinical evidence of end organ damage)
Interventions	T 1: nicardipine hydrochloride 20 mg po tds (5 participants) T 2: captopril 12.5 mg po tds (3 participants) T 3. clonidine hydrochloride 0.1 mg tds (2 participants) C: matching dextrose/starch capsule tds (6 participants) Rx: for 3 days
Outcomes	Supine BP at baseline then every 10 minutes for first hour, then hourly for 6 hours, then 4 hourly BP measured using an automatic monitor (Space Labs, model IEC 601-1)

Lisk 1993 (*Continued*)

	Neurological impairment: NIHSS at baseline and daily SPECT at baseline and at 3 days	
Notes	Exclusion: coma, significant neurological deficit from previous stroke, brain stem stroke, acute MI, severe heart failure or cardiac conduction defect, history of angioedema or collagen vascular disease, liver dysfunction	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	Inadequate

PIL-FAST 2013

Methods	Double-blind parallel-group external pilot controlled trial Both active and control group tablets were blister packed and placed in identical boxes. Each box had a unique study number according to the randomisation code (intervention and control in 1:1 ratio)
Participants	UK, single centre 14 participants. T: 6 C: 8 Median age 73 years Male T: 7, C: 7 Inclusion: conscious ("A" on AVPU scale), ≥ 40 years with new unilateral arm weakness thought to be due to be acute stroke and SBP > 160 mm Hg on 2 consecutive seated or lying readings taken 5 to 10 minutes apart Enrolment within 3 hours of symptom onset FU: not completed for 1 participant
Interventions	T: lisinopril (Modepharma) 5 mg sublingual and second dose of 5 mg given po, sublingual or via nasogastric tube C: matched placebo (Haupt Pharma Wuelfing) Rx: 7 days
Outcomes	BP measured seated or supine 5 to 10 minutes apart before randomisation Primary: feasibility-recruitment rate, compliance with data collection Secondary: change in BP for 7 days (BP measurement methodology during study schedule not given); NIHSS at days 3 and 7; BI, mRS, renal function, death at day 7
Notes	Exclusion: age < 40 years; females, pregnant, lactating or at risk of pregnancy; females < 56 years of age consented by a relative; suspected stroke without unilateral arm weakness; unable to establish whether stroke onset time was within the last 3 hours; SBP < 160 mm Hg; reduced level of consciousness below "A" on AVPU scale; patient not being transported to PIL-FAST trial site; absence of participant or next of kin consent; known to be taking ACE inhibitor or angiotensin II receptor blocker medication already; known sensitivity to lisinopril or other ACE inhibitor medication; pulse > 120 bpm; seizure; hypoglycaemia; unable to walk independently prior to stroke; obvious understanding or memory problems when next of kin is absent; significant head trauma or brain surgery in

PIL-FAST 2013 (*Continued*)

	the last 3 months; known renal failure, liver failure (or currently jaundiced); uncontrolled heart failure (breathlessness at rest); receiving palliative care for known malignancy; participating in a clinical trial assessing a study drug

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation list created by independent statistician
Allocation concealment (selection bias)	Low risk	Both lisinopril and placebo were supplied in identical boxes and each box was packaged into a secondary trial pack. Each pack carried a unique study number linked to the randomisation code
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were assessed by investigators centrally masked to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for, both groups have similar dropout rates; clinical reasoning given
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported
Other bias	Low risk	No other biases evident

PRoFESS 2009

Methods	Double-blind, 2 x 2 factorial trial Randomisation done by central telephone system
Participants	International (35 countries), multicentre (695 centres) 1360 participants. T: 647 , C: 713 Mean age T: 66.8 years, C: 67.1 years Male T: 64.9%, C: 65.1% Inclusion: IS Enrolment within 72 hours FU: no losses

PRoFESS 2009 (*Continued*)

Interventions	T: telmisartan 80 mg once daily C: placebo Rx: 2.5 years
Outcomes	Primary: BP, HR at days 7, 30 and 90 (BP and HR recorded using validated semiautomatic monitor - Omron 705CP) Secondary: mRS day 30, haemorrhagic transformation of the infarct, cerebral oedema, recurrent stroke, MI, composite vascular events (vascular death, non-fatal stroke, or MI) , death at days 7, 30 and 90
Notes	Exclusion: mRS > 3, using or needing ARA at time of randomisation, known severe renal insufficiency or renal artery stenosis, hyperkalaemia, uncorrected volume or sodium depletion, known severe coronary artery disease or recent MI, patients scheduled for carotid endarterectomy

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Adequate
Allocation concealment (selection bias)	Low risk	Central allocation ensured allocation concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Endpoint adjudication committee blinded; independent safety committee blinded
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported
Other bias	Low risk	None

Rashid 2003 10 mg

Methods	Open-label, blinded-endpoint dose comparison controlled trial Randomisation by minimisation (age, gender, SSS, mean arterial pressure) FU: no losses
Participants	UK, single centre 90 participants. T: 20, C: 30 Mean age T: 70.8 years, C: 73.9 years Male T: 28, C: 13 Inclusion: IS or ICH Enrolment within 72 hours of ictus Clinical stroke subtype at baseline and CT scanning within a week of stroke onset Any antihypertensive medication was stopped at the time of admission and recommenced after 10 days once the trial treatment phase was completed
Interventions	T: transdermal GTN 10 mg once daily C: no patch Rx: 10 days
Outcomes	24 hour ambulatory BP monitoring during day and hourly during night at days 0, 1, 4, 5 and 10 mRS, BI, QoL at 3 months
Notes	Exclusion: SBP > 230 mmHg or < 100 mmHg, DBP > 130 mmHg or < 60 mmHg, HR > 130 bpm or < 50 bpm, mild stroke, coma, pre-morbid dependence, or presence of illnesses that could confound neurological or functional evaluation (such as pre-existing neurologic or psychiatric disorders)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate

Rashid 2003 5 mg

Methods	Open-label, blinded-endpoint dose comparison controlled trial Randomisation by minimisation (age, gender, SSS, mean arterial pressure) FU: no losses
Participants	UK, single centre 90 participants. T: 20, C: 30 Mean age T: 70.8 years, C: 73.9 years Male T: 28, C: 13 Inclusion: IS or ICH Enrolment within 72 hours of ictus Clinical stroke subtype at baseline and CT scanning within a week of stroke onset Any antihypertensive medication was stopped at the time of admission and recommenced after 10 days once the trial treatment phase was completed

Rashid 2003 5 mg (*Continued*)

Interventions	T: transdermal GTN 5 mg once daily C: no patch Rx: 10 days
Outcomes	24 hour ambulatory BP monitoring during day and hourly during night at days 0, 1, 4, 5 and 10 mRS, BI, QoL at 3 months
Notes	Exclusion: SBP > 230 mmHg or < 100 mmHg, DBP > 130 mmHg or < 60 mmHg, HR > 130 bpm or < 50 bpm, mild stroke, coma, pre-morbid dependence, or presence of illnesses that could confound neurological or functional evaluation (such as pre-existing neurologic or psychiatric disorders)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Adequate

Rashid 2003 5/10 mg

Methods	Open-label, blinded-endpoint dose comparison controlled trial Randomisation by minimisation (age, gender, SSS, mean arterial pressure) FU: no losses
Participants	UK, single centre 90 participants. T: 20, C: 30 Mean age T: 70.8 years, C: 73.9 years Male T: 28, C: 13 Inclusion: IS or ICH Enrolment within 72 hours of ictus Clinical stroke subtype at baseline and CT scanning within a week of stroke onset Any antihypertensive medication was stopped at the time of admission and recommenced after 10 days once the trial treatment phase was completed
Interventions	T: transdermal GTN 5/10 mg once daily C: no patch Rx: 10 days
Outcomes	24 hour ambulatory BP monitoring during day and hourly during night at days 0, 1, 4, 5 and 10, mRS, BI, QoL at 3 months
Notes	Exclusion: SBP > 230 mmHg or < 100 mmHg, DBP > 130 mmHg or < 60 mmHg, HR > 130 bpm or < 50 bpm, mild stroke, coma, pre-morbid dependence, or presence of illnesses that could confound neurological or functional evaluation (such as pre-existing neurologic or psychiatric disorders)

Rashid 2003 5/10 mg (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Adequate

RIGHT 2013

Methods	Single-blind, blinded-endpoint Randomisation (1:1) Intervention in double non-opaque envelopes carried in ambulance: outer envelope - case report form; inner envelope - gauze dressing +/- GTN patch
Participants	UK, single centre 41 participants. T: 25, C: 16 Mean age T: 79 years, C: 81 years Male T: 15 (60%), C: 7 (43.8%) Inclusion: positive FAST test Enrolment within 4 hours of symptom onset (wake-up stroke defined as onset at bedtime) FU: no losses
Interventions	T: GTN patch C: No GTN patch Blinding: gauze dressing covering patch or similar area of skin
Outcomes	Primary: SBP at 2 hours (BP measured in the ambulance using a semiautomatic sphygmomanometer and in hospital with Omron 705 CP or 705 CP II) Secondary: 15 minutes: SBP, DBP, HR; Day 7: SSS, recurrent stroke, death, hypotension, neurological deterioration (5 point reduction in SSS); Day 90: mRS, BI, EQ-5D, EQ-VAS, MMSE, Zung Depression Scale
Notes	Exclusion: definite need or CI for GTN; GCS $\leq$ 8; blood glucose < 2.5 mmol/L; non-ambulatory prior to symptom onset

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Simple randomisation equally distributed with equal distribution between treatment and control groups
Allocation concealment (selection bias)	Low risk	Adequate. The opaque envelope containing the gauze dressing with or without GTN was opened only after informed consent was obtained; thus the research paramedic did not know or was not able

RIGHT 2013 (*Continued*)

		to guess treatment allocation unless the opaque envelope was opened
Blinding (performance bias and detection bias) All outcomes	Unclear risk	GTN was given in a single-blind design as no manufacturer was able to supply placebo patches. Participants were blinded with placement of a gauze dressing over an area of skin out of view (e.g. back or shoulders) with or without GTN patch a underneath
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	GTN was given in a single-blind design as no manufacturer was able to supply placebo patches. Participants were blinded with placement of a gauze dressing over an area of skin out of view (e.g. back or shoulders) with or without GTN patch a underneath. All participants were to receive best medical care and there was no difference in care between treatment groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were assessed by investigators blinded to all clinical details
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants have been accounted for; no differences between trial groups
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported
Other bias	Low risk	No other biases found

SCAST 2011

Methods	Double-blind, placebo-controlled, blinded-endpoint Randomisation (1:1) by secure Internet website with both participants and investigators masked to treatment allocation
Participants	International (9 countries), multicentre (146 sites) 2029 participants. T: 1017, C: 1012 Mean age T: 70.8 years, C: 71.0 years Male T: 60%, C: 56% Inclusion: IS or ICH Enrolment within 30 hours of stroke onset and elevated SBP > 140 mm Hg FU: 25 losses
Interventions	T: candesartan (Astra Zeneca), doses increasing from 4 mg on day 1 to 16 mg on days 3 to 7 C: placebo

SCAST 2011 (*Continued*)

	Rx: 7 days
Outcomes	BP measured twice with validated automated blood pressure monitor (UA-767 Plus 30, A&D Medical, San Jose, CA, USA) Primary: composite of vascular death, nonfatal MI or non-fatal stroke in first 6 months; mRS at 6 months Secondary: SSS at day 7 and BI; death from all causes; vascular death; recurrent stroke; MI; stroke progression
Notes	Exclusion: CI to, or current treatment with ARA; markedly reduced consciousness (SSS consciousness score $\leq$ 2); clear indication for an ARA during treatment period; clear indication for antihypertensive treatment during the acute phase of stroke; premorbid modified mRS $\geq$ 4; life expectancy of 12 months or less; patient unavailable for follow-up; pregnancy or breastfeeding

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was done by secure Internet system
Allocation concealment (selection bias)	Low risk	Both candesartan and placebo tablets were identical in appearance. Central web-based allocation ensured allocation concealment. If Internet was not available, investigators used the drug pack with the lowest pack number
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No differences between trial groups
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes were reported; no differences between trial groups
Other bias	Unclear risk	No other biases found

TAST 2013

Methods	Double-blind, blinded outcome Randomisation (2:1) by computerised minimisation (age, sex, SBP, SSS, time to first Xenon scan and cortical features according to OCSP classification); randomisation and minimisation were carried out by a single investigator who had no contact with the trial participants or trial data. Randomisation sequence was generated by trial pharmacist
Participants	UK, single centre 19 participants. T: 12, C: 7 Mean age T: 71.9 years, C: 68.3 years Male: T: 10 (83%), C: 4 (57%) Inclusion:CT confirmed or suspected IS Enrolment within 5 days and elevated SBP > 140 mm Hg FU: no losses
Interventions	T: telmisartan 80 mg daily administered orally or by nasogastric tube C: placebo Rx: 90 days
Outcomes	Primary: change in ipsilateral hemispheric CBF Secondary: BP; CBF velocity; CPP; ZFP; mRS at day 90. BP was measured using OmronHEM- 705CP (Omron, 705IT, Kyoto, Japan) semiautomatic sphygmomanometer with participants supine or sitting; measurements were taken in the unaffected arm and done in duplicate with the average of the two readings recorded in the database
Notes	Exclusion: CI to telmisartan or xenon CT scanning, or no enteral access

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were randomised after core data entry was complete by computer and minimised on key prognostic variables
Allocation concealment (selection bias)	Unclear risk	All validations made with treatment allocation blinded
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

TAST 2013 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for; no differences between trial groups
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported
Other bias	Low risk	No other biases evident

Uzuner 1995

Methods	Double-blind, placebo-controlled Randomisation technique not stated Per-protocol analysis FU: no losses
Participants	Turkey, single centre 100 participants. T: 50, C: 50 100% CT pre-entry Enrolment within 24 hours IS: 41 male, 36 female Mean age 63 years ICH: 3 male, 8 female Mean age 65 years
Interventions	T IS: nimodipine 180 mg/day (60 mg tds) po T ICH: nimodipine 2 mg/h iv C: matching po or iv placebo Rx: for 2 days
Outcomes	BP and HR at baseline, 5, 15, 30 and 60 minutes, then every hour for 23 hours (day 1) , then every 2 hours for 24 hours (day 2). BP measured supine using unstated automatic device; LOS; GCS
Notes	Exclusion: 10 participants (T 2, C 8) treated with antihypertensive agents for malignant hypertension and 2 participants with subarachnoid haemorrhage (treated with iv nimodipine) were excluded from our analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	Inadequate

VENTURE 2013

Methods	Prospective, open-labelled, blinded-endpoint Randomisation by computer
Participants	South Korea, multicentre (30 sites) 405 participants, T: 203, C: 202
Interventions	T: valsartan 80 mg po once daily titrated up to 320 mg C: no valsartan Inclusion: IS and SBP 150 to 185 mm Hg Enrolment: within 24 hours Rx: 7 days
Outcomes	BP methodology not known Primary: mRS at 90 days Secondary: early neurological deterioration during the first 7 days; death at day 90
Notes	Exclusion: not known

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	This was an abstract only. The authors describe the study as being randomised open-labelled and blinded-endpoint
Allocation concealment (selection bias)	Unclear risk	No further information available
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The trial was published as an abstract only. The authors describe the study as being open-labelled and blinded-endpoint
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was published as an abstract only. The authors describe the study as being open-labelled and blinded-endpoint
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was published as an abstract only. The authors describe the study was prospective, open-labelled and blinded-endpoint
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient sufficient data were provided in the abstract to assess attrition
Selective reporting (reporting bias)	Unclear risk	This was an abstract only
Other bias	Unclear risk	This was an abstract only

Willmot 2006

Methods	Participant- and measurement-blinded RCT Randomisation by computer (with minimisation on age, sex, baseline SBP, baseline SSS, hours from onset, presence of a visible stroke lesion on CT) FU: no losses
Participants	UK, single centre 18 participants. T: 12, C: 6 Age T: 69 years, C: 70 years Male T: 2, C: 3 Inclusion: IS or ICH, previously independent adult patients with a clinical stroke syndrome and limb weakness 100% CT Enrolment: within 5 days of ictus Prior antihypertensive medication was discontinued at the time of admission
Interventions	T: transdermal GTN 5 mg (Transiderm-Nitro5, Novartis Pharmaceuticals) once daily C: no patch Rx: 7 days
Outcomes	BP was measured immediately before the baseline xenon CT scan and immediately after the post-treatment scan Peripheral SBP and DBP was measured in the non-hemiparetic arm with a validated digital readout oscillometric device (Omron HEM-705CP, Omron Corp, Toyoko, Japan) Central BP was assessed by applanation tonometry of the left radial artery and using the pulse wave analysis (PWA) system (Sphygmocor, Sydney, Australia)
Notes	Exclusion: requirement for or CI to nitrate therapy, had a definite need for prior antihypertensive therapy or vasoactive drugs, unable to co-operate with scanning

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Adequate

ACEI: Angiotensin converting enzyme Inhibitors
ARA: Angiotensin receptor antagonist
AVPU: Alert, Voice, Pain, Unresponsive (AVPU) scale
BI: Barthel Index
BP: blood pressure
bpm: beats per minute
CI: contraindication
C: control group
CBF: cerebral blood flow
CPP: cerebral perfusion pressure
CT: computed tomography
DBP: diastolic blood pressure
ECG: electrocardiogram

EQ-5d: European Quality of life-5 dimensions questionnaire
FU: follow up
GCS: Glasgow coma scale
GTN: glycerol trinitrate
HR: heart rate
ICH: intracerebral haemorrhage
INR: International Normalised Ratio
IS: ischaemic stroke
iv: intravenous
LOS: length of stay in hospital
MAP: mean arterial pressure
MCA: middle cerebral artery
MI: myocardial infarction
MMSE: mini mental state examination
MRI: magnetic resonance imaging
mRS: modified Rankin Scale
NIHSS: National Institutes of Health Stroke Scale
OCSP: Oxford Community Stroke Project classification
po: orally
QoL: quality of life
RCT: randomised controlled trial
rtPA: recombinant tissue plasminogen activator
Rx: treatment
SBP: systolic blood pressure
SSS: Scandinavian stroke scale
T: treatment group
tds: three times daily

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

Study	Reason for exclusion
ACCELERATE 2013	Single-arm, non-blinded trial with all participants enrolled to receive iv clevidipine
Alem 2005	Recruitment of participants was within 3 months and not in the acute stage; compared bendrofluazide and indapamide
ATACH 2006	Prospective open-label study; used single agent intravenous nicardipine comparing 3 tiers of BP lowering
Beer 2012	Trial aim not to alter BP, but assess the effect of irbesartan on infarct size and cerebral blood flow
BEST 1988	Trial aim not about altering BP, but to assess the effect of beta blockers in acute stroke
BIAS 2012	Trial aim not about altering BP, but to assess the effect of neuro and cardioprotective effects of propranolol
BLAST 2007	Withdrawn before recruitment
Bougousslavsky 1990	Trial aim not to alter BP, but to assess the effect of nimodipine on functional outcome

(*Continued*)

Bridgers 1991	Aim of the trial was not to alter BP, but to test the effect of nimodipine in acute stroke
Bursztyn 1985	Head-to-head comparison of nifedipine + betablocker + thiazide versus nifedipine alone
Canwin 1993	Trial aim not about altering BP, but to assess the effect of nimodipine in acute stroke
CAPON 1983	Concealment, treatment losses, exclusion criteria, stroke criteria not available
Carlsson 1993	BP and outcome data not available
Chandra 1995	Head-to-head comparison study comparing intravenous versus oral nimodipine
CHERISH 2010	Head-to-head comparison study comparing cilnidipine versus losartan
Csiba 2012	No data available
Dalal 1995	Tested nimodipine as a neuroprotectant
FIST 1996	Aim not to alter BP, but assessed the effect of flunarizine on functional outcome
Gelmers 1984	Not placebo controlled
Gelmers 1988	Trial tested nimodipine in neurological outcome and survival
German-Austrian 1994	Trial aim not to alter BP, but to assess effect of nimodipine in neurological and functional outcome
Hartmann 2005	Head-to-head comparison study comparing urapidil versus nifedipine
HASTE 2010	No trial design or data available
Heiss 1990	Study compared morphological and functional effect between nimodipine and placebo
Infield 1999	Assessed the effect of nimodipine on cerebral perfusion and outcome
Inzhutova 2007	Study aim not to alter BP, but to assess effect on humoral endothelial dysfunction markers in ischaemic stroke
Kaste 1994	Trial tested the effect of nimodipine on functional outcome, not BP
Koenig 2006	A retrospective chart review of induced hypertension
Kornhuber 1993	Study assessed the effect of flunarizine on functional outcome, not BP
Kwon 2013	Head-to head comparison between amlodipine and losartan
Lamsudin 1995	Assessed functional outcome with nimodipine, not BP

(*Continued*)

Limburg 1990	Trial tested the effect of death and dependency of flunarizine
Lowe 1989	Comparison of death and disability with oral nimodipine versus placebo
Marin Gámez 1988	Published in Spanish. Very little known about treatment group, large number of participants excluded after randomisation
Martinez-Vila 1990	Trial tested the effect of nimodipine on mortality and functional outcome
Marzan 2004	A retrospective evaluation of induced hypertension
Matias Guiu 1988	Study tested nicardipine on cognitive impairment
Meier 1991	BP data not available
Mohr 1992	Aim not to alter BP, but tested the effect of nimodipine on death and functional outcome
MOSES 2005	Head-to-head comparison study comparing eprosartan and nitrendipine
Nag 1998	BP data reported 4 weeks after treatment
Naidech 2003	BP data not available
Nakamura 2007	Head-to-head comparison study comparing perindopril versus candesartan versus conventional antihypertensive therapy
Nazir 2004	SBP and DBP data not available
Nazir 2005	SBP and DBP data not available
NEST 1993	Significant number of participants excluded after randomisation and outcomes not presented in the publication
NICE 2010	Trial aim not to alter BP, but to evaluate nimodipine in preventing cognitive impairment after acute ischaemic stroke
Ning 2007	Trial aim not to alter BP, but to assess the effect of nimodipine in treating perifocal oedema and neurological function after ICH
Oczkowski 1989	Not relevant
PACI 1989	Tested effect of nimodipine on functional outcome and mortality, not BP
Popa 1995	Pre-stroke antihypertensive drugs discontinued (nifedipine, clonidine, furosemide or acetazolamide or both)
Powers 1999	BP data not available

(*Continued*)

Roitberg 2008	Head-to-head comparison between nicardipine and nitroprusside
Rordorf 1997	Retrospective study of induced hypertension
Rosenbaum 1990	Feasibility and safety study
Rosselli 1992	Article published in Italian; only abstract available, insufficient details
Sherman 1986	Trial tested effect of nimodipine versus placebo on clinical outcome, not BP
Shibuya 2005	Study compared clinical outcome between fasudil and placebo
Sze 1998	Not relevant; trial tested the effect of nimodipine on memory
TOPS 2013	Non-randomised study investigating the effects of olmesartan post-stroke
TRUST 1990	Primary aim not to alter BP
Wang 2006	Non-randomised study
Wimalaratna 1994	Study aim not to alter BP
Wityk 2008	No comparator, all participants received intervention to induce hypertension
Yao 1991	Article published in Chinese; nimodipine trial; preliminary study, insufficient details
Yordanov 1984	No details of control group

BP: blood pressure
DBP: diastolic blood pressure
ICH: intracerebral haemorrhage
iv: intraveous
SBP: systolic blood pressure

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

ATTACI 2010

Methods	Prospective, single centre
Participants	Elderly people (> 65 years) with ischaemic stroke
Interventions	Antihypertensive medications added to existing BP medications either morning, afternoon or bedtime

ATTACI 2010 (*Continued*)

Outcomes	BP
Notes	Size: 200 participants Contact person: Dr N Hosomi Department of Clinical Neuroscience and Therapeutics, Hiroshima University Graduate School of Biomedical and Health Sciences, Hiroshima, Japan

ESH-CHL-SHOT 2013

Methods	Factorial 3 x 2 arm, phase 4 study
Participants	People with recent stroke or TIA
Interventions	Randomisation to one of 3 BP targets: • < 145 to 135 mm Hg • < 135 to 125 mm Hg • < 125 mm Hg Random allocation to 1 of 2 lipid-lowering targets: • LDL-C between 2.8 and 1.8 mmol/L • < 1.8 mmol/L
Outcomes	Recurrent stroke Time to recurrent stroke Composite vascular events: cardiovascular death, non-fatal stroke, non-fatal MI and cardiac failure Cognitive impairment and dementia
Notes	Size: 7500 participants Funding: Instituto Auxologico Italiano, Italy

MAPAS 2009

Methods	Single centre, randomised, open-label, parallel assignment
Participants	Non-thrombolysed acute ischaemic stroke patients within 6 hours of ictus onset
Interventions	T1: infusion up to 1 litre of saline and/or norepinephrine T2: infusion of esmolol or sodium nitroprusside
Outcomes	Primary: mRS at day 90 Secondary: treatment feasibility of the antihypertensive treatment, comparing the SBP range for the 24-hour period
Notes	Size: 240 Funding: Hospital de Clinicas de Porto Alegre, Brazil

STABLE-ICAS 2010

Methods	Phase 4 study
Participants	People with subacute ischaemic stroke due to symptomatic severe intracranial atherosclerosis
Interventions	Intensive BP lowering (SBP < 120 mm Hg) compared with modest BP control (SBP < 140mm Hg)
Outcomes	Primary outcomes: ischaemic lesion volume change in the whole forebrain on fluid attenuation inversion recovery (FLAIR) magnetic resonance imaging (MRI); difference between final ischaemic lesions volume and base ischaemic lesions of both hemisphere on FLAIR MRI Secondary outcomes: Ischaemic lesion volume change in the territory of symptomatic intracranial disease on FLAIR MRI difference between final ischaemic lesions volume and base ischaemic lesions in the territory of symptomatic intracranial disease on FLAIR MRI; participants with new ischaemic lesion in the whole forebrain on FLAIR MRI; cardiovascular events; vascular death; number of adverse events and adverse drug reactions
Notes	Size: 156 participants Funding: Asan Medical Center, South Korea

BP: blood pressure
LDL-C: low-density lipoprotein cholesterol
MI: myocardial infarction
mRS: modified Rankin Scale
SBP: systolic blood pressure
TIA: transient ischaemic attack

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

ATACH-2 2011

Trial name or title	Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH II)
Methods	Multicentre, prospective, open-label, phase 3 randomised trial
Participants	People with supratentorial intracerebral haemorrhage
Interventions	Early intensive BP lowering with nicardipine iv, or management according to current American Heart Association guidelines
Outcomes	Primary outcome: combining death and dependency, according to a 4 to 6 score on the mRS at 90 days Secondary outcomes: all cause and cause-specific early neurological deterioration during the first 24 hours; haematoma expansion at 24 hours; quality of life at 3 months
Starting date	2011
Contact information	Prof Adnan I Qureshi University of Minnesota, MMC 295, 420 Delaware St. SE., Minneapolis MN 55455, USA

ATACH-2 2011 (*Continued*)

Notes	Size: 1280 participants Funding: National Institutes of Health, USA

ENCHANTED 2011

Trial name or title	Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED)
Methods	Prospective, international, multicentre, open-label, blinded-endpoint quasi-factorial randomised trial
Participants	People with ischaemic stroke within 4.5 hours of ictus and SBP $\leq$ 185mm Hg
Interventions	• standard dose rtPA or low dose rtPA • intensive BP lowering to SBP 140 to 150 mm Hg, or SBP to < 180 mm Hg
Outcomes	Primary outcome: death and dependency, according to a 2 to 6 score on the mRS Secondary outcomes: early neurological deterioration during the first 72 hours; symptomatic intracerebral haemorrhage during the first 7 days; day 90: discharge: quality of life; length of stay; disposition; mortality
Starting date	2012
Contact information	Prof Craig Anderson, The George Institute, PO Box M 201, Misssenden Road, Sydney NSW 2050, Australia
Notes	Size: 3300 Sponsor: National Health and Medical Research Council of Australia (NHMRC)

FAST-BP 2013

Trial name or title	Field Administration of Stroke Therapy-Blood Pressure Lowering (FAST-BP)
Methods	Single centre, prospective, open-label, safety and feasibility study
Participants	People with ischaemic stroke or intracerebral haemorrhage
Interventions	T1: GTN 5 mg/24 hour patch T2: GTN 10 mg/24 hour patch T3: GTN 5 mg/24 hour patch plus single metered dose 0.4 mg sublingual GTN
Outcomes	Primary outcome: mean BP change 15 minutes after treatment Secondary outcomes: early neurological deterioration (two point or greater worsening in GCS) during the first hour; SBP less than 120 mm Hg; serious adverse events at 90 days
Starting date	2013
Contact information	Dr Nerses Sanossian, Keck School of Medicine of University of South California, 1520 San Pablo St, Los Angeles, CA90033, USA

FAST-BP 2013 (*Continued*)

Notes	Size: 45 Sponsor: University of California Los Angeles, USA

SETIN-HYPERTENSION 2012

Trial name or title	Safety and Efficacy of Therapeutic Induced Hypertension in Acute Non-cardioembolic Ischemic Stroke
Methods	Multicentre, prospective, randomised, open-label, phase 3 study
Participants	Acute ischaemic stroke, confirmed by DWI within 24 hours of onset of ictus, or people who show a 2-point or more increase in NIHSS including one or more increase in the motor score of the affected arm or leg or clear evidence of symptom worsening judged by the investigator confirmed by DWI performed within 24 hours of symptom aggravation
Interventions	T: iv phenylephrine C: no phenylephrine
Outcomes	Primary outcome: NIHSS between day 0 and day 7 Secondary outcomes: Day 7: infarct growth or new ischaemic lesion on MRI; Day 90: mRS, BI; symptomatic intracerebral haemorrhage or cerebral oedema, MI, death from any cause during the first 3 months; intracerebral haemorrhage on follow up MRI and side effects (headache, arrhythmia, chest pain, dysuria, or gastrointestinal haemorrhage) up to 3 months
Starting date	2012
Contact information	Prof Oh Young Bang Samsung Medical Centre, South Korea
Notes	Size: 170 Sponsor: Samsung Medical Centre

BI: Barthel Index
BP: blood pressure
DWI: Diffusion-weighted imaging
GCS: Glasgow Coma Score
GTN: glyceryl trinitrate
iv: intravenous
MI: myocardial infarction
MRI: magnetic resonance imaging
mRS: modified Rankin Score
NIHSS: National Institutes of Health Stroke Scale
rtPA: recombinant tissue plasminogen activator
SBP: systolic blood pressure

DATA AND ANALYSES

Comparison 1. Blood pressure lowering therapy in acute stroke

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or dependency, end of trial by intervention	16	15489	Odds Ratio (IV, Random, 95% CI)	0.98 [0.92, 1.05]
1.1 ACE inhibitors	2	126	Odds Ratio (IV, Random, 95% CI)	1.12 [0.53, 2.36]
1.2 ARA(po)	3	3737	Odds Ratio (IV, Random, 95% CI)	1.07 [0.93, 1.23]
1.3 Beta-blockers	1	86	Odds Ratio (IV, Random, 95% CI)	1.03 [0.42, 2.55]
1.4 Nitric oxide donor	7	4194	Odds Ratio (IV, Random, 95% CI)	0.97 [0.86, 1.10]
1.5 Low BP target	4	7346	Odds Ratio (IV, Random, 95% CI)	0.95 [0.86, 1.04]
2 Death or dependency, end of trial by stroke type	16	15366	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.92, 1.05]
2.1 Ischaemic stroke	8	11015	Odds Ratio (M-H, Random, 95% CI)	1.00 [0.92, 1.08]
2.2 Combined Ischaemic stroke and Intracerebral haemorrhage	5	142	Odds Ratio (M-H, Random, 95% CI)	1.31 [0.64, 2.65]
2.3 Intracerebral haemorrhage	7	4209	Odds Ratio (M-H, Random, 95% CI)	1.01 [0.84, 1.21]
3 Death or dependency, end of trial by stroke location	6	11950	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.87, 1.01]
3.1 Intracerebral haemorrhage, deep	3	2536	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.73, 1.00]
3.2 Intracerebral haemorrhage, superficial	3	851	Odds Ratio (M-H, Random, 95% CI)	1.02 [0.77, 1.35]
3.3 Ischaemic stroke, cortical	4	6180	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.81, 1.09]
3.4 Ischaemic stroke, subcortical	4	2383	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.76, 1.27]
4 Death or dependency, end of trial by time to treatment	16	15489	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.92, 1.05]
4.1 Ultra-acute/pre-hospital	1	41	Odds Ratio (M-H, Random, 95% CI)	0.36 [0.09, 1.43]
4.2 Hyper-acute	3	3506	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.76, 0.99]
4.3 Acute	7	10440	Odds Ratio (M-H, Random, 95% CI)	1.02 [0.94, 1.11]
4.4 Subacute	6	1502	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.84, 1.31]
5 Death, early by intervention	16	10050	Odds Ratio (IV, Random, 95% CI)	0.97 [0.74, 1.28]
5.1 ACE inhibitors (po)	4	164	Odds Ratio (IV, Random, 95% CI)	0.51 [0.06, 4.34]
5.2 ARA (po)	2	1379	Odds Ratio (IV, Random, 95% CI)	0.45 [0.05, 3.97]
5.3 Beta-blockers	1	86	Odds Ratio (IV, Random, 95% CI)	0.25 [0.02, 2.93]
5.4 Calcium channel blockers (po)	1	77	Odds Ratio (IV, Random, 95% CI)	0.65 [0.17, 2.50]
5.5 Calcium channel blockers (iv)	1	11	Odds Ratio (IV, Random, 95% CI)	2.69 [0.10, 73.20]
5.6 Nitric oxide donor	7	4189	Odds Ratio (IV, Random, 95% CI)	0.79 [0.37, 1.72]
5.7 Low BP target	2	4144	Odds Ratio (IV, Random, 95% CI)	1.10 [0.66, 1.83]
6 Death, early by stroke type	13	9925	Odds Ratio (M-H, Random, 95% CI)	1.02 [0.76, 1.35]
6.1 Ischaemic stroke	6	8844	Odds Ratio (M-H, Random, 95% CI)	1.00 [0.73, 1.38]

6.2 Combined ischaemic stroke and intracerebral haemorrhage	6	373	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.25, 2.05]
6.3 Intracerebral haemorrhage	3	708	Odds Ratio (M-H, Random, 95% CI)	1.27 [0.61, 2.61]
7 Death, early by time to treatment	15	10028	Odds Ratio (M-H, Random, 95% CI)	1.03 [0.79, 1.36]
7.1 Ultra-acute/prehospital	2	47	Odds Ratio (M-H, Random, 95% CI)	1.16 [0.09, 14.29]
7.2 Hyper-acute	1	270	Odds Ratio (M-H, Random, 95% CI)	1.55 [0.59, 4.05]
7.3 Acute	6	8182	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.78, 1.41]
7.4 Subacute	7	1529	Odds Ratio (M-H, Random, 95% CI)	0.40 [0.11, 1.42]
8 Death, end of trial by intervention	20	15818	Odds Ratio (IV, Random, 95% CI)	0.95 [0.84, 1.06]
8.1 ACE inhibitors (po)	4	165	Odds Ratio (IV, Random, 95% CI)	0.47 [0.15, 1.48]
8.2 ARA (po)	5	4120	Odds Ratio (IV, Random, 95% CI)	0.92 [0.59, 1.44]
8.3 Beta-blockers	1	86	Odds Ratio (IV, Random, 95% CI)	0.57 [0.17, 1.89]
8.4 Nitric oxide donor	7	4197	Odds Ratio (IV, Random, 95% CI)	0.86 [0.72, 1.04]
8.5 Low BP target	4	7250	Odds Ratio (IV, Random, 95% CI)	1.04 [0.87, 1.25]
9 Death, end of trial by stroke type	20	15750	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.84, 1.07]
9.1 Ischaemic stroke	10	11238	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.78, 1.16]
9.2 Combined ischaemic stroke and intracerebral haemorrhage	7	328	Odds Ratio (M-H, Random, 95% CI)	0.59 [0.29, 1.22]
9.3 Intracerebral haemorrhage	6	4184	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.82, 1.18]
10 Death, end of trial by time to treatment	20	15818	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.75, 1.08]
10.1 Ultra-acute/pre-hospital	2	52	Odds Ratio (M-H, Random, 95% CI)	0.47 [0.11, 2.07]
10.2 Hyper-acute	3	3506	Odds Ratio (M-H, Random, 95% CI)	0.70 [0.38, 1.26]
10.3 Acute	8	10708	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.77, 1.22]
10.4 Subacute	8	1552	Odds Ratio (M-H, Random, 95% CI)	0.92 [0.39, 2.15]
11 Barthel Index, end of trial, by intervention	2	4350	Mean Difference (IV, Random, 95% CI)	0.63 [-3.28, 4.54]
11.1 ARA	1	339	Mean Difference (IV, Random, 95% CI)	-1.90 [-6.46, 2.66]
11.2 Nitric oxide donor	1	4011	Mean Difference (IV, Random, 95% CI)	2.20 [-0.20, 4.60]
12 Barthel Index, end of trial, by stroke type	2	4310	Mean Difference (IV, Random, 95% CI)	1.33 [-1.04, 3.69]
12.1 Ischaemic stroke	2	3681	Mean Difference (IV, Random, 95% CI)	0.84 [-3.21, 4.89]
12.2 Intracerebral haemorrhage	1	629	Mean Difference (IV, Random, 95% CI)	0.90 [-5.18, 6.98]
13 Barthel Index, end of trial, by time to treatment	2	4350	Mean Difference (IV, Random, 95% CI)	-5.43 [-14.19, 3.33]
13.1 Ultra-acute	1	273	Mean Difference (IV, Random, 95% CI)	-18.0 [-25.66, -10.34]
13.2 Acute	2	4077	Mean Difference (IV, Random, 95% CI)	0.30 [-2.64, 3.24]
14 Early neurological deterioration, by intervention	7	7575	Odds Ratio (M-H, Random, 95% CI)	1.07 [0.92, 1.24]
14.1 ACE inhibitors	1	86	Odds Ratio (M-H, Random, 95% CI)	1.59 [0.30, 8.41]
14.2 Beta-blockers	1	86	Odds Ratio (M-H, Random, 95% CI)	0.53 [0.03, 8.74]
14.3 Nitric oxide donor	2	4052	Odds Ratio (M-H, Random, 95% CI)	1.14 [0.66, 1.98]
14.4 Low BP target	4	3351	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.80, 1.18]
15 Early neurological deterioration, by stroke type	7	7507	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.91, 1.24]
15.1 Ischaemic stroke	2	3349	Odds Ratio (M-H, Random, 95% CI)	0.58 [0.09, 3.82]

