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TABLE OF CONTENTS

[Intervention Review]

Vasoactive drugs for acute stroke

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ABSTRACT

Background

It is unclear whether blood pressure (BP) should be altered actively during the acute phase of stroke.

Objectives

To assess the effect of lowering or elevating BP in people with acute stroke, and the effect of different vasoactive drugs on BP in acute stroke.

Search methods

We searched the Cochrane Stroke Group Trials Register (last searched June 2009), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 4, 2009), MEDLINE (1966 to October 2009), EMBASE (1980 to October 2009), and Science Citation Index (1981 to October 2009).

Selection criteria

Randomised trials of interventions that would be expected, on pharmacological grounds, to alter BP in patients within one week of the onset of acute stroke.

Data collection and analysis

Two review authors independently applied the trial inclusion criteria, assessed trial quality, and extracted data.

Main results

We identified 131 trials involving in excess of 18,000 patients; a further 13 trials are ongoing. We obtained data for 43 trials (7649 patients). Among BP-lowering trials, beta receptor antagonists lowered BP (early systolic BP (SBP) mean difference (MD) -6.1 mmHg, 95% CI -11.4 to -0.9; late SBP MD -4.9 mmHg, 95% CI -10.2 to 0.4; late diastolic BP (DBP) MD -4.5 mmHg, 95% CI -7.8 to -1.2). Oral calcium channel blockers (CCB) lowered BP (late SBP MD -3.2 mmHg, 95% CI -5.4 to -1.1; early DBP MD -2.5, 95% CI -5.6 to 0.7; late DBP MD -2.1, 95% CI -3.5 to -0.7). Nitric oxide donors lowered BP (early SBP MD -10.3 mmHg, 95% CI -17.6 to -3.0). Prostacyclin lowered BP (late SBP MD, -7.7 mmHg, 95% CI -15.6 to 0.2; late DBP MD -3.9 mmHg, 95% CI -8.1 to 0.4). Among BP-increasing trials, diaspirin cross-linked haemoglobin (DCLHb) increased BP (early SBP MD 15.3 mmHg, 95% CI 4.0 to 26.6; late SBP MD 15.9 mmHg, 95% CI 1.8 to 30.0). None of the drug classes significantly altered outcome apart from DCLHb which increased combined death or dependency (odds ratio (OR) 5.41, 95% CI 1.87 to 15.64).

Authors' conclusions

There is not enough evidence to evaluate reliably the effect of altering BP on outcome after acute stroke. However, treatment with DCLHb was associated with poor clinical outcomes. Beta receptor antagonists, CCBs, nitric oxide, and prostacyclin each lowered BP during the acute phase of stroke. In contrast, DCLHb increased BP.

PLAIN LANGUAGE SUMMARY

Vasoactive drugs for acute stroke

In patients who have just had a stroke (a sudden catastrophe in the brain either because an artery to the brain blocks, or because an artery in or on the brain ruptures and bleeds) very high and very low blood pressure may be harmful. Drugs which raise low blood pressure or lower high blood pressure might benefit acute stroke patients. This review of 43 trials involving 7649 participants found that there was not enough evidence to decide if drugs which can alter blood pressure should or should not be used in patients with acute stroke. More research is needed.

BACKGROUND

Description of the condition

Stroke is the third most common cause of death and the commonest 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 (International Society of Hypertension 2003). The mechanisms underlying hypertension in stroke are complex but pre-existing hypertension (present in 50% to 60% of patients), hospitalisation stress, activation of the neuro-endocrine pathways, and the Cushing reflex, each contribute (International Society of Hypertension 2003; Sprigg 2005). Low blood pressure is not common in acute stroke but it, like high blood pressure, is associated with a poor outcome (Castillo 2004; Leonardi-Bee 2002; Vemmos 2004). 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).

Description of the intervention

Although debated more than 20 years ago, it still remains unclear whether hypertension 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 higher than 220/120 mmHg, higher than 200/100 mmHg with end organ involvement (hypertensive encephalopathy, aortic dissection, cardiac ischaemia, pulmonary oedema, acute renal failure), or higher than 200/120 mmHg with primary intracerebral haemorrhage (PICH) (AHA-HS 2007; AHA-IS 2007; ESO 2008). Though the evidence is weak (class 1, level of evidence B) guidelines now recommend that patients who have elevated blood pressure and are otherwise eligible for treatment of recombinant tissue plasminogen activator (rtPA) may have their blood pressure lowered so that systolic blood pressure (SBP) is ≤ 185 mmHg and diastolic blood pressure (DBP) is ≤ 110 mmHg before thrombolysis using intravenous labetalol, nitropaste or nicardipine and it should be maintained below 180/105 mmHg for at least the first 24 hours after therapy (AHA-IS 2007; ESO 2008). Similarly, guidelines recommend that causes of low blood pressure in the setting of acute stroke should be sought with a view to correcting reversible causes such as hypovolaemia and cardiac arrhythmias (AHA-IS 2007; ESO 2008).

How the intervention might work

A number of small studies have assessed the relationship between blood pressure and outcome. A meta-analysis of these and other studies found that elevated blood pressure was associated with a poor outcome (Willmot 2004). Data from 17,398 patients in the International Stroke Trial (IST) identified a U-shaped relationship such that both low and high blood pressure was associated independently with increased early death and later death or dependency (Leonardi-Bee 2002). A high blood pressure is also associated with increased early recurrence (Leonardi-Bee 2002; Sprigg 2006). In ischaemic stroke, hypertension also appears to affect adversely through increasing the risk of cerebral oedema, but not haemorrhagic transformation (Leonardi-Bee 2002) as shown in the IST analysis. Haematoma expansion is related to high blood pressure in patients with PICH although this relationship may be confounded by stroke severity and time to presentation (Bath 2003). Since cerebral autoregulation is lost following stroke (Burke 1986; Paulson 1990; Strandgaard 1973) such that cerebral blood flow becomes dependent on systemic blood pressure, some researchers have hypothesised that blood pressure should be increased (Sandercock 1992) after stroke to improve perfusion to the penumbral region, and several case series and small trials have been published. In a recent meta-regression of blood pressure in acute stroke involving data from randomised controlled trials, large increases or reductions in blood pressure were associated with harm whereas moderate reductions were associated with a non-significant reduction in death or dependency (Geeganage 2009).

Why it is important to do this review

This systematic review included randomised controlled trials (RCTs) of interventions that would be expected, on pharmacological grounds, to alter blood pressure in patients within one week of the onset of acute ischaemic or haemorrhagic stroke. A related review restricted inclusion to those trials which specifically studied the effect of changing blood pressure in acute stroke (BASC I). The aim of this review is to assess the effect of lowering or elevating blood pressure in people with acute stroke, and the effect of different vasoactive drugs on blood pressure in acute stroke.

OBJECTIVES

1. To determine whether lowering or elevating blood pressure in patients with acute stroke is safe and effective in reducing the risk of early and late death and functional dependency.
2. To determine the effect of vasoactive drugs on blood pressure patients with acute stroke.

METHODS

Criteria for considering studies for this review

Types of studies

We included published and unpublished randomised or quasi-randomised controlled trials (i.e. trials that used a non-random method of treatment allocation, for example hospital number, date of birth or day of the week), of vasoactive drugs in acute ischaemic stroke or acute primary intracerebral haemorrhage where drug therapy was initiated within one week of stroke onset. We excluded uncontrolled studies, confounded controlled studies where the intervention was compared with another active therapy, and studies of patients with subarachnoid haemorrhage.

Types of participants

Adults (aged 18 years and over) of either sex with acute ischaemic or haemorrhagic stroke (within one week of onset) who were eligible for randomisation to either active treatment or placebo/open control.

Types of interventions

All randomised controlled acute stroke trials where vasoactive drugs were used in the acute treatment of stroke.

Types of outcome measures

Early (within one month) and end-of-trial mortality; early death or deterioration; end-of-trial mortality or dependency; blood pressure

and heart rate at baseline, and during early (less than 24 hours) and late (24 to 72 hours) treatment; length of hospital stay and discharge destination. We defined disability or dependency as a Barthel Index 0 to 55 or Rankin score 3 to 5. We also noted the presence of 'hypotension' (however defined by trialists) where given.

Search methods for identification of studies

See the 'Specialized register' section in the Cochrane Stroke Group module.

We searched the Cochrane Stroke Group Trials Register, which was last searched by the Managing Editor in June 2009 using a search strategy designed to identify all relevant trials. In addition, we searched the Cochrane Database of Systematic Reviews (CDSR) and the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 4, 2009), MEDLINE (1966 to October 2009) (Appendix 1), EMBASE (1980 to October 2009) (Appendix 2), and Science Citation Index (ISI Web of Science, 1981 to October 2009) (Appendix 3). We did not apply any language restrictions.

In an effort to identify further published, unpublished, and ongoing trials:

1. we searched reviews of hypertension in acute stroke from the CDSR and existing Cochrane and other stroke overviews relating to drugs which may alter blood pressure, including: calcium channel blockers (CCBs) (Horn 2001), nitric oxide (Bath 2002), pentoxifylline (Bath 2004/2), amphetamine (Martinsson 2007; Sprigg 2007), tirilazad (Tirilazad International Steering Committee 2001), naftidrofuryl (Leonardi-Bee 2007), vinpocetine (Bereczki 2008) and prostacyclin (Bath 2004/1) as well as other generic reviews (Geeganage 2009);
2. we searched the Ongoing Trials section of *Stroke* and the Internet Stroke Center Stroke Trials Registry (Stroke Center) (October 2009);
3. we scanned the reference lists of relevant trials and existing review articles;
4. we contacted research workers in this field (see Acknowledgements);
5. 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) in 1999 for the previous version of the review.

Data collection and analysis

We identified and independently assessed published and unpublished trials and decided whether to include or exclude them. One review author (CG) identified data in published material and sought additional information from the principal investigators of the trials where necessary. We resolved disagreements by discussion. Where available, we re-analysed individual patient data and used the resulting group data in preference to published data. We recorded information on the methods of randomisation, concealment of allocation, blinding, analysis (intention-to-treat or efficacy analysis), stroke type (ischaemia or haemorrhage), drug dose, route of administration (oral, transdermal or intravenous) and timing, blood pressure and heart rate (before and during treatment), numbers of deaths, functional disability, quality of life, length of stay, and adverse effects such as hypotension,

We assessed the methodological quality of trials, especially relating to concealment of allocation as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). We calculated the weighted estimate of the typical treatment effect across trials (odds ratio (OR) for binary data, mean difference (MD) for continuous data) using aggregated patient data in Review Manager 5.0 (RevMan 2008); this software also tests for heterogeneity between the trials.

RESULTS

Description of studies

Where a trial used more than one dose of a particular drug then the reference is written as author followed by date followed by dose of drug. When referencing the whole trial the references for all the doses will be used (e.g. Saxena 1999 50 mg/Saxena 1999 100 mg). Blood pressure (BP) data were available in 43 trials including 7649 patients (Characteristics of included studies). We excluded more than 80 studies as the relevant data were unobtainable, either because they were not present in trial reports and could not be provided by trialists, or because they had been discarded or they could not be released until publication of the final trial reports (Characteristics of excluded studies).

The trials involved 16 combinations of drug classes and routes of administration: oral or sublingual angiotensin converting enzyme (ACE) inhibitors (perindopril, captopril and lisinopril); oral angiotensin receptor antagonists (ARA) (candesartan); oral beta receptor antagonists (βRA) (atenolol, propanolol); combined alpha and beta receptor antagonists (labetalol); oral thiazide diuretics (bendrofluazide), intravenous CCBs (flunarizine, isradipine, nimodipine); oral CCBs (nimodipine, nicardipine); intravenous DCLHb (a haemoglobin analogue); intravenous magnesium sulphate; intravenous naftidrofuryl; transdermal glyceryl trinitrate (a nitric oxide donor); intravenous piracetam; combined intravenous prostacyclin; intravenous glucose potassium insulin (GKI); intravenous insulin; intravenous phenylephrine; and intravenous and or oral mixed antihypertensive therapy (Characteristics of included studies).

Patients were recruited into trials within six to 168 hours from stroke onset; most were enrolled within 24 to 168 hours (Characteristics of included studies). Nine studies included patients who were hypertensive at the time of recruitment (Characteristics of included studies); the other studies involved patients with a range of BPs. Two trials studied phenylephrine and DCLHb which elevate BP (Saxena 1999 25 mg/Saxena 1999 50 mg/Saxena 1999 100 mg; Hillis 2003). Thirty-eight trials were published and five trials unpublished (IMAGES Pilot; Lowe 1993; Pokrupa 1986; Strand 1984; Uzuner 1995/180 mg). Routes of administration included oral, intravenous (iv), transdermal, sublingual or combinations of these (Characteristics of included studies). The treatment duration varied from 24 hours to nine months (Characteristics of included studies). Some drugs were given in two phases, initially intravenously then orally (CCB, magnesium sulphate, naftidrofuryl, piracetam) (Characteristics of included studies). Combinations of intravenous and oral antihypertensive drugs were used to lower BP in the intensive as well as guideline group of INTERACT pilot trial (INTERACT pilot 2008). Three trials used transdermal glyceryl trinitrate (GTN) 5 mg daily for 12 days (Bath 2000); GTN 5 mg, 5/10 mg, 10 mg (Rashid 2003 5 mg/Rashid 2003 5/10 mg/Rashid 2003 10 mg) for 10 days; GTN 5 mg (Willmot 2006) for seven days. There

was one dose escalation study of 8 mmol, 12 mmol, 16 mmol of magnesium sulphate over 24 hours (Muir 1995).

Risk of bias in included studies

The methods used in the 43 trials are summarised in the Characteristics of included studies table. All trials were double-blind, with the exceptions of one single-blinded (Saxena 1999 100 mg/Saxena 1999 25 mg/Saxena 1999 50 mg), four outcome-blinded (Gray 2007; INTERACT pilot 2008; Rashid 2003 10 mg/Rashid 2003 5 mg/Rashid 2003 5/10 mg; Willmot 2006) and two open studies (Barer 1988 atenolol/Barer 1988 propanolol; Walters 2006). The method of randomisation was only given for 22 trials (Ahmed 2000 1 mg/Ahmed 2000 2 mg; Barer 1988 atenolol/Barer 1988 propanolol; Bath 2000; Bogousslavsky 1990; Dyker 1997; Eames 2005; Eveson 2007; Gray 2007; IMAGES Pilot; INTERACT pilot 2008; Kaste 1994/120 mg; Lees 1995; Limburg 1990; Lowe 1993; PASS 1995; Pokrupa 1986; Potter 2009 labetalol/Potter 2009 lisinopril; Rashid 2003 5 mg/Rashid 2003 5/10 mg/Rashid 2003 10 mg; Strand 1984; Walters 2006; Willmot 2006; Wimalarat 1994/120mg/Wimalarat 1994/240mg). All trials were analysed by the intention-to-treat analysis with the exception of two (Huczynski 1988; Martinez-Vila 1990).