15.2 Combined ischaemic stroke and intracerebral haemorrhage	1	172	Odds Ratio (M-H, Random, 95% CI)	1.23 [0.31, 4.95]
15.3 Intracerebral haemorrhage	6	3986	Odds Ratio (M-H, Random, 95% CI)	1.01 [0.84, 1.22]
16 Early neurological deterioration, by time to treatment	7	7575	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.87, 1.30]
16.1 Ultra-acute	1	41	Odds Ratio (M-H, Random, 95% CI)	0.55 [0.13, 2.32]
16.2 Hyper-acute	3	3506	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.77, 1.13]
16.3 Acute	4	4028	Odds Ratio (M-H, Random, 95% CI)	1.39 [1.07, 1.81]
17 Quality of life (EuroQol) at end of trial, by intervention	3	6881	Mean Difference (IV, Fixed, 95% CI)	0.02 [0.01, 0.04]
17.1 Nitric oxide donor	2	4052	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.01, 0.03]
17.2 Low BP target	1	2829	Mean Difference (IV, Fixed, 95% CI)	0.05 [0.02, 0.08]
18 Quality of life (EuroQoL) at end of trial, by stroke type	3	7502	Mean Difference (IV, Random, 95% CI)	0.03 [-0.01, 0.07]
18.1 Ischaemic stroke	2	4038	Mean Difference (IV, Random, 95% CI)	0.13 [-0.14, 0.40]
18.2 Intracerebral haemorrhage	3	3464	Mean Difference (IV, Random, 95% CI)	0.02 [-0.03, 0.08]
19 Quality of life (EuroQoL) at end of trial, by time to treatment	3	6867	Mean Difference (IV, Random, 95% CI)	0.05 [-0.00, 0.11]
19.1 Ultra-acute	1	27	Mean Difference (IV, Random, 95% CI)	0.29 [0.07, 0.51]
19.2 Hyperacute	2	3102	Mean Difference (IV, Random, 95% CI)	0.06 [0.03, 0.08]
19.3 Acute	1	3738	Mean Difference (IV, Random, 95% CI)	0.0 [-0.02, 0.02]
20 Length of stay, by intervention	4	8295	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.30, 0.28]
20.1 ACE inhibitors	1	86	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-2.11, 1.85]
20.2 Beta-blockers	1	86	Mean Difference (IV, Fixed, 95% CI)	0.21 [-1.76, 2.18]
20.3 Nitric oxide donor	2	4052	Mean Difference (IV, Fixed, 95% CI)	-0.31 [-1.76, 1.14]
20.4 Low BP target	1	4071	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.31, 0.31]
21 Length of stay, by stroke type	3	8194	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.30, 0.29]
21.1 Ischaemic stroke	2	7393	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.33, 0.28]
21.2 Combined ischaemic and Intracerebral haemorrhage	1	172	Mean Difference (IV, Random, 95% CI)	0.20 [-1.20, 1.60]
21.3 Intracerebral haemorrhage	1	629	Mean Difference (IV, Random, 95% CI)	2.60 [-1.49, 6.69]
22 Length of stay, by time to treatment	4	8295	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.30, 0.29]
22.1 Ultra-acute	2	314	Mean Difference (IV, Random, 95% CI)	-1.88 [-6.58, 2.83]
22.2 Acute	3	7981	Mean Difference (IV, Random, 95% CI)	0.00 [-0.29, 0.30]
23 SBP, first after randomisation, by intervention	24	15432	Mean Difference (IV, Random, 95% CI)	-9.83 [-12.11, -7.56]
23.1 ACE inhibitors(po)	5	123	Mean Difference (IV, Random, 95% CI)	-13.68 [-20.03, -7.32]
23.2 ACE inhibitors (s/l)	1	42	Mean Difference (IV, Random, 95% CI)	-4.00 [-17.55, 5.55]
23.3 ARA (po)	3	3408	Mean Difference (IV, Random, 95% CI)	-4.59 [-7.71, -1.48]
23.4 A2AA(po)	1	4	Mean Difference (IV, Random, 95% CI)	-13.67 [-41.48, 14.14]
23.5 Beta-blockers (po)	1	44	Mean Difference (IV, Random, 95% CI)	-11.5 [-20.29, -2.71]
23.6 Beta-blockers (iv)	1	41	Mean Difference (IV, Random, 95% CI)	-16.40 [-27.40, -5.40]

23.7 Calcium channel blockers (po)	3	106	Mean Difference (IV, Random, 95% CI)	-7.62 [-17.21, 1.96]
23.8 Calcium channel blockers (iv)	1	11	Mean Difference (IV, Random, 95% CI)	-9.76 [-24.42, 4.90]
23.9 Nitric oxide donor	7	4192	Mean Difference (IV, Random, 95% CI)	-9.25 [-14.54, -3.96]
23.10 Thiazide-like diuretic (po)	1	40	Mean Difference (IV, Random, 95% CI)	-20.0 [-38.60, -1.40]
23.11 Low BP target	5	7421	Mean Difference (IV, Random, 95% CI)	-11.39 [-15.30, -7.49]
24 SBP, first after randomisation by stroke type	22	15659	Mean Difference (IV, Random, 95% CI)	-8.77 [-11.04, -6.50]
24.1 Ischaemic stroke	10	9256	Mean Difference (IV, Random, 95% CI)	-6.99 [-8.61, -5.38]
24.2 Combined ischaemic stroke and intracerebral haemorrhage	9	2466	Mean Difference (IV, Random, 95% CI)	-7.89 [-12.43, -3.36]
24.3 Intracerebral haemorrhage	4	3937	Mean Difference (IV, Random, 95% CI)	-11.77 [-15.25, -8.30]
25 SBP, first after randomisation by time to treatment	17	15211	Mean Difference (IV, Random, 95% CI)	-9.67 [-12.14, -7.20]
25.1 Ultra-acute/prehospital	2	55	Mean Difference (IV, Random, 95% CI)	-15.98 [-30.43, -1.53]
25.2 Hyper-acute	3	3506	Mean Difference (IV, Random, 95% CI)	-13.38 [-15.41, -11.35]
25.3 Acute	6	10120	Mean Difference (IV, Random, 95% CI)	-7.23 [-9.83, -4.63]
25.4 Subacute	7	1530	Mean Difference (IV, Random, 95% CI)	-7.26 [-10.02, -4.50]
26 SBP, at day 1	18	14203	Mean Difference (IV, Random, 95% CI)	-8.33 [-10.97, -5.69]
26.1 ACE inhibitors (po)	5	120	Mean Difference (IV, Random, 95% CI)	-7.90 [-16.83, 1.03]
26.2 ACE inhibitors (s/l)	1	42	Mean Difference (IV, Random, 95% CI)	-12.0 [-25.60, 1.60]
26.3 ARA (po)	2	2368	Mean Difference (IV, Random, 95% CI)	-0.50 [-2.52, 1.51]
26.4 A2AA (po)	1	4	Mean Difference (IV, Random, 95% CI)	-21.83 [-66.12, 22.46]
26.5 Beta-blockers(po)	1	44	Mean Difference (IV, Random, 95% CI)	-14.00 [-27.28, -0.72]
26.6 Beta-blockers (iv)	1	43	Mean Difference (IV, Random, 95% CI)	-5.0 [-18.44, 8.44]
26.7 Calcium channel blockers (po)	2	84	Mean Difference (IV, Random, 95% CI)	-13.23 [-43.36, 16.91]
26.8 Calcium channel blockers (iv)	1	11	Mean Difference (IV, Random, 95% CI)	-31.90 [-64.73, 0.93]
26.9 Nitric oxide donor	7	4183	Mean Difference (IV, Random, 95% CI)	-12.10 [-19.06, -5.14]
26.10 Low BP target	3	7304	Mean Difference (IV, Random, 95% CI)	-10.04 [-12.47, -7.61]
27 SBP, at day 7	11	15151	Mean Difference (IV, Random, 95% CI)	-6.74 [-9.39, -4.10]
27.1 ACE inhibitors	1	11	Mean Difference (IV, Random, 95% CI)	-26.0 [-43.00, -7.00]
27.2 ARA(po)	4	3747	Mean Difference (IV, Random, 95% CI)	-5.74 [-7.44, -4.03]
27.3 Thiazide-like diuretic (po)	1	37	Mean Difference (IV, Random, 95% CI)	-15.0 [-34.25, 4.25]
27.4 Nitric oxide donor	2	4052	Mean Difference (IV, Random, 95% CI)	-1.16 [-2.63, 0.31]
27.5 Low BP target	3	7304	Mean Difference (IV, Random, 95% CI)	-7.62 [-11.69, -3.56]
28 SBP, at end of treatment	20	15684	Mean Difference (IV, Random, 95% CI)	-8.02 [-10.07, -5.97]

28.1 ACE inhibitors (po)	4	123	Mean Difference (IV, Random, 95% CI)	-17.37 [-23.42, -11.31]
28.2 ACE inhibitors (s/l)	1	42	Mean Difference (IV, Random, 95% CI)	-1.5 [-12.20, 9.20]
28.3 ARA (po)	5	3785	Mean Difference (IV, Random, 95% CI)	-7.37 [-10.19, -4.56]
28.4 A2AA (po)	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
28.5 Beta-blockers (po)	1	44	Mean Difference (IV, Random, 95% CI)	-3.20 [-13.17, 6.77]
28.6 Beta-blockers (iv)	1	43	Mean Difference (IV, Random, 95% CI)	-13.00 [-25.21, -4.79]
28.7 Calcium channel blockers (po)	1	77	Mean Difference (IV, Random, 95% CI)	-7.80 [-17.12, 1.52]
28.8 Calcium channel blockers (iv)	1	11	Mean Difference (IV, Random, 95% CI)	-9.20 [-25.73, 7.33]
28.9 Nitric oxide donor	4	4101	Mean Difference (IV, Random, 95% CI)	-1.05 [-2.50, 0.39]
28.10 Thiazide-like diuretic (po)	1	37	Mean Difference (IV, Random, 95% CI)	3.0 [-11.74, 17.74]
28.11 Low BP target	5	7421	Mean Difference (IV, Random, 95% CI)	-10.06 [-13.58, -6.55]
29 DBP, first after randomisation by intervention	17	12397	Mean Difference (IV, Random, 95% CI)	-3.86 [-5.07, -2.64]
29.1 ACE inhibitors(po)	5	123	Mean Difference (IV, Random, 95% CI)	-4.23 [-9.68, 1.21]
29.2 ACE inhibitors (s/l)	1	42	Mean Difference (IV, Random, 95% CI)	2.20 [-5.50, 9.90]
29.3 ARA (po)	3	3408	Mean Difference (IV, Random, 95% CI)	-2.48 [-4.35, -0.61]
29.4 A2AA	1	4	Mean Difference (IV, Random, 95% CI)	-2.10 [-15.43, 11.23]
29.5 Beta-Blockers (po)	1	43	Mean Difference (IV, Random, 95% CI)	-5.40 [-13.01, 2.21]
29.6 Beta-Blockers (iv)	1	41	Mean Difference (IV, Random, 95% CI)	-17.5 [-25.32, -9.68]
29.7 Calcium channel blockers (po)	1	77	Mean Difference (IV, Random, 95% CI)	-3.30 [-9.28, 2.68]
29.8 Calcium channel blockers (iv)	1	11	Mean Difference (IV, Random, 95% CI)	-12.90 [-31.35, 5.55]
29.9 Nitric oxide donor	6	4173	Mean Difference (IV, Random, 95% CI)	-3.39 [-4.25, -2.52]
29.10 Low BP target	2	4475	Mean Difference (IV, Random, 95% CI)	-6.43 [-12.10, -0.75]
30 DBP, first after randomisation by stroke type	16	14952	Mean Difference (IV, Random, 95% CI)	-3.73 [-4.69, -2.76]
30.1 Ischaemic stroke	6	7500	Mean Difference (IV, Random, 95% CI)	-3.53 [-4.20, -2.87]
30.2 Combined ischaemic stroke and Intracerebral haemorrhage	10	6419	Mean Difference (IV, Random, 95% CI)	-2.85 [-4.26, -1.44]
30.3 Intracerebral haemorrhage	2	1033	Mean Difference (IV, Random, 95% CI)	-6.80 [-11.99, -1.60]
31 DBP, first after randomisation by time to treatment	16	10977	Mean Difference (IV, Random, 95% CI)	-3.80 [-5.06, -2.54]
31.1 Ultra-acute/prehospital	2	55	Mean Difference (IV, Random, 95% CI)	1.39 [-7.71, 10.48]
31.2 Hyper-acute	2	677	Mean Difference (IV, Random, 95% CI)	-6.48 [-12.55, -0.41]
31.3 Acute	6	10076	Mean Difference (IV, Random, 95% CI)	-3.11 [-4.26, -1.97]
31.4 Subacute	7	169	Mean Difference (IV, Random, 95% CI)	-3.88 [-7.98, 0.22]
32 DBP, at day 1	16	11361	Mean Difference (IV, Random, 95% CI)	-3.05 [-4.20, -1.91]
32.1 ACE inhibitors (po)	4	96	Mean Difference (IV, Random, 95% CI)	-3.24 [-8.95, 2.47]
32.2 ACE inhibitors (s/l)	1	42	Mean Difference (IV, Random, 95% CI)	-2.0 [-9.70, 5.70]
32.3 ARA (po)	2	2368	Mean Difference (IV, Random, 95% CI)	1.00 [-3.47, 1.48]
32.4 A2AA (po)	1	4	Mean Difference (IV, Random, 95% CI)	0.17 [-26.77, 27.11]
32.5 Beta-blockers (po)	1	43	Mean Difference (IV, Random, 95% CI)	-1.0 [-8.99, 6.99]

32.6 Beta-blockers (iv)	1	41	Mean Difference (IV, Random, 95% CI)	-5.0 [-13.21, 3.21]
32.7 Calcium channel blockers (po)	2	84	Mean Difference (IV, Random, 95% CI)	-6.10 [-14.08, 1.89]
32.8 Calcium channel blockers (iv)	1	11	Mean Difference (IV, Random, 95% CI)	-12.90 [-31.35, 5.55]
32.9 Nitric oxide donor	7	4197	Mean Difference (IV, Random, 95% CI)	-3.31 [-4.17, -2.44]
32.10 Low BP target	2	4475	Mean Difference (IV, Random, 95% CI)	-5.34 [-9.02, -1.65]
33 DBP, at day 7	10	12686	Mean Difference (IV, Random, 95% CI)	-2.90 [-3.96, -1.83]
33.1 ACE inhibitors	1	11	Mean Difference (IV, Random, 95% CI)	-18.0 [-33.10, -2.90]
33.2 ARA(po)	5	4152	Mean Difference (IV, Random, 95% CI)	-2.47 [-3.24, -1.70]
33.3 Nitric oxide donor	1	4011	Mean Difference (IV, Random, 95% CI)	-1.10 [-2.00, -0.20]
33.4 Thiazide-like diuretic (po)	1	37	Mean Difference (IV, Random, 95% CI)	-5.0 [-16.00, 6.00]
33.5 Low BP target	2	4475	Mean Difference (IV, Random, 95% CI)	-4.49 [-6.18, -2.80]
34 DBP, at end of treatment	15	13050	Mean Difference (IV, Random, 95% CI)	-3.95 [-5.15, -2.75]
34.1 ACE inhibitors (po)	4	123	Mean Difference (IV, Random, 95% CI)	-6.06 [-11.18, -0.95]
34.2 ARA (po)	6	4190	Mean Difference (IV, Random, 95% CI)	-3.61 [-5.61, -1.61]
34.3 ACE inhibitors (s/l)	1	42	Mean Difference (IV, Random, 95% CI)	0.0 [-7.70, 7.70]
34.4 Beta-blockers (po)	1	43	Mean Difference (IV, Random, 95% CI)	0.90 [-7.48, 9.28]
34.5 Beta-Blockers (iv)	1	41	Mean Difference (IV, Random, 95% CI)	-16.40 [-24.22, -8.58]
34.6 Calcium channel blockers (po)	1	77	Mean Difference (IV, Random, 95% CI)	-9.40 [-15.50, -3.30]
34.7 Calcium channel blockers (iv)	1	11	Mean Difference (IV, Random, 95% CI)	-2.90 [-21.35, 15.55]
34.8 Nitric oxide donor	1	4011	Mean Difference (IV, Random, 95% CI)	-1.10 [-2.00, -0.20]
34.9 Thiazide-like diuretic (po)	1	37	Mean Difference (IV, Random, 95% CI)	-4.0 [-13.03, 5.03]
34.10 Low BP target	2	4475	Mean Difference (IV, Random, 95% CI)	-4.24 [-5.62, -2.86]
35 HR at baseline	15	5841	Mean Difference (IV, Random, 95% CI)	0.07 [-0.86, 0.99]
35.1 ACE inhibitors (po)	3	61	Mean Difference (IV, Random, 95% CI)	0.22 [-5.31, 5.75]
35.2 ARA(po)	2	1379	Mean Difference (IV, Random, 95% CI)	-0.34 [-1.57, 0.90]
35.3 A2AA (po)	1	2	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
35.4 Calcium channel blockers (po)	2	79	Mean Difference (IV, Random, 95% CI)	-3.60 [-9.47, 2.27]
35.5 Nitric oxide donor	7	4197	Mean Difference (IV, Random, 95% CI)	2.26 [-1.26, 5.77]
35.6 Thiazide-like diuretic (po)	1	37	Mean Difference (IV, Random, 95% CI)	-4.0 [-10.50, 2.50]
35.7 Calcium channel blockers (iv)	1	11	Mean Difference (IV, Random, 95% CI)	5.30 [-4.21, 14.81]
35.8 Low BP target	1	75	Mean Difference (IV, Random, 95% CI)	-3.0 [-10.53, 4.53]
36 HR, first after randomisation	6	4196	Mean Difference (IV, Random, 95% CI)	2.74 [-1.13, 6.61]
36.1 ACE inhibitors (po)	2	39	Mean Difference (IV, Random, 95% CI)	-0.58 [-9.89, 8.72]
36.2 ARA(po)	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
36.3 Calcium channel blockers (po)	2	82	Mean Difference (IV, Random, 95% CI)	1.28 [-21.89, 24.46]
36.4 A2AA (po)	1	3	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
36.5 Nitric oxide donor	3	4061	Mean Difference (IV, Random, 95% CI)	3.95 [-1.03, 8.93]
36.6 Calcium channel blockers (iv)	1	11	Mean Difference (IV, Random, 95% CI)	10.0 [0.71, 19.29]
37 HR, at day 1	10	4333	Mean Difference (IV, Random, 95% CI)	2.35 [-1.06, 5.76]

37.1 ACE inhibitors (po)	2	39	Mean Difference (IV, Random, 95% CI)	0.03 [-40.45, 40.51]
37.2 Calcium channel blockers (po)	2	83	Mean Difference (IV, Random, 95% CI)	-2.56 [-7.71, 2.59]
37.3 A2AA (po)	1	3	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
37.4 Nitric oxide donor	7	4197	Mean Difference (IV, Random, 95% CI)	4.53 [1.46, 7.60]
37.5 Calcium channel blockers (iv)	1	11	Mean Difference (IV, Random, 95% CI)	-16.90 [-27.35, -6.45]
38 HR, at day 7	4	5449	Mean Difference (IV, Random, 95% CI)	0.47 [-0.24, 1.19]
38.1 Thiazide-like diuretic (po)	1	37	Mean Difference (IV, Random, 95% CI)	0.0 [-6.14, 6.14]
38.2 ARA(po)	1	1360	Mean Difference (IV, Random, 95% CI)	0.10 [-1.07, 1.27]
38.3 Nitric oxide donor	2	4052	Mean Difference (IV, Random, 95% CI)	0.72 [-0.20, 1.63]
39 HR, at end of treatment	4	4124	Mean Difference (IV, Random, 95% CI)	0.70 [-0.21, 1.61]
39.1 ACE inhibitors	1	35	Mean Difference (IV, Random, 95% CI)	2.40 [-62.22, 67.02]
39.2 Thiazide- like diuretic	1	37	Mean Difference (IV, Random, 95% CI)	0.0 [-6.14, 6.14]
39.3 Nitric oxide donor	2	4052	Mean Difference (IV, Random, 95% CI)	0.72 [-0.20, 1.63]

Comparison 2. Blood pressure altering by continue or stop prestroke antihypertensives (C/S)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or dependency, end of trial by C/S	2	2860	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.91, 1.24]
2 Death or dependency, end of trial by stroke type C/S	2	2841	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.91, 1.24]
2.1 Ischaemic stroke	1	1832	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.87, 1.28]
2.2 Combined ischaemic stroke and intracerebral haemorrhage	1	763	Odds Ratio (M-H, Random, 95% CI)	1.10 [0.82, 1.48]
2.3 Intracerebral haemorrhage	1	246	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.55, 1.65]
3 Death or dependency, end of trial by time to treatment	2	2860	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.91, 1.24]
3.1 Ultra-acute	1	143	Odds Ratio (M-H, Random, 95% CI)	1.34 [0.69, 2.61]
3.2 Acute	2	2717	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.89, 1.23]
4 Death early, by C/S	2	2860	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.55, 2.00]
5 Death early, by stroke type C/S	2	2841	Odds Ratio (M-H, Random, 95% CI)	1.03 [0.56, 1.87]
5.1 Ischaemic stroke	1	1832	Odds Ratio (M-H, Random, 95% CI)	1.37 [0.79, 2.36]
5.2 Combined ischaemic stroke and intracerebral haemorrhage	1	763	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.17, 1.98]
5.3 Intracerebral haemorrhage	1	246	Odds Ratio (M-H, Random, 95% CI)	0.53 [0.09, 2.92]
6 Death early, by time to treatment C/S	2	2860	Odds Ratio (M-H, Random, 95% CI)	1.08 [0.60, 1.93]
6.1 Ultra-acute	1	143	Odds Ratio (M-H, Random, 95% CI)	5.68 [0.27, 120.37]
6.2 Acute	2	2717	Odds Ratio (M-H, Random, 95% CI)	1.03 [0.61, 1.76]
7 Death, end of trial by C/S	2	2860	Odds Ratio (M-H, Random, 95% CI)	1.15 [0.92, 1.43]
8 Death end of trial, by stroke type C/S	2	2839	Odds Ratio (M-H, Random, 95% CI)	1.18 [0.94, 1.47]

8.1 Ischaemic stroke	1	1832	Odds Ratio (M-H, Random, 95% CI)	1.24 [0.96, 1.61]
8.2 Combined ischaemic stroke and intracerebral haemorrhage	1	763	Odds Ratio (M-H, Random, 95% CI)	1.13 [0.67, 1.91]
8.3 Intracerebral haemorrhage	1	244	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.45, 1.71]
9 Death, end of trial by time to treatment C/S	2	2860	Odds Ratio (M-H, Random, 95% CI)	1.14 [0.92, 1.42]
9.1 Ultra-acute	1	143	Odds Ratio (M-H, Random, 95% CI)	1.87 [0.68, 5.15]
9.2 Acute	2	2717	Odds Ratio (M-H, Random, 95% CI)	1.12 [0.89, 1.40]
10 Barthel Index, end of trial, by C/S	2	2860	Mean Difference (IV, Random, 95% CI)	-3.18 [-5.80, -0.55]
11 Early neurological deterioration, by C/S	1	2097	Odds Ratio (M-H, Random, 95% CI)	1.27 [0.89, 1.82]
12 Quality of life (EuroQol) at end of trial, by C/S	2	2860	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.05, -0.01]
13 Length of stay, by C/S	1	2097	Mean Difference (IV, Random, 95% CI)	1.20 [-0.87, 3.27]
14 SBP, first after randomisation, by C/S	2	2860	Mean Difference (IV, Random, 95% CI)	-3.11 [-4.75, -1.46]
15 SBP, at day 1 by C/S	2	2860	Mean Difference (IV, Random, 95% CI)	-3.11 [-4.75, -1.46]
16 SBP, at end of treatment by C/S	2	2860	Mean Difference (IV, Random, 95% CI)	-11.30 [-15.20, -7.40]
17 DBP, at baseline by C/S	2	2860	Mean Difference (IV, Random, 95% CI)	-0.69 [-1.65, 0.27]
18 DBP at day 1, by C/S	2	2860	Mean Difference (IV, Random, 95% CI)	-1.16 [-2.24, -0.08]
19 DBP, at end of treatment by C/S	2	2860	Mean Difference (IV, Random, 95% CI)	-6.45 [-9.28, -3.61]
20 HR, at day 1	1	2097	Mean Difference (IV, Fixed, 95% CI)	0.60 [-0.70, 1.90]
21 HR, at end of treatment	1	2097	Mean Difference (IV, Fixed, 95% CI)	-3.20 [-4.51, -1.89]

Comparison 3. Blood pressure elevation therapy in acute stroke

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death early, by intervention	1	15	Odds Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.1 Phenylephrine (iv)	1	15	Odds Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Death early, by stroke type	1	15	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.1 Ischaemic stroke	1	15	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Death end of trial, by intervention	1	15	Odds Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.1 Phenylephrine (iv)	1	15	Odds Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 SBP, at baseline	1	15	Mean Difference (IV, Random, 95% CI)	-27.5 [-50.83, -4.17]
4.1 Phenylephrine (iv)	1	15	Mean Difference (IV, Random, 95% CI)	-27.5 [-50.83, -4.17]
5 SBP, first after randomisation	1	15	Mean Difference (IV, Random, 95% CI)	20.60 [-13.31, 54.51]
6 SBP, at day 1	1	15	Mean Difference (IV, Random, 95% CI)	20.60 [-13.31, 54.51]
7 DBP, at baseline	1	15	Mean Difference (IV, Random, 95% CI)	-8.30 [-19.13, 2.53]
8 DBP, first after randomisation	1	15	Mean Difference (IV, Random, 95% CI)	0.5 [-14.86, 15.86]
9 DBP, at day 1	1	15	Mean Difference (IV, Random, 95% CI)	0.5 [-14.86, 15.86]

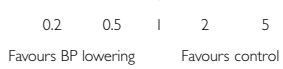
Analysis 1.1. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 1 Death or dependency, end of trial by intervention.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 1 Death or dependency, end of trial by intervention

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
1 ACE inhibitors					
CHHIPS 2009	35/57	17/29		0.5 %	1.12 [0.45, 2.79]
Eveson 2007	7/18	8/22		0.3 %	1.11 [0.31, 4.03]
Subtotal (95% CI)	**75**	**51**		**0.8 %**	**1.12 [0.53, 2.36]**
Total events: 42 (Treatment), 25 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.00, df = 1 (P = 0.99); I^2 =0.0%					
Test for overall effect: Z = 0.30 (P = 0.77)					
2 ARA(po)					
PRoFESS 2009	195/647	211/713		8.0 %	1.03 [0.81, 1.30]
SCAST 2011	348/1000	331/1004		12.6 %	1.09 [0.90, 1.31]
VENTURE 2013	46/187	42/186		1.9 %	1.12 [0.69, 1.80]
Subtotal (95% CI)	**1834**	**1903**		**22.4 %**	**1.07 [0.93, 1.23]**
Total events: 589 (Treatment), 584 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.18, df = 2 (P = 0.92); I^2 =0.0%					
Test for overall effect: Z = 0.91 (P = 0.36)					
3 Beta-blockers					
CHHIPS 2009	34/56	18/30		0.5 %	1.03 [0.42, 2.55]
Subtotal (95% CI)	**56**	**30**		**0.5 %**	**1.03 [0.42, 2.55]**
Total events: 34 (Treatment), 18 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.06 (P = 0.95)					
4 Nitric oxide donor					
Bath 2000	8/16	6/18		0.2 %	2.00 [0.50, 8.00]
ENOS 2014	1205/2000	1227/2011		26.9 %	0.97 [0.85, 1.10]
Rashid 2003 10 mg	13/20	6/10		0.2 %	1.24 [0.26, 5.91]
Rashid 2003 5 mg	12/20	6/10		0.2 %	1.00 [0.21, 4.71]
Rashid 2003 5/10 mg	12/20	6/10		0.2 %	1.00 [0.21, 4.71]
RIGHT 2013	13/25	12/16		0.2 %	0.36 [0.09, 1.43]



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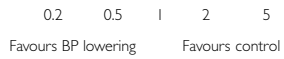
Study or subgroup	Treatment n/N	Control n/N	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
Willmot 2006	5/12	2/6		0.1 %	1.43 [0.18, 11.09]
Subtotal (95% CI)	**2113**	**2081**		**28.0 %**	**0.97 [0.86, 1.10]**
Total events: 1268 (Treatment), 1265 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.26, df = 6 (P = 0.78); I^2 =0.0%					
Test for overall effect: Z = 0.49 (P = 0.63)					
5 Low BP target					
CATIS 2013	683/2038	681/2033		25.4 %	1.00 [0.88, 1.14]
INTERACT pilot 2008	95/203	95/201		2.8 %	0.98 [0.66, 1.45]
INTERACT-2 2013	719/1399	785/1430		19.7 %	0.87 [0.75, 1.01]
Koch 2008	13/21	11/21		0.3 %	1.48 [0.43, 5.05]
Subtotal (95% CI)	**3661**	**3685**		**48.3 %**	**0.95 [0.86, 1.04]**
Total events: 1510 (Treatment), 1572 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.53, df = 3 (P = 0.47); I^2 =0.0%					
Test for overall effect: Z = 1.16 (P = 0.25)					
Total (95% CI)	**7739**	**7750**		**100.0 %**	**0.98 [0.92, 1.05]**
Total events: 3443 (Treatment), 3464 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 8.12, df = 16 (P = 0.95); I^2 =0.0%					
Test for overall effect: Z = 0.60 (P = 0.55)					
Test for subgroup differences: Chi^2 = 2.15, df = 4 (P = 0.71), I^2 =0.0%					

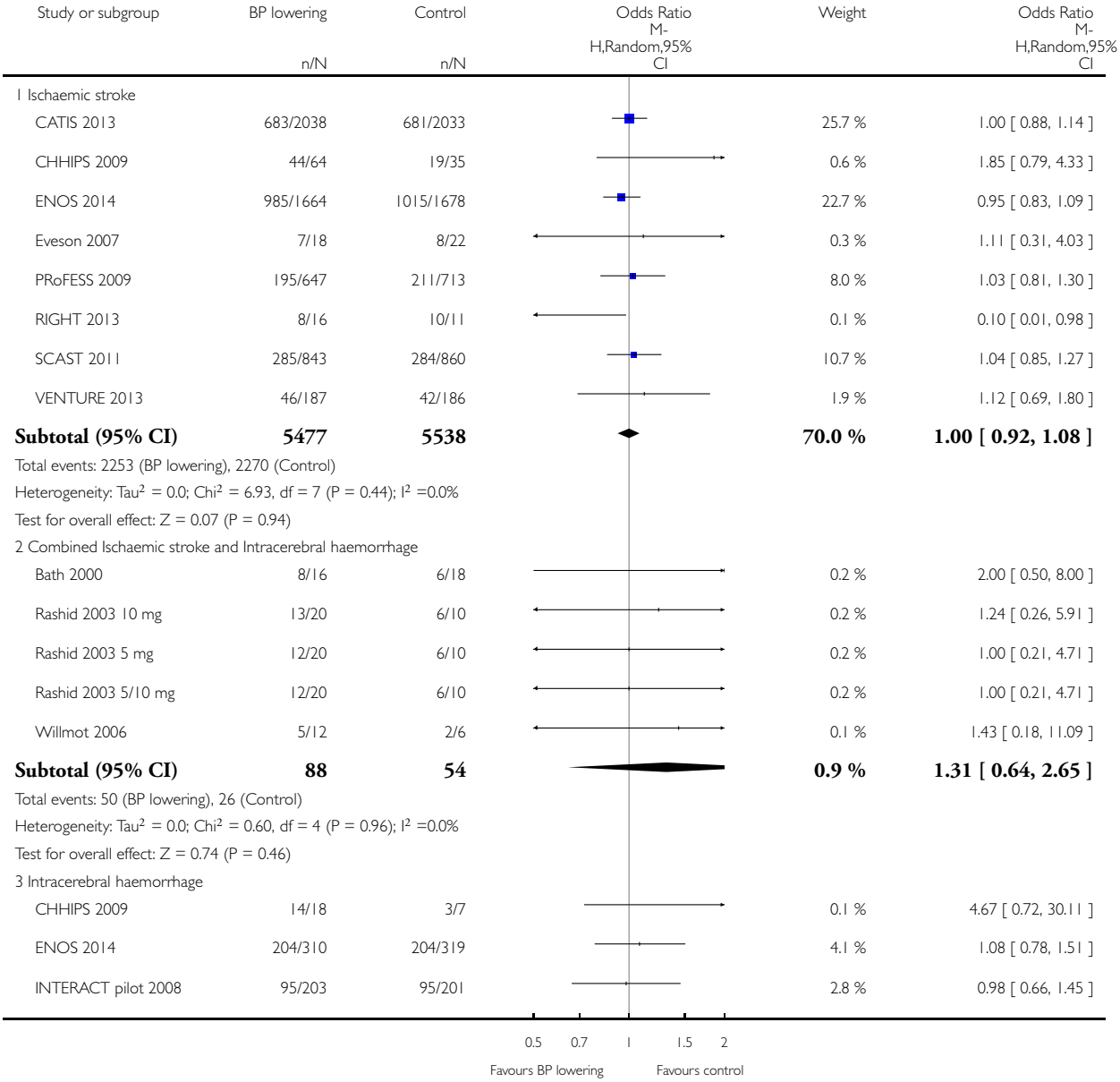


Analysis 1.2. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 2 Death or dependency, end of trial by stroke type.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 2 Death or dependency, end of trial by stroke type



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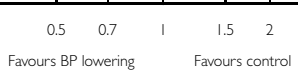
Study or subgroup	BP lowering n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
INTERACT-2 2013	719/1399	785/1430		19.9 %	0.87 [0.75, 1.01]
Koch 2008	13/21	11/21		0.3 %	1.48 [0.43, 5.05]
RIGHT 2013	3/5	1/1		0.0 %	0.47 [0.01, 16.89]
SCAST 2011	63/144	47/130		1.8 %	1.37 [0.84, 2.23]
Subtotal (95% CI)	**2100**	**2109**		**29.1 %**	**1.01 [0.84, 1.21]**
Total events: 1111 (BP lowering), 1146 (Control)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 7.71, df = 6 (P = 0.26); I^2 =22%					
Test for overall effect: Z = 0.08 (P = 0.93)					
Total (95% CI)	**7665**	**7701**		**100.0 %**	**0.98 [0.92, 1.05]**
Total events: 3414 (BP lowering), 3442 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 16.40, df = 19 (P = 0.63); I^2 =0.0%					
Test for overall effect: Z = 0.48 (P = 0.63)					
Test for subgroup differences: Chi^2 = 0.56, df = 2 (P = 0.76), I^2 =0.0%					