There were 23 single-centred trials. All trials used computerised tomography (CT) to exclude patients with PICH with the exception of nine trials that included both types of stroke (Ahmed 2000 1 mg/Ahmed 2000 2 mg; Barer 1988 atenolol/Barer 1988 propanolol; Barer 1988/50 mg/Barer 1988/80 mg; Fagan 1988/120 mg/Fagan 1988/240 mg; Gray 2007; Potter 2009 labetalol/Potter 2009 lisinopril; Rashid 2003 5 mg/Rashid 2003 5/10 mg/Rashid 2003 10 mg; VENUS 1995; Willmot 2006). One trial only included patients with acute spontaneous intracerebral haemorrhage (ICH) diagnosed by CT (INTERACT pilot 2008). For the lisinopril study randomisation was done before neuroimaging and those with non-ischaemic stoke were subsequently withdrawn from the study (Eveson 2007).

Effects of interventions

General

We identified a total of 131 trials involving in excess of 18,000 patients. However, data were only available for 43 trials involving 7649 patients. We excluded 86 trials as BP or outcome data were not available. The patients receiving placebo or control treatment in eight trials (Ahmed 2000 1 mg/Ahmed 2000 2 mg; Barer 1988 atenolol/Barer 1988 propanolol; Barer 1988/50 mg/Barer 1988/80 mg; Fagan 1988/120 mg/Fagan 1988/240 mg; Rashid 2003 5 mg/Rashid 2003 5/10 mg/Rashid 2003 10 mg; Saxena 1999 25 mg/Saxena 1999 50 mg/Saxena 1999 100 mg; Wimalarat 1994/120mg/Wimalarat 1994/240mg; Potter 2009 labetalol/Potter 2009 lisinopril) acted as controls for more than one group of actively treated patients; control participants in these studies were divided equally between each active treatment group to ensure that the total number of control participants was correct. This strategy is recommended by the Cochrane Stroke Group and avoids artificially inflating patient numbers and therefore narrowing confidence intervals.

Blood pressure

Baseline SBP was mismatched between the treatment and control groups across all treatments (MD -1.6 mmHg, 95% CI -2.8 to -0.4) and especially for intravenous CCBs (MD -6.6 mmHg, 95% CI -13.4 to 0.2) (Appendix 4). Several drug classes lowered BP, including: beta receptor antagonists (early SBP, MD -6.1 mmHg, 95% CI -11.4 to -0.9; late SBP MD -4.9 mmHg, 95% CI -10.2 to 0.4; late DBP MD -4.5 mmHg, 95% CI -7.8 to -1.2); oral CCBs (late SBP MD -3.2 mmHg, 95% CI -5.4 to -1.1; early DBP MD -2.5, 95% CI -5.6 to 0.7; late DBP MD -2.1, 95% CI -3.5 to -0.7); nitric oxide donors (early SBP MD -10.3 mmHg, 95% CI -17.6 to -3.0), and prostacyclin (late SBP MD -7.7 mmHg, 95% CI -15.6 to 0.2; late DBP MD -3.9 mmHg, 95% CI -8.1 to 0.4).

BP lowering is also seen for several other antihypertensive agents although the small number of participants studied meant that differences in BP were not always statistically significant. Drugs showing hypotensive properties included: angiotensin converting enzyme inhibitors, angiotensin receptor antagonists, bendrofluazide, intravenous CCBs and GKI. Neither magnesium, naftidrofuryl nor piracetam had appreciable effects on BP. INTERACT pilot 2008 lowered SBP (early MD -14.0 mmHg 95% CI -17.2 to -10.8, late MD -11.0 mmHg, 95% CI -14.0 to -8.0) in the intensive treatment versus guideline treatment arm.

In contrast, DCLHb increased BP (early SBP MD 15.3 mmHg, 95% CI 4.0 to 26.6; late SBP MD 15.9 mmHg, 95% CI 1.8 to 30.0). Intravenous phenylephrine also showed a trend towards an increase in SBP (MD 20.6, 95% CI -13.3 to 54.5) as compared to control.

Heart rate

Heart rate was lowered by beta blockers (early heart rate (HR) MD -6.8 beats/minute, 95% CI -9.6 to -4.0; late HR MD -9.3 beats/minute, 95% CI -12.0 to -6.6); and oral CCBs (late HR MD -2.8 beats/minute, 95% CI -3.9 to -1.7); and increased by nitric oxide donors (MD 6.3 beats/minute 95% CI 2.9 to 9.7). Intravenous CCBs, ACE inhibitors, naftidrofuryl, magnesium, and DCLHb did not alter heart rate.

Death or dependency

There was no evidence of an effect on death for any agent except DCLHb which significantly increased the odds of death or dependency (OR 5.41, 95% CI 1.87 to 15.64). A trend for an increase in combined end of trial death or disability was observed for oral CCBs (odds ratio (OR) 1.30, 95% CI 0.91 to1.86).

Hypotensive events

There was no significant difference for oral CCBs (total events four active, six control, OR 0.73, 95% CI 0.19 to 2.74) and mixed antihypertensive therapy (total events five active, six control, OR 1.24, 95% CI 0.33 to 4.7) in the number of hypotensive events. None of the other agents reported hypotensive events in trial publications.

Relationship between blood pressure and outcome

The numbers of trials and participants with data on BP and outcome were not identical and it was not possible to relate group differences in BP with group differences in outcome. This problem was compounded by biologically important differences in baseline BP between treated and control groups.

DISCUSSION

Beta receptor antagonists, oral calcium channel blockers (CCBs), glyceryl trinitrate (GTN), prostacyclin and mixed antihypertensive therapy lowered blood pressure (BP) during the first three days of

treatment. Angiotensin converting enzyme inhibitors, angiotensin receptor blockers, bendroflumethiazide, intravenous CCBs, insulin and GKI also appeared to lower BP as compared to the controls. In contrast, magnesium, naftidrofuryl, and piracetam had no effect on BP. Nevertheless, these observations may be partly confounded by mismatches in baseline BP (significantly so for intravenous CCBs). Baseline imbalances in BP would have profound effects on outcome and therefore change the BP-outcome relationship. A definitive assessment as to whether these drugs change BP will be dependent on analysis of individual patient data from these trials. Unfortunately, individual patient data were not available for most of the included trials; the presence of these data would have addressed this issue. Further, the apparent BP-reducing effect of GKI may be due to the confounding in the GIST trial, in which the controls were treated with intravenous saline, and the treatment group received intravenous dextrose, so the BP difference may not be attributable to the GKI lowering BP, but to the control group having less hypovolaemia/hypotension because of the saline (Gray 2007).

None of the drug classes altered outcome apart from diaspirin cross-linked haemoglobin (DCLHb) which significantly increased combined death and dependency compared with control. There was no significant difference in outcome for CCBs, beta blockers, ACE-I, magnesium, and nitric oxide. The relationship between BP and outcome could not be studied for methodological reasons in the present review. However, the relationship between BP and outcome based on many of the included trials has been assessed in a meta-regression (Geeganage 2009). The results revealed a U-shaped relationship between BP changes and outcome, with the lowest risk of death or combined death or dependency at the end of follow up in patients with BP reductions ranging from eight to 15 mmHg. Although large falls or increases in BP were associated with a higher risk of poor outcomes, a modest reduction may reduce death and combined death or dependency, although confidence intervals were wide and compatible with an overall benefit or hazard.

AUTHORS' CONCLUSIONS

Implications for practice

Trials of vasoactive drugs in acute stroke reveal that beta receptor antagonists, oral calcium channel blockers (CCBs), glyceryl trinitrate (GTN), prostacyclin and mixed antihypertensive therapy each lower blood pressure (BP). In contrast, diaspirin cross-linked haemoglobin (DCLHb) and phenylephrine increases BP. However, these data do not allow the effect of changing BP on outcome to be assessed. In the absence of definitive information, there is no clear indication for the deliberate alteration of BP during the first few days after stroke.

Implications for research

The existing completed studies of vasoactive drugs in acute stroke are all small or medium sized (fewer than 1000 participants) and, hence, likely to be underpowered. One or more large trials (several thousand participants) are now required to determine whether altering (raising or lowering) BP can be safe and efficacious; such studies are ongoing (ENOS 2006; INTERACT 2 2007; SCAST 2005).

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- Trialists: Ahmed N (Sweden), Asplund K (Sweden), Autret A (France), Barer D (UK), Bath PMW (UK), Bereczki D (Hungary), Bogousslavsky J (Switzerland), Chan YW (Hong Kong), Davis S (Australia), de Deyn PP (Belgium), Donnan G (Australia), Dyker AG (UK), Eveson D (UK), Fogelholm R (Finland), Gelmers HJ (Netherlands), Gray CS (UK), Grotta J (USA), Hachinski V (Canada), Hakim RP (Canada), Heiss WH (Germany), Herrschaft H (Germany), Hillis AB (USA), Horn J (Netherlands), Hsu CY (USA), Huczynski J (Poland), Kaste M (Finland), Koudstall PJ (Netherlands), Kramer G (Switzerland), Lees KR (UK), Limberg M (Netherlands), Lisk R (Cameroon), Lowe G (UK), Muir KW (UK), Mistri A (UK), Murphy JJ (UK), Orgogozo JM (France), Pokrupa RP (Canada), Rashid P (UK), Saxena R (Netherlands), Steiner T (UK), Strand T (Sweden), Uzuner N (Turkey), Wahlgren N (Sweden), Walters MR (UK), Willmot M (UK), Wimalaratna HSK (UK), Wong WJ (Taiwan).
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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	Multicentre, double-blind, placebo-controlled Method of randomisation not known
Participants	Germany 339 patients - T: 173, C:166 Age: T: 68.3 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 systolic or 100 mmHg diastolic C: matching placebo

ACCESS 2003 *(Continued)*

	Rx: 7 days
Outcomes	BP was measured by a nurse or automatically Case fatality and disability using BI 3 months after the end of placebo-controlled 7-day period
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
Adequate sequence generation?	Low risk	Probably done
Allocation concealment?	Unclear risk	Unclear from the publication
Blinding?	Low risk	Probably done
Completeness of follow-up	Unclear risk	Unclear from the publication

Ahmed 2000 1 mg

Methods	As for Ahmed 2000 2 mg
Participants	—
Interventions	—
Outcomes	—
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Probably done
Allocation concealment?	Low risk	According to predetermined randomisation lists
Blinding?	Low risk	Probably done
Completeness of follow-up	High risk	Probably not done 101 patients did not complete 21 days of treatment This includes 2 trial withdrawals

Ahmed 2000 2 mg

Methods	Multicentre, double-blind, placebo-controlled Randomisation by predetermined randomisation list

Ahmed 2000 2 mg *(Continued)*

Participants	Sweden 295 patients: T1: 101, T2: 94, C: 100 Age: T1: 71.9 years , T2: 72.1 years, C: 71 years Male: T1: 45, T2: 45, C: 45 Inclusion: clinical diagnosis of ischaemic stroke in the carotid artery territory Enrolment: within 24 hours of ictus
Interventions	T1: nimodipine iv 1 mg/hour for 5 days followed by oral nimodipine 30 mg qid for 16 days T2: nimodipine iv 2 mg/hour for 5 days followed by po nimodipine 30 mg qid for 16 days C: matching placebo
Outcomes	Transformed Orgogozo score and transformed Barthel index score on the follow up at day 21
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Probably done
Allocation concealment?	Low risk	According to predetermined randomisation lists
Blinding?	Low risk	Probably done
Completeness of follow-up	High risk	Probably not done 101 patients did not complete 21 days of treatment This includes 2 trial withdrawals

ASCLEPIOS 1990

Methods	Multicentre (40), double-blind, placebo-controlled Method of randomisation unknown ITT analysis
Participants	European and Canadian 234 patients - T:120, C:114 Age: 45 to 85 years Males: T: 76, C: 69 Patients with ischaemic MCA stroke presenting with hemiparesis or hemiplegia within 12 hours of onset 100% CT and/or MRI within 72 hours 1 patient > 12 hours (15 hours) and one patient < 45 years (44 years)
Interventions	T: isradipine as continuous iv infusion (80 ug/hour) for 72 hours then po (2.5 mg bd) C: matching iv/po placebo Rx: for 28 days
Outcomes	Assessments at baseline and days 1, 3, 7, 14, 28, 90 Neurological score (modified by Orgogozo et al (1993)); Barthel Index (extended to include death as worst possible outcome) Missing data: day 28: T: 11, C: 6; day 90: T: 4, C: 0 Blood pressure measured at baseline and days 1, 2, 3 (method of measurement unknown)

ASCLEPIOS 1990 *(Continued)*

Notes	Ex: Massive hemispheric damage; very mild stroke (neurological score > 65); any condition where previous neurological deficits might hinder ability to detect improvement from current stroke; other systemic diseases such as gastrointestinal system, liver, kidneys; acute or unstable cardiovascular disease, except AF; exposure to drugs that may interfere with safety or efficacy; pregnancy, lactation Data provided by J-M Orgogozo (principal investigator) TIAs will be excluded and analysed separately

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Probably done
Allocation concealment?	Unclear risk	Unclear from the publication
Blinding?	Low risk	Probably done
Completeness of follow-up	Unclear risk	Unclear from the publication

Barer 1988 atenolol

Methods	Multicentre, open randomised controlled Separate randomisation schemes for each hospital ITT analysis
Participants	UK 55 patients: T1: 18, T2:16, C:21 Mean age: T1: 73 years, T2: 72 years, C: 70 years Males: T1:12, T2:8, C:8 Inclusion: clinically diagnosed hemispheric strokes Patients should be conscious and able to swallow tablets Enrolment within 48 hours
Interventions	T1: atenolol po 50 mg daily T2: propranolol 80 mg po daily Rx: 4 weeks
Outcomes	Same time points used as Barer 1988
Notes	Same exclusions as Barer 1988

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomisation was done in block of 3 with separate schemes for each hospital
Allocation concealment?	Low risk	Probably done
Blinding?	High risk	Open randomised controlled trial
Completeness of follow-up	Unclear risk	Unclear from the publication

Barer 1988 propanolol

Methods	As for Barer 1988 atenolol
Participants	—
Interventions	
Outcomes	—
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Probably done
Allocation concealment?	Low risk	Probably done
Blinding?	High risk	Open randomised controlled
Completeness of follow-up	Unclear risk	38 patients lost to follow up

Barer 1988/50 mg

Methods	Single centre, double-blind, placebo-controlled Method of randomisation not known 38 patients lost to FU PP analysis
Participants	UK 303 patients: T1:102, T2:101, C:100 Mean age: T1: 70.6 years, T2: 68.2 years, C: 69 years Males: T1: 53, T2: 57, C:49 Inclusion: clinically diagnosed hemispheric strokes Patients should be conscious and able to swallow tables CT not used Enrolment within 48 hours
Interventions	T1: atenolol 50 mg po daily T2: slow release propranolol 80 mg po daily C: matching placebo Rx: 3 weeks
Outcomes	Neurological assessments made at days 1 and 8 and months 1 and 6; full functional assessments made from day 8 onwards; death, functional outcome used ADL on an ordinal scale designed for patients with stroke; length of stay Method by which BP measured not given Early and late death and dependency data defined as ADL score of less than or equal to 4 No method given for BP measurements
Notes	Ex: pre-existing major physical or mental disability, taking beta blockers, contraindications to beta blockers i.e. heart rate ≤ 56 beats/minute, SBP < 100 mmHg, second or third degree heart block, heart

Barer 1988/50 mg *(Continued)*

	failure or bronchospasm causing dyspnoea, history of asthma, insulin dependent diabetes, MI, other causes of seriously reduced cerebral perfusion

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomisation was done in block of 3 with separate schemes for each hospital
Allocation concealment?	Low risk	Probably done
Blinding?	High risk	Open randomised controlled trial
Completeness of follow-up	High risk	Unclear from the publication

Barer 1988/80 mg

Methods	As for Barer 1988/50 mg
Participants	—
Interventions	—
Outcomes	—
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Probably done
Allocation concealment?	Low risk	Probably done
Blinding?	High risk	Open randomised controlled
Completeness of follow-up	High risk	38 patients lost to follow up

Bath 2000

Methods	Single centre double-blind, placebo-controlled Randomisation by computer (with minimisation on age and mean arterial BP) ITT analysis
Participants	UK 37 patients. T: 16, C: 21 Age: T: 76 years, C: 72 years Male T: 6, C: 12 Inclusion: ischaemic or haemorrhage stroke 100% CT

Bath 2000 *(Continued)*

	Enrolment within 5 days: T: 4 patients enrolled > 5 days and C: 3 patients > 5 days Stroke type assessed clinically
Interventions	T: transdermal GTN 5 mg C: matching placebo Rx: 12 days
Outcomes	24 hour ambulatory BP was measured before and during GTN treatment at days 0, 1 and 8 Ambulatory BP was monitored using a Spacelabs 90207 set to record thrice hourly during the day and hourly during the night Functional outcome Rankin scale and Barthel Index and case fatality at 3 months Late death and disability used Barthel, but if used Rankin there is 1 less missing value
Notes	Ex: taking part in another trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomisation by computer (with minimisation on age and mean arterial BP)
Allocation concealment?	Low risk	Probably done
Blinding?	Low risk	Probably done
Completeness of follow-up	Low risk	No loss of follow up

Bogousslavsky 1990

Methods	Single centre, double-blind, placebo-controlled Randomisation by next random number on list 60 patients randomised but 8 excluded due to incorrect diagnosis Data from paper, PP analysis
Participants	German 52 patients: T: 24, C: 28 Mean age T: 64, C: 65 (efficacy) Males 38 Inclusion: ischaemic stroke of mild to moderate severity (Mathew scale sum between 50 and 75), > 39 years and < 85 years Diagnosis: clinical and 100% CT scan Enrolment within 48 hours
Interventions	T: nimodipine 30 mg po qid C: matching po placebo Rx: for 14 days Medical therapy allowed such as drugs against infection, hypertension, mild hypnotics, analgesics, volume substitution (including Dextran 40), low-dose heparin (2 x 500 U/day)
Outcomes	Impairment: Mathews score on day 1, 3, 5, 7, and 14, week 4 and month 4 BP and heart rate were checked twice daily and on week 4 and month 4 Number of hypotensives noted Method used for taking BP not given
Notes	Ex: TIA, progressing stroke, coma, brain stem, ICH, SAH, recent MI, CCF, systemic infection, renal/hepatic failure, SBP < 100, DBP > 105, bradycardia (heart rate < 50 beats/minute), AV conduction distur-

Bogousslavsky 1990 *(Continued)*

	bances, concomitant use of CCBs, piracetam, pentoxifylline, naftidrofuryl hydrogenoxalate, dihydroergotoxine, alpha methyl dopa Follow up 4 weeks and 4 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomisation by next random number on the list
Allocation concealment?	Low risk	Probably done
Blinding?	Low risk	Probably done
Completeness of follow-up	Unclear risk	Unclear from the publication

Dyker 1997

Methods	Double-blind, placebo-controlled Method of randomisation: computer-generated random list prepared and held by Pharmacy Trials Department ITT analysis
Participants	UK, single centre 28 patients: T: 14, C: 14 Mean age: 70 years Males: T: 9, C: 8 Inclusion: strokes with mild to moderate hypertension (170 to 250/95 to 120 mm Hg) 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: 4 mg perindopril po once daily C: matching placebo Rx: 2 weeks
Outcomes	BP measured semi-automatically pre-treatment and hourly to 10 hours repeated at 24 hours and at 2 weeks Clinical and neurological assessment according to the NIH Stroke Scale made before study entry and repeated on day 15
Notes	Ex: severe carotid disease

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computer-generated random list prepared and held by pharmacy trials department
Allocation concealment?	Low risk	Probably done
Blinding?	Low risk	Probably done

Dyker 1997 *(Continued)*

Completeness of follow-up	High risk	28 recruited to the study with 24 completing the protocol

Eames 2005

Methods	Double-blind, placebo-controlled, parallel group Block randomisation (4 per block)
Participants	UK, single centre 37 patients: T: 18, C: 19 Age: 68 years Male: 86% Inclusion: neuroradiologically diagnosed ischaemic stroke with 24 hour 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)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Probably done
Allocation concealment?	Low risk	Probably done
Blinding?	Low risk	Probably done
Completeness of follow-up	Low risk	38 participants randomised, 19 to each group

Eveson 2007

Methods	Double-blind, placebo-controlled, parallel group Randomisation by prepared and numbered identical study packs
Participants	UK, single centre 40 patients. T: 18, C: 22 Age: T: 73 years, C: 75 years Male: 63% Inclusion: acute ischaemic stroke within the previous 24 hours with a mean casual SBP level ≥ 140 mm Hg or DBP level ≥ 90 mm Hg Randomisation done before neuroimaging and those with non-ischaemic stroke were withdrawn from the study

Eveson 2007 *(Continued)*

Interventions	T: 5 mg lisinopril po once daily C: matching placebo Rx: 14 days Dose was increased to 10 mg or 2 placebos on day 7 if SBP ≥ 140 mmHg or DBP ≥ 90 mmHg
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, Barthel score and modified Rankin scale at day 14 and day 90
Notes	Ex: severe carotid stenosis, significant aortic stenosis, cardiac failure, MI within past 6 months, dysphagia, dehydration, adverse reactions to ACEI, and pre-stroke modified Rankin score > 2

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Probably done
Allocation concealment?	Low risk	Probably done
Blinding?	Low risk	Probably done
Completeness of follow-up	High risk	During 90-day follow up 1 patient from lisinopril died, 2 placebo-treated patients underwent rating before day 90 (1 moved to another hospital and 1 declined further study participation after the treatment period)

Fagan 1988/120 mg

Methods	Multicentre, double-blind, placebo-controlled Randomisation technique not stated ITT analysis
Participants	USA, 19 participants Age: > 45 years No genders given Inclusion: IS diagnosed on history and neurological examination Enrolment times not given
Interventions	T: nimodipine (Miles Pharmaceuticals, USA) 120 mg/day po in 6 divided doses 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 DBP estimated from SBP and MAP given in paper
Notes	Ex: concurrent calcium channel antagonists, antihypertensive agents (other than beta blockers) Admission times of concurrent medication always separated from study drug administration by at least 2 hours Part of a larger unpublished trial to evaluate the safety and efficacy of nimodipine

Risk of bias

Bias	Authors' judgement	Support for judgement

Fagan 1988/120 mg *(Continued)*

Adequate sequence generation?	Low risk	Probably done
Allocation concealment?	Unclear risk	Unclear from the publication
Blinding?	Low risk	Probably done
Completeness of follow-up	Unclear risk	Unclear from the publication

Fagan 1988/240 mg

Methods	Multicentre, double-blind, placebo-controlled Randomisation technique not stated ITT analysis
Participants	USA, 19 participants 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 po in 6 divided doses 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 DBP estimated from SBP and MAP given in paper
Notes	Ex: concurrent calcium channel antagonists, antihypertensive agents (other than beta blockers) Admission times of concurrent medication always separated from study drug administration by at least 2 hours Part of a larger unpublished trial to evaluate the safety and efficacy of nimodipine

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Probably done
Allocation concealment?	Unclear risk	Unclear from the publication
Blinding?	Low risk	Probably done
Completeness of follow-up	Unclear risk	Unclear from the publication

German-Austrian 120mg

Methods	Multicentre, double-blind, placebo-controlled Method of randomisation not known ITT analysis

German-Austrian 120mg *(Continued)*

Participants	Germany and Austria, 16 centres 482 patients: T: 239, C: 243 Age: 40 to 80 years Inclusion: infarcts in anterior circulation 100% CT Enrolment within 48 hours
Interventions	T: po nimodipine 30 mg qid C: matching placebo Optional concomitant drugs were haemodilution, low-dose heparin, acetylsalicylic acid, digitalis, diuretics, antihypertensives, and sedatives Rx: 21 days
Outcomes	Modified Mathew scale at baseline and days 1, 3, 5, 7, 14, 21 and 6 months Barthel Index at days 1 and 21. Method for measuring BP not given BP estimated from graphs in paper
Notes	Ex: TIA, progressive stroke, vertebrobasilar ischaemia, coma, intracerebral bleeding or tumour, SAH, pregnancy, cardiac surgery within last 3 months, severe systemic illness, acute severe hepatic disease, bradycardia < 50 beats/minute, hypotension SBP < 100 mmHg, severe AV conduction block, renal insufficiency, severe systemic infections, severe cardiac insufficiency within last 3 months, other CCBs, PTX, naftidrofuryl, fetal bovine serum, piracetam, dihydroergotoxine, steroids and osmotic drugs Data taken from the paper

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Probably done
Allocation concealment?	Unclear risk	Unclear from the publication
Blinding?	Low risk	Probably done
Completeness of follow-up	Unclear risk	Unclear from the publication

Gray 2007

Methods	Multicentre, randomised controlled trial Blinded outcome assessments Randomisation: first 571 patients sealed envelopes, the rest by central randomisation service ITT analysis
Participants	UK, 933 patients T: 464, C: 469 Mean age: 75 years Male: 45% Inclusion: acute ischaemic stroke or primary intracerebral haemorrhage with admission venous plasma glucose 6 to 17 mmol/L Enrolment within 24 hours of stroke onset
Interventions	T: 500 ml GKI (of 10% dextrose, 20 mmol potassium chloride and 16U soluble recombinant human insulin) continuous iv infusion C: 0.9% normal saline

Gray 2007 *(Continued)*

	Rx: 24 hours
Outcomes	Death at 90 days, European stroke scale score, OCSP subtype, Glasgow Coma Scale at baseline Barthel index, mRS at 30 and 90 days
Notes	Ex: SAH, isolated posterior circulation syndromes no physical disability, pure language disorders, renal failure, anaemia, coma, established history of insulin treated diabetes, previous disabling stroke, dementia or symptomatic cardiac failure

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Probably done
Allocation concealment?	Low risk	Treatment allocation was concealed
Blinding?	High risk	Probably not done
Completeness of follow-up	High risk	Probably not done No loss of follow up for death at 90 days Day 90 mRS missing for 5 patients Day 90 Bartel Index missing for 30 patients

Herrschaft 1988

Methods	Single centre, double-blind, placebo-controlled Randomisation technique not stated PP analysis FU: 4 lost
Participants	German 44 participants: T: 24, C: 20 Mean age: T: 59 years, C: 54 years Males: T: 17, C:10 Inclusion: IS diagnosed on neurological examination and 100% CT, first stroke Enrolment within 5 days Proof of vascular stenoses or occlusions of the supplying or intracranial brain vessels by means of doppler sonography or cerebral angiography
Interventions	T and C: continuous iv of 1000 ml Dextran 40 plus 2 x 150 ml Sorbit 40% daily during the first 3 days T and C: over 4 to 6 hours a daily infusion of 500 ml Dextran 40 from day 4 to day 14 T: 3 x 4 g/20 ml piracetam iv bolus day 1 to day 14; FU 28 days C: matching placebo T: 4.8 g piracetam po daily for following 14 days C: matching placebo po daily for following 14 days
Outcomes	Neurological and psychiatric assessments using own scales at baseline and days 7, 14, 28 Organic brain psychosyndrome was determined using Lehrl and Erizgkeit short syndrome test Method of measuring BP not known
Notes	Ex: patients with severe internal disease (heart and lung disease), liver or renal insufficiency, DM, fixed hypertonia, neoplasia, hematological and systemic diseases, patients who had earlier neurological diseases of a different nature, drug or alcohol abuse

Herrschaft 1988 *(Continued)*

	4 patients were lost to follow up for following reasons: cardiac insufficiency, cardiac infarctus, pneumonia, gastrointestinal bleeding (T:1, C:3)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Probably done
Allocation concealment?	Unclear risk	Unclear from the publication
Blinding?	Low risk	Probably done
Completeness of follow-up	High risk	4 lost to follow up

Hillis 2003

Methods	Pilot randomised controlled trial Method of randomisation not known FU: no losses
Participants	USA, single centre 15 patients: T: 9, C: 6 Age: T: 59.1 years, C: 67.8 years Male: T: 2, C: 2 Inclusion: IS > 20% diffusion-perfusion mismatch, quantifiable, stable or worsening aphasia, hemispatial neglect and/or hemiparesis Enrolment: up to 7 days from the onset of stroke symptoms Patients on any previous antihypertensive medication were discontinued prior to the initiation of the study 100% CT, MRI
Interventions	T: iv phenylephrine was titrated to reach 10% to 20% increase MAP and continued for maximum of 72 hours After 24 hours the patients were started on midodrine (up to 10 mg), fludrocortisone (up to 0.2 mg) and sodium chloride tablets while simultaneously weaning the iv phenylephrine By 4 weeks, midodrine, fludrocortisone, and sodium chloride were tapered as long as there was no concomitant clinical deterioration C: conventional management
Outcomes	MAP measured 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
Adequate sequence generation?	Low risk	Probably done