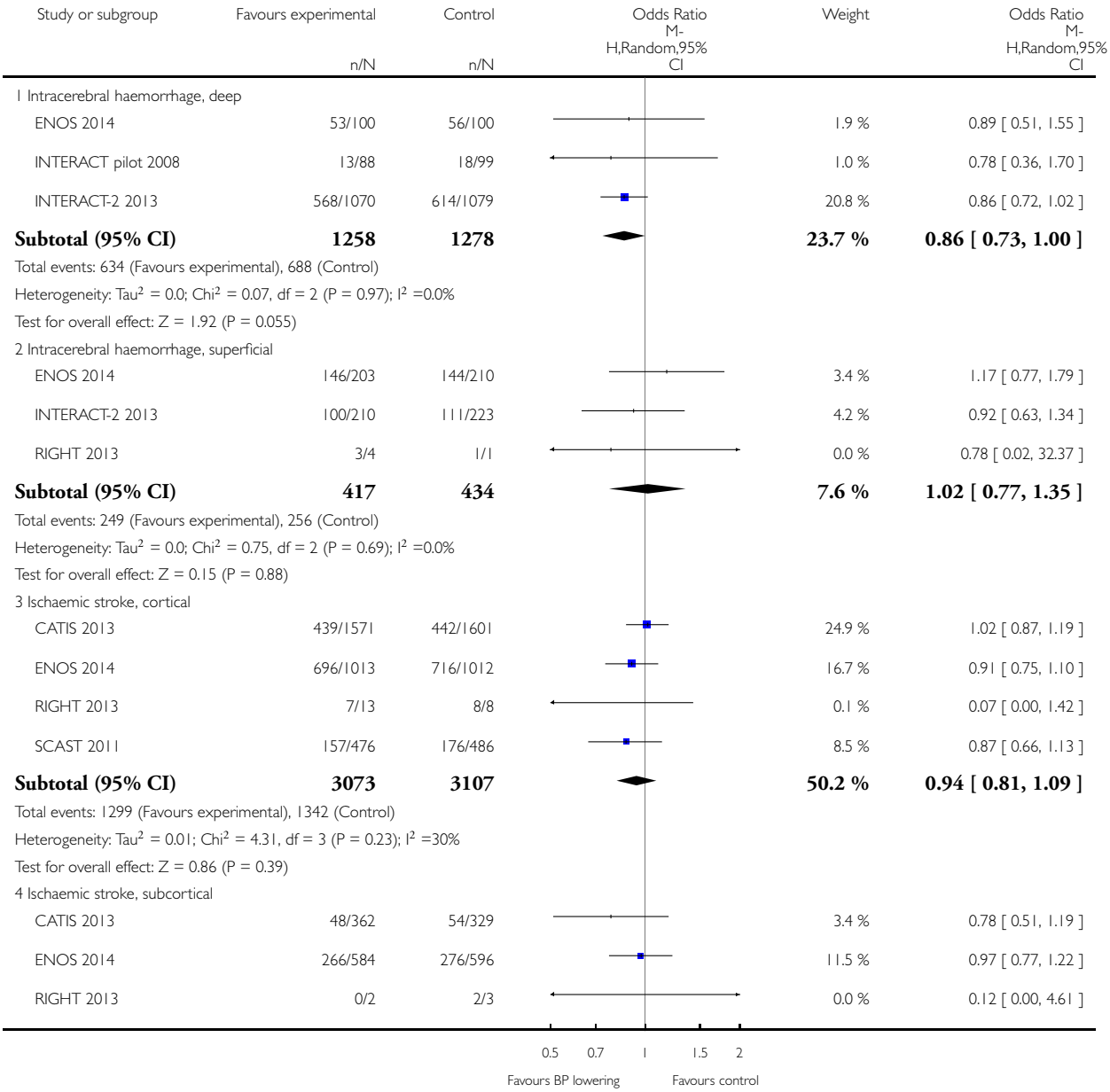


Analysis 1.3. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 3 Death or dependency, end of trial by stroke location.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 3 Death or dependency, end of trial by stroke location



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Study or subgroup	Favours experimental n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
SCAST 2011	64/242	57/265		3.6 %	1.31 [0.87, 1.98]
Subtotal (95% CI)	**1190**	**1193**		**18.5 %**	**0.98 [0.76, 1.27]**
Total events: 378 (Favours experimental), 389 (Control)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 4.38$, df = 3 (P = 0.22); $I^2 = 32\%$					
Test for overall effect: Z = 0.13 (P = 0.90)					
Total (95% CI)	**5938**	**6012**		**100.0 %**	**0.94 [0.87, 1.01]**
Total events: 2560 (Favours experimental), 2675 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 11.45$, df = 13 (P = 0.57); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.63 (P = 0.10)					
Test for subgroup differences: $Chi^2 = 1.65$, df = 3 (P = 0.65), $I^2 = 0.0\%$					

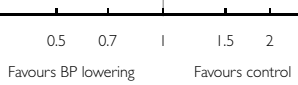
Analysis 1.4. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 4 Death or dependency, end of trial by time to treatment.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 4 Death or dependency, end of trial by time to treatment

Study or subgroup	BP lowering n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Ultra-acute/pre-hospital					
RIGHT 2013	13/25	12/16		0.2 %	0.36 [0.09, 1.43]
Subtotal (95% CI)	**25**	**16**		**0.2 %**	**0.36 [0.09, 1.43]**
Total events: 13 (BP lowering), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.45 (P = 0.15)					
2 Hyper-acute					
INTERACT pilot 2008	95/203	95/201		2.8 %	0.98 [0.66, 1.45]
INTERACT-2 2013	719/1399	785/1430		19.7 %	0.87 [0.75, 1.01]
ENOS 2014	74/144	78/129		1.9 %	0.69 [0.43, 1.12]
Subtotal (95% CI)	**1746**	**1760**		**24.4 %**	**0.87 [0.76, 0.99]**
Total events: 888 (BP lowering), 958 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.24, df = 2 (P = 0.54); I^2 =0.0%					
Test for overall effect: Z = 2.12 (P = 0.034)					
3 Acute					
CHHIPS 2009	69/113	35/59		1.0 %	1.08 [0.57, 2.04]
CATIS 2013	683/2038	681/2033		25.5 %	1.00 [0.88, 1.14]
SCAST 2011	348/1000	331/1004		12.6 %	1.09 [0.90, 1.31]
Eveson 2007	7/18	8/22		0.3 %	1.11 [0.31, 4.03]
VENTURE 2013	46/187	42/186		1.9 %	1.12 [0.69, 1.80]
Koch 2008	13/21	11/21		0.3 %	1.48 [0.43, 5.05]
ENOS 2014	1131/1856	1149/1882		25.0 %	1.00 [0.87, 1.14]
Subtotal (95% CI)	**5233**	**5207**		**66.5 %**	**1.02 [0.94, 1.11]**
Total events: 2297 (BP lowering), 2257 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.18, df = 6 (P = 0.98); I^2 =0.0%					
Test for overall effect: Z = 0.50 (P = 0.62)					
4 Subacute					
Bath 2000	8/16	6/18		0.2 %	2.00 [0.50, 8.00]
Rashid 2003 10 mg	13/20	6/10		0.2 %	1.24 [0.26, 5.91]



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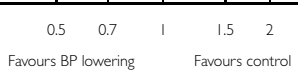
Study or subgroup	BP lowering n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Rashid 2003 5/10 mg	12/20	6/10		0.2 %	1.00 [0.21, 4.71]
Rashid 2003 5 mg	12/20	6/10		0.2 %	1.00 [0.21, 4.71]
Willmot 2006	5/12	2/6		0.1 %	1.43 [0.18, 11.09]
PRoFESS 2009	195/647	211/713		8.0 %	1.03 [0.81, 1.30]
Subtotal (95% CI)	**735**	**767**		**8.8 %**	**1.05 [0.84, 1.31]**
Total events: 245 (BP lowering), 237 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.00$, df = 5 (P = 0.96); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.44 (P = 0.66)					
Total (95% CI)	**7739**	**7750**		**100.0 %**	**0.98 [0.92, 1.05]**
Total events: 3443 (BP lowering), 3464 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 10.14$, df = 16 (P = 0.86); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.58 (P = 0.56)					
Test for subgroup differences: $Chi^2 = 6.71$, df = 3 (P = 0.08), $I^2 = 55\%$					

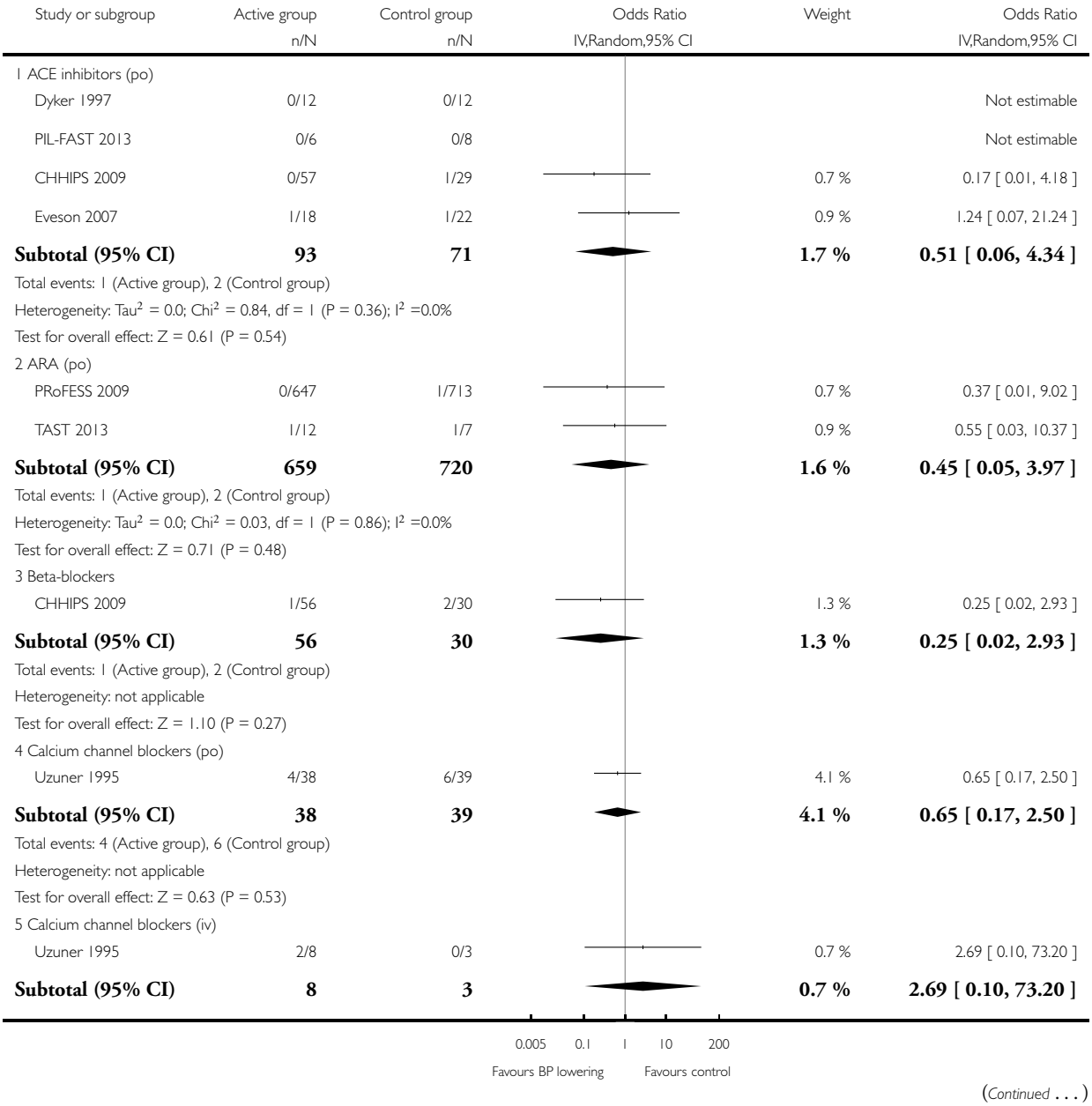


Analysis 1.5. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 5 Death, early by intervention.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 5 Death, early by intervention



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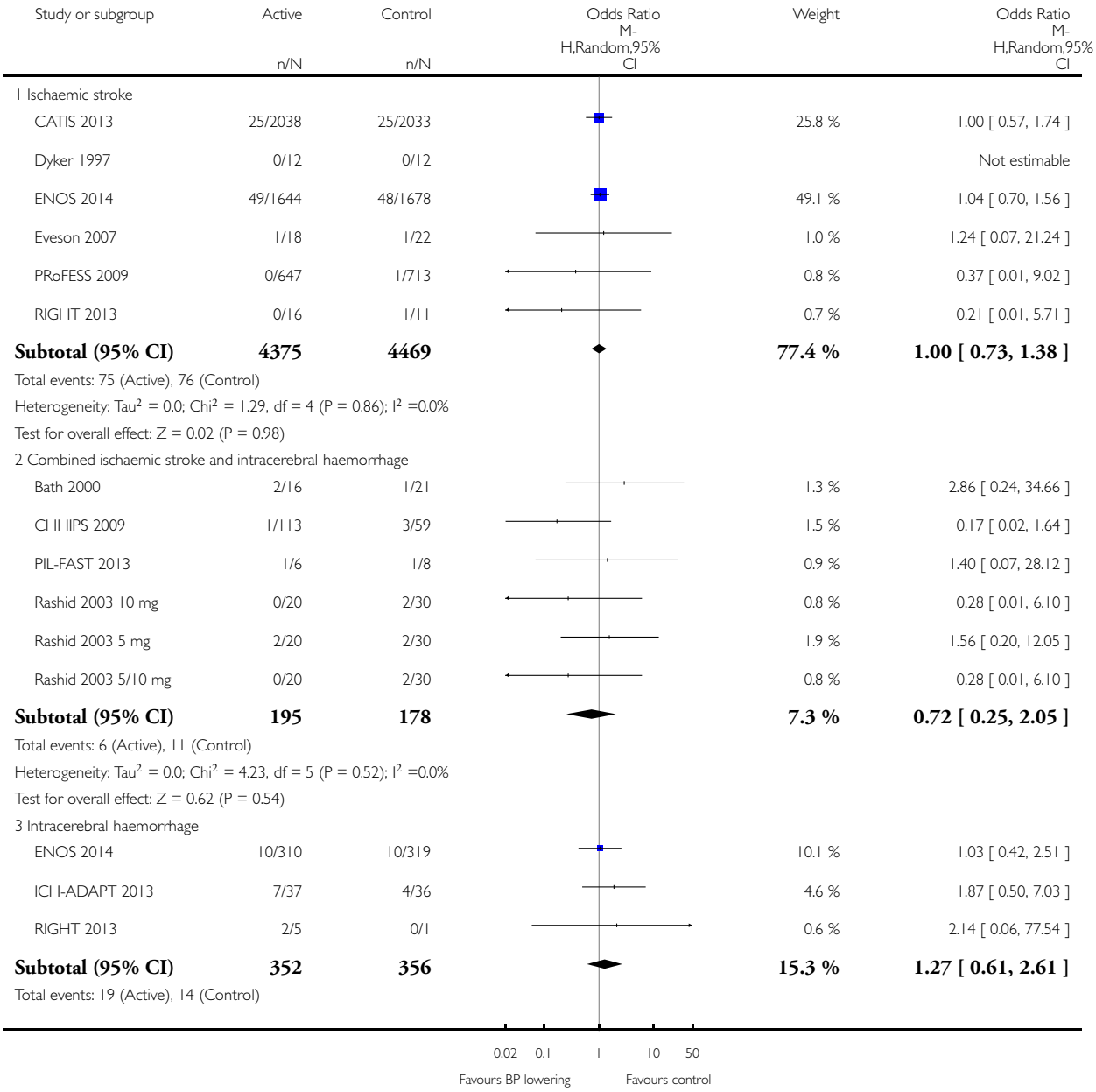
Study or subgroup	Active group n/N	Control group n/N	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
Total events: 2 (Active group), 0 (Control group)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.59 (P = 0.56)					
6 Nitric oxide donor					
Willmot 2006	0/12	0/6			Not estimable
Rashid 2003 5/10 mg	0/20	2/10		0.8 %	0.08 [0.00, 1.92]
Rashid 2003 10 mg	0/20	2/10		0.8 %	0.08 [0.00, 1.92]
Rashid 2003 5 mg	2/20	2/10		1.7 %	0.44 [0.05, 3.74]
ENOS 2014	61/2000	58/2011		56.6 %	1.06 [0.74, 1.53]
RIGHT 2013	2/21	1/12		1.2 %	1.16 [0.09, 14.29]
Bath 2000	2/16	1/21		1.2 %	2.86 [0.24, 34.66]
Subtotal (95% CI)	**2109**	**2080**		**62.2 %**	**0.79 [0.37, 1.72]**
Total events: 67 (Active group), 66 (Control group)					
Heterogeneity: Tau^2 = 0.22; Chi^2 = 6.17, df = 5 (P = 0.29); I^2 =19%					
Test for overall effect: Z = 0.59 (P = 0.56)					
7 Low BP target					
CATIS 2013	25/2038	25/2033		24.2 %	1.00 [0.57, 1.74]
ICH-ADAPT 2013	7/37	4/36		4.3 %	1.87 [0.50, 7.03]
Subtotal (95% CI)	**2075**	**2069**		**28.5 %**	**1.10 [0.66, 1.83]**
Total events: 32 (Active group), 29 (Control group)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.73, df = 1 (P = 0.39); I^2 =0.0%					
Test for overall effect: Z = 0.35 (P = 0.73)					
Total (95% CI)	**5038**	**5012**		**100.0 %**	**0.97 [0.74, 1.28]**
Total events: 108 (Active group), 107 (Control group)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 10.68, df = 14 (P = 0.71); I^2 =0.0%					
Test for overall effect: Z = 0.22 (P = 0.83)					
Test for subgroup differences: Chi^2 = 2.99, df = 6 (P = 0.81), I^2 =0.0%					

Analysis 1.6. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 6 Death, early by stroke type.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 6 Death, early by stroke type



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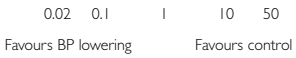
Study or subgroup	Active n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.62, df = 2 (P = 0.73); I^2 =0.0%					
Test for overall effect: Z = 0.64 (P = 0.52)					
Total (95% CI)	**4922**	**5003**		**100.0 %**	**1.02 [0.76, 1.35]**
Total events: 100 (Active), 101 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 6.91, df = 13 (P = 0.91); I^2 =0.0%					
Test for overall effect: Z = 0.10 (P = 0.92)					
Test for subgroup differences: Chi^2 = 0.78, df = 2 (P = 0.68), I^2 =0.0%					



Analysis 1.7. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 7 Death, early by time to treatment.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 7 Death, early by time to treatment

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Ultra-acute/prehospital					
PIL-FAST 2013	0/6	0/8			Not estimable
RIGHT 2013	2/21	1/12		1.2 %	1.16 [0.09, 14.29]
Subtotal (95% CI)	**27**	**20**		**1.2 %**	**1.16 [0.09, 14.29]**
Total events: 2 (Experimental), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.11 (P = 0.91)					
2 Hyper-acute					
ENOS 2014	12/144	7/126		8.0 %	1.55 [0.59, 4.05]
Subtotal (95% CI)	**144**	**126**		**8.0 %**	**1.55 [0.59, 4.05]**
Total events: 12 (Experimental), 7 (Control)					
Heterogeneity: not applicable					

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Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Test for overall effect: Z = 0.88 (P = 0.38)					
3 Acute					
CATIS 2013	25/2038	25/2033		23.8 %	1.00 [0.57, 1.74]
CHHIPS 2009	1/113	3/59		1.4 %	0.17 [0.02, 1.64]
ENOS 2014	56/1856	52/1882		50.5 %	1.09 [0.75, 1.61]
Eveson 2007	1/18	1/22		0.9 %	1.24 [0.07, 21.24]
ICH-ADAPT 2013	7/37	4/36		4.2 %	1.87 [0.50, 7.03]
Uzuner 1995	6/46	6/42		5.0 %	0.90 [0.27, 3.04]
Subtotal (95% CI)	**4108**	**4074**		**85.8 %**	**1.05 [0.78, 1.41]**
Total events: 96 (Experimental), 91 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.37, df = 5 (P = 0.64); I^2 =0.0%					
Test for overall effect: Z = 0.33 (P = 0.74)					
4 Subacute					
Bath 2000	2/16	1/21		1.2 %	2.86 [0.24, 34.66]
Dyker 1997	0/12	0/12			Not estimable
PRoFESS 2009	0/647	1/713		0.7 %	0.37 [0.01, 9.02]
Rashid 2003 10 mg	0/20	2/10		0.8 %	0.08 [0.00, 1.92]
Rashid 2003 5 mg	2/20	2/10		1.6 %	0.44 [0.05, 3.74]
Rashid 2003 5/10 mg	0/20	2/10		0.8 %	0.08 [0.00, 1.92]
Willmot 2006	0/12	0/6			Not estimable
Subtotal (95% CI)	**747**	**782**		**5.0 %**	**0.40 [0.11, 1.42]**
Total events: 4 (Experimental), 8 (Control)					
Heterogeneity: Tau^2 = 0.16; Chi^2 = 4.33, df = 4 (P = 0.36); I^2 =8%					
Test for overall effect: Z = 1.42 (P = 0.16)					
Total (95% CI)	**5026**	**5002**		**100.0 %**	**1.03 [0.79, 1.36]**
Total events: 114 (Experimental), 107 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 10.69, df = 12 (P = 0.56); I^2 =0.0%					
Test for overall effect: Z = 0.24 (P = 0.81)					
Test for subgroup differences: Chi^2 = 2.85, df = 3 (P = 0.42), I^2 =0.0%					

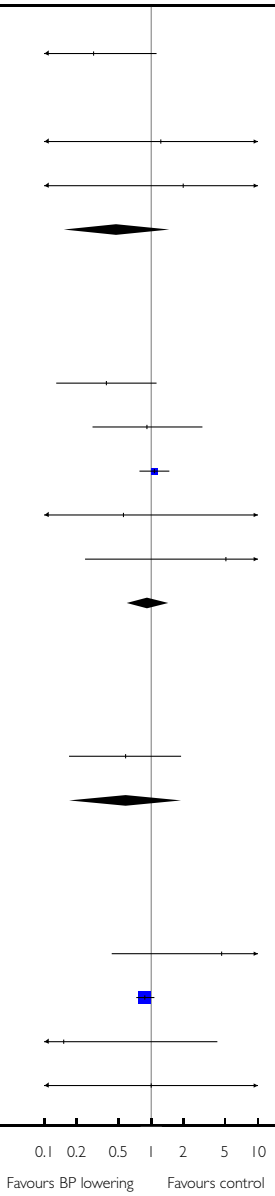
Analysis 1.8. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 8 Death, end of trial by intervention.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 8 Death, end of trial by intervention

Study or subgroup	Active group n/N	Control group n/N	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
1 ACE inhibitors (po)					
CHHIPS 2009	4/57	6/29		0.8 %	0.29 [0.07, 1.12]
Dyker 1997	0/14	0/14			Not estimable
Eveson 2007	1/18	1/22		0.2 %	1.24 [0.07, 21.24]
PIL-FAST 2013	1/4	1/7		0.1 %	2.00 [0.09, 44.35]
Subtotal (95% CI)	**93**	**72**		**1.1 %**	**0.47 [0.15, 1.48]**
Total events: 6 (Active group), 8 (Control group)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.77$, df = 2 (P = 0.41); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.28 (P = 0.20)					
2 ARA (po)					
ACCESS 2003	5/173	12/166		1.2 %	0.38 [0.13, 1.11]
PRoFESS 2009	5/647	6/713		1.0 %	0.92 [0.28, 3.02]
SCAST 2011	84/1017	78/1012		13.5 %	1.08 [0.78, 1.49]
TAST 2013	1/12	1/7		0.2 %	0.55 [0.03, 10.37]
VENTURE 2013	2/187	0/186		0.1 %	5.03 [0.24, 105.42]
Subtotal (95% CI)	**2036**	**2084**		**16.0 %**	**0.92 [0.59, 1.44]**
Total events: 97 (Active group), 97 (Control group)					
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 4.60$, df = 4 (P = 0.33); $I^2 = 13\%$					
Test for overall effect: Z = 0.37 (P = 0.71)					
3 Beta-blockers					
CHHIPS 2009	7/56	6/30		1.0 %	0.57 [0.17, 1.89]
Subtotal (95% CI)	**56**	**30**		**1.0 %**	**0.57 [0.17, 1.89]**
Total events: 7 (Active group), 6 (Control group)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.92 (P = 0.36)					
4 Nitric oxide donor					
Bath 2000	3/16	1/21		0.2 %	4.62 [0.43, 49.30]
ENOS 2014	233/2000	263/2011		39.2 %	0.88 [0.73, 1.06]
Rashid 2003 10 mg	0/20	1/10		0.1 %	0.15 [0.01, 4.15]
Rashid 2003 5 mg	2/20	1/10		0.2 %	1.00 [0.08, 12.56]



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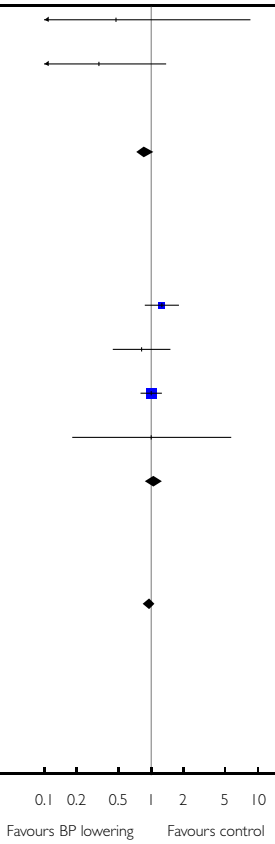
Study or subgroup	Active group n/N	Control group n/N	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
Rashid 2003 5/10 mg	1/20	1/10		0.2 %	0.47 [0.03, 8.46]
RIGHT 2013	4/25	6/16		0.6 %	0.32 [0.07, 1.38]
Willmot 2006	0/12	0/6			Not estimable
Subtotal (95% CI)	**2113**	**2084**		**40.6 %**	**0.86 [0.72, 1.04]**
Total events: 243 (Active group), 273 (Control group)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 4.95$, df = 5 (P = 0.42); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.54 (P = 0.12)					
5 Low BP target					
CATIS 2013	68/1988	54/1987		10.6 %	1.27 [0.88, 1.82]
INTERACT pilot 2008	21/203	25/201		3.7 %	0.81 [0.44, 1.50]
INTERACT-2 2013	166/1399	170/1430		26.8 %	1.00 [0.79, 1.25]
Koch 2008	3/21	3/21		0.5 %	1.00 [0.18, 5.63]
Subtotal (95% CI)	**3611**	**3639**		**41.4 %**	**1.04 [0.87, 1.25]**
Total events: 258 (Active group), 252 (Control group)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.89$, df = 3 (P = 0.60); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.44 (P = 0.66)					
Total (95% CI)	**7909**	**7909**		**100.0 %**	**0.95 [0.84, 1.06]**
Total events: 611 (Active group), 636 (Control group)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 17.39$, df = 18 (P = 0.50); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.94 (P = 0.35)					
Test for subgroup differences: $Chi^2 = 4.04$, df = 4 (P = 0.40), $I^2 = 1\%$					

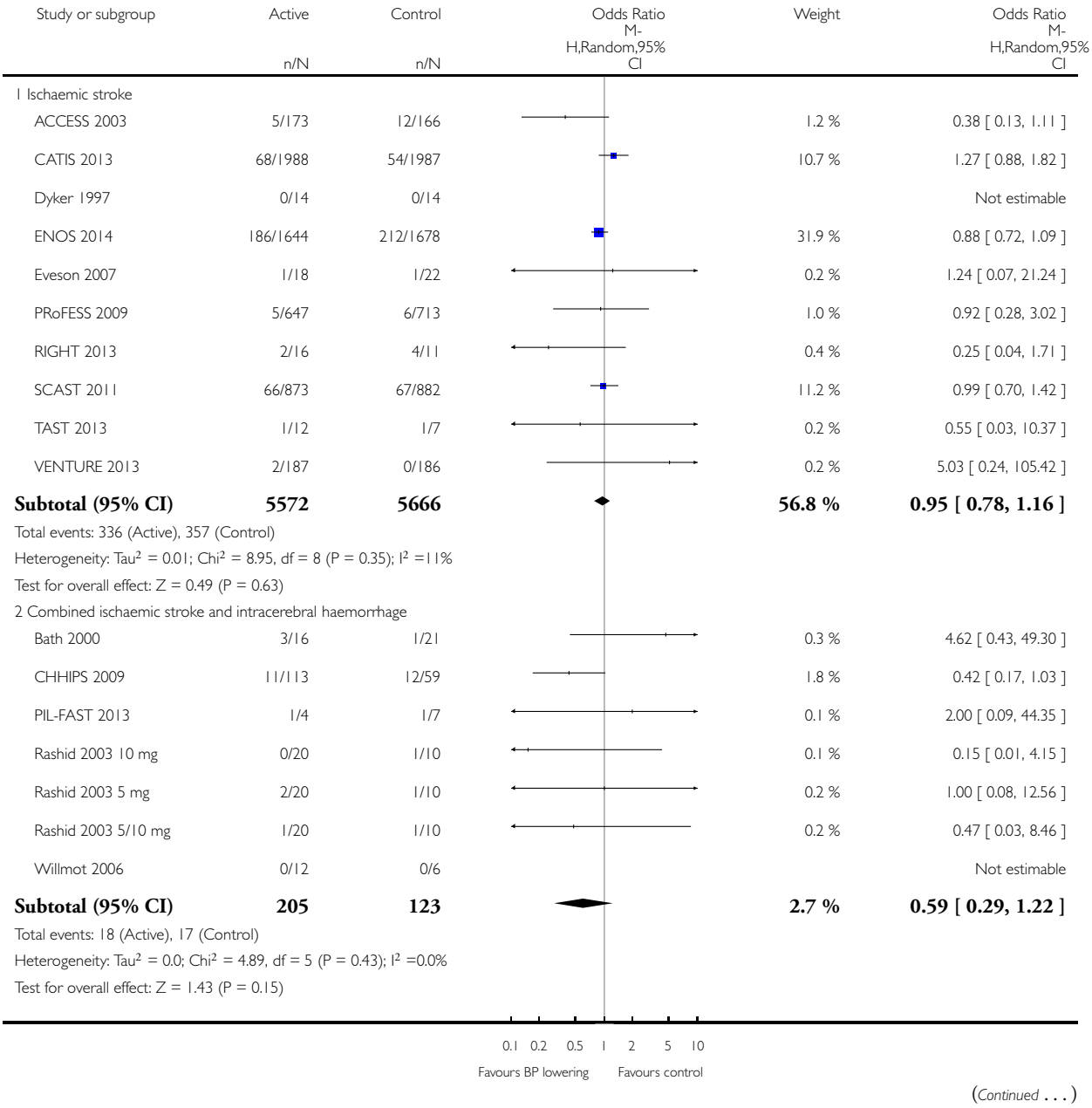


Analysis 1.9. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 9 Death, end of trial by stroke type.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 9 Death, end of trial by stroke type



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Study or subgroup	Active n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
3 Intracerebral haemorrhage					
ENOS 2014	42/310	47/319		7.0 %	0.91 [0.58, 1.42]
INTERACT pilot 2008	21/203	25/201		3.7 %	0.81 [0.44, 1.50]
INTERACT-2 2013	166/1399	170/1430		27.0 %	1.00 [0.79, 1.25]
Koch 2008	3/21	3/21		0.5 %	1.00 [0.18, 5.63]
RIGHT 2013	2/5	1/1		0.1 %	0.24 [0.01, 8.62]
SCAST 2011	18/144	11/130		2.2 %	1.55 [0.70, 3.41]
Subtotal (95% CI)	**2082**	**2102**		**40.5 %**	**0.98 [0.82, 1.18]**
Total events: 252 (Active), 257 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.37, df = 5 (P = 0.80); I^2 =0.0%					
Test for overall effect: Z = 0.18 (P = 0.86)					
Total (95% CI)	**7859**	**7891**		**100.0 %**	**0.95 [0.84, 1.07]**
Total events: 606 (Active), 631 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 17.98, df = 20 (P = 0.59); I^2 =0.0%					
Test for overall effect: Z = 0.87 (P = 0.39)					
Test for subgroup differences: Chi^2 = 1.79, df = 2 (P = 0.41), I^2 =0.0%					

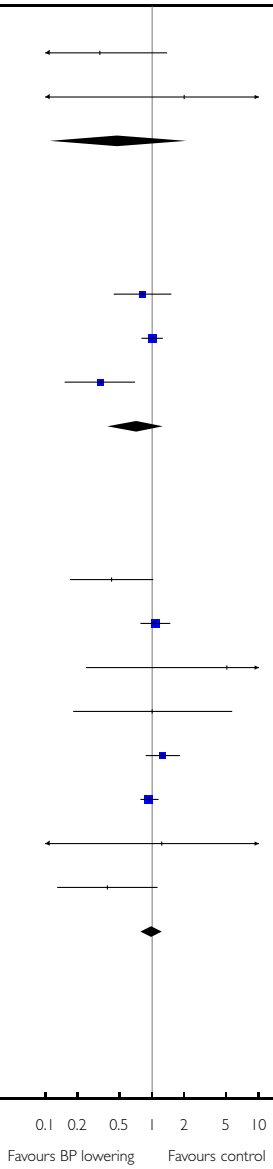
Analysis 1.10. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 10 Death, end of trial by time to treatment.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 10 Death, end of trial by time to treatment

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Ultra-acute/pre-hospital					
RIGHT 2013	4/25	6/16		1.5 %	0.32 [0.07, 1.38]
PIL-FAST 2013	1/4	1/7		0.3 %	2.00 [0.09, 44.35]
Subtotal (95% CI)	**29**	**23**		**1.8 %**	**0.47 [0.11, 2.07]**
Total events: 5 (Experimental), 7 (Control)					
Heterogeneity: Tau² = 0.16; Chi² = 1.11, df = 1 (P = 0.29); I² =10%					
Test for overall effect: Z = 1.00 (P = 0.32)					
2 Hyper-acute					
INTERACT pilot 2008	21/203	25/201		6.9 %	0.81 [0.44, 1.50]
INTERACT-2 2013	166/1399	170/1430		20.9 %	1.00 [0.79, 1.25]
ENOS 2014	11/144	26/129		5.0 %	0.33 [0.15, 0.69]
Subtotal (95% CI)	**1746**	**1760**		**32.8 %**	**0.70 [0.38, 1.26]**
Total events: 198 (Experimental), 221 (Control)					
Heterogeneity: Tau² = 0.20; Chi² = 7.86, df = 2 (P = 0.02); I² =75%					
Test for overall effect: Z = 1.19 (P = 0.24)					
3 Acute					
CHHIPS 2009	11/113	12/59		3.7 %	0.42 [0.17, 1.03]
SCAST 2011	84/1017	78/1012		15.9 %	1.08 [0.78, 1.49]
VENTURE 2013	2/187	0/186		0.4 %	5.03 [0.24, 105.42]
Koch 2008	3/21	3/21		1.1 %	1.00 [0.18, 5.63]
CATIS 2013	68/1988	54/1987		14.0 %	1.27 [0.88, 1.82]
ENOS 2014	222/1856	237/1882		22.8 %	0.94 [0.78, 1.15]
Eveson 2007	1/18	1/22		0.4 %	1.24 [0.07, 21.24]
ACCESS 2003	5/173	12/166		2.7 %	0.38 [0.13, 1.11]
Subtotal (95% CI)	**5373**	**5335**		**61.0 %**	**0.97 [0.77, 1.22]**
Total events: 396 (Experimental), 397 (Control)					
Heterogeneity: Tau² = 0.03; Chi² = 10.01, df = 7 (P = 0.19); I² =30%					
Test for overall effect: Z = 0.27 (P = 0.79)					
4 Subacute					



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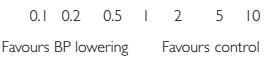
Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Willmot 2006	0/12	0/6			Not estimable
Bath 2000	3/16	1/21		0.6 %	4.62 [0.43, 49.30]
Dyker 1997	0/14	0/14			Not estimable
PRoFESS 2009	5/647	6/713		2.2 %	0.92 [0.28, 3.02]
TAST 2013	1/12	1/7		0.4 %	0.55 [0.03, 10.37]
Rashid 2003 10 mg	0/20	1/10		0.3 %	0.15 [0.01, 4.15]
Rashid 2003 5 mg	2/20	1/10		0.5 %	1.00 [0.08, 12.56]
Rashid 2003 5/10 mg	1/20	1/10		0.4 %	0.47 [0.03, 8.46]
Subtotal (95% CI)	**761**	**791**		**4.4 %**	**0.92 [0.39, 2.15]**
Total events: 12 (Experimental), 11 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.24$, df = 5 (P = 0.66); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.20 (P = 0.84)					
Total (95% CI)	**7909**	**7909**		**100.0 %**	**0.90 [0.75, 1.08]**
Total events: 611 (Experimental), 636 (Control)					
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 23.98$, df = 18 (P = 0.16); $I^2 = 25\%$					
Test for overall effect: Z = 1.17 (P = 0.24)					
Test for subgroup differences: $Chi^2 = 1.79$, df = 3 (P = 0.62), $I^2 = 0.0\%$					



Analysis 1.11. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 11 Barthel Index, end of trial, by intervention.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 11 Barthel Index, end of trial, by intervention

Study or subgroup	Active N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 ARA							
ACCESS 2003	173	87 (22.9)	166	88.9 (19.9)		38.3 %	-1.90 [-6.46, 2.66]
Subtotal (95% CI)	**173**		**166**			**38.3 %**	**-1.90 [-6.46, 2.66]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.82 (P = 0.41)							
2 Nitric oxide donor							
ENOS 2014	2000	65.5 (38.1)	2011	63.3 (39.4)		61.7 %	2.20 [-0.20, 4.60]
Subtotal (95% CI)	**2000**		**2011**			**61.7 %**	**2.20 [-0.20, 4.60]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.80 (P = 0.072)							
Total (95% CI)	**2173**		**2177**			**100.0 %**	**0.63 [-3.28, 4.54]**
Heterogeneity: Tau^2 = 4.95; Chi^2 = 2.43, df = 1 (P = 0.12); I^2 =59%							
Test for overall effect: Z = 0.31 (P = 0.75)							
Test for subgroup differences: Chi^2 = 2.43, df = 1 (P = 0.12), I^2 =59%							