Hillis 2003 *(Continued)*

Allocation concealment?	Unclear risk	Unclear from the publication
Blinding?	Low risk	Probably done
Completeness of follow-up	Low risk	15 patients (T: 9, C: 6) no loss of follow up

Hsu 1987

Methods	Multicentre, double-blind, placebo-controlled Randomisation technique not stated, stratified by thrombotic and embolic stroke ITT analysis
Participants	USA, 5 centres T: 43, C: 37 Mean age: 65 years 49 male, 31 female Inclusion: IS 100% CT pre-entry Enrolment within 24 hours
Interventions	T: PGI2 (epoprostenol sodium, Upjohn Co, USA, and Wellcome, UK) iv infusion started at 1 ng/kg/min increased every 30 minutes until maximum rate of 10 ng/kg/min; infusion for 72 hours with gradual reduction of dose during last 12 hours C: solvent Rx: 3 days
Outcomes	Death at 4 weeks (Neurological impairment assessed using Turnhill score at entry, day 3, weeks 1, 2 + 4) Method of BP measurement not known
Notes	Ex: stupor, coma, psychiatric disorder, clinical intracranial hypertension, organ or systemic disease, bleeding risk, heparin Further information unavailable because original data discarded Data from unpublished manuscript

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Probably done
Allocation concealment?	Unclear risk	Unclear from the publication
Blinding?	Low risk	Probably done
Completeness of follow-up	Unclear risk	Unclear from the publication

Huczynski 1988

Methods	Single centre, double-blind, placebo-controlled Randomisation technique not stated PP analysis 5 lost to FU

Huczynski 1988 *(Continued)*

	Withdrawals: T: 4, C: 1
Participants	Poland 30 patients: T: 15, C: 15 Mean age 61 years 16 male and 14 female Inclusion: IS in the territory of the internal carotid artery 100% EEG and CSF pre-entry Enrolment 24 to 72 hours
Interventions	T: PGI2 (Wellcome, UK, or Chinoin, WRL), daily 6 hour iv infusions at 2.5 to 5 ng/kg/min C: glycine solvent Rx: 2 weeks All patients given low-molecular-weight dextran
Outcomes	Death at 4 weeks, neurological impairment assessed using modified Matthew score assessed at baseline, after each infusion, 3, 4 and 12 weeks Barthel and Rankin at 1, 2, 4, 12, 24 and 48 weeks
Notes	Ex: heart failure, hyperglycaemia, uraemia, arrhythmia, hyperpyrexia, previous stroke, mild stroke

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Probably done
Allocation concealment?	Unclear risk	Unclear from the publication
Blinding?	Low risk	Probably done
Completeness of follow-up	High risk	5 lost to follow up

IMAGES Pilot

Methods	Multicentre, double-blind, placebo-controlled Randomisation by telephone service provided by Clinphone ITT analysis
Participants	UK 51 patients: T: 26, C: 25 Inclusion: clinically diagnosed acute stroke with limb weakness (NIHSS ≥ 1), symptoms present for at least an hour and treatment initiation possible within 12 hours of onset Age 18 or greater Previously independent in activities of daily living
Interventions	T: iv magnesium sulphate given as 16 mmol over 15 minutes followed by 65 mmol over 24 hours C: matching placebo
Outcomes	Death and death and disability at 3 months Disability < 60 on the Barthel Index
Notes	Ex: co-existing disease which is likely to prevent outcome assessment, renal impairment, intracerebral pathology other than IS, participation in another acute clinical trial, pregnancy, contraindication to magnesium

IMAGES Pilot *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomisation by telephone service provided by Clinphone
Allocation concealment?	Low risk	Probably done
Blinding?	Low risk	Probably done
Completeness of follow-up	Low risk	No loss of follow up

INTERACT pilot 2008

Methods	Open, blinded outcome, randomised trial Randomisation was done with minimisation through a password protected Internet-based system ITT analysis
Participants	International, multicentre 404 patients: T: 203, C: 201 Age: 63 years Male: 65% 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
Interventions	T: early intensive lowering of BP (target SBP 140 mmHg) C: standard guideline based management of BP (target SBP 180 mmHg) Both groups have received oral as well as iv agents for lowering blood pressure 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, contraindication 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 Glasgow Coma Scale), pre-stroke disability or medical illness, and early planned decompressive neurosurgical intervention

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomisation was done with minimisation through a password-protected Internet based system
Allocation concealment?	Low risk	Probably done
Blinding?	High risk	Open blinded outcome trial
Completeness of follow-up	High risk	1 patient from each group was lost to follow up at 90 days A further 9 patients were known to be alive, but dependency was not assessed at 90 days due to being unable to contact the patient or a relative

Kaste 1994/120 mg

Methods	Multicentre, double-blind, placebo-controlled Randomisation used sealed envelopes, stratified by onset of therapy, age and stroke severity Tablets provided in identical numbered vials ITT analysis
Participants	Finland, 3 centres 350 patients: T: 176, C: 174 Mean age: T: 57 years, C: 58 years Males: T: 122, C: 113 Inclusion: acute ischaemic hemispheric stroke 100% CT Enrolment within 48 hours
Interventions	T: 30 mg nimodipine qid C: matching placebo Rx: 21 days
Outcomes	Neurological evaluation (own score) at baseline, day 1, 7, 21 and months 3 and 12; mobility at 12 months Functional outcome, Rankin at 3 and 12 months - grades 1 and 2 representing independence were considered good outcome Primary end points: Rankin at 12 months, neurological scale and death Used Rankin > 3 for dependence in this review Rankin scale missing 2 living patients in control and 1 living patient in treatment group Method of BP measurement unknown
Notes	Ex: unconsciousness, dysphagia, TIA, dependence in ADL before stroke, brain stem infarction, complicated migraine, pregnancy, renal or hepatic or cardiac failure, severe systemic infection, serious psychiatric disturbance, terminal malignancy Data from published paper and author

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomisation used sealed envelopes, stratified by onset of therapy, age and stroke severity
Allocation concealment?	Low risk	Probably done
Blinding?	Low risk	Probably done
Completeness of follow-up	Unclear risk	Unclear from the publication

Lamsudin 1997

Methods	Multicentre, double-blind, placebo-controlled Method of randomisation not given ITT analysis
Participants	Indonesia, 5 departments 150 patients Males: T: 46, C: 50 Inclusion: acute IS

Lamsudin 1997 *(Continued)*

	Enrolment within 24 hours
Interventions	T1: 30 mg nimodipine tds and 500 mg aspirin tds T2: 500 mg aspirin tds Rx: 28 hours
Outcomes	Canadian Neurological Scale at baseline, 7, 14, 21 and 28 days Barthel Index at baseline, 7 and 14 days
Notes	Ex: coma, haemorrhage, tumour, infection, trauma, serious organic brain disease other than IS, need for ventilation, current use of CCBs, allergy to aspirin, pregnancy, hypotension (SBP < 100 mmHg), bradycardia (rate < 50), second or third degree heart block if patient did not have pacemaker, hepatic or renal dysfunction, congestive heart failure, pneumonia

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Probably done
Allocation concealment?	Low risk	Unclear from the publication
Blinding?	Low risk	Probably done
Completeness of follow-up	Unclear risk	Unclear from the publication

Lees 1995

Methods	Single centre, double-blind, placebo-controlled Randomisation performed in blocks of 10 according to a code devised and held by pharmacy ITT analysis
Participants	UK 60 participants: T: 30, C: 30 Mean age: T: 69.2 years, C: 65.9 years 30 males and 30 females Inclusion: MCA strokes 100% CT scan Enrolment within 12 hours
Interventions	T1: magnesium sulfate 8 mmol in 50 mL saline iv over 15 minutes, then 65 mmol in 100 mL saline continuous iv over 24 hours C: matching volumes of normal saline
Outcomes	MCA Neurological Score (N score) and NIHSS at baseline days 5 and 90 Barthel Index and Rankin Scale at days 5 and 90 Assess of 10 metre walking time made Method of BP measurement not known
Notes	Ex: pregnancy, renal failure, pre-existing functional impairment such that post-stroke assessment would be impaired (mRS ≤ 3)

Risk of bias

Bias	Authors' judgement	Support for judgement

Lees 1995 *(Continued)*

Adequate sequence generation?	Low risk	Randomisation was performed in blocks of 10 according to a code devised and held by the pharmacy
Allocation concealment?	Low risk	Probably done
Blinding?	Low risk	Medical staff and patients were blind to treatment
Completeness of follow-up	Unclear risk	Unclear from the publication

Limburg 1990

Methods	Single centre, double-blind, placebo-controlled Randomisation using tables from manufacturer ITT analysis
Participants	Netherlands 26 patients: T: 12, C: 14 Mean age: T: 67 years, C: 66 years Males: T: 3, C: 6 Inclusion: acute supratentorial brain infarction 100% CT Enrolment within 24 hours of ictus
Interventions	T: flunarizine, iv bolus of 0.1 mg/kg body weight in 5% glucose solution, followed after 3 hours by continuous infusion of 0.3 mg/kg/24 hours during 72 hours, then po flunarizine for 11 days C: identical placebo Rx: 14 days
Outcomes	Motricity Index, Rankin scale, Barthel Index, death Last follow up 6 months Barthel and Rankin used in review Method for measurement of BP not known
Notes	Ex: lacunar syndromes, serious underlying diseases, previous disabling stroke, using CCBs

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Randomisation using tables from manufacturer
Allocation concealment?	Low risk	Probably done
Blinding?	Low risk	Probably done
Completeness of follow-up	Unclear risk	Unclear from the publication

Lisk 1993

Methods	Single centre, double-blind, placebo-controlled Randomisation technique not stated ITT analysis

Lisk 1993 *(Continued)*

Participants	USA 16 patients: T1: 5, T2: 3, T3: 2, C: 6 Mean age: 66 years 4 male, 12 female Inclusion: all patients except 2 had MCA territory infarct SBP ≥ 170 mmHg or ≤ 220 mmHg, DBP ≥ 95 mmHg or ≤ 120 mmHg 100% CT pre-entry Enrolment within 72 hours History or family with hypertension 6 had SBP < 170 mmHg and 3 had DBP < 95 mmHg (baseline measurements)
Interventions	T1: po 20 mg nicardipine hydrochloride T2: 12.5 mg captopril T3: 0.1 mg clonidine hydrochloride C: placebo (dextrose and starch) every 8 hours for 3 days
Outcomes	Neurological impairment assessed using NIHSS at baseline and daily BP taken in supine position with automatic monitors; every 10 minutes for the first hour after first dose of drug, then every hour for 6 hours Thereafter BP measured at 4-hourly intervals during sleep and waking hours (standing where possible to check for postural hypotension)
Notes	Ex: coma, significant neurological deficit from previous stroke, unstable cardiac disease including acute MI, severe heart failure or conduction defects, history of angioedema and collagen vascular disease, liver dysfunction with aspartate aminotransferase and or bilirubin levels greater than twice normal, brain stem strokes Data from published paper and individual patient data provided by author

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Probably done
Allocation concealment?	Unclear risk	Unclear from the publication
Blinding?	Low risk	Probably done
Completeness of follow-up	Low risk	16 patients were entered into the study: 6 received placebo, 10 had antihypertensive drugs All had follow-up data

Lowe 1993

Methods	Single centre, double-blind, randomised, placebo-controlled Stratification at entry into: A - normal consciousness/face-arm paresis B - normal consciousness/hemiparesis or hemiplegia C - altered consciousness/hemiparesis or hemiplegia Method of randomisation used, statistical table using 6 groups of 4 possible sequences of individual treatment ITT analysis
Participants	UK

Lowe 1993 *(Continued)*

	112 patients: T: 56, C: 56 Age: 45 to 85 years Males: T: 37, C: 29 Inclusion: clinical diagnosis of acute cerebral hemispheric infarction, Barthel < 65 100% CT scan within 7 days Enrolment within 48 hours: T: 6 patients delay > 48 hours, C: 9 patients delay > 48 hours
Interventions	If patients able to swallow po treatment may be initiated from the start of the trial T: 40 mg nimodipine tds C: identical placebo Rx: 16 weeks If concomitant therapy used like beta blockers or methyl dopa, iv treatment was to be initially titrated against BP
Outcomes	Neurological outcome assessed by a 10-item grading system and using the Medical Research Council (MRC) numeric grading for each item when applicable Functional outcome assessed by the Barthel Index Assessments at days 1, 4, 7, 10 and weeks 2, 4, 8, 12, 16, 20, 24 Barthel at 1 month missing 12 in treatment group and 6 in placebo group Barthel at 12 weeks missing 12 in treatment group and 6 in placebo group At 24 weeks 16 missing in treatment group and 10 in placebo group 1 patient died at day 215, i.e. later than 6 months BP measured at baseline, 24, 96 hours and 7, 10, 14 days and 1, 2, 3, 4, 5, 6 months Method used to measure BP not known
Notes	Ex: disability due to other causes, MI in previous 4 weeks or decompensated heart failure, liver or renal failure, brainstem stroke, patient whose survival is not expected, causes of neurological deficits other than ischaemic hemispheric infarction

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Probably done
Allocation concealment?	Low risk	Probably done
Blinding?	Low risk	Probably done
Completeness of follow-up	Unclear risk	Unclear from available data

Martinez-Vila 1990

Methods	Multicentre, placebo-controlled Method of randomisation not given PP analysis 41 patients excluded blindly from efficacy analysis
Participants	Spain, 4 centres 164 patients: T: 81, C: 83 Age range: 45 to 92 years Males: T:43, C:43 Inclusion: IS in internal carotid artery territory as by clinical examination 100% CT within 3 days Enrolment within 48 hours

Martinez-Vila 1990 *(Continued)*

Interventions	T: 30 mg qid nimodipine po C: identical placebo Rx: 28 days Allowed drugs included heparin (5000 IU bid) and agents indicated for cerebral oedema and cardiovascular drugs (not CCBs) and antibiotic or anxiolytic drugs
Outcomes	Slightly modified Mathews scale by Gelmers et al at baseline, 1, 3, 5, 7, 14, 21, 28 days BP data obtained from paper, using PP numbers Death data taken from paper using ITT data BP estimated from graphs in paper
Notes	Ex: MI, renal failure, liver failure, severe systemic infections, poorly controlled DM, SBP < 100 mmHg, terminal malignancy, TIA, evolving strokes, coma

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Probably done
Allocation concealment?	Unclear risk	Unclear from the publication
Blinding?	Low risk	Probably done
Completeness of follow-up	Unclear risk	Unclear from the publication

Muir 1995

Methods	Single centre, double-blind, randomised, placebo-controlled Randomisation of 6 participants per group was planned ITT analysis
Participants	UK 25 patients: T: 19, C: 6 Mean age: T1: 75 years, T2: 65 years, T3: 71 years, C: 68 years Males: T1: 4, T2: 5, T3: 4, C: 3 Inclusion: clinically diagnosed stroke CT within 72 hours of stroke Enrolment within 24 hours of ictus Stroke types classified according to OCSP criteria
Interventions	T1: 8 mmol MgSO4 over 24 hours T2: 12 mmol MgSO4 over 24 hours T3: 16 mmol MgSO4 over 24 hours C: matching placebo
Outcomes	Barthel ADL score and mRS on days 30 and 60 BP and heart rate were measured semi-automatically by oscillometric recorders (Marquette) Method used for measuring BP not known
Notes	Ex: pregnancy, coma, renal failure

Risk of bias

Muir 1995 *(Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Probably done
Allocation concealment?	Unclear risk	Unclear from the publication
Blinding?	Low risk	Probably done
Completeness of follow-up	Low risk	All completed the study protocol

Norris 1994

Methods	Single centre, double-blind, placebo-controlled Randomisation method not given No method for concealment of allocation given 189 patients randomised, 164 analysed in paper - due to 25 protocol violations Paper analysis PP, calculations here based on ITT data
Participants	Canada 189 patients: T: 96, C: 93 Mean age: T: 71.1 years, C: 72.1 years Inclusion: IS, Toronto stroke scores of > 20 100% CT Enrolment within 48 hours 4 patients with delay > 48 hours: T: 3, C: 1
Interventions	T: iv nimodipine for first 10 days, 2 mg/hour, then po 180 mg/day for next 6 months C: identical placebo Rx: 6 months
Outcomes	Neurological disability using Toronto scale at baseline 10, 15, and 30 days Functional disability at baseline, 6 months, and 1 year using 3 simple categories: minor or no disability, moderate disability and patients who were severely disabled or bedridden (used severely disabled for disability scoring) Toronto stroke scale missing 6 in treatment group and 14 in control group BP was measured at baseline then 2-hourly for first day then 4-hourly for day 2 and 8-hourly day 3 to 10 Method by which BP was measured not given
Notes	Ex: comatose patients, no motor weakness (e.g. aphasia only), brain stem strokes, previous strokes, CT scan not compatible with IS, on CCBs, terminal illness, renal or hepatic failure or heart block Data from published paper and from Bayer Canada

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Probably done
Allocation concealment?	Unclear risk	Unclear from the publication
Blinding?	Unclear risk	Unclear from the publication

Norris 1994 *(Continued)*

Completeness of follow-up	Unclear risk	Unclear from the publication

Paci 1989/120 mg

Methods	Single centre, double-blind, placebo-controlled Method of randomisation unknown ITT analysis
Participants	Italy 41 patients: T: 19, C: 22 Mean age: T: 62 years, C: 63 years Males: T: 11, C: 17 Inclusion: patients with sudden and persistent neurological deterioration due to a focal event in the carotid artery distribution 100% CT Enrolment within 12 hours
Interventions	T: nimodipine 40 mg tds C: identical matching placebo Rx: 28 days Patients given supportive medication of 20% mannitol, antihypertensive agents and antibiotics
Outcomes	Neurological deficit (Mathews slightly modified by Gelmers) baseline and at days 1, 2, 3, 5, 7, 14, 21, 28 Global assessment made at end of treatment - good/fair/poor BP and heart rate recorded twice daily, method of recording not given
Notes	Ex: TIA, progressing stroke, primary intracerebral haemorrhage (CT scan), systemic disorders, recent MI, CCF, abnormal hepatic, renal or pulmonary functions, previous history of complete stroke Data from published paper

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Probably done
Allocation concealment?	Unclear risk	Unclear from the publication
Blinding?	Low risk	Probably done
Completeness of follow-up	High risk	Probably not complete 41 entered the study (T: 19, C: 22) and at the end of period of observation 18 nimodipine-treated patients with 1 possible loss of follow up

PASS 1995

Methods	Multicentre, double-blind, placebo-controlled Computer-generated randomisation schedule stratified by study centre
Participants	55 centres in 10 European countries 927 patients: T: 464, C: 463 Mean age: T: 70 years, C: 71 years Males: T: 241, C: 238

PASS 1995 *(Continued)*

	Inclusion: clinical diagnosis of acute ischaemic supratentorial stroke with Orgogozo Scale of > 5 and < 70 100% CT within 24 hours of ictus Enrolment within 12 hours
Interventions	T: 12 g piracetam (Nootropil) as initial iv bolus over 20 minutes, then 12 g daily for 4 weeks and 4.8 g daily for 8 weeks C: matching placebo RX: 12 weeks
Outcomes	Assessment at 1 and 3 days and 1, 2, 4, 8 and 12 weeks Primary outcome: MCA neurological scale at week 4 Secondary outcome: modified Barthel at 12 weeks, first used after 3 days Method for BP measurement not given
Notes	Ex: haemorrhage, coma (< 5 on Glasgow Coma Scale), previous stroke, confounding neurological or systemic illness, thrombolytic agents and haemodilution Dipyridamole and ticlopidine were prohibited during the first 4 weeks Non-study medications allowed were CCBs, osmotic diuretics and heparin Concomitant aspirin not recommended for at least 24 hours

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Probably done
Allocation concealment?	Low risk	Probably done
Blinding?	Low risk	Probably done
Completeness of follow-up	Unclear risk	Unclear from the publication

Pokrupa 1986

Methods	Single centre, double-blind, placebo-controlled Randomisation by sealed numbered opaque envelope ITT analysis
Participants	Canada 23 patients: T: 11, C: 12 Mean age: 63 years Males: T: 5, C: 6 Inclusion: completed cerebrovascular accidents 100% CT pre-entry Enrolment within 48 hours of ictus 5 patients enrolled > 48 hours
Interventions	T: PGI2 ("Cycloprostin", Upjohn Co, USA) 5 daily 8-hour consecutive infusions weaned up from 2 to 10 mg/kg/min and tapered over last hour C: sterile diluent buffer (NaCl 0.147 w/v, glycine 0.188 w/v, NaOH, pH 10.5 +/- 0.3) Rx: 5 days
Outcomes	Death at 5 days and 1, 2, and 4 weeks. (Neurological impairment rating at 5 days, and 1, 2, and 4 weeks; CT and PET at 5 to 9 days.)

Pokrupa 1986 *(Continued)*

	Method for measuring BP not known
Notes	Ex: coma, complicating neurological conditions, heparin, malignant hypertension, uncontrolled DM, heart attack within 2 months, recent surgery Mixture of data used

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomisation by sealed numbered opaque envelope
Allocation concealment?	Unclear risk	Unclear from the publication
Blinding?	Low risk	Probably done
Completeness of follow-up	Unclear risk	Unclear from the publication

Potter 2009 labetalol

Methods	Multicentre, double-blind, placebo-controlled Randomisation by secure Internet central randomisation (with block size of 6) ITT analysis
Participants	UK 172 patients: T: 56, C: 29 Mean age: 74 years Male 57% Inclusion: > 18 years of age, fixed neurological deficit > 60 minutes, clinical diagnosis of acute stroke Enrolment within 36 hours of ictus
Interventions	Labetalol 50 mg po or matching placebo was initially given with the opportunity to repeat this at 4 hours and 8 hours after randomisation Thereafter patients were continued on 50 to 150 mg of labetalol twice daily for 2 weeks, including for dysphagic patients (after 72 hours intravenous labetalol was converted to oral or nasogastric labetalol depending on swallowing status in dysphagic patients)
Outcomes	Death or dependency at 2 weeks Supine BP was measured with a validated A&D UA-767 BP monitor with a cuff of a suitable size
Notes	Ex: hypertensive encephalopathy, co-existing cardiac or vascular emergency, SBP > 200 mmHg and/or DBP > 120 mmHg in association with primary intracerebral haemorrhage, pre-existing antihypertensive therapy in patients without dysphagia, impaired level of consciousness, contraindication to trial therapy, premorbid mRS > 3, coexisting life threatening condition with life expectancy < 6 months, diagnosis of non-stroke on subsequent neuroimaging

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomly assigned by secure Internet central randomisation (with a block size of 6)
Allocation concealment?	Low risk	Probably done

Potter 2009 labetalol *(Continued)*

Blinding?	Low risk	Probably done
Completeness of follow-up	High risk	179 patients randomly assigned, 6 withdrawn due to a protocol violation or non-stroke diagnosis and 1 withdrew consent

Potter 2009 lisinopril

Methods	Multicentre, double-blind, placebo-controlled Randomisation by secure Internet central randomisation (with block size of 6) ITT analysis
Participants	UK 172 patients: T: 56, C: 29 Mean age: 74 years Male 57% Inclusion: > 18 years of age, fixed neurological deficit > 60 minutes, clinical diagnosis of acute stroke Enrolment within 36 hours of ictus
Interventions	Lisinopril or matching placebo was initially given at 5 mg po with an opportunity to repeat the dose at 4 hours and 8 hours after randomisation, with participants then continued on 5 to 15 mg of lisinopril once daily for up to 2 weeks
Outcomes	Death or dependency at 2 weeks Supine BP was measured with a validated A&D UA-767 BP monitor with a cuff of a suitable size
Notes	Ex: hypertensive encephalopathy, co-existing cardiac or vascular emergency, SBP > 200 mmHg and/or DBP > 120 mmHg in association with primary intracerebral haemorrhage, pre-existing antihypertensive therapy in patients without dysphagia, impaired level of consciousness, contraindication to trial therapy, premorbid mRS > 3, coexisting life threatening condition with life expectancy < 6 months, diagnosis of non-stroke on subsequent neuroimaging

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Randomly assigned by secure Internet central randomisation (with a block size of 6)
Allocation concealment?	Low risk	Probably done
Blinding?	Low risk	Probably done
Completeness of follow-up	High risk	179 patients randomly assigned, 6 withdrawn due to a protocol violation or non-stroke diagnosis and 1 withdrew consent

PRISTINE

Methods	Multicentre, double-blind, placebo-controlled Randomisation by minimisation Stratified by age and stroke severity ITT and PP analysis
Participants	UK, Netherlands, Sweden: 9 centres 620 patients: T: 313, C: 307

PRISTINE *(Continued)*

	Age: T: 72 years, C: 72 years Male: T: 161, C: 160 Inclusion: ACHI 100% CT Enrolment within 48 hours
Interventions	T: naftidrofuryl fumarate 633 mg/day iv continuous for 7 days then orally for 6 months C: solvent and identical looking tablets Rx: 6 months
Outcomes	Death Assessments were at entry and intervals to 1 year Method used for BP measurement not given
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Randomisation by minimisation
Allocation concealment?	Unclear risk	Unclear from the publication
Blinding?	Unclear risk	Probably done
Completeness of follow-up	Unclear risk	Unclear from the publication

Rashid 2003 10 mg

Methods	Open label blinded-endpoint Dose comparison Controlled trial Randomisation by computer (with minimisation on age, gender, Scandinavian Neurological Stroke Scale and mean arterial pressure) FU: no losses ITT analysis
Participants	UK, single centre 90 patients: T: 60, C: 30 Mean age: T: 70.8 years, C: 73.9 years Male: T: 28, C: 13 Inclusion: ischaemic or haemorrhagic stroke 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	Transdermal glyceryl trinitrate once daily: T1: 5 mg , T2: 5/10 mg, T3: 10 mg C: no patch Rx: 10 days
Outcomes	24 hour ambulatory BP monitoring was set to record 3 times per hour during the day and hourly during the night at days 0, 1, 4, 5 and 10 mRS, Barthel index and quality of life at 3 months

Rashid 2003 10 mg *(Continued)*

Notes	Ex: SBP > 230 mmHg or < 100 mmHg, DBP > 130 mmHg or < 60 mmHg, heart rate > 130 beats/minute or < 50 beats/minute, 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
Adequate sequence generation?	Low risk	Randomisation by computer (with minimisation on age, gender, Scandinavian Neurological Stroke Scale and mean arterial pressure)
Allocation concealment?	Low risk	Probably done
Blinding?	High risk	Probably not done
Completeness of follow-up	Low risk	No loss of follow up

Rashid 2003 5 mg

Methods	As for Rashid 2003 10 mg
Participants	—
Interventions	—
Outcomes	—
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomisation by computer (with minimisation on age, gender, Scandinavian Neurological Stroke Scale and mean arterial pressure)
Allocation concealment?	Low risk	Probably done
Blinding?	High risk	Probably not done
Completeness of follow-up	Low risk	No loss of follow up

Rashid 2003 5/10 mg

Methods	As for Rashid 2003 10 mg
Participants	—
Interventions	—
Outcomes	—

Rashid 2003 5/10 mg *(Continued)*

Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomisation by computer (with minimisation on age, gender, Scandinavian Neurological Stroke Scale and mean arterial pressure)
Allocation concealment?	Low risk	Probably done
Blinding?	High risk	Probably not done
Completeness of follow-up	Low risk	No loss of follow up

Saxena 1999 100 mg

Methods	As for Saxena 1999 25 mg
Participants	—
Interventions	—
Outcomes	—
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Probably done
Allocation concealment?	Unclear risk	Unclear from publications
Blinding?	High risk	Study was single-blinded because of the prominent colour of the drug and the difficulty in manufacturing a proper placebo
Completeness of follow-up	Unclear risk	Unclear from publications

Saxena 1999 25 mg

Methods	Multicentre, single-blind, placebo-controlled Randomisation method not stated ITT analysis
Participants	Europe 85 patients: T1: 10, T2: 10, T3: 20, C: 45 Mean age: T1, T2, T3: 68 years, C: 65 years 39 male and 46 female Inclusion: IS in the anterior circulation 100% CT scans

Saxena 1999 25 mg *(Continued)*

	Enrolment within 18 hours
Interventions	T1: 25 mg/kg 10% DCLHb T2: 50 mg/kg 10% DCLHb T3: 100 mg/kg 10%DCLHb C: equal volume of 0.9% normal saline given every 6 hours for 73 hours Rx: 3 days
Outcomes	Rankin at 3 months BP and heart rate measured every 15 minutes for approximately 72 hours
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Probably done
Allocation concealment?	Unclear risk	Unclear from publications
Blinding?	High risk	Study was single-blinded because of the prominent colour of the drug and the difficulty in manufacturing a proper placebo
Completeness of follow-up	Unclear risk	Unclear from publications

Saxena 1999 50 mg

Methods	As for Saxena 1999 25 mg
Participants	
Interventions	
Outcomes	—
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Probably done
Allocation concealment?	Unclear risk	Unclear from publications
Blinding?	High risk	Study was single-blinded because of the prominent colour of the drug and the difficulty in manufacturing a proper placebo
Completeness of follow-up	Unclear risk	Unclear from publications