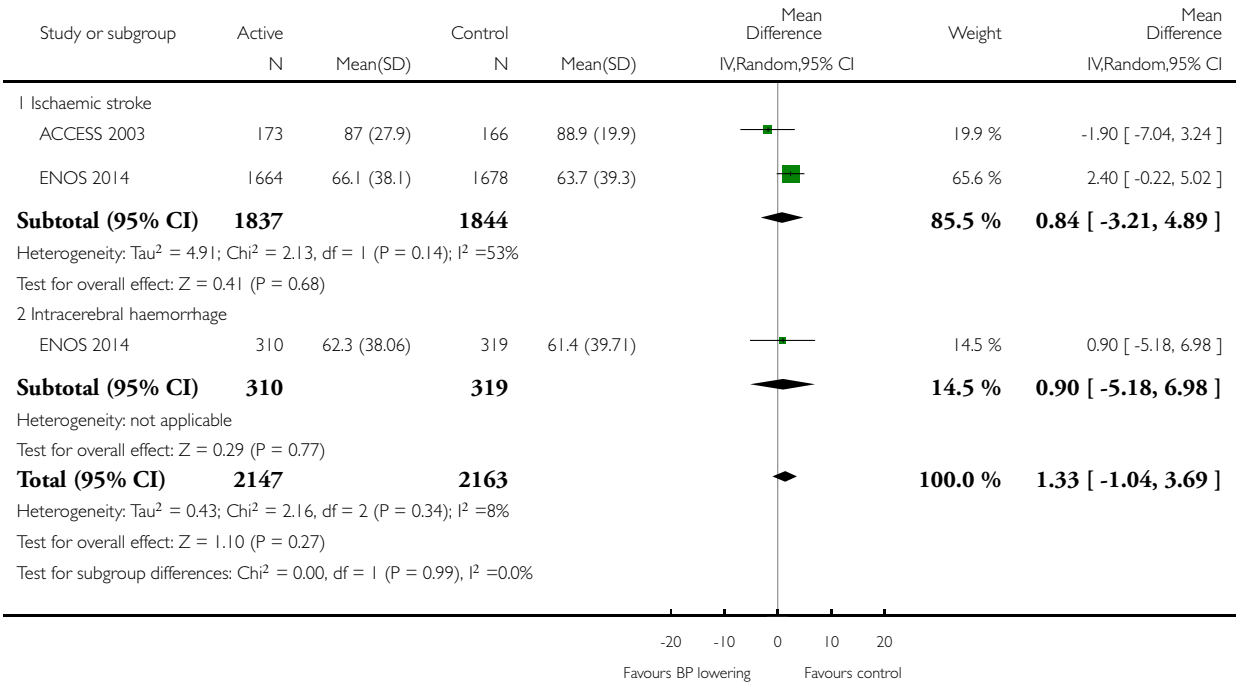
Analysis 1.12. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 12 Barthel Index, end of trial, by stroke type.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 12 Barthel Index, end of trial, by stroke type

Study or subgroup	Active N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Ischaemic stroke							
ACCESS 2003	173	87 (27.9)	166	88.9 (19.9)		19.9 %	-1.90 [-7.04, 3.24]
ENOS 2014	1664	66.1 (38.1)	1678	63.7 (39.3)		65.6 %	2.40 [-0.22, 5.02]
Subtotal (95% CI)	**1837**		**1844**			**85.5 %**	**0.84 [-3.21, 4.89]**
Heterogeneity: $Tau^2 = 4.91$; $Chi^2 = 2.13$, df = 1 (P = 0.14); $I^2 = 53\%$							
Test for overall effect: Z = 0.41 (P = 0.68)							
2 Intracerebral haemorrhage							
ENOS 2014	310	62.3 (38.06)	319	61.4 (39.71)		14.5 %	0.90 [-5.18, 6.98]
Subtotal (95% CI)	**310**		**319**			**14.5 %**	**0.90 [-5.18, 6.98]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.29 (P = 0.77)							
Total (95% CI)	**2147**		**2163**			**100.0 %**	**1.33 [-1.04, 3.69]**
Heterogeneity: $Tau^2 = 0.43$; $Chi^2 = 2.16$, df = 2 (P = 0.34); $I^2 = 8\%$							
Test for overall effect: Z = 1.10 (P = 0.27)							
Test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 0.99), $I^2 = 0.0\%$							

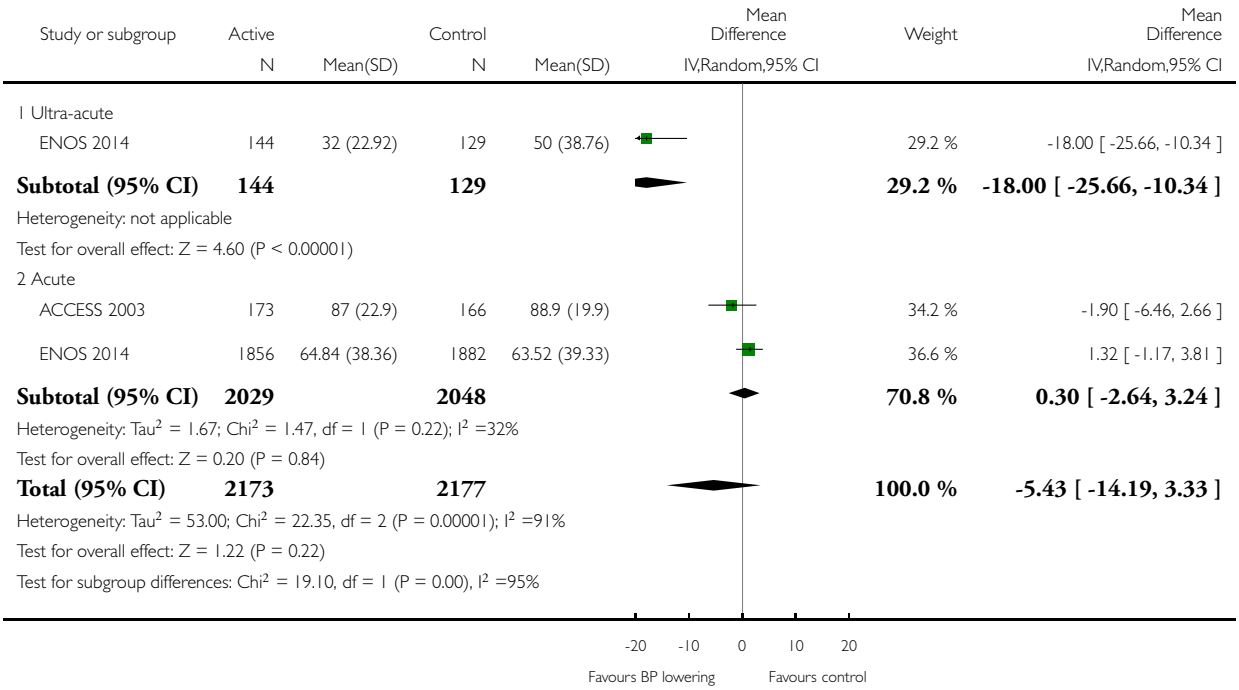


Analysis 1.13. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 13 Barthel Index, end of trial, by time to treatment.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 13 Barthel Index, end of trial, by time to treatment

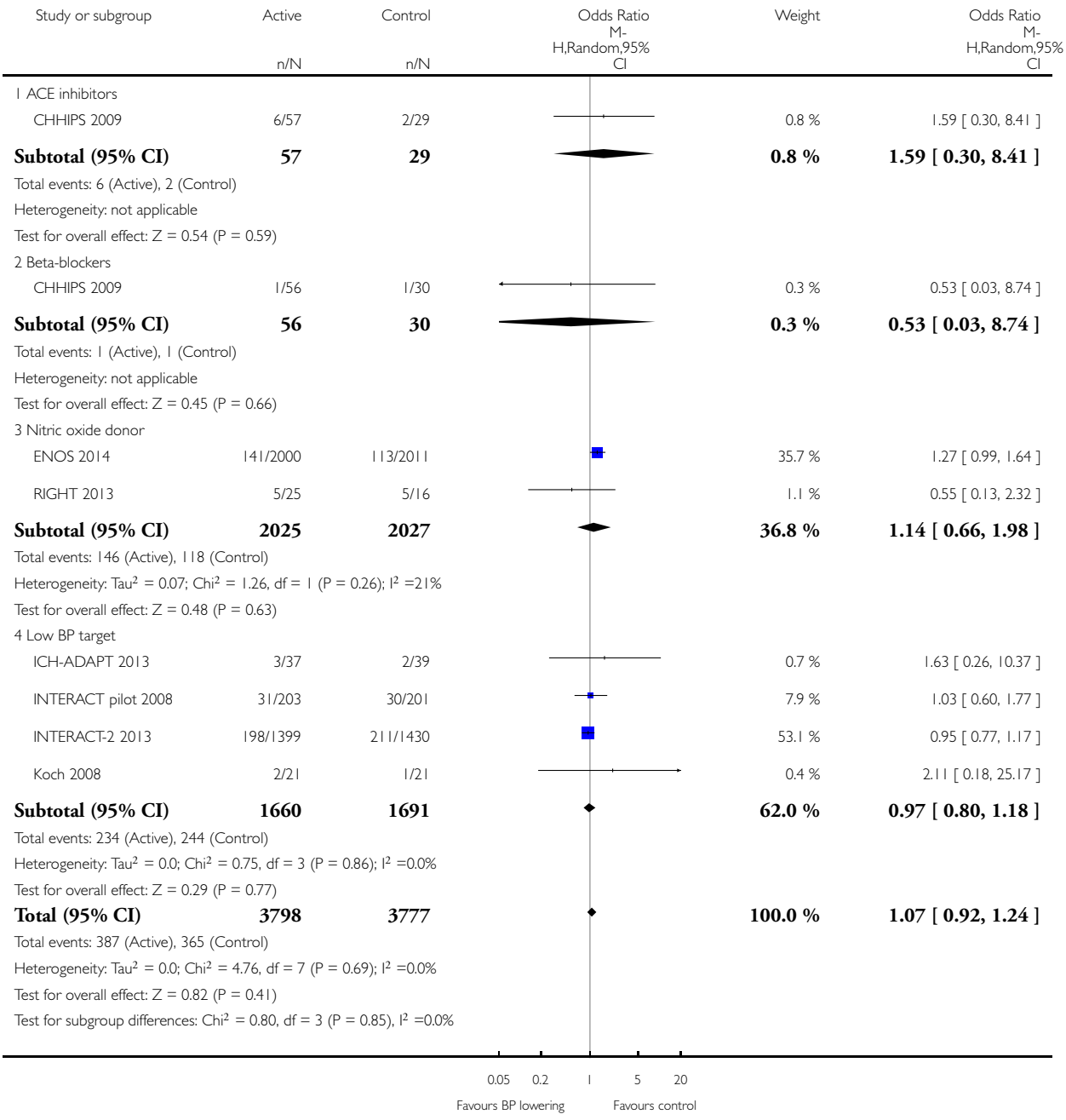


Analysis 1.14. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 14 Early neurological deterioration, by intervention.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 14 Early neurological deterioration, by intervention

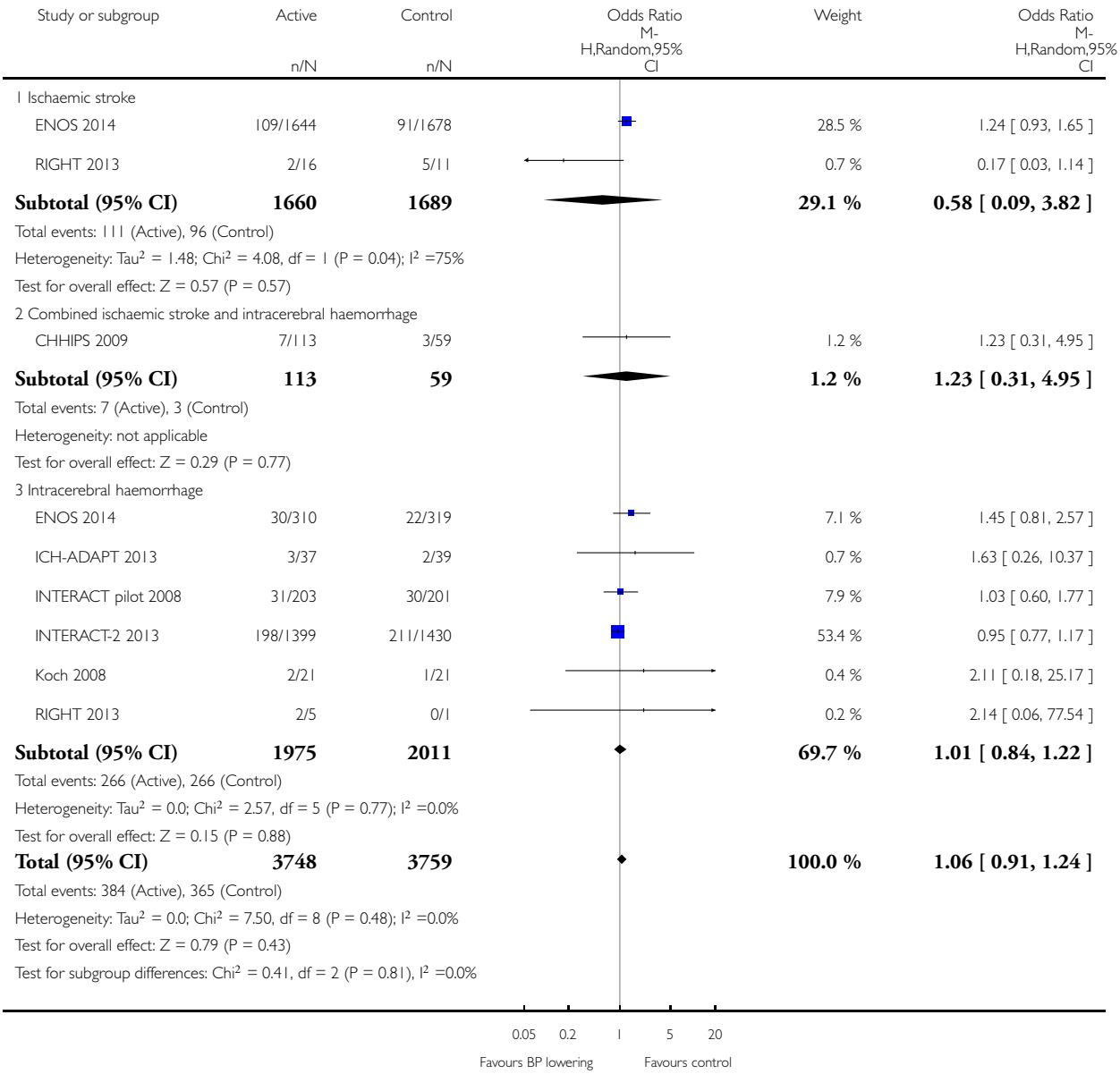


Analysis 1.15. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 15 Early neurological deterioration, by stroke type.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 15 Early neurological deterioration, by stroke type

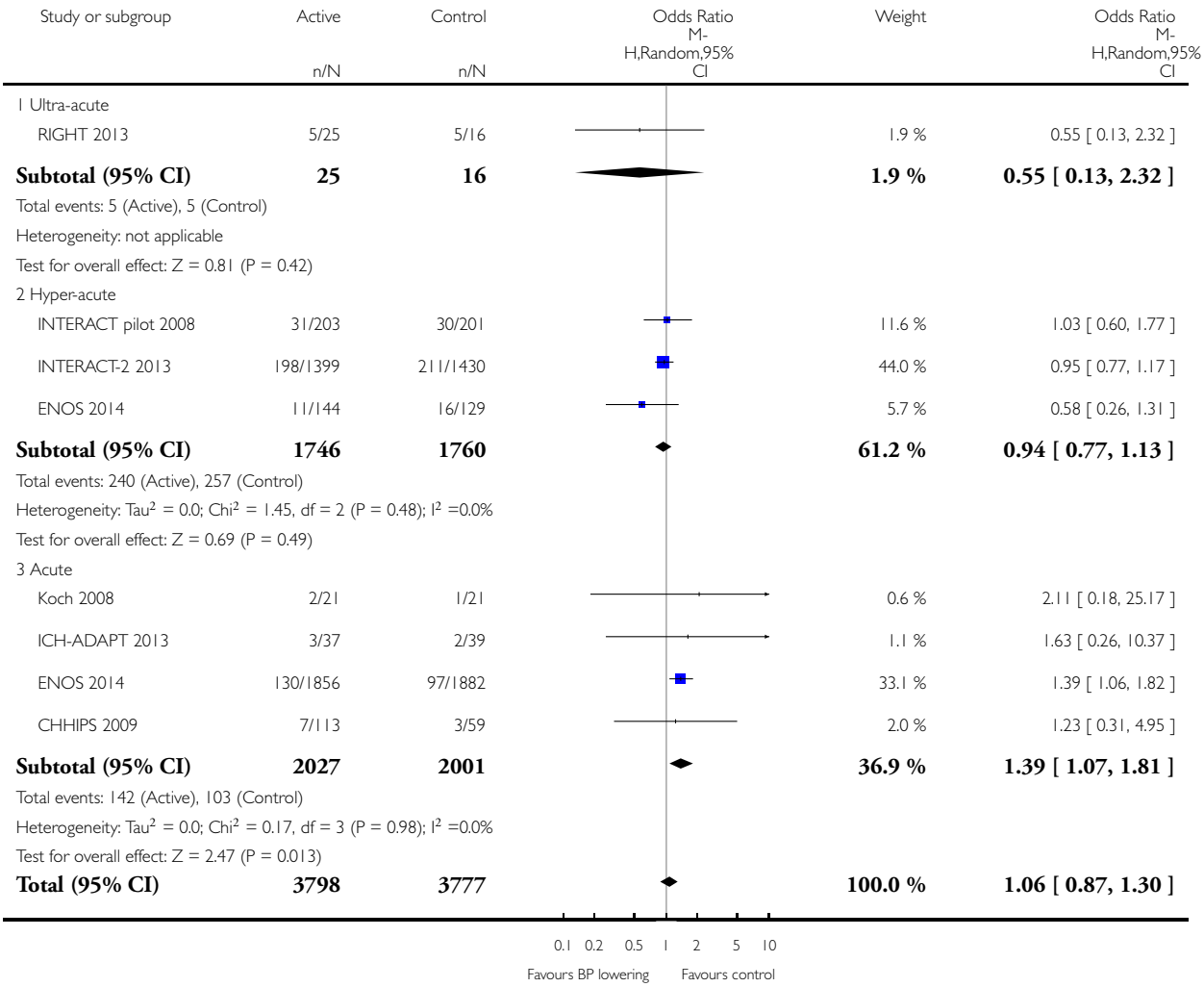


Analysis 1.16. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 16 Early neurological deterioration, by time to treatment.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 16 Early neurological deterioration, by time to treatment



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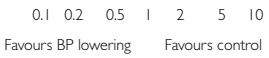
Study or subgroup	Active n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Total events: 387 (Active), 365 (Control)					
Heterogeneity: Tau² = 0.01; Chi² = 8.20, df = 7 (P = 0.32); I² =15%					
Test for overall effect: Z = 0.62 (P = 0.54)					
Test for subgroup differences: Chi² = 6.59, df = 2 (P = 0.04), I² =70%					



Analysis 1.17. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 17 Quality of life (EuroQol) at end of trial, by intervention.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 17 Quality of life (EuroQol) at end of trial, by intervention

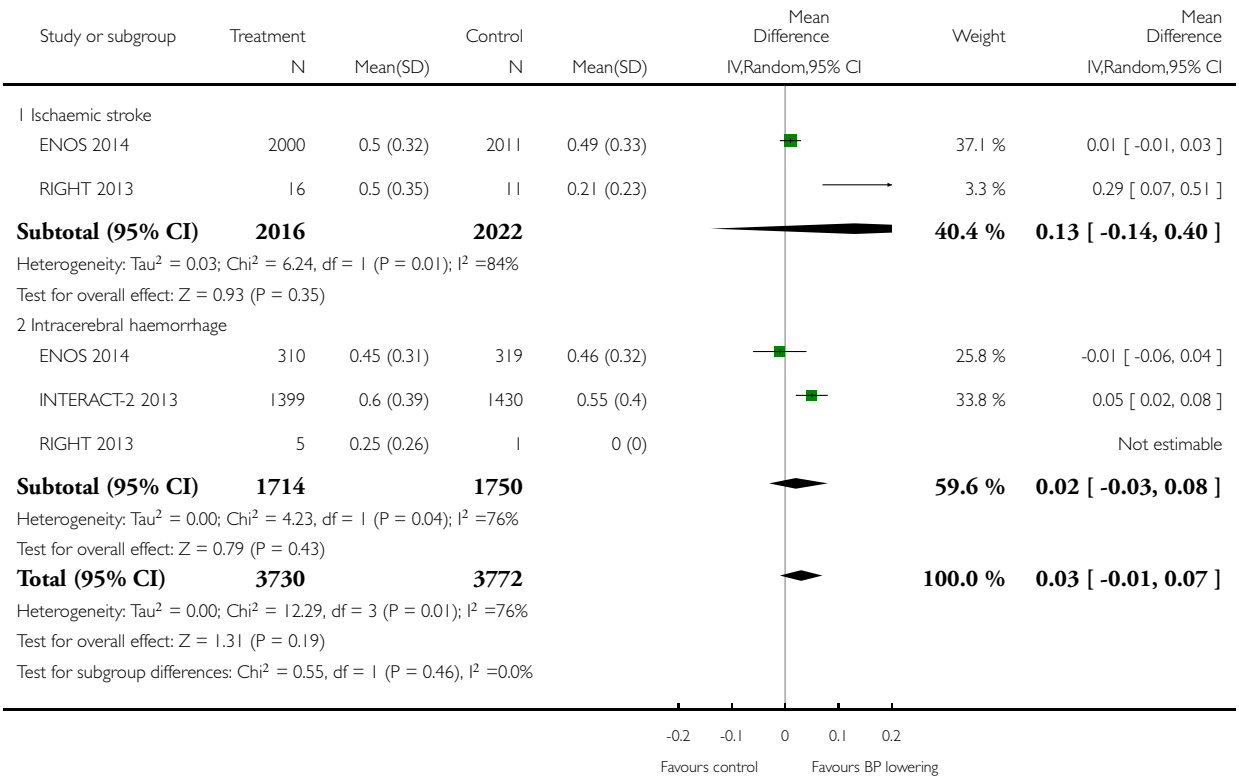
Study or subgroup	Active N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Nitric oxide donor							
ENOS 2014	2000	0.49 (0.32)	2011	0.48 (0.33)		67.1 %	0.01 [-0.01, 0.03]
RIGHT 2013	25	0.45 (0.33)	16	0.25 (0.26)		0.8 %	0.20 [0.02, 0.38]
Subtotal (95% CI)	**2025**		**2027**			**67.9 %**	**0.01 [-0.01, 0.03]**
Heterogeneity: Chi² = 4.16, df = 1 (P = 0.04); I² =76%							
Test for overall effect: Z = 1.21 (P = 0.23)							
2 Low BP target							
INTERACT-2 2013	1399	0.6 (0.39)	1430	0.55 (0.4)		32.1 %	0.05 [0.02, 0.08]
Subtotal (95% CI)	**1399**		**1430**			**32.1 %**	**0.05 [0.02, 0.08]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.37 (P = 0.00076)							
Total (95% CI)	**3424**		**3457**			**100.0 %**	**0.02 [0.01, 0.04]**
Heterogeneity: Chi² = 8.53, df = 2 (P = 0.01); I² =77%							
Test for overall effect: Z = 2.90 (P = 0.0037)							
Test for subgroup differences: Chi² = 4.38, df = 1 (P = 0.04), I² =77%							

Analysis 1.18. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 18 Quality of life (EuroQoL) at end of trial, by stroke type.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 18 Quality of life (EuroQoL) at end of trial, by stroke type

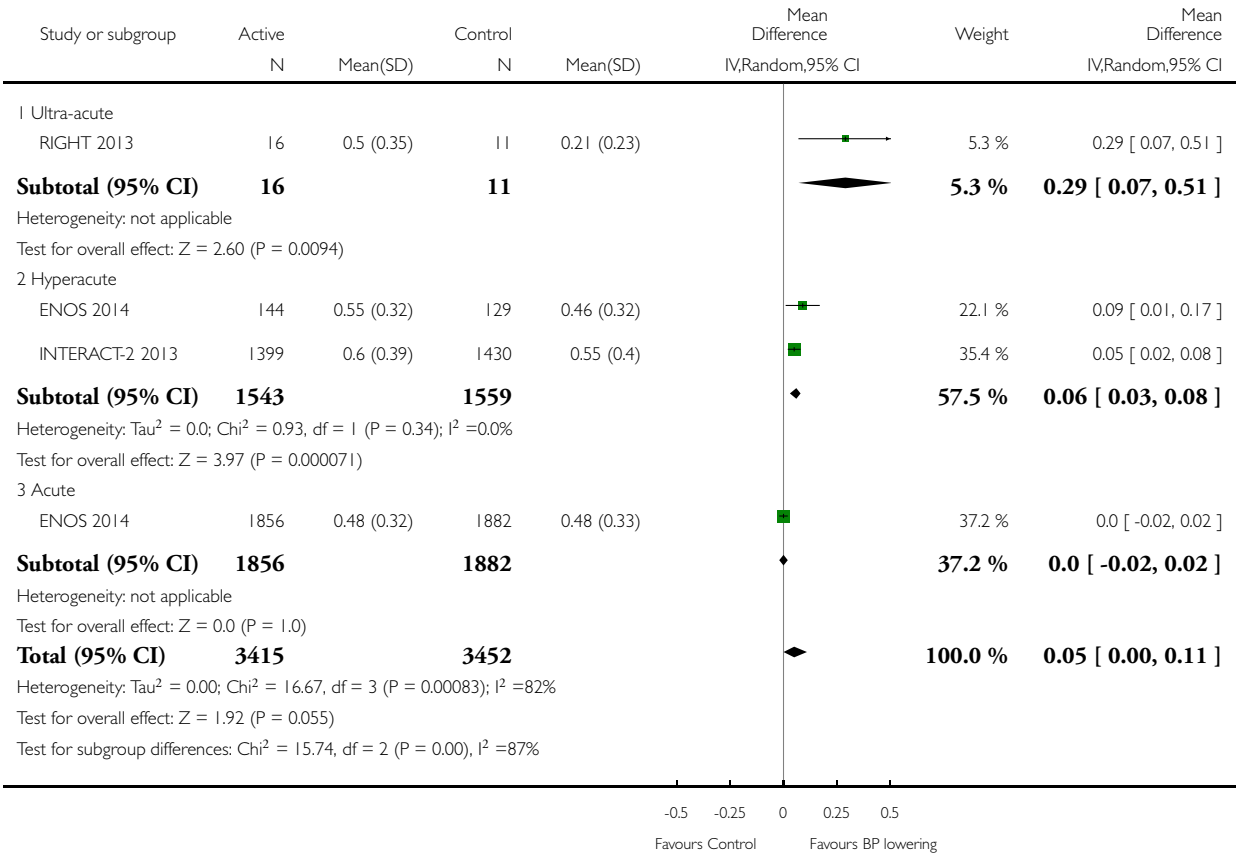


Analysis 1.19. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 19 Quality of life (EuroQoL) at end of trial, by time to treatment.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 19 Quality of life (EuroQoL) at end of trial, by time to treatment



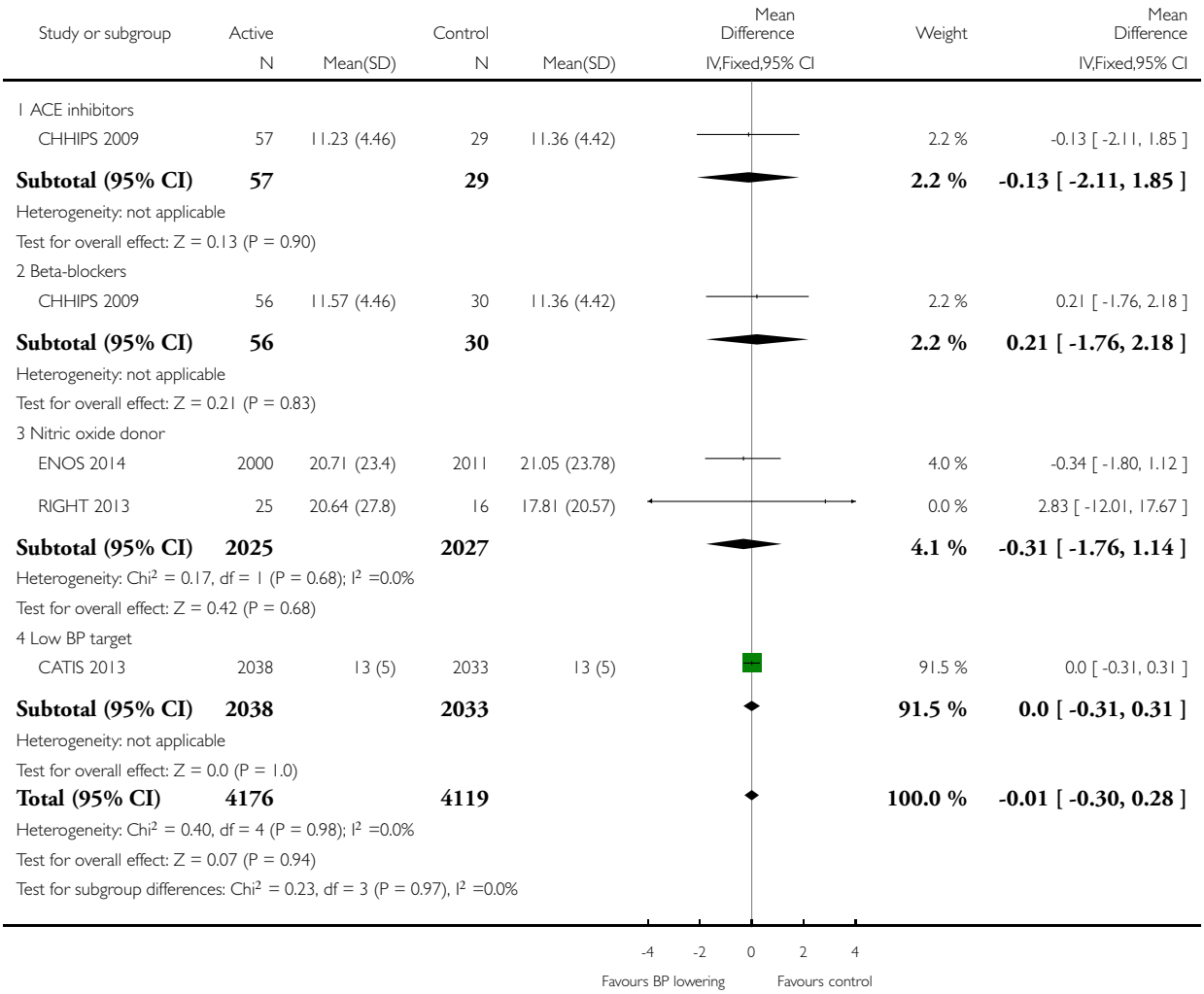
Analysis 1.20. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 20 Length of stay, by intervention.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 20 Length of stay, by intervention

Study or subgroup	Active N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 ACE inhibitors							
CHHIPS 2009	57	11.23 (4.46)	29	11.36 (4.42)		2.2 %	-0.13 [-2.11, 1.85]
Subtotal (95% CI)	**57**		**29**			**2.2 %**	**-0.13 [-2.11, 1.85]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.13 (P = 0.90)							
2 Beta-blockers							
CHHIPS 2009	56	11.57 (4.46)	30	11.36 (4.42)		2.2 %	0.21 [-1.76, 2.18]
Subtotal (95% CI)	**56**		**30**			**2.2 %**	**0.21 [-1.76, 2.18]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.21 (P = 0.83)							
3 Nitric oxide donor							
ENOS 2014	2000	20.71 (23.4)	2011	21.05 (23.78)		4.0 %	-0.34 [-1.80, 1.12]
RIGHT 2013	25	20.64 (27.8)	16	17.81 (20.57)		0.0 %	2.83 [-12.01, 17.67]
Subtotal (95% CI)	**2025**		**2027**			**4.1 %**	**-0.31 [-1.76, 1.14]**
Heterogeneity: Chi^2 = 0.17, df = 1 (P = 0.68); I^2 =0.0%							
Test for overall effect: Z = 0.42 (P = 0.68)							
4 Low BP target							
CATIS 2013	2038	13 (5)	2033	13 (5)		91.5 %	0.0 [-0.31, 0.31]
Subtotal (95% CI)	**2038**		**2033**			**91.5 %**	**0.0 [-0.31, 0.31]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
Total (95% CI)	**4176**		**4119**			**100.0 %**	**-0.01 [-0.30, 0.28]**
Heterogeneity: Chi^2 = 0.40, df = 4 (P = 0.98); I^2 =0.0%							
Test for overall effect: Z = 0.07 (P = 0.94)							
Test for subgroup differences: Chi^2 = 0.23, df = 3 (P = 0.97), I^2 =0.0%							



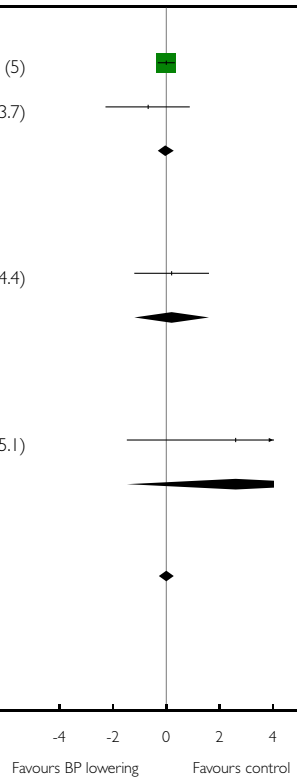
Analysis 1.21. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 21 Length of stay, by stroke type.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 21 Length of stay, by stroke type

Study or subgroup	Active N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Ischaemic stroke							
CATIS 2013	2038	13 (5)	2033	13 (5)		91.6 %	0.0 [-0.31, 0.31]
ENOS 2014	1644	20.2 (22.7)	1678	20.9 (23.7)		3.5 %	-0.70 [-2.28, 0.88]
Subtotal (95% CI)	**3682**		**3711**			**95.0 %**	**-0.03 [-0.33, 0.28]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.73$, df = 1 (P = 0.39); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.17 (P = 0.87)							
2 Combined ischaemic and Intracerebral haemorrhage							
CHHIPS 2009	113	11.6 (4.5)	59	11.4 (4.4)		4.4 %	0.20 [-1.20, 1.60]
Subtotal (95% CI)	**113**		**59**			**4.4 %**	**0.20 [-1.20, 1.60]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.28 (P = 0.78)							
3 Intracerebral haemorrhage							
ENOS 2014	310	24.6 (27.1)	319	22 (25.1)		0.5 %	2.60 [-1.49, 6.69]
Subtotal (95% CI)	**310**		**319**			**0.5 %**	**2.60 [-1.49, 6.69]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.25 (P = 0.21)							
Total (95% CI)	**4105**		**4089**			**100.0 %**	**0.00 [-0.30, 0.29]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.39$, df = 3 (P = 0.50); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.01 (P = 0.99)							
Test for subgroup differences: $Chi^2 = 1.66$, df = 2 (P = 0.44), $I^2 = 0.0\%$							



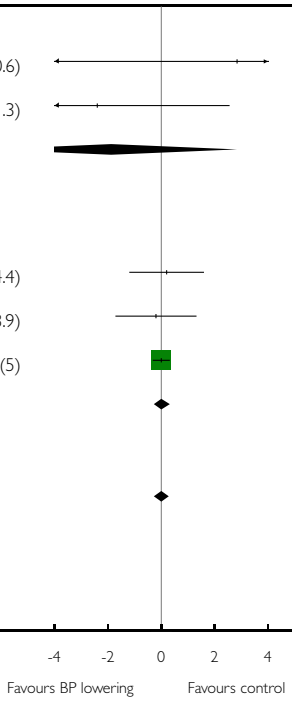
Analysis 1.22. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 22 Length of stay, by time to treatment.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 22 Length of stay, by time to treatment

Study or subgroup	Active N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Ultra-acute							
RIGHT 2013	25	20.64 (27.8)	16	17.81 (20.6)		0.0 %	2.83 [-12.02, 17.68]
ENOS 2014	144	15.5 (20.4)	129	17.9 (21.3)		0.4 %	-2.40 [-7.36, 2.56]
Subtotal (95% CI)	**169**		**145**			**0.4 %**	**-1.88 [-6.58, 2.83]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.43$, df = 1 (P = 0.51); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.78 (P = 0.43)							
2 Acute							
CHHIPS 2009	113	11.6 (4.5)	59	11.4 (4.4)		4.4 %	0.20 [-1.20, 1.60]
ENOS 2014	1856	21.1 (23.6)	1882	21.3 (23.9)		3.7 %	-0.20 [-1.72, 1.32]
CATIS 2013	2038	13 (5)	2033	13 (5)		91.5 %	0.0 [-0.31, 0.31]
Subtotal (95% CI)	**4007**		**3974**			**99.6 %**	**0.00 [-0.29, 0.30]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.15$, df = 2 (P = 0.93); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.01 (P = 0.99)							
Total (95% CI)	**4176**		**4119**			**100.0 %**	**-0.01 [-0.30, 0.29]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.18$, df = 4 (P = 0.88); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.04 (P = 0.97)							
Test for subgroup differences: $Chi^2 = 0.61$, df = 1 (P = 0.44), $I^2 = 0.0\%$							



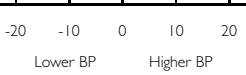
Analysis 1.23. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 23 SBP, first after randomisation, by intervention.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 23 SBP, first after randomisation, by intervention

Study or subgroup	Active N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 ACE inhibitors(po)							
CHHIPS 2009	29	161.2 (18)	16	172.6 (13)		3.8 %	-11.40 [-20.54, -2.26]
Dyker 1997	12	150 (21)	12	173 (23)		1.4 %	-23.00 [-40.62, -5.38]
Eveson 2007	17	153.8 (20.2)	18	169.1 (14.5)		2.7 %	-15.30 [-27.01, -3.59]
Lisk 1993	3	168.3 (23.6)	2	159.17 (18.5)		0.4 %	9.13 [-27.89, 46.15]
PIL-FAST 2013	6	171 (30)	8	186 (13)		0.7 %	-15.00 [-40.64, 10.64]
Subtotal (95% CI)	**67**		**56**			**9.0 %**	**-13.68 [-20.03, -7.32]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.86$, df = 4 (P = 0.58); $I^2 = 0.0\%$							
Test for overall effect: Z = 4.22 (P = 0.000025)							
2 ACE inhibitors (s/l)							
CHHIPS 2009	28	161.1 (18)	14	167.1 (18)		2.8 %	-6.00 [-17.55, 5.55]
Subtotal (95% CI)	**28**		**14**			**2.8 %**	**-6.00 [-17.55, 5.55]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.02 (P = 0.31)							
3 ARA (po)							
PRoFESS 2009	647	135.3 (17.8)	713	141.4 (17)		9.1 %	-6.10 [-7.95, -4.25]
SCAST 2011	1017	157.1 (19)	1012	159.8 (19.2)		9.2 %	-2.70 [-4.36, -1.04]
TAST 2013	12	164.5 (12.5)	7	173.9 (16.7)		2.0 %	-9.40 [-23.65, 4.85]
Subtotal (95% CI)	**1676**		**1732**			**20.4 %**	**-4.59 [-7.71, -1.48]**
Heterogeneity: $Tau^2 = 4.47$; $Chi^2 = 7.67$, df = 2 (P = 0.02); $I^2 = 74\%$							
Test for overall effect: Z = 2.89 (P = 0.0038)							
4 A2AA(po)							
Lisk 1993	2	145.5 (7.77)	2	159.17 (18.5)		0.6 %	-13.67 [-41.48, 14.14]
Subtotal (95% CI)	**2**		**2**			**0.6 %**	**-13.67 [-41.48, 14.14]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.96 (P = 0.34)							
5 Beta-blockers (po)							
CHHIPS 2009	29	161.1 (16)	15	172.6 (13)		4.0 %	-11.50 [-20.29, -2.71]
Subtotal (95% CI)	**29**		**15**			**4.0 %**	**-11.50 [-20.29, -2.71]**
Heterogeneity: not applicable							



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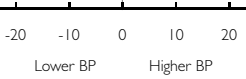
Study or subgroup	Active N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Test for overall effect: Z = 2.57 (P = 0.010)							
6 Beta-blockers (iv)							
CHHIPS 2009	27	153.1 (15)	14	169.5 (18)		3.0 %	-16.40 [-27.40, -5.40]
Subtotal (95% CI)	**27**		**14**			**3.0 %**	**-16.40 [-27.40, -5.40]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.92 (P = 0.0035)							
7 Calcium channel blockers (po)							
Fagan 1988 120 mg	10	139 (22)	5	141 (24)		0.8 %	-2.00 [-27.07, 23.07]
Fagan 1988 240 mg	10	133 (17)	4	141 (24)		0.7 %	-8.00 [-33.77, 17.77]
Uzuner 1995	38	136.2 (21.2)	39	144.9 (29)		2.8 %	-8.70 [-20.03, 2.63]
Subtotal (95% CI)	**58**		**48**			**4.3 %**	**-7.62 [-17.21, 1.96]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.23, df = 2 (P = 0.89); I^2 =0.0%							
Test for overall effect: Z = 1.56 (P = 0.12)							
8 Calcium channel blockers (iv)							
Uzuner 1995	8	146.9 (19)	3	156.66 (5.7)		1.9 %	-9.76 [-24.42, 4.90]
Subtotal (95% CI)	**8**		**3**			**1.9 %**	**-9.76 [-24.42, 4.90]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.30 (P = 0.19)							
9 Nitric oxide donor							
Bath 2000	13	159.23 (29.37)	19	152.63 (22.1)		1.3 %	6.60 [-12.21, 25.41]
ENOS 2014	2000	156.6 (22.6)	2011	163.7 (22.5)		9.4 %	-7.10 [-8.50, -5.70]
Rashid 2003 10 mg	20	139.2 (15.7)	10	151.7 (22.7)		1.7 %	-12.50 [-28.16, 3.16]
Rashid 2003 5 mg	20	141.1 (18.4)	10	151.1 (22.7)		1.6 %	-10.00 [-26.22, 6.22]
Rashid 2003 5/10 mg	20	142.5 (20.3)	10	151.1 (22.7)		1.6 %	-8.60 [-25.25, 8.05]
RIGHT 2013	25	157.5 (26.8)	16	177.2 (27.1)		1.5 %	-19.70 [-36.63, -2.77]
Willmot 2006	12	159.5 (22.94)	6	185.17 (18.82)		1.2 %	-25.67 [-45.55, -5.79]
Subtotal (95% CI)	**2110**		**2082**			**18.2 %**	**-9.25 [-14.54, -3.96]**
Heterogeneity: Tau^2 = 13.55; Chi^2 = 8.07, df = 6 (P = 0.23); I^2 =26%							
Test for overall effect: Z = 3.43 (P = 0.00061)							
10 Thiazide-like diuretic (po)							
Eames 2005	18	156 (26)	22	176 (34)		1.3 %	-20.00 [-38.60, -1.40]
Subtotal (95% CI)	**18**		**22**			**1.3 %**	**-20.00 [-38.60, -1.40]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.11 (P = 0.035)							
11 Low BP target							
CATIS 2013	2038	144.7 (15)	2033	152.9 (15.9)		9.5 %	-8.20 [-9.15, -7.25]
ICH-ADAPT 2013	39	159.4 (20)	36	167.9 (25)		3.2 %	-8.50 [-18.80, 1.80]



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Study or subgroup	Active N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
INTERACT pilot 2008	203	153 (18)	201	167 (19)		7.8 %	-14.00 [-17.61, -10.39]
INTERACT-2 2013	1399	150 (17)	1430	164 (17)		9.4 %	-14.00 [-15.25, -12.75]
Koch 2008	21	113.8 (13)	21	124.1 (12.8)		4.5 %	-10.30 [-18.10, -2.50]
Subtotal (95% CI)	**3700**		**3721**			**34.5 %**	**-11.39 [-15.30, -7.49]**
Heterogeneity: Tau^2 = 14.16; Chi^2 = 56.26, df = 4 (P<0.00001); I^2 =93%							
Test for overall effect: Z = 5.72 (P < 0.00001)							
Total (95% CI)	**7723**		**7709**			**100.0 %**	**-9.83 [-12.11, -7.56]**
Heterogeneity: Tau^2 = 13.87; Chi^2 = 157.60, df = 28 (P<0.00001); I^2 =82%							
Test for overall effect: Z = 8.47 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 15.00, df = 10 (P = 0.13), I^2 =33%							

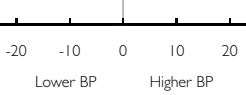
Analysis 1.24. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 24 SBP, first after randomisation by stroke type.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 24 SBP, first after randomisation by stroke type

Study or subgroup	Active N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Ischaemic stroke							
ACCESS 2003	173	165.8 (20.9)	166	168.4 (19.7)		7.0 %	-2.60 [-6.92, 1.72]
CATIS 2013	2038	144.7 (15)	2033	152.9 (15.9)		9.3 %	-8.20 [-9.15, -7.25]
Dyker 1997	12	150 (21)	12	173 (23)		1.4 %	-23.00 [-40.62, -5.38]
Eames 2005	18	156 (26)	19	176 (34)		1.2 %	-20.00 [-39.44, -0.56]
ENOS 2014	1664	155.8 (22)	1678	162.4 (22.1)		9.1 %	-6.60 [-8.10, -5.10]
Eveson 2007	17	153.8 (20.2)	18	169.1 (14.5)		2.7 %	-15.30 [-27.01, -3.59]
Fagan 1988 120 mg	10	139 (22)	5	141 (24)		0.8 %	-2.00 [-27.07, 23.07]
Fagan 1988 240 mg	10	133 (17)	4	141 (24)		0.7 %	-8.00 [-33.77, 17.77]
PRoFESS 2009	647	135.3 (17.8)	713	141.4 (17)		8.9 %	-6.10 [-7.95, -4.25]
TAST 2013	12	164.5 (12.5)	7	173.9 (16.7)		2.0 %	-9.40 [-23.65, 4.85]
Subtotal (95% CI)	**4601**		**4655**			**43.0 %**	**-6.99 [-8.61, -5.38]**
Heterogeneity: Tau^2 = 1.86; Chi^2 = 17.08, df = 9 (P = 0.05); I^2 =47%							
Test for overall effect: Z = 8.51 (P < 0.00001)							
2 Combined ischaemic stroke and intracerebral haemorrhage							
Bath 2000	13	159.23 (29.37)	19	152.63 (22.1)		1.3 %	6.60 [-12.21, 25.41]
CHHIPS 2009	113	161.5 (14)	59	171.9 (11)		7.4 %	-10.40 [-14.21, -6.59]
PIL-FAST 2013	6	171 (30)	8	186 (13)		0.7 %	-15.00 [-40.64, 10.64]
Rashid 2003 10 mg	20	139.2 (15.7)	10	151.1 (22.7)		1.7 %	-11.90 [-27.56, 3.76]
Rashid 2003 5 mg	20	141.1 (18.4)	10	151.1 (22.7)		1.6 %	-10.00 [-26.22, 6.22]
Rashid 2003 5/10 mg	20	142.5 (20.3)	10	151.1 (22.7)		1.6 %	-8.60 [-25.25, 8.05]
RIGHT 2013	25	157.5 (26.8)	16	177.2 (27.1)		1.5 %	-19.70 [-36.63, -2.77]
SCAST 2011	1017	157.1 (19)	1012	159.8 (19.2)		9.0 %	-2.70 [-4.36, -1.04]
Uzuner 1995	38	136.2 (21.2)	39	144.9 (29)		2.8 %	-8.70 [-20.03, 2.63]
Uzuner 1995	8	146.9 (19)	3	156.66 (5.7)		1.9 %	-9.76 [-24.42, 4.90]
Subtotal (95% CI)	**1280**		**1186**			**29.5 %**	**-7.89 [-12.43, -3.36]**



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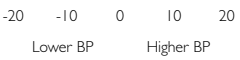
Study or subgroup	Active N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Heterogeneity: Tau² = 18.94; Chi² = 21.27, df = 9 (P = 0.01); I² =58%							
Test for overall effect: Z = 3.41 (P = 0.00065)							
3 Intracerebral haemorrhage							
ENOS 2014	310	162.7 (24.6)	319	170.2 (23.3)		7.5 %	-7.50 [-11.25, -3.75]
ICH-ADAPT 2013	39	159.4 (20)	36	167.9 (25)		3.2 %	-8.50 [-18.80, 1.80]
INTERACT pilot 2008	203	153 (18)	201	167 (19)		7.6 %	-14.00 [-17.61, -10.39]
INTERACT-2 2013	1399	150 (17)	1430	164 (17)		9.2 %	-14.00 [-15.25, -12.75]
Subtotal (95% CI)	**1951**		**1986**			**27.5 %**	**-11.77 [-15.25, -8.30]**
Heterogeneity: Tau² = 8.08; Chi² = 11.38, df = 3 (P = 0.01); I² =74%							
Test for overall effect: Z = 6.64 (P < 0.00001)							
Total (95% CI)	**7832**		**7827**			**100.0 %**	**-8.77 [-11.04, -6.50]**
Heterogeneity: Tau² = 14.24; Chi² = 161.25, df = 23 (P<0.00001); I² =86%							
Test for overall effect: Z = 7.57 (P < 0.00001)							
Test for subgroup differences: Chi² = 5.98, df = 2 (P = 0.05), I² =67%							



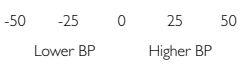
Analysis 1.25. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 25 SBP, first after randomisation by time to treatment.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 25 SBP, first after randomisation by time to treatment

Study or subgroup	Active N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Ultra-acute/prehospital							
PIL-FAST 2013	6	171 (30)	8	177 (20)		0.7 %	-6.00 [-33.72, 21.72]
RIGHT 2013	25	157.5 (26.8)	16	177.2 (27.1)		1.8 %	-19.70 [-36.63, -2.77]
Subtotal (95% CI)	**31**		**24**			**2.5 %**	**-15.98 [-30.43, -1.53]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.68$, df = 1 (P = 0.41); $I^2 = 0.0\%$							
Test for overall effect: Z = 2.17 (P = 0.030)							
2 Hyper-acute							
INTERACT pilot 2008	203	153 (18)	201	167 (19)		9.0 %	-14.00 [-17.61, -10.39]
INTERACT-2 2013	1399	150 (17)	1430	164 (17)		10.9 %	-14.00 [-15.25, -12.75]
ENOS 2014	144	154.4 (22.3)	129	163.8 (20.4)		7.6 %	-9.40 [-14.47, -4.33]
Subtotal (95% CI)	**1746**		**1760**			**27.5 %**	**-13.38 [-15.41, -11.35]**
Heterogeneity: $Tau^2 = 1.28$; $Chi^2 = 3.00$, df = 2 (P = 0.22); $I^2 = 33\%$							
Test for overall effect: Z = 12.91 (P < 0.00001)							
3 Acute							
SCAST 2011	1017	157.1 (19)	1012	159.8 (19.2)		10.6 %	-2.70 [-4.36, -1.04]
CATIS 2013	2038	144.7 (15)	2033	152.9 (15.9)		11.0 %	-8.20 [-9.15, -7.25]
ICH-ADAPT 2013	39	159.4 (20)	36	167.9 (25)		3.8 %	-8.50 [-18.80, 1.80]
CHHIPS 2009	113	161.5 (14)	59	171.9 (11)		8.8 %	-10.40 [-14.21, -6.59]
Eveson 2007	17	153.8 (20.2)	18	169.1 (14.5)		3.2 %	-15.30 [-27.01, -3.59]
ENOS 2014	1856	156.8 (22.6)	1882	163.6 (22.6)		10.8 %	-6.80 [-8.25, -5.35]
Subtotal (95% CI)	**5080**		**5040**			**48.2 %**	**-7.23 [-9.83, -4.63]**
Heterogeneity: $Tau^2 = 6.66$; $Chi^2 = 36.98$, df = 5 (P<0.00001); $I^2 = 86\%$							
Test for overall effect: Z = 5.44 (P < 0.00001)							
4 Subacute							
Eames 2005	18	156 (26)	19	176 (34)		1.4 %	-20.00 [-39.44, -0.56]
Dyker 1997	12	150 (21)	12	173 (23)		1.7 %	-23.00 [-40.62, -5.38]
PRoFESS 2009	647	135.3 (17.8)	713	141.4 (17)		10.5 %	-6.10 [-7.95, -4.25]
Rashid 2003 5 mg	20	141.1 (18.4)	10	151.1 (22.7)		1.9 %	-10.00 [-26.22, 6.22]



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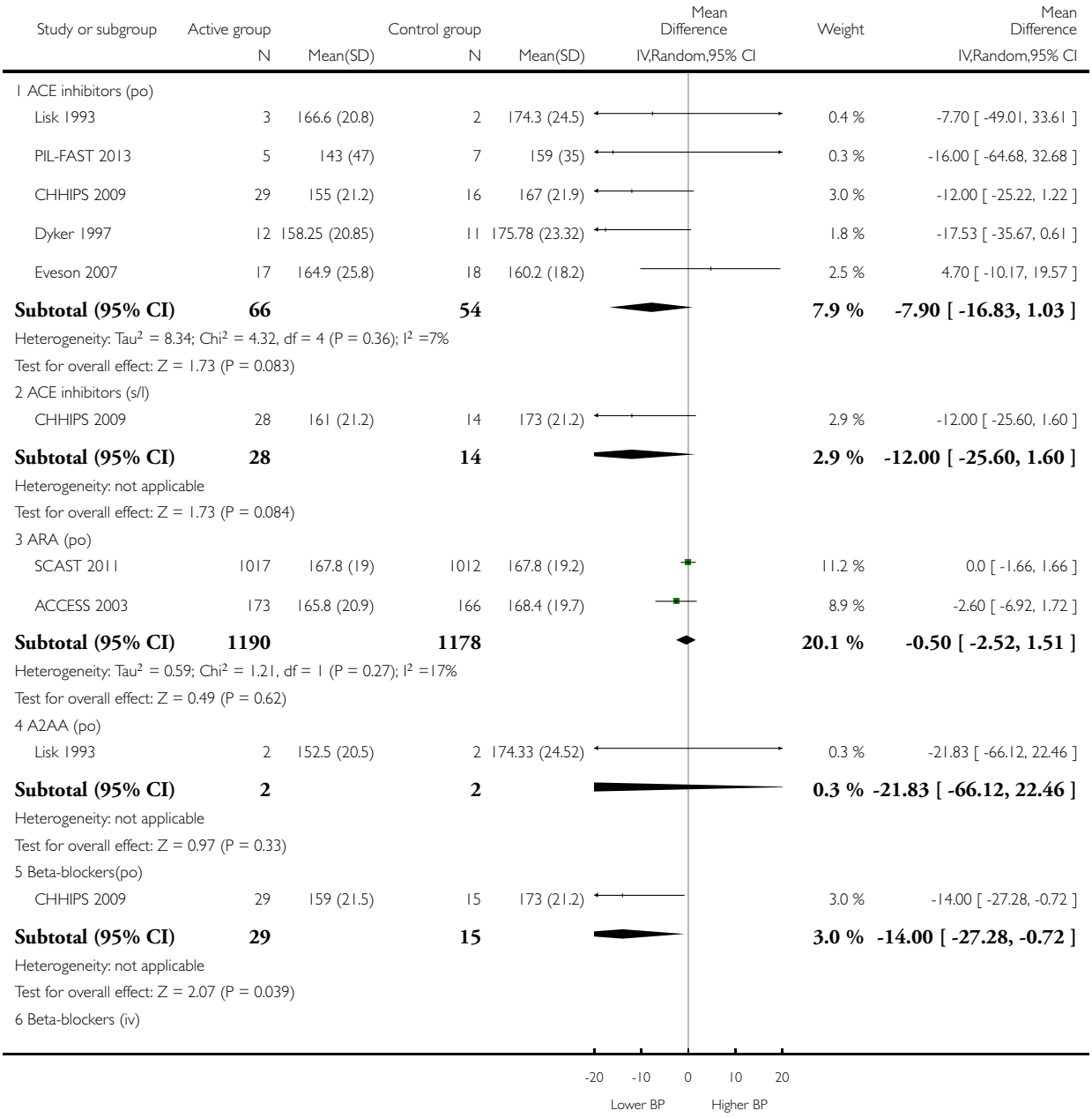
Study or subgroup	Active N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Rashid 2003 5/10 mg	20	142.5 (20.3)	10	151.1 (22.7)		1.8 %	-8.60 [-25.25, 8.05]
Rashid 2003 10 mg	20	139.2 (15.7)	10	151.1 (22.7)		2.0 %	-11.90 [-27.56, 3.76]
TAST 2013	12	164.5 (12.5)	7	173.9 (16.7)		2.4 %	-9.40 [-23.65, 4.85]
Subtotal (95% CI)	**749**		**781**		◆	**21.8 %**	**-7.26 [-10.02, -4.50]**
Heterogeneity: Tau^2 = 1.49; Chi^2 = 6.24, df = 6 (P = 0.40); I^2 =4%							
Test for overall effect: Z = 5.15 (P < 0.00001)							
Total (95% CI)	**7606**		**7605**		◆	**100.0 %**	**-9.67 [-12.14, -7.20]**
Heterogeneity: Tau^2 = 14.24; Chi^2 = 149.93, df = 17 (P<0.00001); I^2 =89%							
Test for overall effect: Z = 7.67 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 19.39, df = 3 (P = 0.00), I^2 =85%							

Analysis 1.26. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 26 SBP, at day 1.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 26 SBP, at day 1



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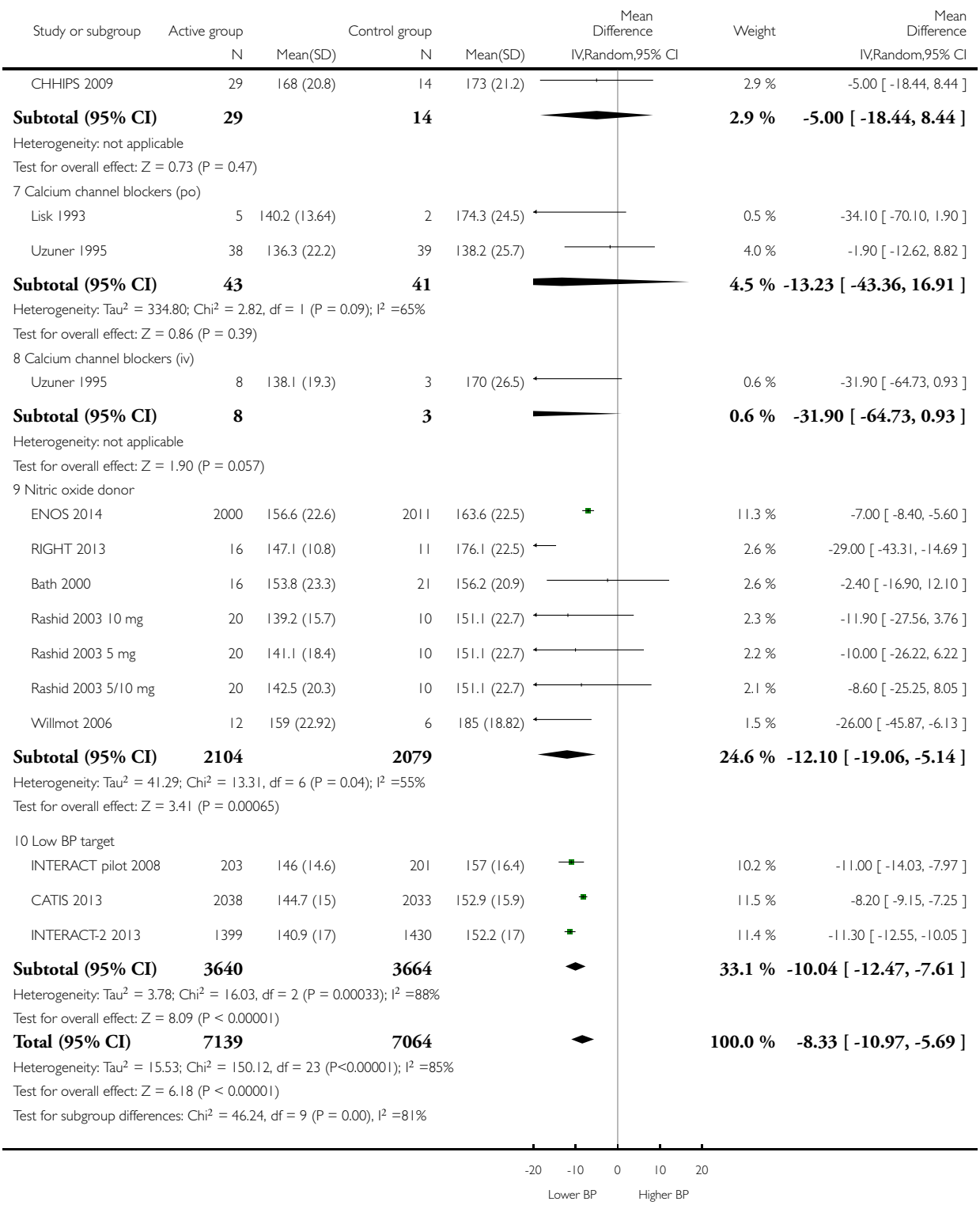
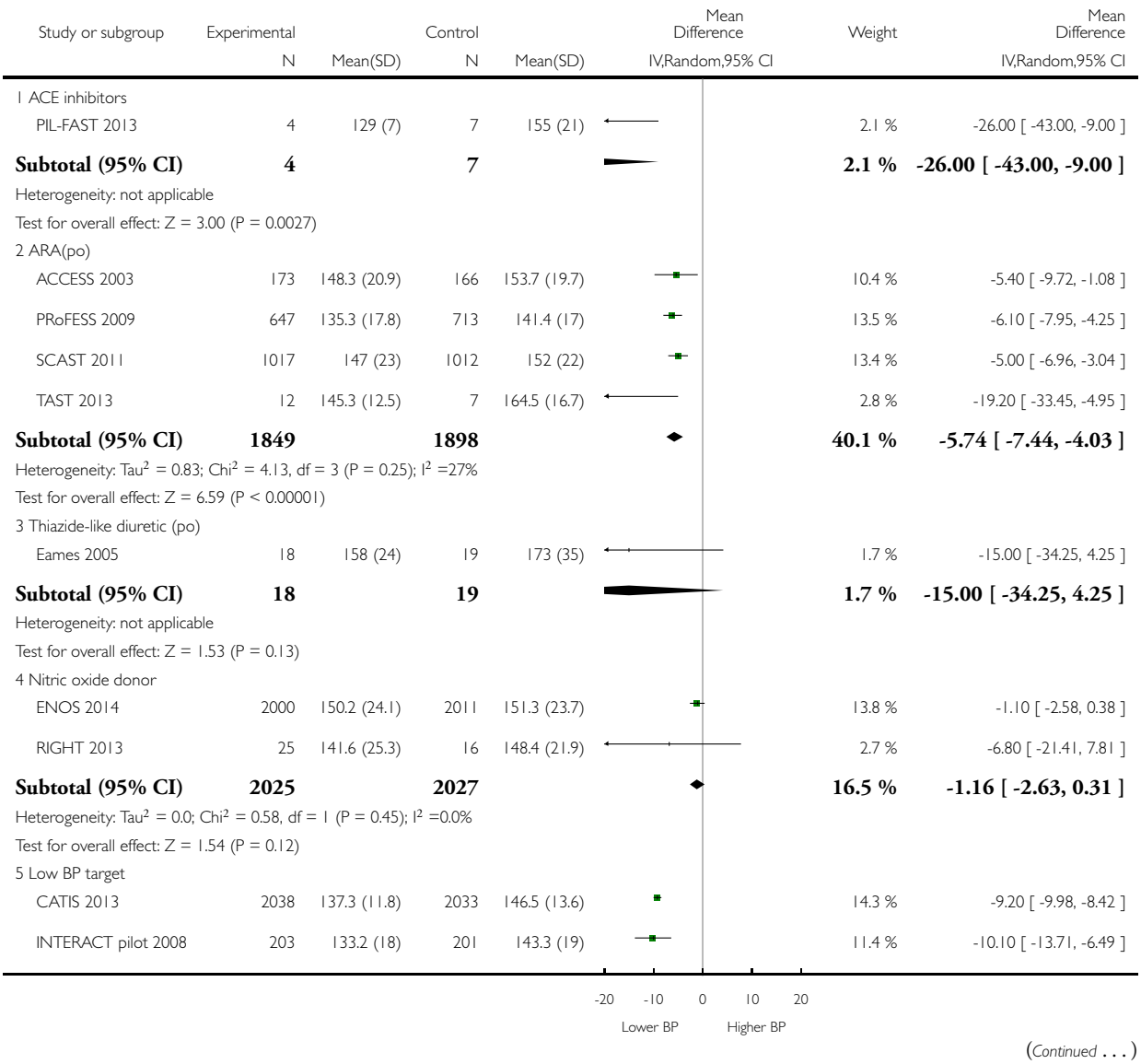


Analysis 1.27. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 27 SBP, at day 7.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 27 SBP, at day 7



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Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
INTERACT-2 2013	1399	137.5 (17)	1430	141.53 (17)		14.0 %	-4.03 [-5.28, -2.78]
Subtotal (95% CI)	**3640**		**3664**			**39.7 %**	**-7.62 [-11.69, -3.56]**
Heterogeneity: Tau^2 = 11.73; Chi^2 = 48.63, df = 2 (P<0.00001); I^2 =96%							
Test for overall effect: Z = 3.68 (P = 0.00024)							
Total (95% CI)	**7536**		**7615**			**100.0 %**	**-6.74 [-9.39, -4.10]**
Heterogeneity: Tau^2 = 12.61; Chi^2 = 127.17, df = 10 (P<0.00001); I^2 =92%							
Test for overall effect: Z = 4.99 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 28.38, df = 4 (P = 0.00), I^2 =86%							

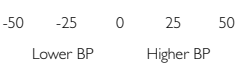
Analysis 1.28. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 28 SBP, at end of treatment.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 28 SBP, at end of treatment

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 ACE inhibitors (po)							
CHHIPS 2009	29	145 (16)	16	155 (17)		2.7 %	-10.00 [-20.16, 0.16]
Dyker 1997	14	152.4 (17)	14	170.5 (21)		1.7 %	-18.10 [-32.25, -3.95]
Eveson 2007	18	136 (13)	21	156 (14)		3.4 %	-20.00 [-28.48, -11.52]
PIL-FAST 2013	4	129 (7)	7	155 (21)		1.2 %	-26.00 [-43.00, -9.00]
Subtotal (95% CI)	**65**		**58**			**9.1 %**	**-17.37 [-23.42, -11.31]**
Heterogeneity: Tau^2 = 4.62; Chi^2 = 3.39, df = 3 (P = 0.34); I^2 =11%							
Test for overall effect: Z = 5.62 (P < 0.00001)							
2 ACE inhibitors (s/l)							
CHHIPS 2009	28	157.1 (16)	14	158.6 (17)		2.5 %	-1.50 [-12.20, 9.20]



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Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Subtotal (95% CI)	**28**		**14**			**2.5 %**	**-1.50 [-12.20, 9.20]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.27 (P = 0.78)							
3 ARA (po)							
ACCESS 2003	173	150.5 (20.9)	166	157 (19.7)		6.0 %	-6.50 [-10.82, -2.18]
ACCOST 2006	19	142.6 (3.5)	19	154.1 (5.3)		7.1 %	-11.50 [-14.36, -8.64]
PRoFESS 2009	647	134.5 (19.9)	713	140.3 (19)		7.6 %	-5.80 [-7.87, -3.73]
SCAST 2011	1017	147 (23)	1012	152 (22)		7.7 %	-5.00 [-6.96, -3.04]
TAST 2013	12	142.9 (12.5)	7	157.5 (16.7)		1.7 %	-14.60 [-28.85, -0.35]
Subtotal (95% CI)	**1868**		**1917**			**30.0 %**	**-7.37 [-10.19, -4.56]**
Heterogeneity: Tau² = 6.50; Chi² = 15.65, df = 4 (P = 0.004); I² =74%							
Test for overall effect: Z = 5.14 (P < 0.00001)							
4 A2AA (po)							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
5 Beta-blockers (po)							
CHHIPS 2009	29	153.3 (16)	15	156.5 (16)		2.8 %	-3.20 [-13.17, 6.77]
Subtotal (95% CI)	**29**		**15**			**2.8 %**	**-3.20 [-13.17, 6.77]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.63 (P = 0.53)							
6 Beta-blockers (iv)							
CHHIPS 2009	29	145 (16)	14	160 (16)		2.7 %	-15.00 [-25.21, -4.79]
Subtotal (95% CI)	**29**		**14**			**2.7 %**	**-15.00 [-25.21, -4.79]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.88 (P = 0.0040)							
7 Calcium channel blockers (po)							
Uzuner 1995	38	128.2 (16.7)	39	136 (24.4)		3.1 %	-7.80 [-17.12, 1.52]
Subtotal (95% CI)	**38**		**39**			**3.1 %**	**-7.80 [-17.12, 1.52]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.64 (P = 0.10)							
8 Calcium channel blockers (iv)							
Uzuner 1995	8	147.5 (21.9)	3	156.7 (5.8)		1.3 %	-9.20 [-25.73, 7.33]
Subtotal (95% CI)	**8**		**3**			**1.3 %**	**-9.20 [-25.73, 7.33]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.09 (P = 0.28)							
9 Nitric oxide donor							
ENOS 2014	2000	150.2 (24.1)	2011	151.3 (23.7)		7.9 %	-1.10 [-2.58, 0.38]
Rashid 2003 10 mg	20	101.5 (13.6)	10	100.1 (15.7)		2.3 %	1.40 [-10.01, 12.81]

-50 -25 0 25 50

Lower BP Higher BP

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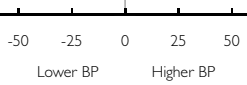
Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Rashid 2003 5 mg	20	101.7 (12.4)	10	100.1 (15.7)		2.4 %	1.60 [-9.55, 12.75]
Rashid 2003 5/10 mg	20	96.8 (10.1)	10	100.1 (15.7)		2.5 %	-3.30 [-13.99, 7.39]
Subtotal (95% CI)	**2060**		**2041**			**15.2 %**	**-1.05 [-2.50, 0.39]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.57, df = 3 (P = 0.90); I^2 =0.0%							
Test for overall effect: Z = 1.43 (P = 0.15)							
10 Thiazide-like diuretic (po)							
Eames 2005	18	167 (26)	19	164 (19)		1.6 %	3.00 [-11.74, 17.74]
Subtotal (95% CI)	**18**		**19**			**1.6 %**	**3.00 [-11.74, 17.74]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.40 (P = 0.69)							
11 Low BP target							
CATIS 2013	2038	135.2 (10.4)	2033	143.7 (14)		8.1 %	-8.50 [-9.26, -7.74]
ICH-ADAPT 2013	39	140 (19)	36	162 (12)		4.1 %	-22.00 [-29.14, -14.86]
INTERACT pilot 2008	203	133.2 (18)	201	143.3 (19)		6.6 %	-10.10 [-13.71, -6.49]
INTERACT-2 2013	1399	137.5 (17)	1430	141.53 (17)		8.0 %	-4.03 [-5.28, -2.78]
Koch 2008	21	101.1 (11.5)	21	113.9 (6.8)		5.0 %	-12.80 [-18.51, -7.09]
Subtotal (95% CI)	**3700**		**3721**			**31.8 %**	**-10.06 [-13.58, -6.55]**
Heterogeneity: Tau^2 = 12.27; Chi^2 = 57.26, df = 4 (P<0.00001); I^2 =93%							
Test for overall effect: Z = 5.61 (P < 0.00001)							
Total (95% CI)	**7843**		**7841**			**100.0 %**	**-8.02 [-10.07, -5.97]**
Heterogeneity: Tau^2 = 13.33; Chi^2 = 162.68, df = 23 (P<0.00001); I^2 =86%							
Test for overall effect: Z = 7.66 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 58.27, df = 9 (P = 0.00), I^2 =85%							



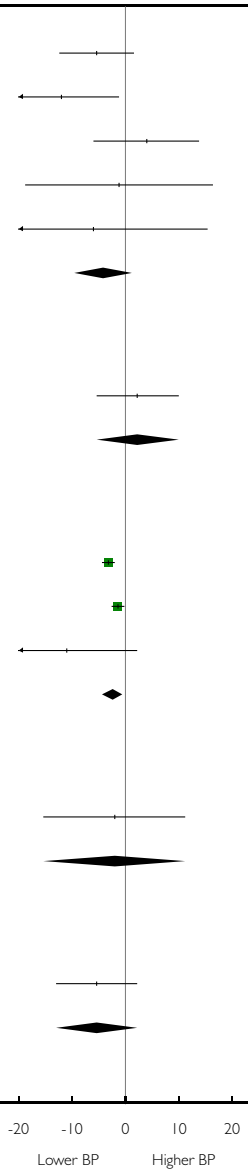
Analysis 1.29. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 29 DBP, first after randomisation by intervention.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 29 DBP, first after randomisation by intervention