Squire 1996

Methods	Multicentre, double-blind, placebo-controlled Stratified for age and time of stroke onset ITT analysis
Participants	UK, 16 centres 147 patients: T: 75, C: 72 Age: T: 69 years, C: 69 years Males: T: 50, C: 32 Inclusion: first ever IS, pre-treatment motor arm or motor leg (NIHSS scale) of 2 or 3 100% CT scan within 72 hours Enrolment within 12 hours
Interventions	T: lifarizine 250 ug/kg iv immediately plus lifarizine 60 mg bd C: matching placebo Rx: 6 days
Outcomes	Death, NIH motor scores and Canadian Neurological scales days 26 to 30 and week 13; Rankin and Barthel scores at days 26 to 30 and week 13 T: 5 missing for Barthel at 4 weeks C: 8 missing for Barthel at 4 weeks T: 6 missing for Barthel at 3 months C: 9 missing for Barthel at 3 months Method for BP measurement not known
Notes	Ex: NIH scale level of consciousness 2 or 3, previous stroke or neurological condition that may interfere with neurological or functional assessments, MI within last 4 months, left ventricular failure, SBP < 120 and DBP < 80 mmHg, history of ventricular arrhythmias or existing ECG abnormalities, AV block or IVCD, on CCBs or lipophilic beta blockers, premenopausal female, TIA, pre-existing life-threatening disease or systemic illness, endarterectomy or enrolled in other trial Data from paper and authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Probably done
Allocation concealment?	Unclear risk	Unclear from publications
Blinding?	Low risk	Probably done
Completeness of follow-up	Unclear risk	Unclear from publication

Steiner 1986

Methods	Single centre, double-blind, placebo-controlled Stratification based upon procedure similar to minimisation 18 patients secondarily excluded and 3 withdrawn 11 patients entered a short-term active treatment group, these are included in the treatment arm ITT analysis
Participants	UK, single centre 980 patients screened, 100 randomised: T: 55, C: 45 Mean age: 69.4 years (1 patient 81 years) 54 males

Steiner 1986 *(Continued)*

	Inclusion: ACHI, disabling hemiparesis, age 40 to 80 years 100% CT Enrolment within 1 week
Interventions	T1: 600 mg naftidrofuryl iv daily for 10 days then 100 mg tds po for 9 months C: inactive vehicles to match T2: 1 in 3 patients starting treatment within 12 hours received active infusion and placebo capsules T1 and T2 treated as one here Rx: 9 months
Outcomes	Neurological deficit measured at 24 and 48 to 72 hours, day 10 and disability and functional capacity (7-point scale where 0 = normal, 5 = severely disabled and 6 = comatose, adapted from Rankins gradings) at weeks 3, 9, 10, 15, 24, 36, 52 Method for BP measurements not given
Notes	Ex: coma, stroke but not ACHI, severe disability, severe intercurrent illness, incompatible medication on admission

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Assignment to active or placebo therapy followed stratification
Allocation concealment?	Unclear risk	Unclear from publication
Blinding?	Low risk	Probably done
Completeness of follow-up	High risk	18 patients secondarily excluded and 3 withdrawn

Strand 1984

Methods	Single centre, double-blind, placebo-controlled Randomisation using serially numbered sealed envelopes; the code was held by pharmacy Stratified by delay of symptoms to randomisation, age and severity of symptoms ITT analysis
Participants	Sweden 26 participants: T: 13, C: 13 Mean age: 74 years, T: 76.3 years, C: 71.5 years 14 males, 12 females 100% CT Enrolment within 36 hours
Interventions	T: loading dose of 4 mmol magnesium sulfate iv over 10 minutes followed by continuous iv of 4 mmol magnesium sulfate during the following 8 hours, then after iv infusion one 250 mg magnesium hydroxide po, then 250 mg magnesium hydroxide po 8-hourly for following 5 days C: equal volumes of isotonic saline and placebo pills Rx: 5 days
Outcomes	Scandinavian Stroke Study Group (neurological score) at baseline, day 6 and 6 months Method of BP measurement not known
Notes	Ex: SBP < 110 mmHg on admission, AV-block II-III, major renal impairment, respiratory insufficiency, pre-existing functional impairment confusing proper evaluation of therapeutic effects, concomitant se-

Strand 1984 *(Continued)*

	vere disorders, and ongoing anticoagulant treatment, plasma creatinine > 200 umol/l and EKG showing AV-block II-III

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomisation using serially numbered sealed envelopes
Allocation concealment?	Low risk	Randomisation code were held by pharmacy
Blinding?	Low risk	Probably done
Completeness of follow-up	Unclear risk	Unclear from publication

Uzuner 1995/180 mg

Methods	Single centre, randomised controlled trial ITT analysis
Participants	Turkey 100 patients: T: 50, C: 50 IS: mean age: 63 years, 41 males and 36 females Primary intracerebral haemorrhage: mean age 65 years, 3 male, 8 female Inclusion: ischaemic and haemorrhagic strokes 100% CT pre-entry Enrolment within 24 hours 16 patients enrolled after 24 hours (1 iv, 15 po)
Interventions	T: IS - nimodipine 180 mg/day (60 mg tds) po T: primary intracerebral haemorrhage: nimodipine 2 mg/hour iv for SAH or intracerebral haemorrhage C: matching po or iv placebo Rx: 2 days
Outcomes	BP and pulse rate measured at basal and at 5, 15, 30 and 60 minutes in first hour and then every hour within the first 23 hours, then every 2 hours in the next 24 hours BP measured supine using automatic monitor (PETAS) Length of stay Glasgow Coma Scale
Notes	Ex: 10 patients (T: 2, C: 8) treated with antihypertensive agents for malignant hypertension 2 patients with SAH (treated with iv nimodipine) excluded from our analysis We used unpublished paper and data supplied by author

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Probably done
Allocation concealment?	Unclear risk	Unclear from available data
Blinding?	Unclear risk	Unclear from available data

Uzuner 1995/180 mg *(Continued)*

Completeness of follow-up	Unclear risk	Unclear from available data

VENUS 1995

Methods	Multicentre, double-blind, randomised controlled trial Method of randomisation not known Patients randomised by general practitioners ITT analysis
Participants	Netherlands, GP lead 454 patients: T: 225, C: 229 Males: T: 127, C: 142 Mean age: T: 70.5 years, C: 71.1 years Enrolment within 6 hours of ictus
Interventions	T: nimodipine po 30 mg qid C: matching placebo Rx: 10 days
Outcomes	Death, Barthel and Rankin done by telephone at 3 months Method for BP measurement not known
Notes	Ex: SBP > 220 mmHg

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Randomised in equal blocks of 10, according to computer-generated lists Numbered blocks contained 1 complete treatment or identical placebo course were sequentially distributed
Allocation concealment?	Low risk	Probably done
Blinding?	Low risk	Probably done
Completeness of follow-up	Unclear risk	Unclear from publication

Walters 2006

Methods	Single centre Randomisation done using standard algorithm by the local pharmacy production unit Allocation to insulin or control done in an open label design
Participants	UK 25 patients: T: 13, C: 12 Mean age: 75 years Inclusion: acute ischaemic stroke Enrolment: within 24 hours of ictus 100% CT scan
Interventions	T: iv insulin at a variable rate adjusted for target glucose concentration of 5 to 8 mmol/l C: iv crystalloid

Walters 2006 *(Continued)*

	Rx: 2 days
Outcomes	Mortality at 1 month
Notes	Ex: known insulin requiring DM, patients with severe metabolic derangement, patients with clinical evidence of infection or CCF

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Randomisation performed using standard algorithm by the local pharmacy production unit
Allocation concealment?	Low risk	Probably done
Blinding?	High risk	Open label design
Completeness of follow-up	Unclear risk	25 patients recruited (T: 13, C: 12); no mention of loss of follow-up

Willmot 2006

Methods	Single centre Patient and measurement-blinded Randomised controlled trial Randomisation by computer (with minimisation on age, sex, baseline SBP, baseline Scandinavian Stroke Score, hours from onset, presence of a visible stroke lesion on CT) FU: no losses ITT analysis
Participants	UK 18 patients: T: 12, C: 6 Age: T: 69 years, C: 70.3 years Male: T: 2, C: 3 Inclusion: 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 glyceryl trinitrate 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, Tokyo, 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	Ex: requirement for or contraindication to nitrate therapy, had a definite need for prior antihypertensive therapy or vasoactive drugs, co-operate with scanning

Risk of bias

Bias	Authors' judgement	Support for judgement

Willmot 2006 *(Continued)*

Adequate sequence generation?	Low risk	Randomly assigned using computerised minimisation
Allocation concealment?	Low risk	Probably done
Blinding?	High risk	Patient and measurement-blinded
Completeness of follow-up	Low risk	No loss of follow up

Wimalarat 1994/120mg

Methods	Multicentre, double-blind, randomised controlled trial Randomised by next random number on list Stratified according to the severity of stroke Treatment within 24 hours of stroke 34 patients secondarily excluded, leaving 181 with cerebral infarction PP analysis Comparing 2 different doses of nimodipine: 120 mg and 240 mg
Participants	UK, 3 centres 215 patients: T: 58, C: 60; 181 patients analysed Mean age: T: 70 years, C: 71 years Males: T: 36, C: 33 Inclusion criteria: ischaemic cerebral hemisphere infarction, age range 45 to 85 years and with Barthel Index score of < 65 at entry 100% CT scan Enrolment within 24 hours
Interventions	T1: 120 mg nimodipine daily for 16 weeks T2: 240 mg nimodipine daily for 16 weeks C: identical placebo
Outcomes	Neurological assessment using Medical Research Council (MRC) score Functional assessment using Barthel Index All assessments at baseline, days 1, 4, 7 and weeks 2, 4, 8, 12, 16, 20 and 24 Method used for monitoring BP not known Deaths in this review are only out of those who completed and excluded withdrawals and secondary exclusions
Notes	Ex: haemorrhage on CT scan, disability due to other causes inseparable from acute stroke, MI with last 6 months, renal or hepatic failure, patient in whom survival was not expected at the initial assessment, brain stem strokes Data used here not intention-to-treat 34 patients secondary excluded and 30 patients withdrawn BP measurements and outcome data obtained from author Data used was from the author and from the paper

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Probably done
Allocation concealment?	Unclear risk	Unclear from publication

Wimalarat 1994/120mg *(Continued)*

Blinding?	Low risk	Probably done
Completeness of follow-up	High risk	30 patients withdrawn

Wimalarat 1994/240mg

Methods	As for Wimalarat 1994/120mg but using 240 mg nimodipine T: 63 patients, C: 60 patients
Participants	—
Interventions	—
Outcomes	—
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Probably done
Allocation concealment?	Unclear risk	Unclear from publication
Blinding?	Low risk	Probably done
Completeness of follow-up	High risk	30 patients withdrawn

ACEI: angiotensin-converting enzyme inhibitor
ACHI: acute cerebral hemisphere infarction
ADL: activities of daily living
AF: atrial fibrillation
AV: atrioventricular
bd: twice a day
BP: blood pressure
C: control treatment
CCB: calcium channel blocker
CCF: congestive cardiac failure
CI: cardiac index
CSF: cerebrospinal fluid
CT: computerised tomography
DBP: diastolic blood pressure
DHCLHb: diaspirin cross-linked haemoglobin
DM: diabetes mellitus
ECG: echocardiogram
EEG: electroencephalography
Ex: exclusions
FU: follow up
GKI: glucose-potassium-insulin
GTN: glyceryl trinitrate
ICH: intracerebral haemorrhage
IS: ischaemic stroke
ITT: Intention to treat

IU: international unit
iv: intravenous
MAP: mean arterial pressure
MCA: middle cerebral artery
MI: myocardial infarction
MRI: magnetic resonance imaging
mRS: modified Rankin Score
NIHSS: National Institutes of Health Stroke Scale
OCSP: Oxfordshire Community Stroke Project
PET: positron emission tomography
po: oral
PP: per protocol
PTX: pentoxifylline
PGI2: prostacyclin
PICH: primary intra cerebral haemorrhage
qid: four times per day
Rx: treatment
SAH: subarachnoid haemorrhage
SBP: systolic blood pressure
sl: sublingual
T: active treatment
tds: three times per day
TIA: transient ischaemic attack

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

Study	Reason for exclusion
Albers 1995a	BP data not available
Albers 1995b	BP data not available
Ameriso 1992	Haemorheological variables are studied This is part of the JP Mohr study
ANS 1992	BP data in the immediate post-stroke period not available
ATTACH 2006	No control group
Autret 1992	BP data not available
Bogousslavsky 2002	Standard deviations for BP data not available
Britton 1980	Unable to obtain data from the author
Brola 1998	Unable to obtain data
Busse 1985	Unable to obtain BP data
Cao 2003	Confounded study (nimodipine + mannitol versus mannitol)
Capon 1983	Unable to obtain data
CARING 2005	Ongoing study Confounded (2 doses of nicardipine)
Chan 1993	Unable to get BP data
Chandra 1995	Oral versus intravenous nimodipine

Study	Reason for exclusion
	No control group
CHERISH 2006	Confounded study (clinidipine versus losartan)
Davalos 1989	Unable to obtain BP data
Dekoninck 1978	Unable to obtain data
Domzal 1986	Confounded study (vinpocetine versus aminophylline)
FIST 1996	BP data not available
Galeas 1998	Unable to obtain data
Gamez 1988	Unable to obtain BP and outcome data
Geismar 1976	Unable to obtain data from the author
Gelmers 1984/120	BP data not available
Gelmers 1988/120	BP data not available
Gladstone 2006	BP data not available
Gray 1990	On-treatment BP data not available
Haley 1994/0.6	Unable to obtain on-treatment BP data
Haley 1994/2	Unable to obtain on-treatment BP data
Haley 1994/6	Unable to obtain on-treatment BP data
Hartmann 2005	Confounded study (urapidil versus nifedipine)
Hoechst 1986	After much correspondence the company Hoechst was unable to provide the data We continue to correspond
Holthoff 1990	Unable to obtain BP data
Hsu 1988	Author did not keep the raw BP data and referred us to Hoechst who seem unable to provide the data
Huber 1993	Author did not have raw data for the trial but suggested Hoechst would We have corresponded over a period of 2 years with Hoechst and still unable to obtain the data
IMAGES 2004	Unable to obtain BP data from authors
Infeld 1999	BP data not available
Karoutas 1990	Dr Karoutas died and the paper was never published No data could be retrieved from his personal archives
Kornhuber 1993	Unable to obtain BP data
Lampl 2001	BP data not available