Study or subgroup	Active N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 ACE inhibitors(po)							
CHHIPS 2009	29	86.8 (12)	16	92.2 (11)		2.6 %	-5.40 [-12.34, 1.54]
Dyker 1997	12	79 (14)	12	91 (13)		1.2 %	-12.00 [-22.81, -1.19]
Eveson 2007	17	92.6 (16.5)	18	88.7 (13.4)		1.4 %	3.90 [-6.09, 13.89]
Lisk 1993	3	93 (10.8)	2	94.16 (9.17)		0.5 %	-1.16 [-18.79, 16.47]
PIL-FAST 2013	6	91 (23)	8	97 (16)		0.3 %	-6.00 [-27.49, 15.49]
Subtotal (95% CI)	**67**		**56**			**6.0 %**	**-4.23 [-9.68, 1.21]**
Heterogeneity: Tau^2 = 6.57; Chi^2 = 4.78, df = 4 (P = 0.31); I^2 =16%							
Test for overall effect: Z = 1.52 (P = 0.13)							
2 ACE inhibitors (s/l)							
CHHIPS 2009	28	94.9 (12)	14	92.7 (12)		2.2 %	2.20 [-5.50, 9.90]
Subtotal (95% CI)	**28**		**14**			**2.2 %**	**2.20 [-5.50, 9.90]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.56 (P = 0.58)							
3 ARA (po)							
PRoFESS 2009	647	78.4 (10.8)	713	81.6 (11)		15.8 %	-3.20 [-4.36, -2.04]
SCAST 2011	1017	85.2 (13.9)	1012	86.6 (14.2)		15.5 %	-1.40 [-2.62, -0.18]
TAST 2013	12	81.1 (16.8)	7	92.2 (12.4)		0.8 %	-11.10 [-24.32, 2.12]
Subtotal (95% CI)	**1676**		**1732**			**32.1 %**	**-2.48 [-4.35, -0.61]**
Heterogeneity: Tau^2 = 1.48; Chi^2 = 6.06, df = 2 (P = 0.05); I^2 =67%							
Test for overall effect: Z = 2.60 (P = 0.0093)							
4 A2AA							
Lisk 1993	2	92 (2.8)	2	94.1 (9.2)		0.8 %	-2.10 [-15.43, 11.23]
Subtotal (95% CI)	**2**		**2**			**0.8 %**	**-2.10 [-15.43, 11.23]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.31 (P = 0.76)							
5 Beta-Blockers (po)							
CHHIPS 2009	28	86.8 (14)	15	92.2 (11)		2.3 %	-5.40 [-13.01, 2.21]
Subtotal (95% CI)	**28**		**15**			**2.3 %**	**-5.40 [-13.01, 2.21]**
Heterogeneity: not applicable							



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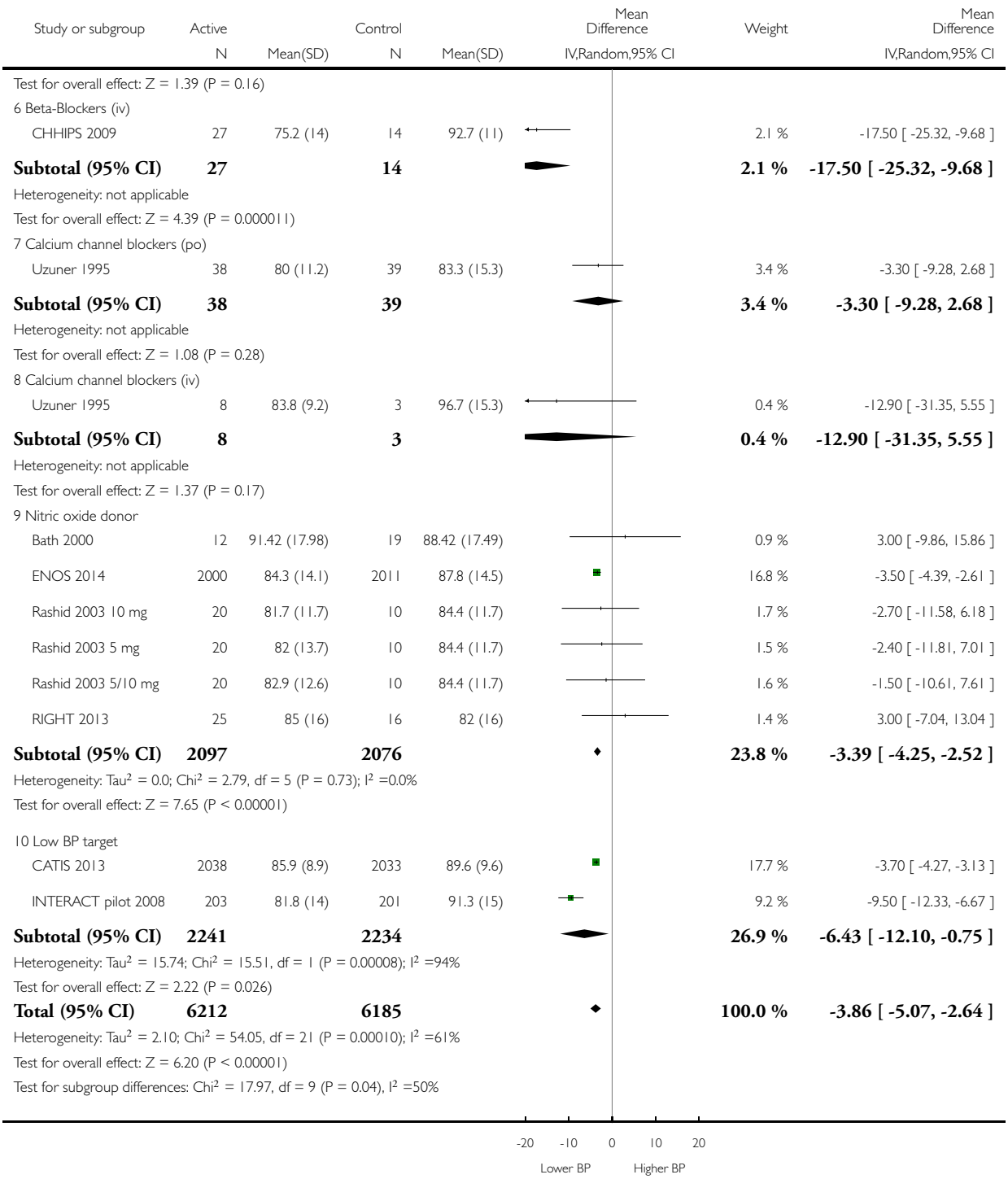

Analysis 1.30. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 30 DBP, first after randomisation by stroke type.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 30 DBP, first after randomisation by stroke type

Study or subgroup	Active N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Ischaemic stroke							
CATIS 2013	2038	85.9 (8.9)	2033	89.6 (9.6)		19.0 %	-3.70 [-4.27, -3.13]
Dyker 1997	12	79 (14)	12	91 (13)		0.8 %	-12.00 [-22.81, -1.19]
ENOS 2014	1664	83.7 (13.7)	1678	86.9 (14.2)		17.0 %	-3.20 [-4.15, -2.25]
Eveson 2007	17	92.6 (16.5)	18	88.7 (13.4)		0.9 %	3.90 [-6.09, 13.89]
Lisk 1993	3	93 (10.8)	2	94.16 (9.17)		0.3 %	-1.16 [-18.79, 16.47]
Lisk 1993	2	92 (2.8)	2	94.2 (9.2)		0.5 %	-2.20 [-15.53, 11.13]
TAST 2013	12	81.1 (16.8)	7	92.2 (12.4)		0.5 %	-11.10 [-24.32, 2.12]
Subtotal (95% CI)	**3748**		**3752**			**39.0 %**	**-3.53 [-4.20, -2.87]**
Heterogeneity: Tau² = 0.10; Chi² = 6.63, df = 6 (P = 0.36); I² =10%							
Test for overall effect: Z = 10.41 (P < 0.00001)							
2 Combined ischaemic stroke and Intracerebral haemorrhage							
Bath 2000	12	91.42 (17.98)	19	88.42 (17.49)		0.5 %	3.00 [-9.86, 15.86]
CHHIPS 2009	56	83.8 (12)	59	89.8 (11)		4.2 %	-6.00 [-10.21, -1.79]
ENOS 2014	2000	84.1 (13)	2011	87.8 (13.3)		17.8 %	-3.70 [-4.51, -2.89]
PIL-FAST 2013	6	91 (23)	8	97 (16)		0.2 %	-6.00 [-27.49, 15.49]
Rashid 2003 10 mg	20	81.7 (11.7)	10	84.4 (11.7)		1.1 %	-2.70 [-11.58, 6.18]
Rashid 2003 5 mg	20	82 (13.7)	10	84.4 (11.7)		1.0 %	-2.40 [-11.81, 7.01]
Rashid 2003 5/10 mg	20	82.9 (12.6)	10	84.4 (11.7)		1.1 %	-1.50 [-10.61, 7.61]
RIGHT 2013	25	85 (16)	16	82 (16)		0.9 %	3.00 [-7.04, 13.04]
SCAST 2011	1017	85.2 (13.9)	1012	86.6 (14.2)		15.3 %	-1.40 [-2.62, -0.18]
Uzuner 1995	38	80 (11.2)	39	83.3 (15.3)		2.3 %	-3.30 [-9.28, 2.68]
Uzuner 1995	8	83.8 (9.2)	3	96.7 (15.3)		0.3 %	-12.90 [-31.35, 5.55]
Subtotal (95% CI)	**3222**		**3197**			**44.6 %**	**-2.85 [-4.26, -1.44]**
Heterogeneity: Tau² = 1.11; Chi² = 14.88, df = 10 (P = 0.14); I² =33%							

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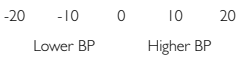
Study or subgroup	Active N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Test for overall effect: Z = 3.95 (P = 0.000078)							
3 Intracerebral haemorrhage							
ENOS 2014	310	88.1 (15.2)	319	92.3 (15.6)		9.0 %	-4.20 [-6.61, -1.79]
INTERACT pilot 2008	203	81.8 (14)	201	91.3 (15)		7.4 %	-9.50 [-12.33, -6.67]
Subtotal (95% CI)	**513**		**520**			**16.3 %**	**-6.80 [-11.99, -1.60]**
Heterogeneity: Tau^2 = 12.25; Chi^2 = 7.82, df = 1 (P = 0.01); I^2 =87%							
Test for overall effect: Z = 2.56 (P = 0.010)							
Total (95% CI)	**7483**		**7469**			**100.0 %**	**-3.73 [-4.69, -2.76]**
Heterogeneity: Tau^2 = 1.18; Chi^2 = 41.13, df = 19 (P = 0.002); I^2 =54%							
Test for overall effect: Z = 7.59 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 2.36, df = 2 (P = 0.31), I^2 =15%							



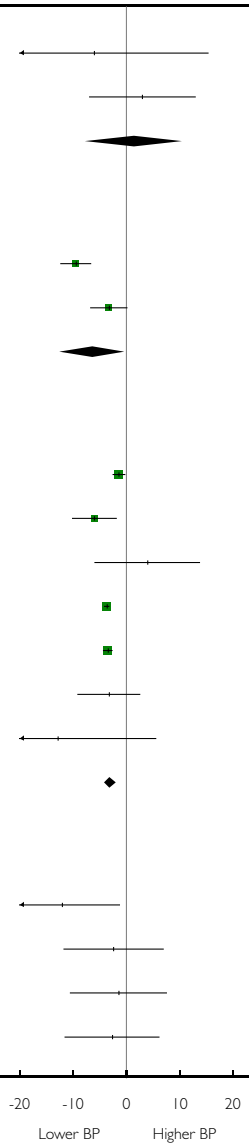
Analysis 1.31. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 31 DBP, first after randomisation by time to treatment.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 31 DBP, first after randomisation by time to treatment

Study or subgroup	Active N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Ultra-acute/prehospital							
PIL-FAST 2013	6	91 (23)	8	97 (16)		0.3 %	-6.00 [-27.49, 15.49]
RIGHT 2013	25	85 (16)	16	82 (16)		1.5 %	3.00 [-7.04, 13.04]
Subtotal (95% CI)	**31**		**24**			**1.8 %**	**1.39 [-7.71, 10.48]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.55$, df = 1 (P = 0.46); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.30 (P = 0.77)							
2 Hyper-acute							
INTERACT pilot 2008	203	81.8 (14)	201	91.3 (15)		10.4 %	-9.50 [-12.33, -6.67]
ENOS 2014	144	84.5 (15)	129	87.8 (14)		8.3 %	-3.30 [-6.74, 0.14]
Subtotal (95% CI)	**347**		**330**			**18.7 %**	**-6.48 [-12.55, -0.41]**
Heterogeneity: $Tau^2 = 16.64$; $Chi^2 = 7.44$, df = 1 (P = 0.01); $I^2 = 87\%$							
Test for overall effect: Z = 2.09 (P = 0.037)							
3 Acute							
SCAST 2011	1017	85.2 (13.9)	1012	86.6 (14.2)		18.1 %	-1.40 [-2.62, -0.18]
CHHIPS 2009	56	83.8 (12)	59	89.8 (11)		6.4 %	-6.00 [-10.21, -1.79]
Eveson 2007	17	92.6 (16.5)	18	88.7 (13.4)		1.5 %	3.90 [-6.09, 13.89]
CATIS 2013	2038	85.9 (8.9)	2033	89.6 (9.6)		20.9 %	-3.70 [-4.27, -3.13]
ENOS 2014	1856	84.3 (14)	1882	87.8 (14.6)		19.6 %	-3.50 [-4.42, -2.58]
Uzuner 1995	38	80 (11.2)	39	83.3 (15.3)		3.7 %	-3.30 [-9.28, 2.68]
Uzuner 1995	8	83.8 (9.2)	3	96.7 (15.3)		0.5 %	-12.90 [-31.35, 5.55]
Subtotal (95% CI)	**5030**		**5046**			**70.6 %**	**-3.11 [-4.26, -1.97]**
Heterogeneity: $Tau^2 = 0.93$; $Chi^2 = 15.90$, df = 6 (P = 0.01); $I^2 = 62\%$							
Test for overall effect: Z = 5.35 (P < 0.00001)							
4 Subacute							
Dyker 1997	12	79 (14)	12	91 (13)		1.3 %	-12.00 [-22.81, -1.19]
Rashid 2003 5 mg	20	82 (13.7)	10	84.4 (11.7)		1.7 %	-2.40 [-11.81, 7.01]
Rashid 2003 5/10 mg	20	82.9 (12.6)	10	84.4 (11.7)		1.8 %	-1.50 [-10.61, 7.61]
Rashid 2003 10 mg	20	81.7 (11.7)	10	84.4 (11.7)		1.8 %	-2.70 [-11.58, 6.18]



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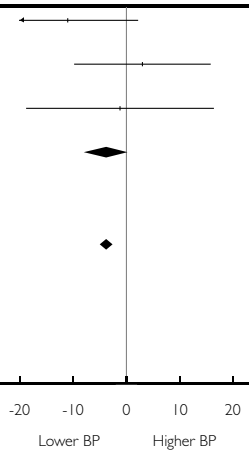
Study or subgroup	Active N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
TAST 2013	12	81.1 (16.8)	7	92.2 (12.4)		0.9 %	-11.10 [-24.32, 2.12]
Bath 2000	12	91.42 (17.98)	19	88.42 (17.49)		0.9 %	3.00 [-9.86, 15.86]
Lisk 1993	3	93 (10.8)	2	94.16 (9.17)		0.5 %	-1.16 [-18.79, 16.47]
Subtotal (95% CI)	**99**		**70**			**8.8 %**	**-3.88 [-7.98, 0.22]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 4.93, df = 6 (P = 0.55); I^2 =0.0%							
Test for overall effect: Z = 1.86 (P = 0.063)							
Total (95% CI)	**5507**		**5470**			**100.0 %**	**-3.80 [-5.06, -2.54]**
Heterogeneity: Tau^2 = 1.90; Chi^2 = 40.17, df = 17 (P = 0.001); I^2 =58%							
Test for overall effect: Z = 5.91 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 2.23, df = 3 (P = 0.53), I^2 =0.0%							

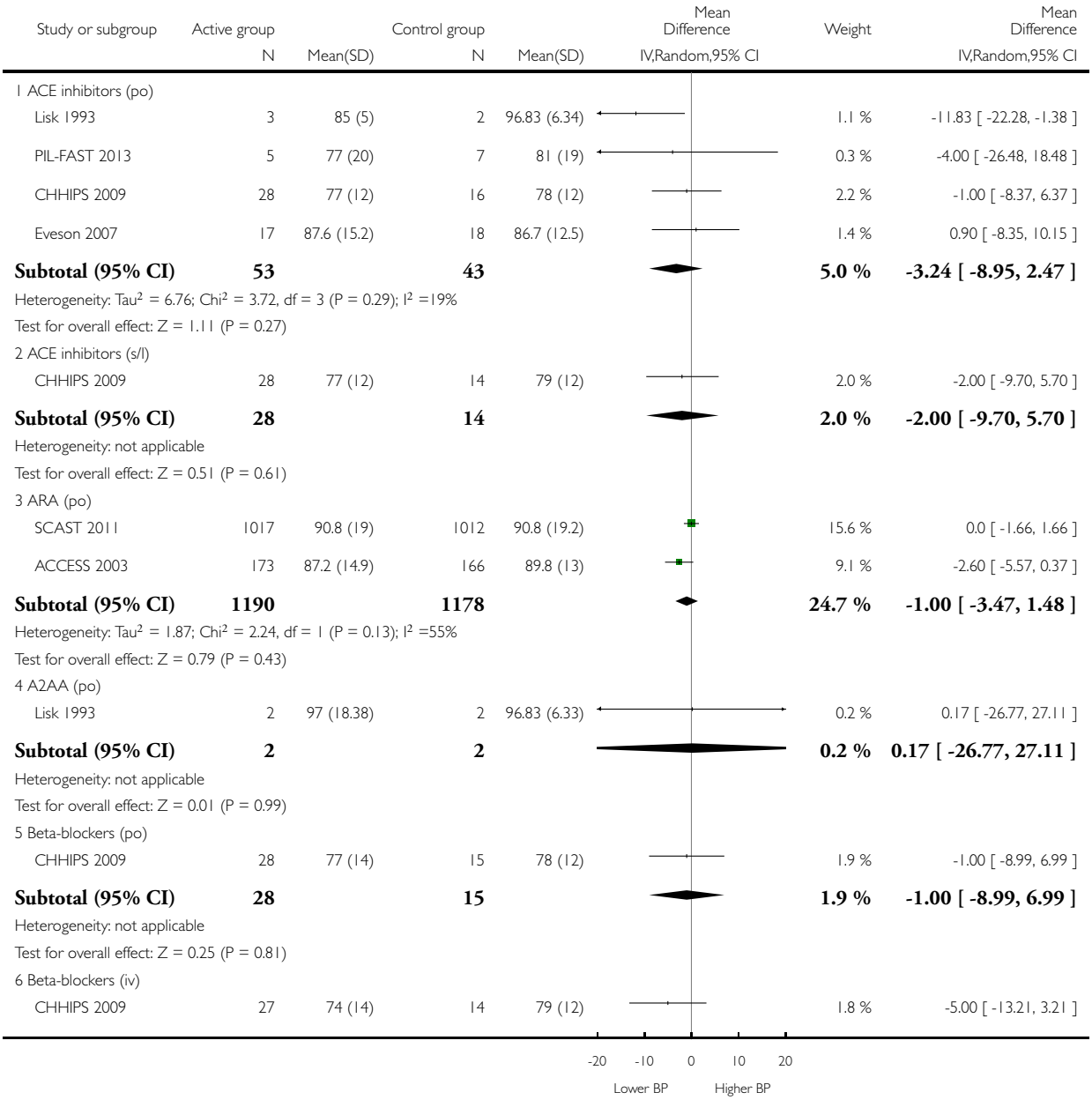


Analysis 1.32. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 32 DBP, at day 1.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 32 DBP, at day 1



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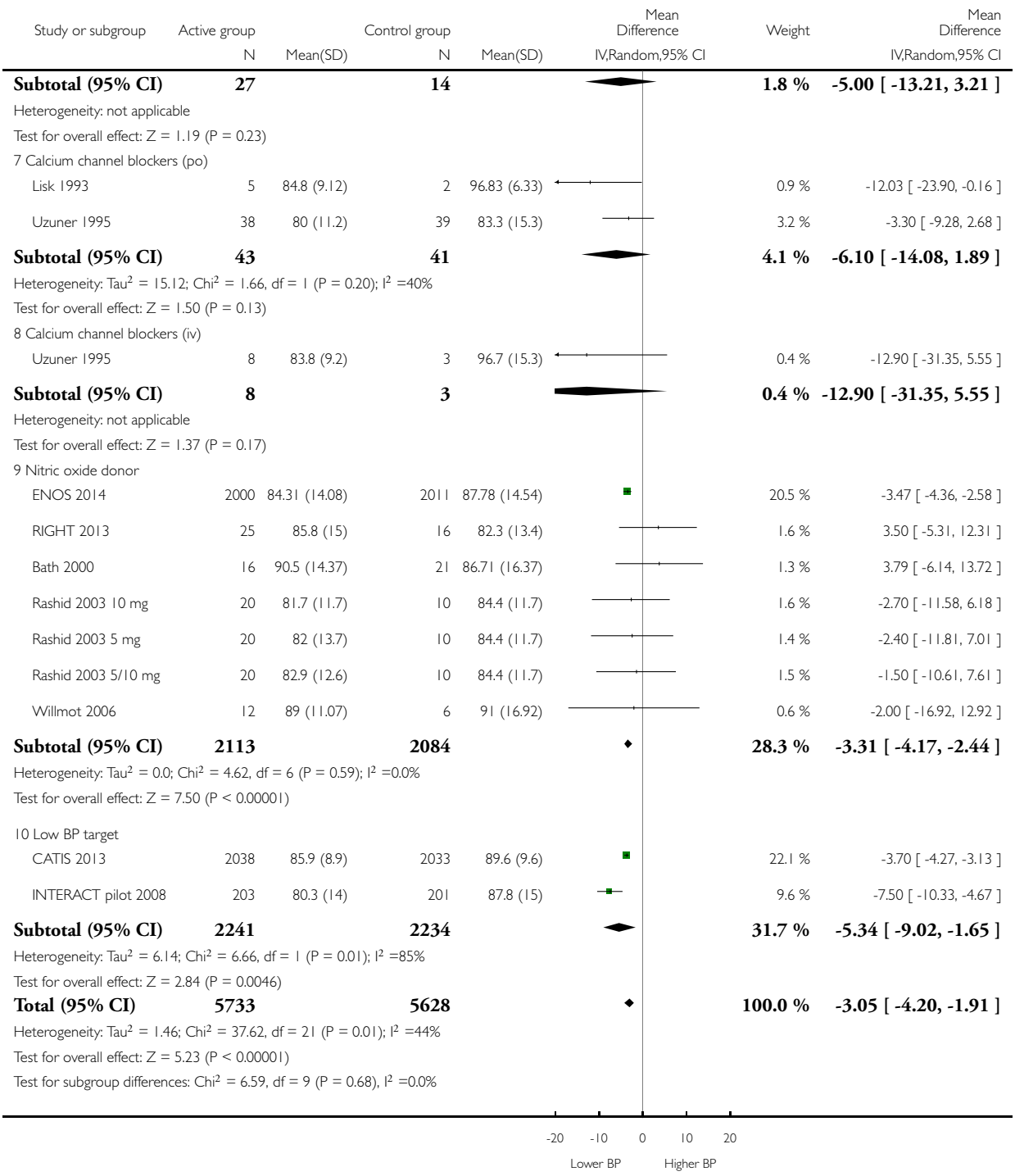


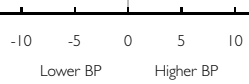
Analysis 1.33. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 33 DBP, at day 7.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 33 DBP, at day 7

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 ACE inhibitors							
PIL-FAST 2013	4	73 (3)	7	91 (20)		0.5 %	-18.00 [-33.10, -2.90]
Subtotal (95% CI)	**4**		**7**			**0.5 %**	**-18.00 [-33.10, -2.90]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.34 (P = 0.020)							
2 ARA(po)							
ACCESS 2003	173	75.8 (20.9)	166	75.8 (19.7)		4.6 %	0.0 [-4.32, 4.32]
PRoFESS 2009	647	78.4 (10.8)	713	81.6 (11)		15.7 %	-3.20 [-4.36, -2.04]
SCAST 2011	1017	82 (14)	1012	84 (14)		15.4 %	-2.00 [-3.22, -0.78]
TAST 2013	12	78.2 (16.8)	7	92.2 (12.4)		0.6 %	-14.00 [-27.22, -0.78]
VENTURE 2013	203	84.7 (2.5)	202	87.1 (2.7)		18.5 %	-2.40 [-2.91, -1.89]
Subtotal (95% CI)	**2052**		**2100**			**54.9 %**	**-2.47 [-3.24, -1.70]**
Heterogeneity: Tau^2 = 0.26; Chi^2 = 6.34, df = 4 (P = 0.18); I^2 =37%							
Test for overall effect: Z = 6.31 (P < 0.00001)							
3 Nitric oxide donor							
ENOS 2014	2000	82.9 (14.7)	2011	84 (14.4)		17.0 %	-1.10 [-2.00, -0.20]
Subtotal (95% CI)	**2000**		**2011**			**17.0 %**	**-1.10 [-2.00, -0.20]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.39 (P = 0.017)							
4 Thiazide-like diuretic (po)							
Eames 2005	18	78 (15)	19	83 (19)		0.9 %	-5.00 [-16.00, 6.00]
Subtotal (95% CI)	**18**		**19**			**0.9 %**	**-5.00 [-16.00, 6.00]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.89 (P = 0.37)							
5 Low BP target							
CATIS 2013	2038	82.4 (7.2)	2033	86.4 (8.1)		18.6 %	-4.00 [-4.47, -3.53]
INTERACT pilot 2008	203	77.2 (14)	201	83.2 (15)		8.2 %	-6.00 [-8.83, -3.17]
Subtotal (95% CI)	**2241**		**2234**			**26.8 %**	**-4.49 [-6.18, -2.80]**
Heterogeneity: Tau^2 = 0.93; Chi^2 = 1.87, df = 1 (P = 0.17); I^2 =46%							
Test for overall effect: Z = 5.21 (P < 0.00001)							
Total (95% CI)	**6315**		**6371**			**100.0 %**	**-2.90 [-3.96, -1.83]**



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Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Heterogeneity: Tau² = 1.53; Chi² = 55.21, df = 9 (P<0.00001); I² =84%							
Test for overall effect: Z = 5.33 (P < 0.00001)							
Test for subgroup differences: Chi² = 17.75, df = 4 (P = 0.00), I² =77%							

Analysis 1.34. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 34 DBP, at end of treatment.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 34 DBP, at end of treatment

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 ACE inhibitors (po)							
CHHIPS 2009	29	86.8 (12)	16	90.8 (11)		2.4 %	-4.00 [-10.94, 2.94]
Dyker 1997	14	83 (9)	14	83 (14)		1.6 %	0.0 [-8.72, 8.72]
Eveson 2007	18	78 (6)	21	86 (9)		4.2 %	-8.00 [-12.74, -3.26]
PIL-FAST 2013	4	73 (3)	7	91 (20)		0.6 %	-18.00 [-33.10, -2.90]
Subtotal (95% CI)	**65**		**58**			**8.8 %**	**-6.06 [-11.18, -0.95]**
Heterogeneity: Tau² = 11.28; Chi² = 5.23, df = 3 (P = 0.16); I² =43%							
Test for overall effect: Z = 2.32 (P = 0.020)							
2 ARA (po)							
ACCESS 2003	173	77.4 (14.9)	166	77.4 (13)		7.0 %	0.0 [-2.97, 2.97]
ACCOST 2006	19	82.3 (3.5)	19	92.4 (3.6)		8.5 %	-10.10 [-12.36, -7.84]
PRoFESS 2009	647	79.2 (11.1)	713	81.5 (11.2)		10.9 %	-2.30 [-3.49, -1.11]
SCAST 2011	1012	82 (14)	1017	84 (14)		10.8 %	-2.00 [-3.22, -0.78]
TAST 2013	12	79.9 (16.8)	7	97.5 (12.4)		0.8 %	-17.60 [-30.82, -4.38]

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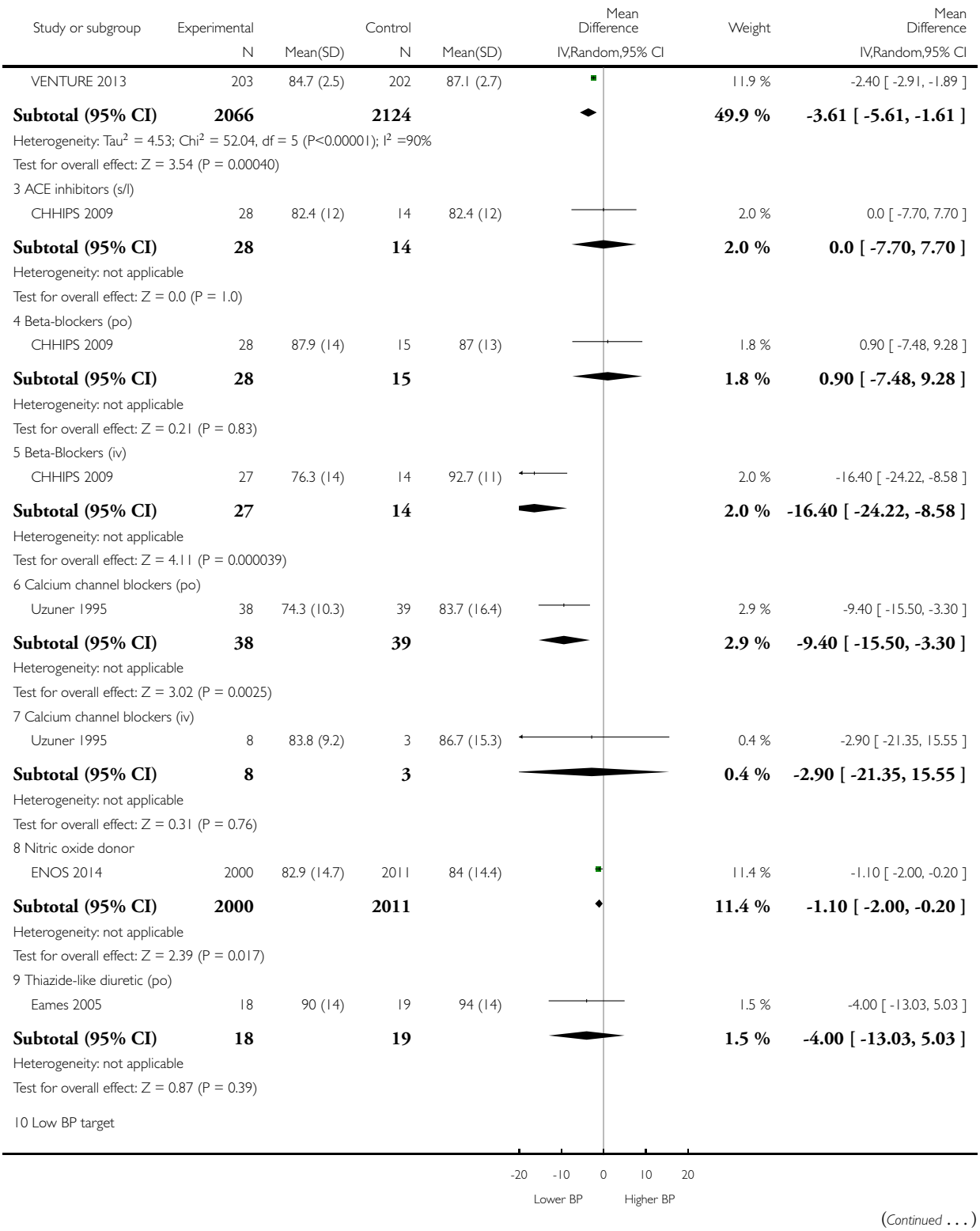

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Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
CATIS 2013	2038	81.4 (7.4)	2033	85.3 (8.3)		12.0 %	-3.90 [-4.38, -3.42]
INTERACT pilot 2008	203	77.4 (14)	201	83.1 (15)		7.3 %	-5.70 [-8.53, -2.87]
Subtotal (95% CI)	**2241**		**2234**			**19.2 %**	**-4.24 [-5.62, -2.86]**
Heterogeneity: Tau^2 = 0.55; Chi^2 = 1.51, df = 1 (P = 0.22); I^2 =34%							
Test for overall effect: Z = 6.03 (P < 0.00001)							
Total (95% CI)	**6519**		**6531**			**100.0 %**	**-3.95 [-5.15, -2.75]**
Heterogeneity: Tau^2 = 3.08; Chi^2 = 115.40, df = 18 (P<0.00001); I^2 =84%							
Test for overall effect: Z = 6.46 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 36.65, df = 9 (P = 0.00), I^2 =75%							

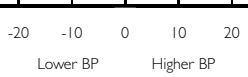
Analysis 1.35. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 35 HR at baseline.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 35 HR at baseline

Study or subgroup	Active group N	Mean(SD)	Control group N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 ACE inhibitors (po)							
Lisk 1993	1	63 (0)	1	79.5 (22.64)			Not estimable
Dyker 1997	12	69.75 (8.71)	12	68.73 (8.82)		1.7 %	1.02 [-5.99, 8.03]
Eveson 2007	17	73.1 (10)	18	74.2 (16.5)		1.0 %	-1.10 [-10.08, 7.88]
Subtotal (95% CI)	**30**		**31**			**2.7 %**	**0.22 [-5.31, 5.75]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.13, df = 1 (P = 0.72); I^2 =0.0%							
Test for overall effect: Z = 0.08 (P = 0.94)							
2 ARA(po)							
PRoFESS 2009	647	72.8 (11.9)	713	73.1 (11.4)		35.5 %	-0.30 [-1.54, 0.94]
TAST 2013	12	69.6 (15.8)	7	74.6 (14.6)		0.4 %	-5.00 [-19.03, 9.03]



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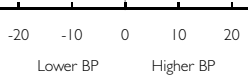
Study or subgroup	Active group N	Mean(SD)	Control group N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Subtotal (95% CI)	**659**		**720**			**35.9 %**	**-0.34 [-1.57, 0.90]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.43, df = 1 (P = 0.51); I^2 =0.0%							
Test for overall effect: Z = 0.53 (P = 0.59)							
3 A2AA (po)							
Lisk 1993	1	76 (0)	1	79.5 (22.6)			Not estimable
Subtotal (95% CI)	**1**		**1**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
4 Calcium channel blockers (po)							
Lisk 1993	1	71 (0)	1	79.5 (22.64)			Not estimable
Uzuner 1995	38	86.6 (10.67)	39	90.2 (15.27)		2.4 %	-3.60 [-9.47, 2.27]
Subtotal (95% CI)	**39**		**40**			**2.4 %**	**-3.60 [-9.47, 2.27]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.20 (P = 0.23)							
5 Nitric oxide donor							
RIGHT 2013	25	85.6 (18.6)	16	78.1 (16.4)		0.7 %	7.50 [-3.35, 18.35]
ENOS 2014	2000	77.69 (14.79)	2011	77.34 (14.64)		50.4 %	0.35 [-0.56, 1.26]
Bath 2000	16	83.63 (17.04)	21	71.19 (12.32)		0.9 %	12.44 [2.57, 22.31]
Rashid 2003 10 mg	20	75.05 (9.64)	10	77.83 (14.01)		0.9 %	-2.78 [-12.44, 6.88]
Rashid 2003 5 mg	20	81.55 (16.62)	10	77.83 (14.01)		0.7 %	3.72 [-7.61, 15.05]
Rashid 2003 5/10 mg	20	77.3 (19.55)	10	77.83 (14.01)		0.6 %	-0.53 [-12.73, 11.67]
Willmot 2006	12	69.42 (13.87)	6	65.83 (15.12)		0.4 %	3.59 [-10.83, 18.01]
Subtotal (95% CI)	**2113**		**2084**			**54.5 %**	**2.26 [-1.26, 5.77]**
Heterogeneity: Tau^2 = 6.22; Chi^2 = 8.28, df = 6 (P = 0.22); I^2 =28%							
Test for overall effect: Z = 1.26 (P = 0.21)							
6 Thiazide-like diuretic (po)							
Eames 2005	18	68 (11)	19	72 (9)		2.0 %	-4.00 [-10.50, 2.50]
Subtotal (95% CI)	**18**		**19**			**2.0 %**	**-4.00 [-10.50, 2.50]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.21 (P = 0.23)							
7 Calcium channel blockers (iv)							
Uzuner 1995	8	97.3 (7.6)	3	92 (7)		0.9 %	5.30 [-4.21, 14.81]
Subtotal (95% CI)	**8**		**3**			**0.9 %**	**5.30 [-4.21, 14.81]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.09 (P = 0.27)							
8 Low BP target							
ICH-ADAPT 2013	39	76 (15)	36	79 (18)		1.5 %	-3.00 [-10.53, 4.53]
Subtotal (95% CI)	**39**		**36**			**1.5 %**	**-3.00 [-10.53, 4.53]**



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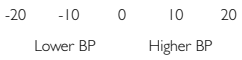
Study or subgroup	Active group N	Mean(SD)	Control group N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Heterogeneity: not applicable							
Test for overall effect: Z = 0.78 (P = 0.44)							
Total (95% CI)	**2907**		**2934**			**100.0 %**	**0.07 [-0.86, 0.99]**
Heterogeneity: Tau^2 = 0.22; Chi^2 = 14.94, df = 14 (P = 0.38); I^2 =6%							
Test for overall effect: Z = 0.14 (P = 0.89)							
Test for subgroup differences: Chi^2 = 6.35, df = 6 (P = 0.39), I^2 =6%							