Study	Reason for exclusion
Lipani 1984	Cross-over study Patients with TIA and other diseases (Parkinsonian syndrome) were also included
Martin 1985	Raw data lost
Martinsson 2002	BP data not available
MAST-I	No BP data available in paper or from author
Meier 1991	No BP data available for active and control groups
Miller 1984	No control group
Ming 1990	Unable to obtain BP data
Misra 2005	BP data not available
Mohr 1992/120	Unable to obtain BP data
Mohr 1992/240	Unable to obtain BP data
Mohr 1992/60	Unable to obtain BP data
Molnar 1979	Confounded study
Mousavi 2004	BP data not available
Nakamura 2007	Confounded study (perindopril, candesartan or conventional therapy)
Nazir 2004	On-treatment BP data not available
NEST 1994/120	On-treatment BP data not available
NIMPAS 1997	BP not taken
Oczkowski 1989	BP data not available
Ohtomo 1986	Confounded
Ohtomo 1987a	Unable to obtain any information for this study Author does not answer any correspondence
Ohtomo 1987b	Unable to obtain BP data
Orgogozo	Unable to obtain BP data
Piradov 1992	Unable to obtain BP data
Piriyawat 2003	No control group
Platt 1993	Unable to obtain BP data
Popa 1995	Not a trial of treatment but stopping
Rosenbaum 1991	No control group

Study	Reason for exclusion
Saver 2004	No control group
Sherman 1986/120	Unable to obtain BP data
Sprigg 2007	Study involves both acute and subacute stroke patients
Su 2004	BP and outcome data not available
Suslina 1999	Confounded study
Szakall 1998	Sub-acute trial and no placebo
Szczechowski 1994	Unable to obtain data
TRUST 1990/120	BP data not available
Vamosi 1976	Study is confounded
Vamosi 1979	Study is confounded
Wang 2004	BP data not available
Wang 2006	BP data not available
Wasilewski 1985	Dr R Wasilewski now retired and all old documentation has been destroyed
Werner 1986	No BP data available
Wong 1987	Unable to get BP data
Woollard 1978	Authors no longer have data; trying pharmaceutical company
Yu 2003	Confounded study
Zhao 2003	Unable to get BP data
Zorzon 1987	An open non-randomised clinical trial

BP: blood pressure
TIA: transient ischaemic attack

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

ACCOST 2006

Trial name or title	Acute Candesartan Cilexetil Outcomes Stroke Trial
Methods	Double-blind, placebo-controlled, phase IV randomised controlled trial
Participants	Patients presenting with a stroke within 72 hours having a mean BP >120/70
Interventions	Candesartan cilexetil or matched placebo
Outcomes	Primary outcome: all-cause mortality and mortality due to vascular causes

ACCOST 2006 *(Continued)*

	Secondary outcomes: neurological recovery at 3 months (NIHSS), functional recovery at 3 months (mRS, Barthel)
Starting date	2004
Contact information	Christopher Gray, Sunderland Royal Hospital, Sunderland, Tyne and Wear, SR4 7TP, UK
Notes	Size: 50 participants Funding: City Hospitals Sunderland NHS Foundation Trust

ASTART 2005

Trial name or title	Acute Stroke Treatment with Atorvastatin and Irbesartan (ASTART)
Methods	Randomised, placebo-controlled
Participants	Clinical diagnosis of acute ischaemic stroke within 72 hours of onset
Interventions	Atorvastatin (80 mg) + irbesartan (150 mg) versus placebo
Outcomes	Effect on infarct size, cerebral perfusion and clinical outcome at 30 days
Starting date	—
Contact information	WA Centre for Health & Ageing (M573), University of Western Australia, 35 Stirling Highway, Crawley WA 6009, Australia
Notes	—

ATACH-2 2008

Trial name or title	Antihypertensive Treatment in Acute Cerebral Hemorrhage
Methods	5-year international, multicentre, open-labelled, randomised, controlled, phase III clinical trial
Participants	Patients with co-morbid hypertension and spontaneous ICH
Interventions	CCB, nicardipine iv
Outcomes	Efficacy of early, intensive antihypertensive treatment using iv nicardipine
Starting date	2008
Contact information	Adnan I Qureshi, University of Minnesota 12-100 PWB 516 Delware St, SE Minneapolis, MN 55455
Notes	Size: 60 participants Funding: NIH

BLAST 2007

Trial name or title	Blood Pressure Lowering in Acute Stroke Trial
Methods	Randomised, double-blind, placebo-controlled
Participants	Acute ischaemic stroke patients with elevated BP within 48 hours of symptom onset
Interventions	Valsartan versus placebo orally daily for 7 days or until discharge
Outcomes	30-day Glasgow Outcome Scale, 30-day modified Rankin scale and 30-day Barthel Index
Starting date	2007
Contact information	Gregory W Albers, Stanford University School of Medicine
Notes	Funding: Stanford University, Novartis

COSSACS 2005

Trial name or title	Continue Or Stop post-Stroke Antihypertensives Collaborative Study
Methods	Multicentre, prospective, randomised, open, blinded endpoint study
Participants	Patients within 24 hours of acute ischaemic or hemorrhagic stroke and within 24 hours of last dose of antihypertensive therapy
Interventions	Continue or stop current antihypertensive therapy
Outcomes	Primary outcome: proportion of patients who are dead or dependent (defined by a mRS score > 2) at 14 days post-stroke Secondary outcomes: BP changes, and neurological and functional status at 2 weeks and at 6 months post ictus
Starting date	2002
Contact information	T Robinson, Department of Cardiovascular Sciences, Aging and Stroke Research Group, University of Leicester, UK
Notes	Funding: The Health Foundation

ENOS 2006

Trial name or title	Efficacy of Nitric Oxide in Stroke Trial
Methods	Prospective, international, multicentre, randomised, parallel group, double-blind, placebo-controlled, collaborative trial
Participants	Patients with hemorrhagic or ischaemic stroke who show motor weakness for at least 1 hour, who can be treated within 48 hours, and who have a pre-stroke Rankin score > 3
Interventions	Transdermal glyceryl trinitrate or placebo for 7 days
Outcomes	Primary outcome: mortality rate and Rankin score at 3 months

ENOS 2006 *(Continued)*

	Secondary outcomes: recurrent stroke, symptomatic deep vein thrombosis, symptomatic pulmonary embolism, or symptomatic intracranial haemorrhage at 7 days, major extracranial haemorrhage at 10 days, BP recorded during 7-day treatment, length of hospital stay, discharge disposition, Barthel Index, quality of life as measured by EuroQol and abbreviated mental test score at 3 months
Starting date	2001
Contact information	Philip MW Bath, Division of Stroke Medicine, University of Nottingham, Clinical Sciences Building, City Hospital Campus, Hucknall Road, Nottingham NG5 1PB, UK
Notes	Size: 5000 participants (100 centres) Funding: BUPA Foundation, The Hypertension Trust, MRC, University of Nottingham

FAST-MAG 2005

Trial name or title	Field Administration of Stroke Therapy - Magnesium Phase III Trial
Methods	Multicentre, randomised, double-blind, placebo-controlled trial
Participants	Patients (both cerebral infarction and intracerebral haemorrhage patients) as identified by the Los Angeles Prehospital Stroke Screen (LAPSS) whose neurological deficits have been present for at least 15 minutes, and who can be treated within 2 hours of symptom onset
Interventions	Magnesium sulphate iv or a matched placebo
Outcomes	Primary outcome: functional outcome at 90 days as measured by the mRS
Starting date	2005
Contact information	Jeffrey L Saver, Department of Neurology, UCLA Stroke Center, Los Angeles, California
Notes	Funding: National Institute for Neurological Disorders and Stroke, NIH, American Heart Association

GRASP 2005

Trial name or title	Glucose Regulation in Acute Stroke Patients trial
Methods	Multicentre, randomised, controlled trial with 3 treatment arms
Participants	Adult acute ischaemic stroke patients with hyperglycaemia (glucose > 110 mg/dL) within 24 hours of stroke symptoms
Interventions	Tight glucose control, loose glucose control, or usual care
Outcomes	Primary outcome: rate of hypoglycaemic events (glucose < 55 mg/dL) The primary feasibility outcome is the frequency of participants in target range within 24 hours of treatment initiation
Starting date	2005
Contact information	Christiana E Hall, Karen C Johnston, University of Virginia, Department of Neurology #800394, Charlottesville, VA 22908

GRASP 2005 *(Continued)*

	Telephone: +1 434 9245323
Notes	Funding: NIH-NINDS

ICH ADAPT 2007

Trial name or title	IntraCerebral Hemorrahge Acutely Decreasing Arterial Pressure Trial
Methods	Multicentre, randomised, open label, blinded endpoint trial
Participants	Patients who have acute ICH, confirmed by CT diagnosis
Interventions	10 mg iv bolus of labetalol or control
Outcomes	Primary outcome: imaging marker (peri-hematomal rCBF, as measured with CT perfusion 2 hours after anti-hypertensive therapy is initiated)
Starting date	2007
Contact information	Ken Butcher, Division of Neurology, 2E3.13 Walter C Mackenzie Health Sciences Centre, 8440 112 St, Edmonton, Alberta, T6G 2B7, Canada
Notes	Funding: University of Alberta University Hospital Foundation

INTERACT 2 2007

Trial name or title	Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage
Methods	Randomised, open label, active control, parallel assignment, safety/efficacy study
Participants	Patients with acute stroke due to spontaneous ICH confirmed by clinical history and CT scan; at least 2 SBP measurements of ≥ 150 mmHg and ≤ 200 mmHg; recorded 2 or more minutes apart; within 6 hours of stroke onset
Interventions	Early intensive lowering of BP (target SBP 140 mmHg) or standard guideline based management of BP (target SBP 180 mmHg)
Outcomes	Primary outcome: mortality and dependency (according to a 3 to 5 score on the mRS at 3 months)
Starting date	2007
Contact information	Emma Heeley, The George Institute, Level 10, King George V Building, Royal Prince Alfred Hospital, Missenden Road, Camperdown NSW 2050, Australia
Notes	Funding: National Health and Medical Research Council of Australia (NHMRC)

PASS II 1998

Trial name or title	Piracetam Acute Stroke Study II

PASS II 1998 *(Continued)*

Methods	Double-blind, 2 parallel group, placebo-controlled, multicentre trial
Participants	Acute stroke patients
Interventions	Piracetam iv or placebo
Outcomes	Primary outcome: aphasia at 4 and 12 weeks by the Frenchay Aphasia Screening Test
Starting date	1999
Contact information	Prof JM Orgogozo, Hospital Pellegrin, Place Amelie Raba-Leon, France
Notes	Funding: UCB SA Belgium

SCAST 2005

Trial name or title	Scandinavian Candesartan Acute Stroke Trial
Methods	Randomised, double-blind, placebo-controlled, multicentre phase III trial
Participants	Patients presenting with acute stroke within 30 hours and having a SBP ≥ 140 mmHg
Interventions	Candesarten cilexetil po (dose increasing from 4 to 16 mg daily) or placebo for 7 days
Outcomes	Primary outcome: death or disability at 6 months; combination of vascular death, MI or stroke during the first 6 months Secondary outcome: SSS at 7 days and 6 months; mRS at 1, 3 and 6 months; MMS score at 6 months; EuroQol score at 6 months
Starting date	2005
Contact information	Rune Aakvik, Department of Internal Medicine, University Hospital, N-0407, Oslo, Norway
Notes	Size: 2500 participants Funding: Helse Øst RHF, AstraZeneca

TAST 2007

Trial name or title	Effect of an angiotensin receptor antagonist on cerebral blood flow, cerebral perfusion pressure, and systemic and peripheral haemodynamics in patients with acute stroke
Methods	Single centre, interventional, randomised, double-blind, placebo-controlled trial
Participants	Ischaemic or haemorrhagic stroke within 5 days and systolic blood pressure > 140 mmHg
Interventions	Telmisartan 80 mg once a day or matched placebo
Outcomes	Quantitative cerebral blood flow (xenon CT figure) before and 1.5 hours after first treatment
Starting date	2007

TAST 2007 *(Continued)*

Contact information	Division of Stroke Medicine, Clinical Sciences Building, City Hospital, Nottingham, NG5 1PB, United Kingdom
Notes	Funding: British Heart Foundation, University of Nottingham

BP: blood pressure
CCB: calcium channel blocker
CT: computerised tomography
ICH: intracerebral haemorrhage
iv: intravenous
MI: myocardial infarction
MMS: Mini-Mental State
mRS: modified Rankin Score
NIH: National Institutes of Health
rCBF: regional cerebral blood flow
SBP: systolic blood pressure
SSS: Scandinavian Stroke Scale