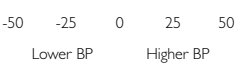
Analysis 1.36. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 36 HR, first after randomisation.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 36 HR, first after randomisation

Study or subgroup	Active group N	Mean(SD)	Control group N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 ACE inhibitors (po)							
Lisk 1993	2	94 (36.76)	2	74.4 (21.3)		0.4 %	19.60 [-39.28, 78.48]
Eveson 2007	17	74 (10.8)	18	75.1 (17.1)		11.7 %	-1.10 [-10.52, 8.32]
Subtotal (95% CI)	**19**		**20**			**12.1 %**	**-0.58 [-9.89, 8.72]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.46, df = 1 (P = 0.50); I^2 =0.0%							
Test for overall effect: Z = 0.12 (P = 0.90)							
2 ARA(po)							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
3 Calcium channel blockers (po)							
Lisk 1993	3	98.66 (28.72)	2	74.4 (21.3)		0.8 %	24.26 [-19.64, 68.16]
Uzuner 1995	38	83.8 (11.5)	39	88.6 (17)		18.5 %	-4.80 [-11.27, 1.67]



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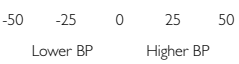
Study or subgroup	Active group N	Mean(SD)	Control group N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Subtotal (95% CI)	**41**		**41**			**19.2 %**	**1.28 [-21.89, 24.46]**
Heterogeneity: Tau^2 = 165.90; Chi^2 = 1.65, df = 1 (P = 0.20); I^2 =39%							
Test for overall effect: Z = 0.11 (P = 0.91)							
4 A2AA (po)							
Lisk 1993	1	0 (0)	2	74.4 (21.31)			Not estimable
Subtotal (95% CI)	**1**		**2**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
5 Nitric oxide donor							
ENOS 2014	2000	79 (15.1)	2011	77.3 (14.9)		37.3 %	1.70 [0.77, 2.63]
Bath 2000	13	79.1 (15.2)	19	69.5 (12.7)		10.7 %	9.60 [-0.44, 19.64]
Willmot 2006	12	72.83 (11.1)	6	65.5 (12.16)		8.6 %	7.33 [-4.25, 18.91]
Subtotal (95% CI)	**2025**		**2036**			**56.7 %**	**3.95 [-1.03, 8.93]**
Heterogeneity: Tau^2 = 9.38; Chi^2 = 3.24, df = 2 (P = 0.20); I^2 =38%							
Test for overall effect: Z = 1.56 (P = 0.12)							
6 Calcium channel blockers (iv)							
Uzuner 1995	8	98 (11.7)	3	88 (4)		11.9 %	10.00 [0.71, 19.29]
Subtotal (95% CI)	**8**		**3**			**11.9 %**	**10.00 [0.71, 19.29]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.11 (P = 0.035)							
Total (95% CI)	**2094**		**2102**			**100.0 %**	**2.74 [-1.13, 6.61]**
Heterogeneity: Tau^2 = 10.23; Chi^2 = 11.94, df = 7 (P = 0.10); I^2 =41%							
Test for overall effect: Z = 1.39 (P = 0.17)							
Test for subgroup differences: Chi^2 = 2.58, df = 3 (P = 0.46), I^2 =0.0%							

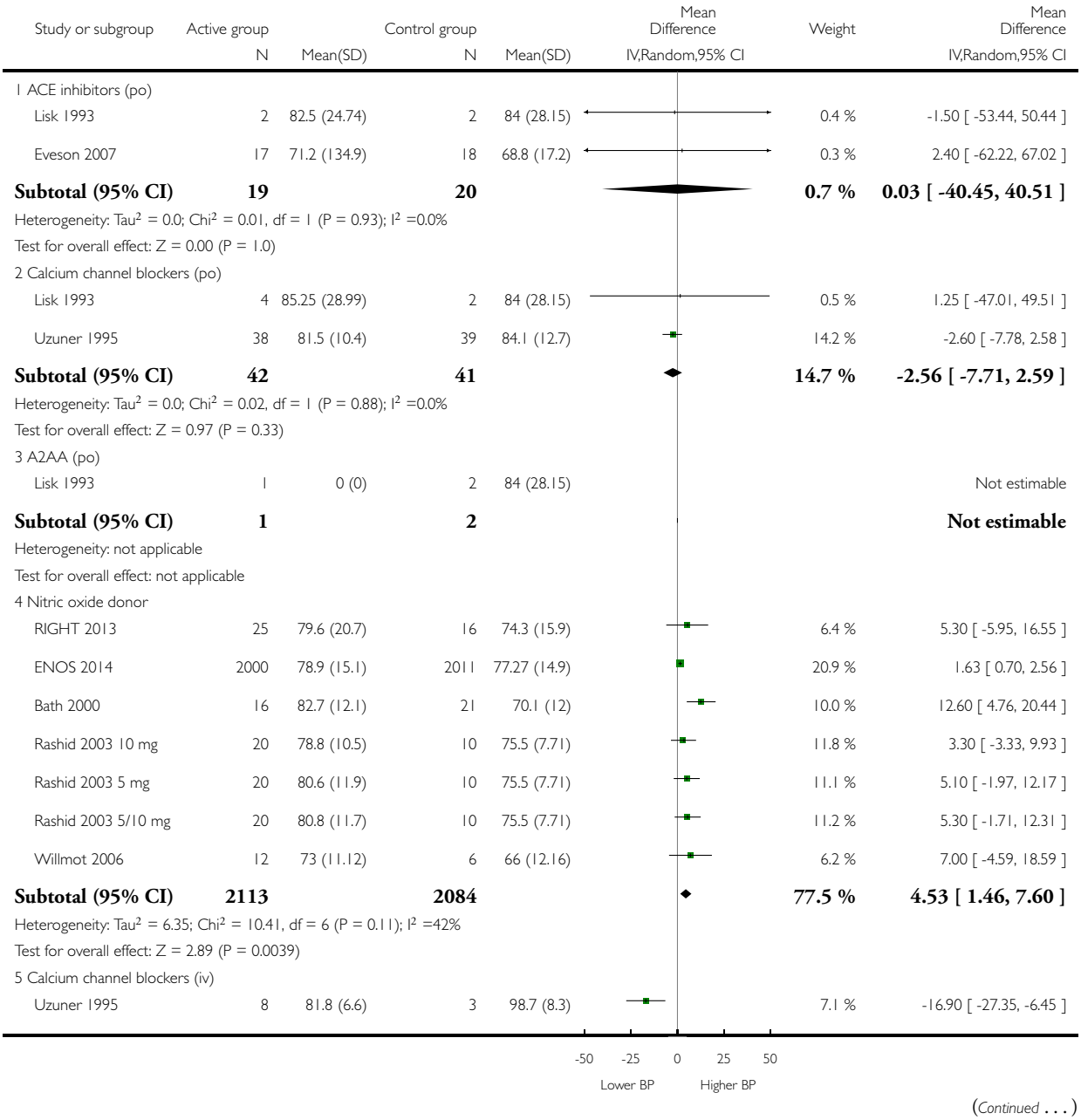


Analysis 1.37. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 37 HR, at day 1.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 37 HR, at day 1



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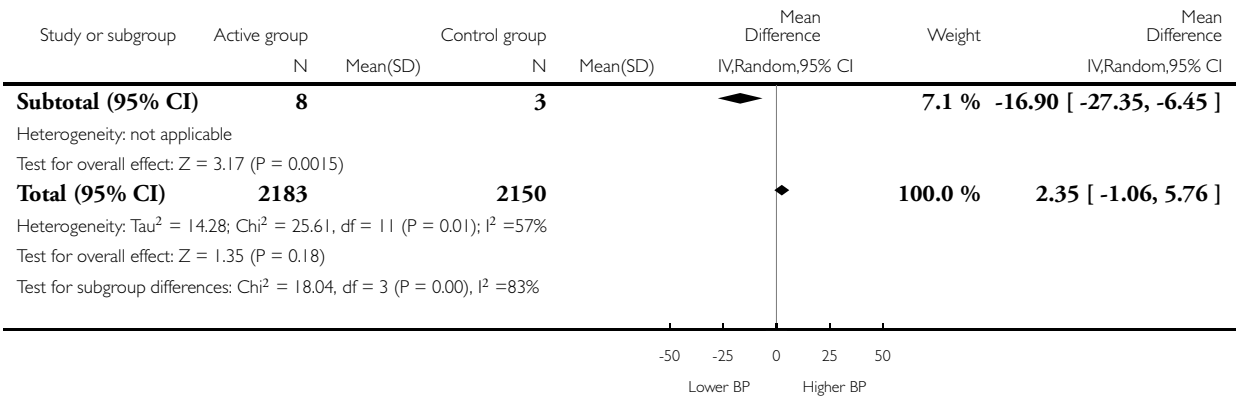
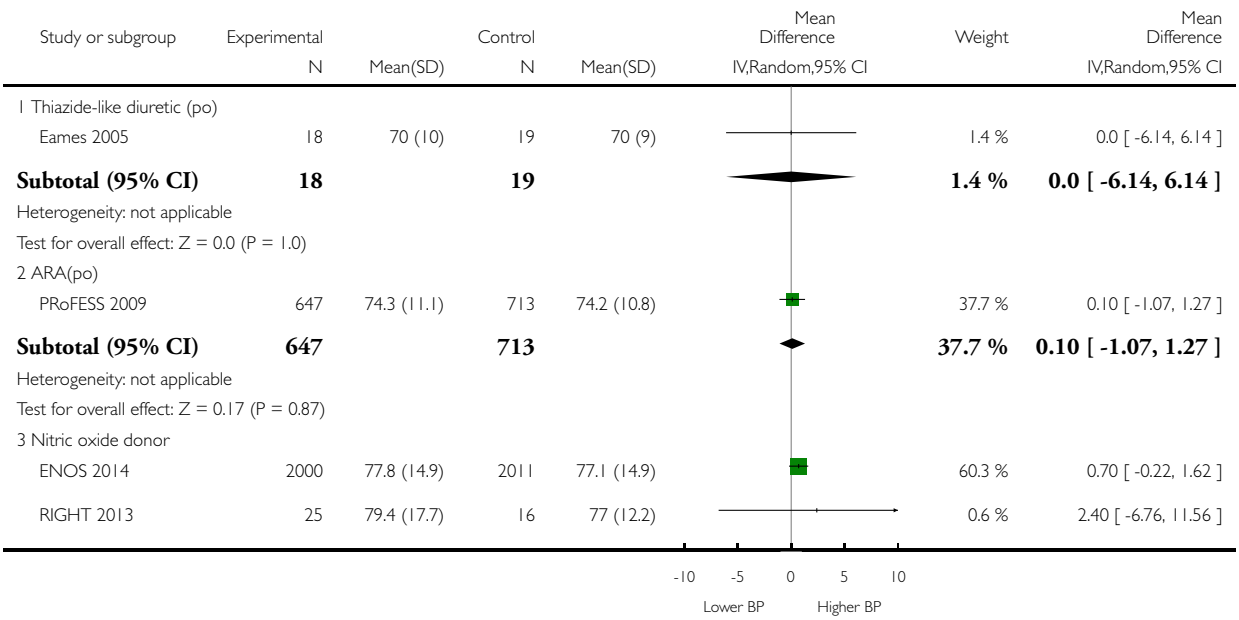


Analysis 1.38. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 38 HR, at day 7.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 38 HR, at day 7



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Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Subtotal (95% CI)	**2025**		**2027**			**60.9 %**	**0.72 [-0.20, 1.63]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.13, df = 1 (P = 0.72); I^2 =0.0%							
Test for overall effect: Z = 1.53 (P = 0.13)							
Total (95% CI)	**2690**		**2759**			**100.0 %**	**0.47 [-0.24, 1.19]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.82, df = 3 (P = 0.85); I^2 =0.0%							
Test for overall effect: Z = 1.30 (P = 0.19)							
Test for subgroup differences: Chi^2 = 0.69, df = 2 (P = 0.71), I^2 =0.0%							

Analysis 1.39. Comparison 1 Blood pressure lowering therapy in acute stroke, Outcome 39 HR, at end of treatment.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 1 Blood pressure lowering therapy in acute stroke

Outcome: 39 HR, at end of treatment

Study or subgroup	Active N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 ACE inhibitors							
Eveson 2007	17	71.2 (134.9)	18	68.8 (17.2)		0.0 %	2.40 [-62.22, 67.02]
Subtotal (95% CI)	**17**		**18**			**0.0 %**	**2.40 [-62.22, 67.02]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.07 (P = 0.94)							
2 Thiazide- like diuretic							
Eames 2005	18	70 (10)	19	70 (9)		2.2 %	0.0 [-6.14, 6.14]
Subtotal (95% CI)	**18**		**19**			**2.2 %**	**0.0 [-6.14, 6.14]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
3 Nitric oxide donor							
ENOS 2014	2000	77.8 (14.9)	2011	77.1 (14.9)		96.8 %	0.70 [-0.22, 1.62]

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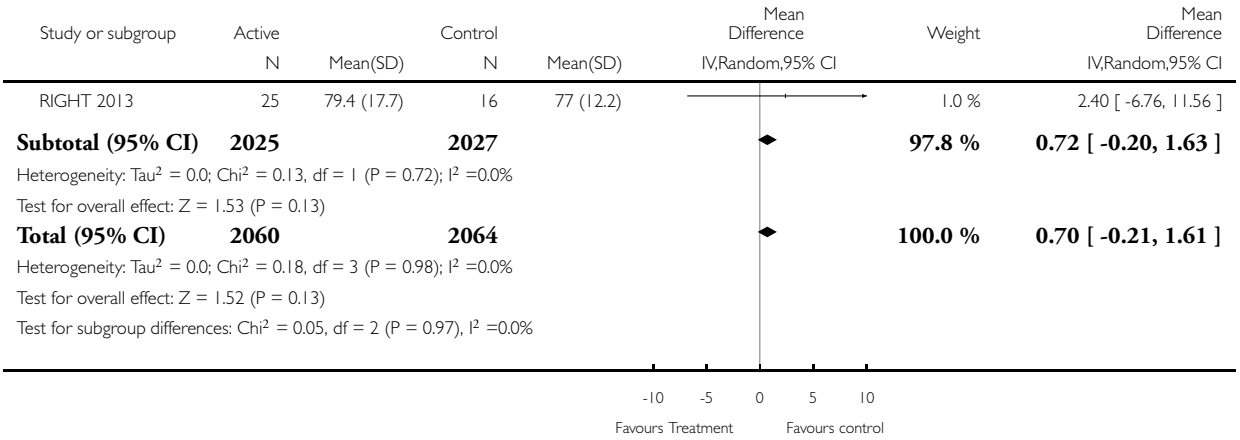
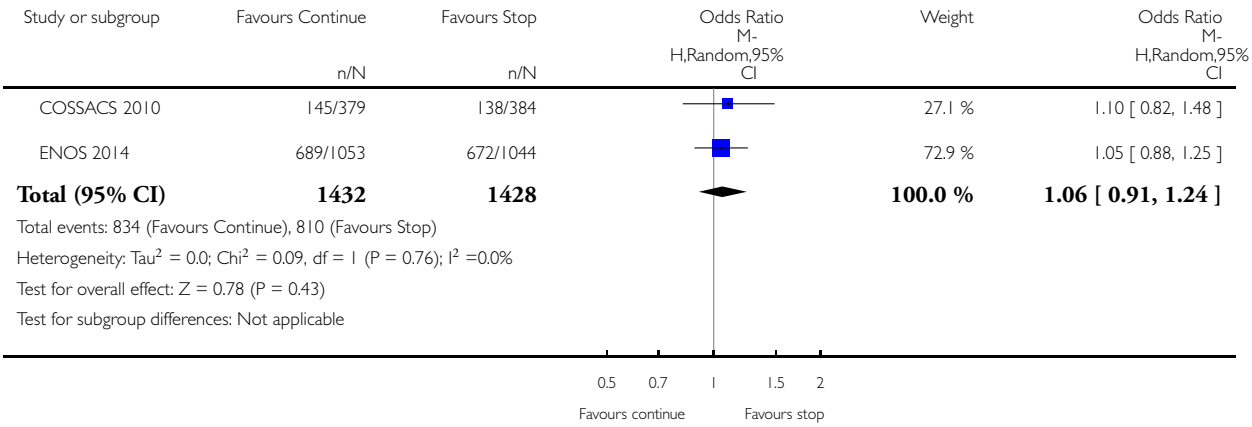


Analysis 2.1. Comparison 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S), Outcome 1 Death or dependency, end of trial by C/S.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S)

Outcome: 1 Death or dependency, end of trial by C/S

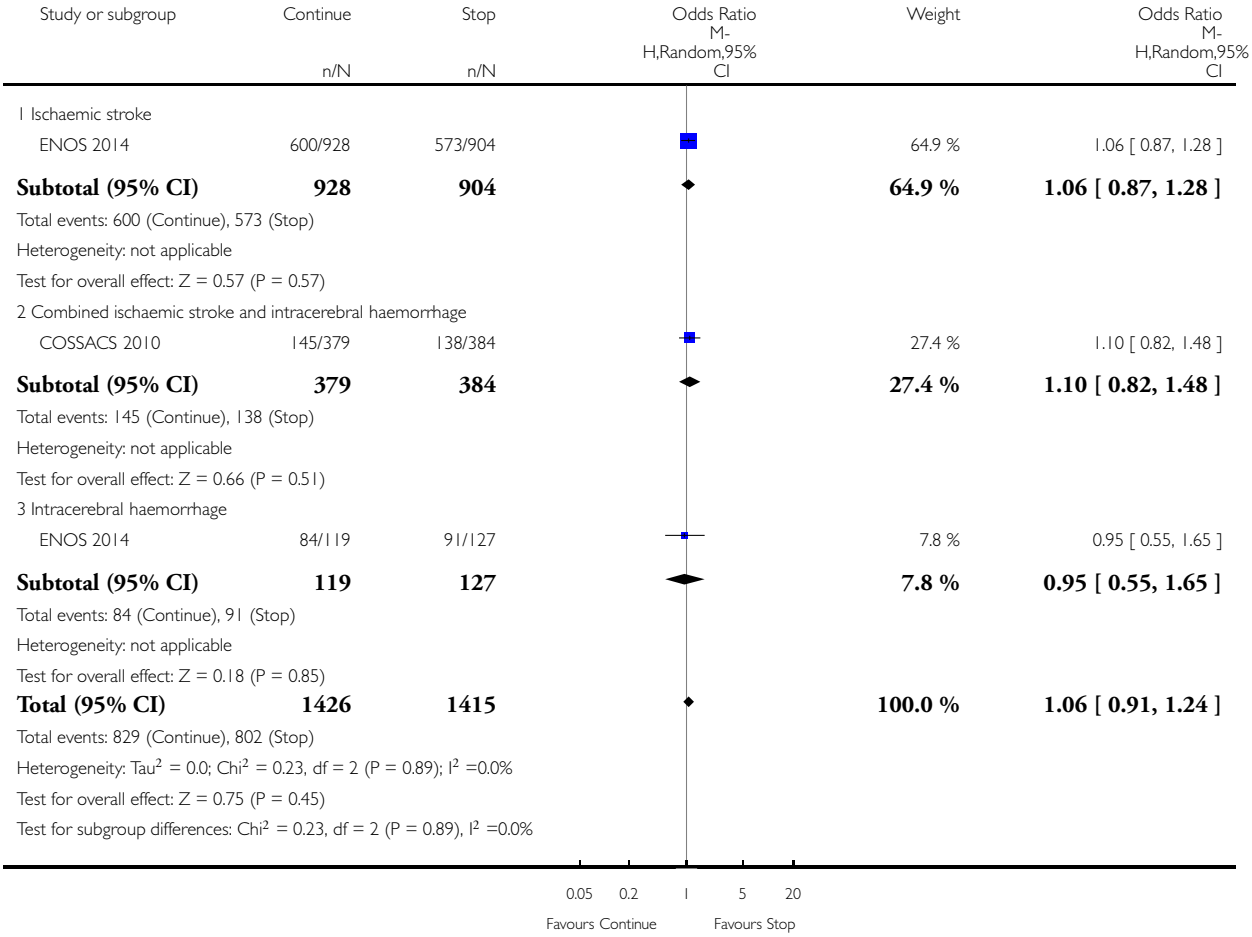


Analysis 2.2. Comparison 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S), Outcome 2 Death or dependency, end of trial by stroke type C/S.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S)

Outcome: 2 Death or dependency, end of trial by stroke type C/S



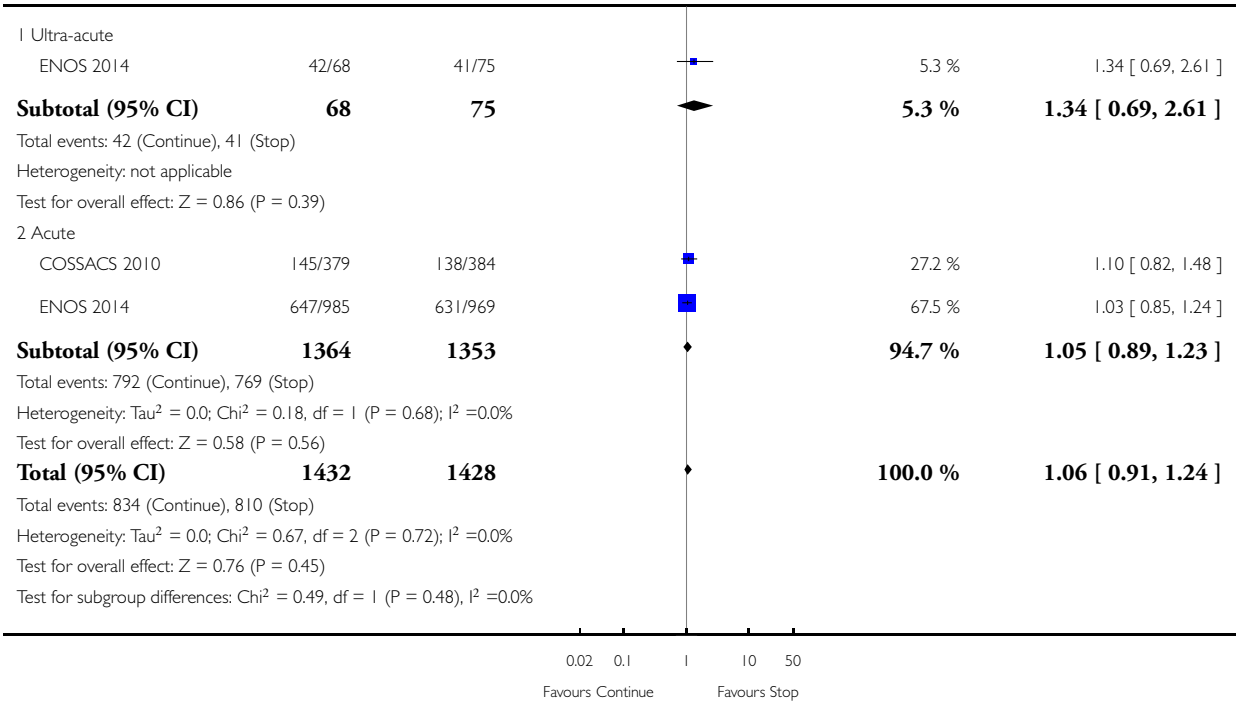
Analysis 2.3. Comparison 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S), Outcome 3 Death or dependency, end of trial by time to treatment.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S)

Outcome: 3 Death or dependency, end of trial by time to treatment

Study or subgroup	Continue n/N	Stop n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Ultra-acute					
ENOS 2014	42/68	41/75		5.3 %	1.34 [0.69, 2.61]
Subtotal (95% CI)	**68**	**75**		**5.3 %**	**1.34 [0.69, 2.61]**
Total events: 42 (Continue), 41 (Stop)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.86 (P = 0.39)					
2 Acute					
COSSACS 2010	145/379	138/384		27.2 %	1.10 [0.82, 1.48]
ENOS 2014	647/985	631/969		67.5 %	1.03 [0.85, 1.24]
Subtotal (95% CI)	**1364**	**1353**		**94.7 %**	**1.05 [0.89, 1.23]**
Total events: 792 (Continue), 769 (Stop)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.18, df = 1 (P = 0.68); I^2 =0.0%					
Test for overall effect: Z = 0.58 (P = 0.56)					
Total (95% CI)	**1432**	**1428**		**100.0 %**	**1.06 [0.91, 1.24]**
Total events: 834 (Continue), 810 (Stop)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.67, df = 2 (P = 0.72); I^2 =0.0%					
Test for overall effect: Z = 0.76 (P = 0.45)					
Test for subgroup differences: Chi^2 = 0.49, df = 1 (P = 0.48), I^2 =0.0%					



Analysis 2.4. Comparison 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S), Outcome 4 Death early, by C/S.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S)

Outcome: 4 Death early, by C/S

Study or subgroup	Continue n/N	Stop n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
COSSACS 2010	4/379	7/384		23.1 %	0.57 [0.17, 1.98]
ENOS 2014	34/1053	27/1044		76.9 %	1.26 [0.75, 2.10]
Total (95% CI)	**1432**	**1428**		**100.0 %**	**1.05 [0.55, 2.00]**

Total events: 38 (Continue), 34 (Stop)

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 1.31$, df = 1 (P = 0.25); $I^2 = 24\%$

Test for overall effect: Z = 0.14 (P = 0.89)

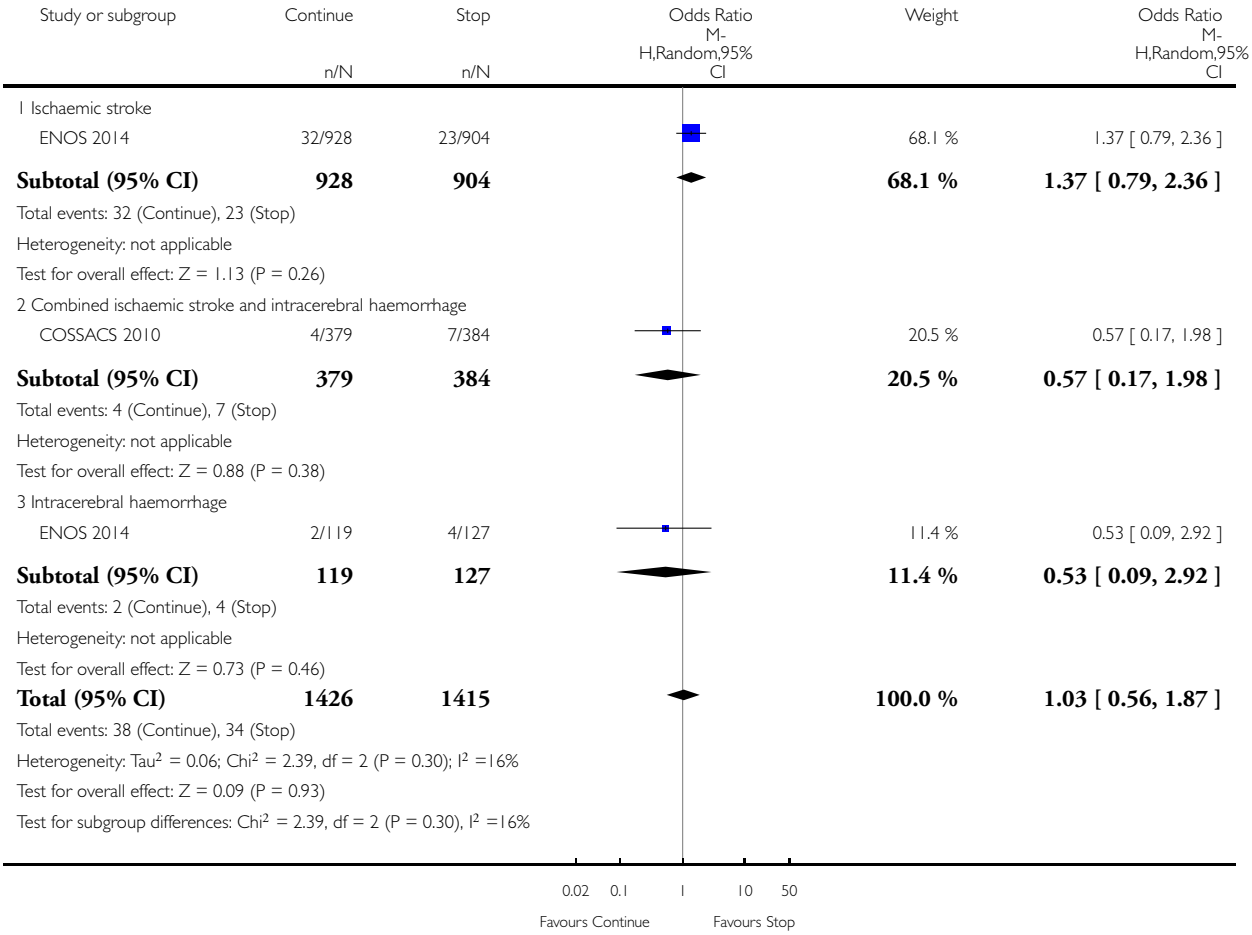
Test for subgroup differences: Not applicable

Analysis 2.5. Comparison 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S), Outcome 5 Death early, by stroke type C/S.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S)

Outcome: 5 Death early, by stroke type C/S

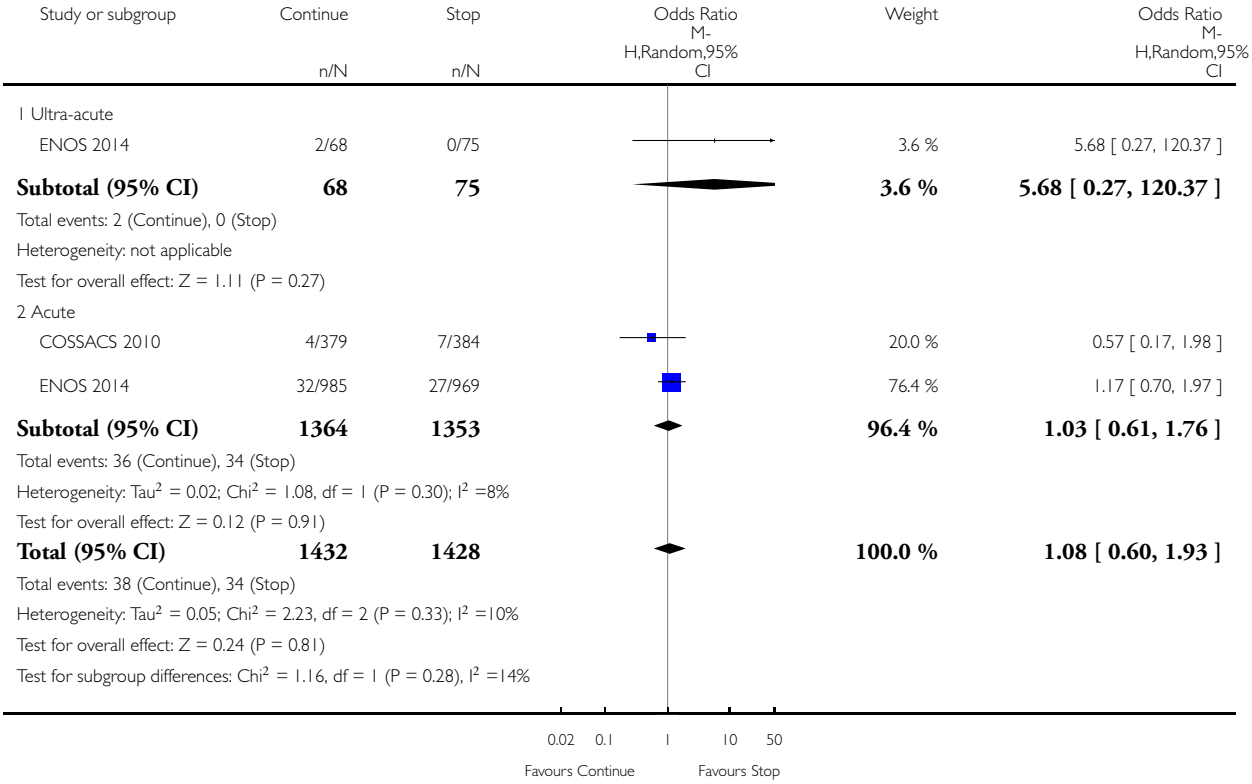


Analysis 2.6. Comparison 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S), Outcome 6 Death early, by time to treatment C/S.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S)

Outcome: 6 Death early, by time to treatment C/S



Analysis 2.7. Comparison 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S), Outcome 7 Death, end of trial by C/S.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S)

Outcome: 7 Death, end of trial by C/S

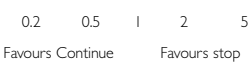
Study or subgroup	Continue n/N	Stop n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
COSSACS 2010	32/379	30/384		17.7 %	1.09 [0.65, 1.83]
ENOS 2014	167/1053	146/1044		82.3 %	1.16 [0.91, 1.47]
Total (95% CI)	**1432**	**1428**		**100.0 %**	**1.15 [0.92, 1.43]**

Total events: 199 (Continue), 176 (Stop)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.05$, df = 1 (P = 0.83); $I^2 = 0.0\%$

Test for overall effect: Z = 1.23 (P = 0.22)

Test for subgroup differences: Not applicable

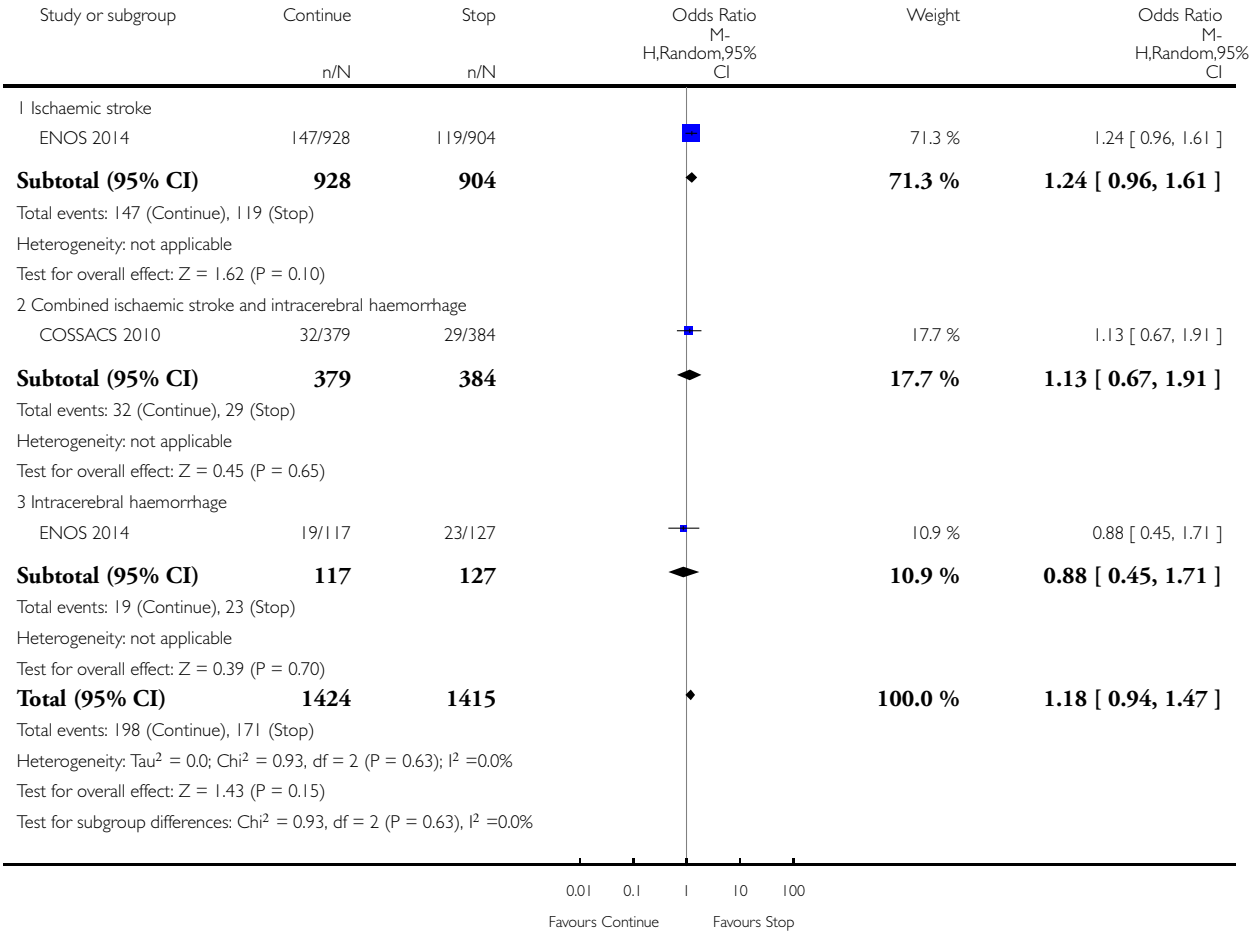


Analysis 2.8. Comparison 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S), Outcome 8 Death end of trial, by stroke type C/S.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S)

Outcome: 8 Death end of trial, by stroke type C/S



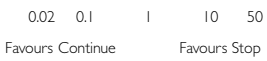
Analysis 2.9. Comparison 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S), Outcome 9 Death, end of trial by time to treatment C/S.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S)

Outcome: 9 Death, end of trial by time to treatment C/S

Study or subgroup	Continue n/N	Stop n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Ultra-acute					
ENOS 2014	11/68	7/75		4.7 %	1.87 [0.68, 5.15]
Subtotal (95% CI)	**68**	**75**		**4.7 %**	**1.87 [0.68, 5.15]**
Total events: 11 (Continue), 7 (Stop)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.22 (P = 0.22)					
2 Acute					
COSSACS 2010	32/379	30/384		17.7 %	1.09 [0.65, 1.83]
ENOS 2014	156/985	139/969		77.6 %	1.12 [0.88, 1.44]
Subtotal (95% CI)	**1364**	**1353**		**95.3 %**	**1.12 [0.89, 1.40]**
Total events: 188 (Continue), 169 (Stop)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.01, df = 1 (P = 0.91); I^2 =0.0%					
Test for overall effect: Z = 0.97 (P = 0.33)					
Total (95% CI)	**1432**	**1428**		**100.0 %**	**1.14 [0.92, 1.42]**
Total events: 199 (Continue), 176 (Stop)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.97, df = 2 (P = 0.61); I^2 =0.0%					
Test for overall effect: Z = 1.21 (P = 0.23)					
Test for subgroup differences: Chi^2 = 0.96, df = 1 (P = 0.33), I^2 =0.0%					



Analysis 2.10. Comparison 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S), Outcome 10 Barthel Index, end of trial, by C/S.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S)

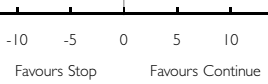
Outcome: 10 Barthel Index, end of trial, by C/S

Study or subgroup	Continue N	Mean(SD)	Stop N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
COSSACS 2010	379	77.9 (29.4)	384	80.2 (28)		41.5 %	-2.30 [-6.37, 1.77]
ENOS 2014	1053	58.1 (40.8)	1044	61.9 (39.4)		58.5 %	-3.80 [-7.23, -0.37]
Total (95% CI)	**1432**		**1428**			**100.0 %**	**-3.18 [-5.80, -0.55]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.30$, df = 1 (P = 0.58); $I^2 = 0.0\%$

Test for overall effect: Z = 2.37 (P = 0.018)

Test for subgroup differences: Not applicable



Analysis 2.11. Comparison 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S), Outcome 11 Early neurological deterioration, by C/S.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S)

Outcome: 11 Early neurological deterioration, by C/S

Study or subgroup	Continue n/N	Stop n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
ENOS 2014	72/1053	57/1044		100.0 %	1.27 [0.89, 1.82]
Total (95% CI)	**1053**	**1044**		**100.0 %**	**1.27 [0.89, 1.82]**

Total events: 72 (Continue), 57 (Stop)

Heterogeneity: not applicable

Test for overall effect: Z = 1.31 (P = 0.19)

Test for subgroup differences: Not applicable

Analysis 2.12. Comparison 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S), Outcome 12 Quality of life (EuroQol) at end of trial, by C/S.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S)

Outcome: 12 Quality of life (EuroQol) at end of trial, by C/S

Study or subgroup	Continue N	Mean(SD)	Stop N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
COSSACS 2010	379	0.68 (0.26)	384	0.71 (0.25)		37.8 %	-0.03 [-0.07, 0.01]
ENOS 2014	1053	0.44 (0.33)	1044	0.47 (0.33)		62.2 %	-0.03 [-0.06, 0.00]
Total (95% CI)	**1432**		**1428**			**100.0 %**	**-0.03 [-0.05, -0.01]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 1 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 2.64 (P = 0.0083)

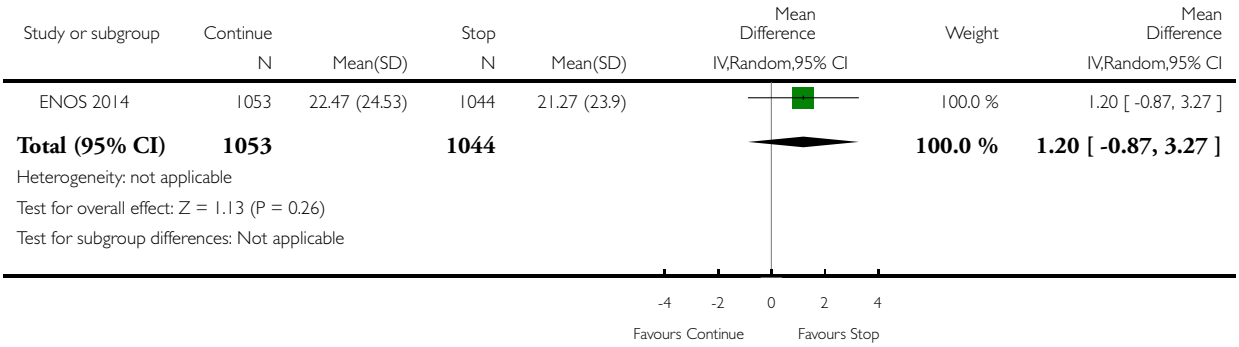
Test for subgroup differences: Not applicable

Analysis 2.13. Comparison 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S), Outcome 13 Length of stay, by C/S.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S)

Outcome: 13 Length of stay, by C/S

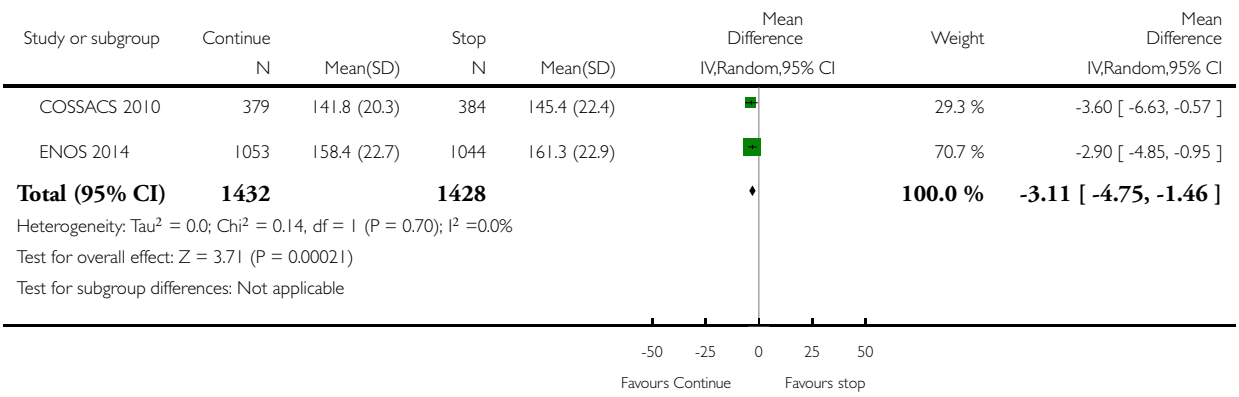


Analysis 2.14. Comparison 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S), Outcome 14 SBP, first after randomisation, by C/S.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S)

Outcome: 14 SBP, first after randomisation, by C/S



Analysis 2.15. Comparison 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S), Outcome 15 SBP, at day 1 by C/S.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S)

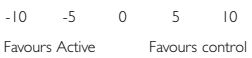
Outcome: 15 SBP, at day 1 by C/S

Study or subgroup	Continue N	Mean(SD)	Stop N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
COSSACS 2010	379	141.8 (20.3)	384	145.4 (22.4)		29.3 %	-3.60 [-6.63, -0.57]
ENOS 2014	1053	158.4 (22.7)	1044	161.3 (22.9)		70.7 %	-2.90 [-4.85, -0.95]
Total (95% CI)	**1432**		**1428**			**100.0 %**	**-3.11 [-4.75, -1.46]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.14$, df = 1 (P = 0.70); $I^2 = 0.0\%$

Test for overall effect: Z = 3.71 (P = 0.00021)

Test for subgroup differences: Not applicable



Analysis 2.16. Comparison 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S), Outcome 16 SBP, at end of treatment by C/S.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S)

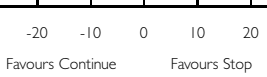
Outcome: 16 SBP, at end of treatment by C/S

Study or subgroup	Continue N	Mean(SD)	Stop N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
COSSACS 2010	379	140 (22)	384	153.5 (23.8)		44.9 %	-13.50 [-16.75, -10.25]
ENOS 2014	1053	145.6 (24.5)	1044	155.1 (23.9)		55.1 %	-9.50 [-11.57, -7.43]
Total (95% CI)	**1432**		**1428**			**100.0 %**	**-11.30 [-15.20, -7.40]**

Heterogeneity: $Tau^2 = 6.07$; $Chi^2 = 4.14$, df = 1 (P = 0.04); $I^2 = 76\%$

Test for overall effect: Z = 5.68 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 2.17. Comparison 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S), Outcome 17 DBP, at baseline by C/S.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S)

Outcome: 17 DBP, at baseline by C/S

Study or subgroup	Continue N	Mean(SD)	Stop N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
COSSACS 2010	379	79.9 (12.9)	384	81.4 (13.6)		26.1 %	-1.50 [-3.38, 0.38]
ENOS 2014	1053	88.1 (13.1)	1044	88.5 (13)		73.9 %	-0.40 [-1.52, 0.72]
Total (95% CI)	**1432**		**1428**			**100.0 %**	**-0.69 [-1.65, 0.27]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.97$, df = 1 (P = 0.32); $I^2 = 0.0\%$

Test for overall effect: Z = 1.40 (P = 0.16)

Test for subgroup differences: Not applicable

Analysis 2.18. Comparison 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S), Outcome 18 DBP at day 1, by C/S.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S)

Outcome: 18 DBP at day 1, by C/S

Study or subgroup	Continue		Stop		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
COSSACS 2010	379	77 (12.4)	384	79 (14.6)		30.2 %	-2.00 [-3.92, -0.08]
ENOS 2014	1053	84.7 (14.2)	1044	85.5 (14.4)		69.8 %	-0.80 [-2.02, 0.42]
Total (95% CI)	**1432**		**1428**			**100.0 %**	**-1.16 [-2.24, -0.08]**

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 1.07$, df = 1 (P = 0.30); $I^2 = 6\%$

Test for overall effect: Z = 2.11 (P = 0.035)

Test for subgroup differences: Not applicable

Analysis 2.19. Comparison 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S), Outcome 19 DBP, at end of treatment by C/S.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S)

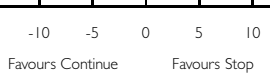
Outcome: 19 DBP, at end of treatment by C/S

Study or subgroup	Continue		Stop		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
COSSACS 2010	379	76.1 (13.7)	384	84.1 (13.8)		46.5 %	-8.00 [-9.95, -6.05]
ENOS 2014	1053	80 (14.7)	1044	85.1 (14.3)		53.5 %	-5.10 [-6.34, -3.86]
Total (95% CI)	**1432**		**1428**			**100.0 %**	**-6.45 [-9.28, -3.61]**

Heterogeneity: $Tau^2 = 3.51$; $Chi^2 = 6.04$, df = 1 (P = 0.01); $I^2 = 83\%$

Test for overall effect: Z = 4.46 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 2.20. Comparison 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S), Outcome 20 HR, at day 1.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S)

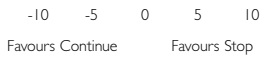
Outcome: 20 HR, at day 1

Study or subgroup	Continue		Stop		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
ENOS 2014	1053	77.4 (15.5)	1044	76.8 (14.9)		100.0 %	0.60 [-0.70, 1.90]
Total (95% CI)	**1053**		**1044**			**100.0 %**	**0.60 [-0.70, 1.90]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.90 (P = 0.37)

Test for subgroup differences: Not applicable



Analysis 2.21. Comparison 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S), Outcome 21 HR, at end of treatment.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 2 Blood pressure altering by continue or stop prestroke antihypertensives (C/S)

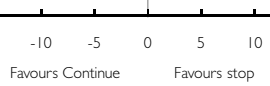
Outcome: 21 HR, at end of treatment

Study or subgroup	Continue N	Mean(SD)	Stop N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
ENOS 2014	1053	76.3 (15.9)	1044	79.5 (14.8)		100.0 %	-3.20 [-4.51, -1.89]
Total (95% CI)	**1053**		**1044**			**100.0 %**	**-3.20 [-4.51, -1.89]**

Heterogeneity: not applicable

Test for overall effect: Z = 4.77 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 3.1. Comparison 3 Blood pressure elevation therapy in acute stroke, Outcome 1 Death early, by intervention.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 3 Blood pressure elevation therapy in acute stroke

Outcome: 1 Death early, by intervention

Study or subgroup	Active n/N	Control n/N	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
1 Phenylephrine (iv)					
Hillis 2003	0/9	0/6			Not estimable
Total (95% CI)	**9**	**6**			**Not estimable**

Total events: 0 (Active), 0 (Control)

Heterogeneity: not applicable

Test for overall effect: not applicable

Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%

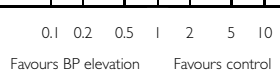
Analysis 3.2. Comparison 3 Blood pressure elevation therapy in acute stroke, Outcome 2 Death early, by stroke type.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 3 Blood pressure elevation therapy in acute stroke

Outcome: 2 Death early, by stroke type

Study or subgroup	Active n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Ischaemic stroke					
Hillis 2003	0/9	0/6			Not estimable
Total (95% CI)	**9**	**6**			**Not estimable**
Total events: 0 (Active), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%					



Analysis 3.3. Comparison 3 Blood pressure elevation therapy in acute stroke, Outcome 3 Death end of trial, by intervention.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 3 Blood pressure elevation therapy in acute stroke

Outcome: 3 Death end of trial, by intervention

Study or subgroup	Active n/N	Control n/N	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
1 Phenylephrine (iv)					
Hillis 2003	0/9	0/6			Not estimable
Total (95% CI)	**9**	**6**			**Not estimable**
Total events: 0 (Active), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%					

Analysis 3.4. Comparison 3 Blood pressure elevation therapy in acute stroke, Outcome 4 SBP, at baseline.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 3 Blood pressure elevation therapy in acute stroke

Outcome: 4 SBP, at baseline

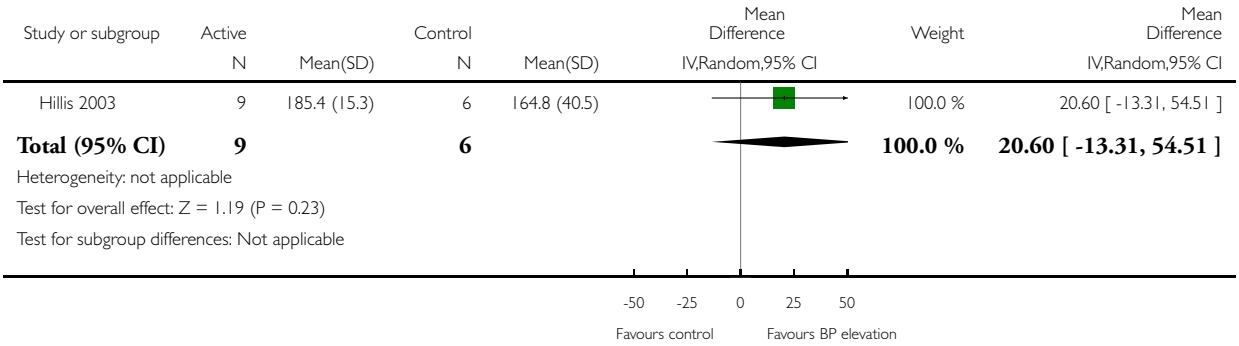
Study or subgroup	Active N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Phenylephrine (iv)							
Hillis 2003	9	138.7 (28.1)	6	166.2 (18)		100.0 %	-27.50 [-50.83, -4.17]
Total (95% CI)	**9**		**6**			**100.0 %**	**-27.50 [-50.83, -4.17]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.31 (P = 0.021)							
Test for subgroup differences: Not applicable							

Analysis 3.5. Comparison 3 Blood pressure elevation therapy in acute stroke, Outcome 5 SBP, first after randomisation.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 3 Blood pressure elevation therapy in acute stroke

Outcome: 5 SBP, first after randomisation

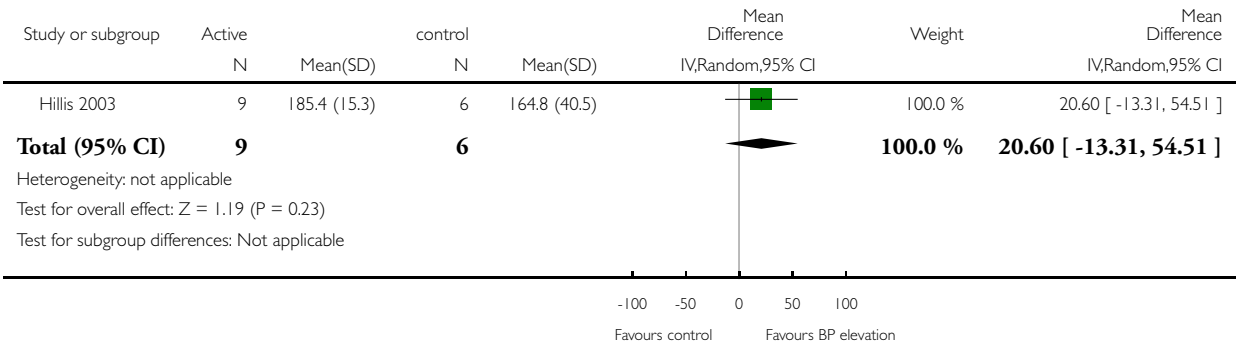


Analysis 3.6. Comparison 3 Blood pressure elevation therapy in acute stroke, Outcome 6 SBP, at day 1.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 3 Blood pressure elevation therapy in acute stroke

Outcome: 6 SBP, at day 1

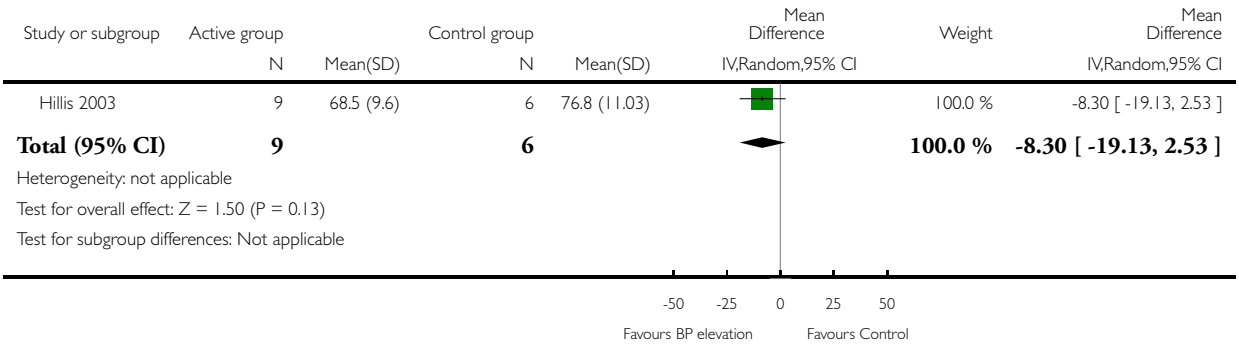


Analysis 3.7. Comparison 3 Blood pressure elevation therapy in acute stroke, Outcome 7 DBP, at baseline.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 3 Blood pressure elevation therapy in acute stroke

Outcome: 7 DBP, at baseline

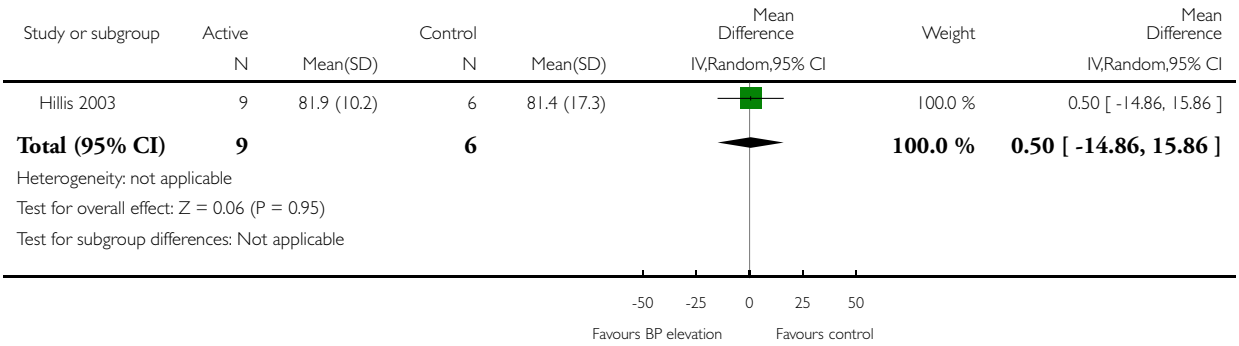


Analysis 3.8. Comparison 3 Blood pressure elevation therapy in acute stroke, Outcome 8 DBP, first after randomisation.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 3 Blood pressure elevation therapy in acute stroke

Outcome: 8 DBP, first after randomisation

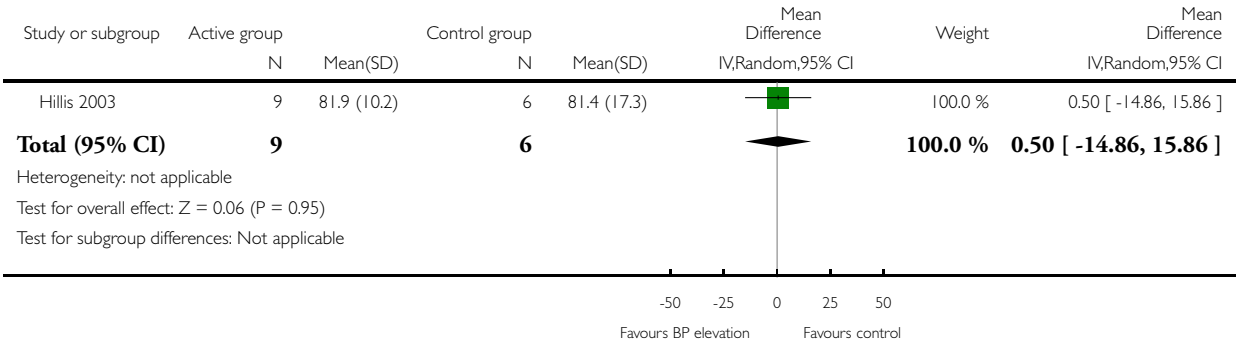


Analysis 3.9. Comparison 3 Blood pressure elevation therapy in acute stroke, Outcome 9 DBP, at day 1.

Review: Interventions for deliberately altering blood pressure in acute stroke

Comparison: 3 Blood pressure elevation therapy in acute stroke

Outcome: 9 DBP, at day 1



ADDITIONAL TABLES

Table 1. Blood pressure changes after first dose

Type	Trials	Participants	SBP	95% CI	I2 %	DBP	95% CI	I2%
Type of intervention								
ACE-I, oral	5	123	-13.7	-20.0 to -7.3	0	-4.2	-9.7 to 1.2	16
ACE-I, sublingual	1	42	-6.0	-17.6 to 5.6	-	+2.2	-5.5 to 9.9	-
ARA	3	3408	-4.6	-8 to -1	74	-2.5	-4.3 to -0.6	67
α-2 adrenoceptor agonist	1	4	-13.7	-41.5 to 14.1	-	-2.1	-15.4 to 11.2	-
ß-receptor antagonist, oral	1	44	-11.5	-20.3 to -2.7	-	-5.4	-13 to 2.2	-
ß-receptor antagonist, iv	1	41	-16.4	-27.4 to -5.4	-	-17.5	-25.3 to -9.7	-

Table 1. Blood pressure changes after first dose (*Continued*)

Calcium channel blocker, oral	3	106	-7.6	-17.2 to 1.9	0	-3.3	-9.3 to 2.7	-
Calcium channel blocker, iv	1	11	-9.7	-24.4 to 4.9	-	-12.9	-31.4 to 5.6	-
Nitric oxide donor	5	4192	-9.3	-14.5 to -4	26	-3.6	-4.4 to -2.8	0
Diuretic, thiazide-like	1	40	-20.0	-38.6 to -1.4	-	-	-	-
Low BP target	5	7421	-11.4	-15.3 to -7.5	93	-6.9	-15.7 to 1.9	94
Overall	27	15432	-11.2	-13.7, -8.7	86	-3.9	-5.4 to -2.6	61

ACE-I: angiotensin converting enzyme inhibitors
ARA: angiotensin receptor antagonist
BP: blood pressure
DBP: diastolic blood pressure
SBP: systolic blood pressure
iv: intravenous

Table 2. Blood pressure changes by type of intervention

SBP	First	Day 1	Day 7
Type of intervention			
ACE-I, oral	-21.0	-7.9	-26
ACE-I, sublingual	-6.0	-12	-
Angiotensin receptor antagonist	-4.6	-0.5	-6
Alpha-2 adrenoceptor agonist	-13.7	-21.8	-
Beta-receptor antagonist, oral	-11.5	-14	-
Beta-receptor antagonist, iv	-16.4	-5	-

Table 2. Blood pressure changes by type of intervention (*Continued*)

Calcium channel blocker, oral	-7.6	-13.2	-
Calcium channel blocker, iv	-9.8	-31.9	-
Nitric oxide donor	-9.3	-7	-1
Diuretic, thiazide-like	-20.0	-	-15
Low BP target	-11.4	-10	-8
Overall	-11.2	-7.7	-7

ACE-I: angiotensin converting enzyme inhibitors
BP: blood pressure
SBP: systolic blood pressure
iv: intravenous

Table 3. Heart rate changes at day 1

Type of intervention	Trials	Participants	Day 1	95% CI
ACE (oral)	2	39	0.03	-40.4 to 40.5
Alpha-2 adrenoceptor agonist	1	3	-	-
Calcium channel blocker, oral	2	83	-2.6	-7.7 to 2.6
Calcium channel blocker, iv	1	11	-16.9	-27.4 to -6.5
Nitric oxide donor	5	4197	4.5	1.5 to 7.6

ACE: angiotensin converting enzyme
iv: intravenous

APPENDICES

Appendix 1. MEDLINE search strategy

1. blood pressure.tw.
2. hypertension.tw
3. acute/
4. stroke.tw.
5. or/1-4
6. and/1-4
7. 1-4.kf.
8.1-4.ti.
9. trials
10. 1-4 and 9
11. 1-4 and 9.ti.
12. ischaemic stroke.tw/ti.
13. haemorrhagic stroke.tw/ti.
14. intracerebral haemorrhage.tw./ti.
15. blood pressure lowering/
16. blood pressure increase/
17. 1-4 or 12
18. 1-4 or 13
19. 1-4 or 14
20. 1-4 and 15
21.1-4 and 16
22. cerebr
23. 1-4 or 22
24. vasoactive/
25. 12-16 or 24
26. nitrate.tw.
27. glyceryl trinitrate/GTN.tw
28. nitric Oxide Donors.tw.
29. 1-4 and/or 26-28
30. 9, 12-13, 16 and/or 26-28
31. thiazide.tw.
32. bendrofluazide.tw.
33. bendroflumethiazide.tw.
34. hydrochrlothiazide/HCT.tw.
35. 31-34 and/or 1-4
36. 31-34 and/or 12-15
37. beta blockers.tw
38. atenolol.tw.
39. propanalol.tw.
40. 37-39 and/or 1-4
41. 37-39 and or 12-15
42. calcium channel blockers.tw.
43. nimodipine.tw.
44. nicardipine.tw.
45. amilodipine.tw.
46. felodipine.tw.
47. isradipine.tw.
48. nifedipine.tw.
49. nisolodipine.tw.

50. 42-49 and or 1-4
51. 42-49 and or 12-15
52. angiotensin-converting enzyme inhibitors/ACE inhibitors.tw
53. captopril.tw.
54. enalapril.tw.
55. lisinopril.tw.
56. perindopril.tw.
57. ramipril.tw.
58. 52-57 and or 1-4
59. 52-57 and or 12-15
60. angiotensin receptor blockers/antagonists.tw.
61. candesartan.tw
62. losartan.tw.
63. telmisartan.tw
64. valsartan.tw.
65. clonidine.tw.
65. 60-65 and or 1-4
66. 60-65 and or 12-15
67. vasoconstrictors.tw.
68. dopamine.tw.
69. dobutamine.tw.
70. noradrenaline.tw.
71. phenylephrine.tw.
72. 67-71 and or 3, 4, 9, 16
73. cerebral blood flow
74. autoregulation
75. stroke outcome
76. 73-75 and or 1-4
77. 73-75 and or 12-16

Appendix 2. EMBASE search strategy

1. blood pressure.tw.
2. hypertension.tw
3. acute/
4. stroke.tw.
5. or/1-4
6. and/1-4
7. 1-4.kf.
8.1-4.ti.
9. trials
10. 1-4 and 9
11. 1-4 and 9.ti.
12. ischaemic stroke.tw/ti.
13. haemorrhagic stroke.tw/ti.
14. intracerebral haemorrhage.tw./ti.
15. blood pressure lowering/
16. blood pressure increase/
17. 1-4 or 12
18. 1-4 or 13
19. 1-4 or 14
20. 1-4 and 15

21.1-4 and 16
22. cerebr
23. 1-4 or 22
24. vasoactive/
25. 12-16 or 24
26. nitrate.tw.
27. glyceryl trinitrate/GTN.tw
28. nitric Oxide Donors.tw.
29. 1-4 and/or 26-28
30. 9, 12-13, 16 and/or 26-28
31. thiazide.tw.
32. bendrofluazide.tw.
33. bendroflumethiazide.tw.
34. hydrochrlothiazide/HCT.tw.
35. 31-34 and/or 1-4
36. 31-34 and/or 12-15
37. beta blockers.tw
38. atenolol.tw.
39. propanalol.tw.
40. 37-39 and/or 1-4
41. 37-39 and or 12-15
42. calcium channel blockers.tw.
43. nimodipine.tw.
44. nicardipine.tw.
45. amilodipine.tw.
46. felodipine.tw.
47. isradipine.tw.
48. nifedipine.tw.
49. nisolodipine.tw.
50. 42-49 and or 1-4
51. 42-49 and or 12-15
52. angiotensin-converting enzyme inhibitors/ACE inhibitors.tw
53. captopril.tw.
54. enalapril.tw.
55. lisinopril.tw.
56. perindopril.tw.
57. ramipril.tw.
58. 52-57 and or 1-4
59. 52-57 and or 12-15
60. angiotensin receptor blockers/antagonists.tw.
61. candesartan.tw
62. losartan.tw.
63. telmisartan.tw
64. valsartan.tw.
65. clonidine.tw.
65. 60-65 and or 1-4
66. 60-65 and or 12-15
67. vasoconstrictors.tw.
68. dopamine.tw.
69. dobutamine.tw.
70. noradrenaline.tw.
71. phenylephrine.tw.
72. 67-71 and or 3, 4, 9, 16

73. cerebral blood flow
74. autoregulation
75. stroke outcome
76. 73-75 and or 1-4
77. 73-75 and or 12-16

Appendix 3. Science Citation Index search strategy

1. blood pressure.TI.
2. hypertension.TI
3. acute/
4. stroke.TS.
5. OR/1-4
6. AND/1-4
7. 1-4.TI.
8.1-4.TI.
9. trials
10. 1-4 AND 9
11. 1-4 AND 9.ti.
12. ischaemic stroke.TI/TS.
13. haemorrhagic stroke.TI/TS.
14. intracerebral haemorrhage.TI./TS.
15. blood pressure lowering/
16. blood pressure increase/
17. 1-4 OR 12
18. 1-4 OR 13
19. 1-4 OR 14
20. 1-4 AND 15
21.1-4 AND 16
22. cerebr
23. 1-4 OR 22
24. vasoactive/
25. 12-16 OR 24
26. nitrate.TI./TS
27. glyceryl trinitrate/GTN.TI/TS
28. nitric Oxide Donors.TI./TS
29. 1-4 AND/OR 26-28
30. 9, 12-13, 16 AND/OR 26-28
31. thiazide.TI.
32. bendrofluazide.TI.
33. bendroflumethiazide.TI.
34. hydrochrlothiazide/HCT.TI.
35. 31-34 AND/OR 1-4
36. 31-34 AND/OR 12-15
37. beta blockers.TI
38. atenolol.TI.
39. propanalol.TI.
40. 37-39 AND/OR 1-4
41. 37-39 AND/OR 12-15
42. calcium channel blockers.TI.
43. nimodipine.TI.
44. nicardipine.TI.

45. amilodipine.TI.
46. felodipine.TI.
47. isradipine.TI.
48. nifedipine.TI.
49. nisolodipine.TI.
50. 42-49 AND/OR 1-4
51. 42-49 AND/OR 12-15
52. angiotensin-converting enzyme inhibitors/ACE inhibitors.TI
53. captopril.TI.
54. enalapril.TI.
55. lisinopril.TI.
56. perindopril.TI.
57. ramipril.TI.
58. 52-57 AND/ OR 1-4
59. 52-57 AND/OR 12-15
60. angiotensin receptor blockers/antagonists.TI.
61. candesartan.TI.
62. losartan.TI.
63. telmisartan.TI.
64. valsartan.TI.
65. clonidine.TI.
65. 60-65 AND/OR 1-4
66. 60-65 AND/OR 12-15
67. vasoconstrictors.TI.
68. dopamine.TI.
69. dobutamine.TI.
70. noradrenaline.TI.
71. phenylephrine.TI.
72. 67-71 AND/OR 3, 4, 9, 16
73. cerebral blood flow
74. autoregulation
75. stroke outcome
76. 73-75 AND/OR 1-4
77. 73-75 AND/OR 12-16

F E E D B A C K

'BEST' Trial

Summary

The 'Beta-blockade in acute stroke trial (BEST)' done in Nottingham in the 1980s (which compared atenolol, propranolol and placebo) is not included in this review. Although lowering blood pressure was not the major aim of the trial, lower blood pressures did occur in the intervention group. Should the study not be included in the review, or be explicitly excluded?
Reference: Barer DH, Cruickshank JM, Ebrahim SB, Mitchell JR. Low dose beta blockade in acute stroke ("BEST" trial): an evaluation. Br Med J 1988;296:737-741.

Reply

The BEST trial was not included since the trial's primary aim was not about altering blood pressure, but rather assessing the effect of beta blockers in acute stroke. However, BEST is included in our related review published in the Cochrane Database of Systematic Reviews: Vasoactive drugs for acute stroke. We have drawn this distinction since there are methodological differences between studies which aim to alter blood pressure, and those which may, or not, have measured blood pressure as part of their protocol.

Contributors

Shah Ebrahim

WHAT'S NEW

Last assessed as up-to-date: 8 July 2014.

Date	Event	Description
8 July 2014	New search has been performed	The searches have been updated to May 2014. We have added 14 new trials (including 15,858 participants). This brings the total number of included studies to 26, involving 17,011 participants. We have added new subgroup analyses
8 July 2014	New citation required but conclusions have not changed	Change in authorship. Whilst substantially more information is now available compared with the previous version, the core questions remain unanswered so the basic conclusion that more data are needed remains unchanged

HISTORY

Protocol first published: Issue 1, 1996

Review first published: Issue 4, 1997

Date	Event	Description
24 October 2008	New search has been performed	Contact details updated.
1 April 2008	New search has been performed	Review was updated: (1) Addition of seven completed trials (ACCESS 2003; Hillis 2003; Rashid 2003; Eames 2005; Willmot 2006; Eveson 2007; INTERACT pilot 2008) involving 943 patients; (2) Addition of nine ongoing or planned trials (COSSACS 2002; CHIPPS 2005; SCAST 2005; ACCOST 2006; ATACH 2006; TAST 2006; Geeganage 2007; Intracerebral haemorrhage ADAPT-E 2007; INTERACT2 2008) The previous version of the review included five trials involving 210 patients. The conclusions of this review have not changed with the addition of the new

(*Continued*)

		data Change of authors.
25 March 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

PMW Bath was involved with the design, development of search strategies, analysis and writing. He is the study guarantor.

K Krishnan was involved with searches for studies, input of data into the latest version, analysis of the latest version, and writing.

DECLARATIONS OF INTEREST

PMWB was involved with eight completed trials (Bath 2000; Rashid 2003 5 mg/Rashid 2003 5/10 mg/Rashid 2003 10 mg; Willmot 2006; PRoFESS 2009; SCAST 2011; RIGHT 2013; TAST 2013; ENOS 2014), each of which are included in this review.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- South Thames NHS Executive (1995-1997), UK.
- Wolfson Foundation (1993-1998), UK.
- Trent NHS Executive (1998-2000), UK.
- The Stroke Association (1998-2015), UK.
- Medical Research Council (2006-2014), UK.
- British Heart Foundation (2006-2008), UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None relevant.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Blood Pressure [*drug effects]; Calcium Channel Blockers [*therapeutic use]; Hypertension [drug therapy]; Randomized Controlled Trials as Topic; Risk; Stroke [physiopathology; *prevention & control]; Time-to-Treatment [statistics & numerical data]; Vasodilator Agents [*therapeutic use]

MeSH check words

Humans