DATA AND ANALYSES

Comparison 1. Drug versus control in stroke: blood pressure lowering therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Early death (≤ 1 month)	36	5134	Odds Ratio (IV, Random, 95% CI)	1.15 [0.98, 1.36]
1.1 ACE inhibitors (po)	3	164	Odds Ratio (IV, Random, 95% CI)	0.91 [0.26, 3.14]
1.2 Beta blockers (po)	5	434	Odds Ratio (IV, Random, 95% CI)	1.33 [0.58, 3.03]
1.3 Calcium channel blockers (iv)	6	738	Odds Ratio (IV, Random, 95% CI)	1.13 [0.76, 1.67]
1.4 Calcium channel blockers (po)	8	1802	Odds Ratio (IV, Random, 95% CI)	0.94 [0.63, 1.40]
1.5 Insulin (iv)	1	25	Odds Ratio (IV, Random, 95% CI)	3.00 [0.11, 80.95]
1.6 Magnesium (iv)	1	25	Odds Ratio (IV, Random, 95% CI)	1.05 [0.04, 29.24]
1.7 Naftidrofuryl	2	710	Odds Ratio (IV, Random, 95% CI)	1.16 [0.77, 1.75]
1.8 Nitric oxide	5	145	Odds Ratio (IV, Random, 95% CI)	1.00 [0.16, 6.11]
1.9 Piracetam	2	967	Odds Ratio (IV, Random, 95% CI)	1.38 [0.99, 1.92]
1.10 Prostacyclin (iv)	3	124	Odds Ratio (IV, Random, 95% CI)	0.51 [0.12, 2.23]
2 Death at end of trial	41	6648	Odds Ratio (IV, Random, 95% CI)	1.09 [0.96, 1.24]
2.1 ACE inhibitors (po)	3	155	Odds Ratio (IV, Random, 95% CI)	0.63 [0.21, 1.90]
2.2 ARA (po)	1	339	Odds Ratio (IV, Random, 95% CI)	0.38 [0.13, 1.11]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 Beta blockers (po)	5	442	Odds Ratio (IV, Random, 95% CI)	1.10 [0.57, 2.14]
2.4 Calcium channel blockers (iv)	6	751	Odds Ratio (IV, Random, 95% CI)	1.17 [0.84, 1.63]
2.5 Calcium channel blockers (po)	10	1534	Odds Ratio (IV, Random, 95% CI)	0.97 [0.72, 1.29]
2.6 GKI (iv)	1	933	Odds Ratio (IV, Random, 95% CI)	1.14 [0.86, 1.51]
2.7 Magnesium (iv)	4	162	Odds Ratio (IV, Random, 95% CI)	0.64 [0.28, 1.48]
2.8 Naftidrofuryl	2	710	Odds Ratio (IV, Random, 95% CI)	1.19 [0.80, 1.77]
2.9 Nitric oxide	4	127	Odds Ratio (IV, Random, 95% CI)	1.01 [0.26, 4.00]
2.10 Pentoxifylline	0	0	Odds Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.11 Piracetam	2	967	Odds Ratio (IV, Random, 95% CI)	1.32 [0.96, 1.81]
2.12 Prostacyclin (iv)	3	124	Odds Ratio (IV, Random, 95% CI)	0.96 [0.17, 5.38]
2.13 Unclassified or combined	1	404	Odds Ratio (IV, Random, 95% CI)	0.81 [0.44, 1.50]
3 Early death or deterioration (≤ 1month)	15	2175	Odds Ratio (IV, Random, 95% CI)	1.07 [0.90, 1.28]
3.1 ACE inhibitors (po)	0	0	Odds Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Beta blockers (po)	4	357	Odds Ratio (IV, Random, 95% CI)	1.32 [0.84, 2.06]
3.3 Calcium channel blockers (iv)	3	254	Odds Ratio (IV, Random, 95% CI)	1.24 [0.75, 2.07]
3.4 Calcium channel blockers (po)	5	787	Odds Ratio (IV, Random, 95% CI)	1.04 [0.78, 1.39]
3.5 Magnesium (iv)	0	0	Odds Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.6 Naftidrofuryl	2	710	Odds Ratio (IV, Random, 95% CI)	0.96 [0.71, 1.32]
3.7 Nitric oxide	0	0	Odds Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.8 Piracetam	1	40	Odds Ratio (IV, Random, 95% CI)	0.21 [0.02, 2.25]
3.9 Prostacyclin (iv)	1	27	Odds Ratio (IV, Random, 95% CI)	1.96 [0.39, 9.93]
4 Death or disability at end of trial	29	3302	Odds Ratio (IV, Random, 95% CI)	1.11 [0.96, 1.29]
4.1 ACE inhibitors (po)	1	40	Odds Ratio (IV, Random, 95% CI)	1.11 [0.31, 4.03]
4.2 Beta blockers (po)	4	353	Odds Ratio (IV, Random, 95% CI)	1.19 [0.76, 1.85]
4.3 Calcium channel blockers (iv)	5	720	Odds Ratio (IV, Random, 95% CI)	1.13 [0.67, 1.91]
4.4 Calcium channel blockers (po)	6	1106	Odds Ratio (IV, Random, 95% CI)	1.30 [0.91, 1.86]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4.5 Magnesium (iv)	4	162	Odds Ratio (IV, Random, 95% CI)	0.73 [0.38, 1.43]
4.6 Naftidrofuryl	2	710	Odds Ratio (IV, Random, 95% CI)	0.97 [0.72, 1.32]
4.7 Nitric oxide	5	142	Odds Ratio (IV, Random, 95% CI)	1.31 [0.64, 2.65]
4.8 Piracetam	1	40	Odds Ratio (IV, Random, 95% CI)	0.37 [0.10, 1.36]
4.9 Prostacyclin (iv)	1	29	Odds Ratio (IV, Random, 95% CI)	2.60 [0.39, 17.16]
5 Systolic blood pressure, early	30	3473	Mean Difference (IV, Random, 95% CI)	-6.95 [-9.40, -4.51]
5.1 ACE inhibitors (po)	4	150	Mean Difference (IV, Random, 95% CI)	-5.68 [-18.32, 6.96]
5.2 ARA (po)	1	339	Mean Difference (IV, Random, 95% CI)	-2.60 [-6.92, 1.72]
5.3 Beta blockers (po)	5	397	Mean Difference (IV, Random, 95% CI)	-6.14 [-11.42, -0.87]
5.4 Calcium channel blockers (iv)	5	676	Mean Difference (IV, Random, 95% CI)	-5.40 [-12.86, 2.07]
5.5 Calcium channel blockers (po)	5	253	Mean Difference (IV, Random, 95% CI)	-4.89 [-11.01, 1.23]
5.6 GKI (iv)	1	933	Mean Difference (IV, Random, 95% CI)	-11.10 [-14.61, -7.59]
5.7 Insulin (iv)	1	25	Mean Difference (IV, Random, 95% CI)	-2.20 [-11.30, 6.90]
5.8 Magnesium (iv)	4	147	Mean Difference (IV, Random, 95% CI)	-6.32 [-14.64, 2.01]
5.9 Nitric oxide	5	145	Mean Difference (IV, Random, 95% CI)	-10.32 [-17.62, -3.02]
5.10 Other vasodilators (po)	1	4	Mean Difference (IV, Random, 95% CI)	-7.16 [-17.11, 2.79]
5.11 Unclassified or combined	1	404	Mean Difference (IV, Random, 95% CI)	-14.0 [-17.20, -10.80]
6 Systolic blood pressure, late	35	5175	Mean Difference (IV, Random, 95% CI)	-4.60 [-6.64, -2.57]
6.1 ACE inhibitors (po)	2	29	Mean Difference (IV, Random, 95% CI)	-8.70 [-30.37, 12.98]
6.2 Beta blockers (po)	4	338	Mean Difference (IV, Random, 95% CI)	-4.92 [-10.22, 0.37]

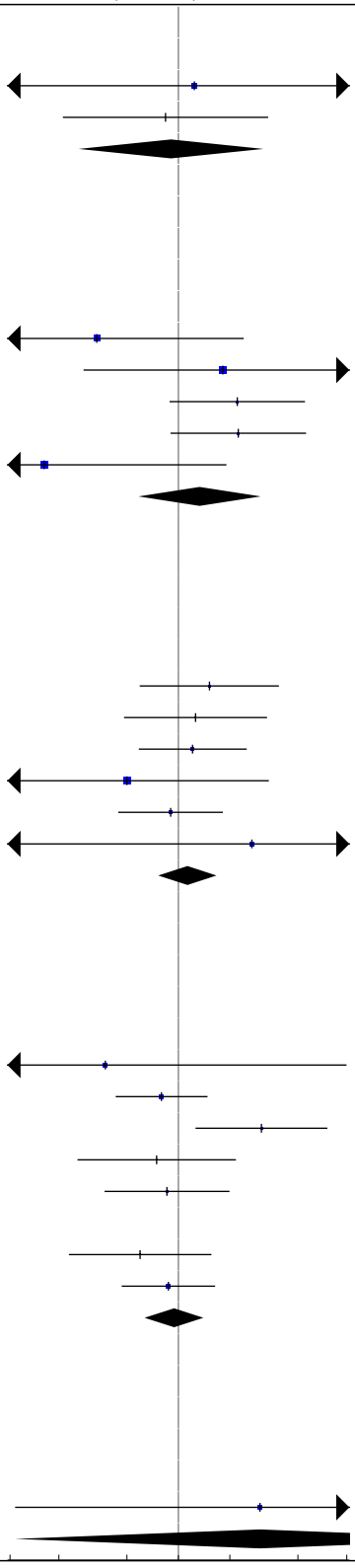
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
6.3 Calcium channel blockers (iv)	4	389	Mean Difference (IV, Random, 95% CI)	-8.57 [-19.08, 1.93]
6.4 Calcium channel blockers (po)	13	2119	Mean Difference (IV, Random, 95% CI)	-3.21 [-5.36, -1.06]
6.5 Insulin (iv)	1	25	Mean Difference (IV, Random, 95% CI)	-4.90 [-13.66, 3.86]
6.6 Magnesium (iv)	4	147	Mean Difference (IV, Random, 95% CI)	1.60 [-10.62, 13.83]
6.7 Naftidrofuryl	2	698	Mean Difference (IV, Random, 95% CI)	-1.67 [-9.86, 6.52]
6.8 Nitric oxide	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.9 Other vasodilators	1	4	Mean Difference (IV, Random, 95% CI)	-23.5 [-45.32, -1.68]
6.10 Piracetam	2	854	Mean Difference (IV, Random, 95% CI)	-2.46 [-5.56, 0.64]
6.11 Prostacyclin (iv)	3	131	Mean Difference (IV, Random, 95% CI)	-7.66 [-15.55, 0.23]
6.12 Thiazide diuretics (po)	1	37	Mean Difference (IV, Random, 95% CI)	-15.0 [-34.25, 4.25]
6.13 Unclassified or combined	1	404	Mean Difference (IV, Random, 95% CI)	-9.00 [-14.03, -7.97]
7 Diastolic blood pressure, early	28	2135	Mean Difference (IV, Random, 95% CI)	-2.53 [-4.07, -0.99]
7.1 ACE inhibitors (po)	4	150	Mean Difference (IV, Random, 95% CI)	-2.71 [-6.94, 1.52]
7.2 ARA (po)	1	339	Mean Difference (IV, Random, 95% CI)	-2.60 [-5.57, 0.37]
7.3 Beta blockers (po)	5	397	Mean Difference (IV, Random, 95% CI)	-2.46 [-5.92, 1.00]
7.4 Calcium channel blockers (iv)	5	675	Mean Difference (IV, Random, 95% CI)	-3.24 [-9.26, 2.77]
7.5 Calcium channel blockers (po)	5	253	Mean Difference (IV, Random, 95% CI)	-2.49 [-5.64, 0.66]
7.6 Insulin (iv)	1	25	Mean Difference (IV, Random, 95% CI)	1.0 [-6.10, 8.10]

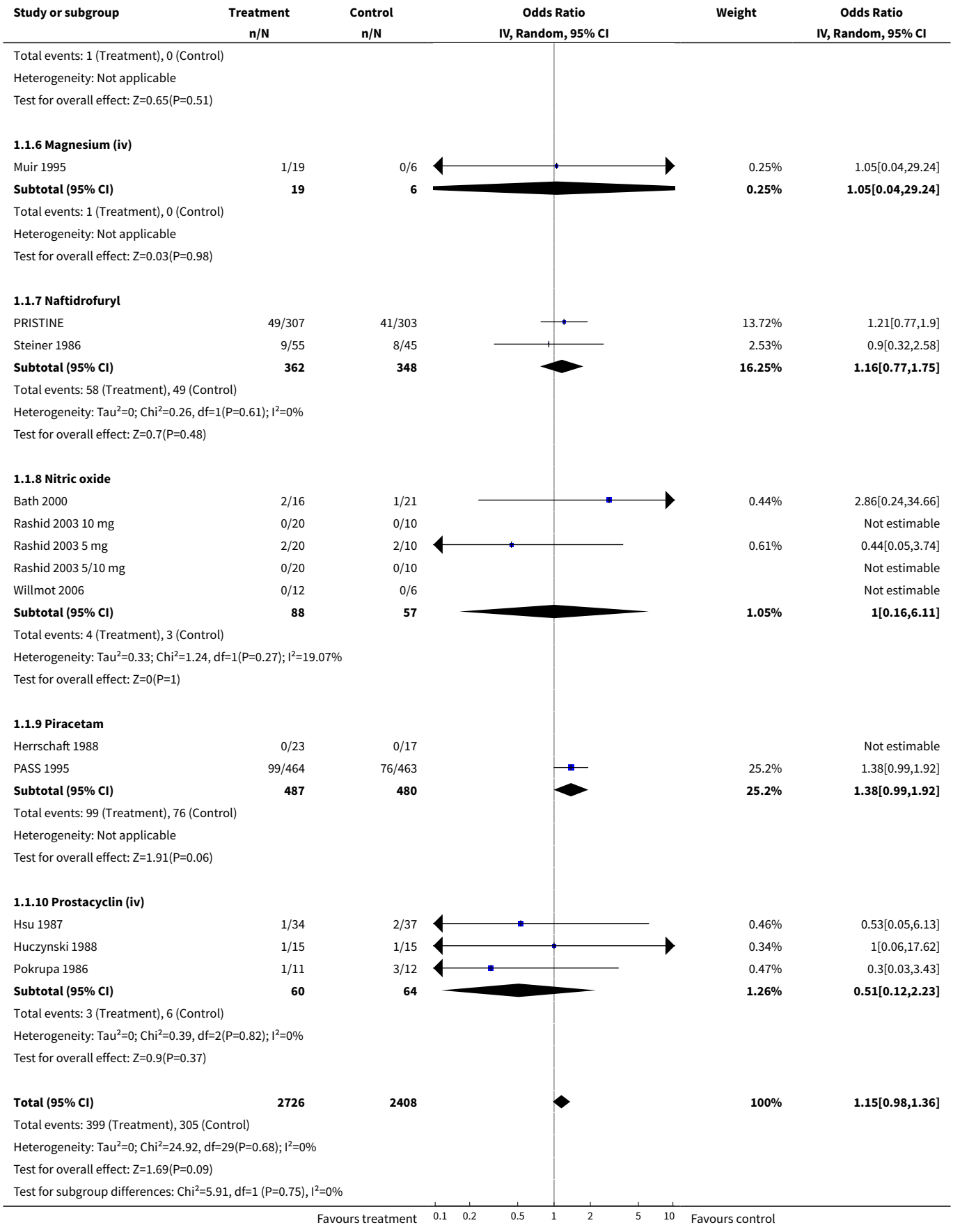
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.7 Magnesium (iv)	4	147	Mean Difference (IV, Random, 95% CI)	-3.53 [-8.37, 1.30]
7.8 Nitric oxide	5	145	Mean Difference (IV, Random, 95% CI)	-0.99 [-5.43, 3.46]
7.9 Other vasodilators	1	4	Mean Difference (IV, Random, 95% CI)	2.67 [-11.78, 17.12]
8 Diastolic blood pressure, late	34	4768	Mean Difference (IV, Random, 95% CI)	-2.63 [-3.90, -1.36]
8.1 ACE inhibitors (po)	2	29	Mean Difference (IV, Random, 95% CI)	-2.64 [-11.96, 6.69]
8.2 Beta blockers (po)	4	338	Mean Difference (IV, Random, 95% CI)	-4.46 [-7.77, -1.15]
8.3 Calcium channel blockers (iv)	4	389	Mean Difference (IV, Random, 95% CI)	-5.35 [-12.76, 2.06]
8.4 Calcium channel blockers (po)	13	2117	Mean Difference (IV, Random, 95% CI)	-2.05 [-3.45, -0.65]
8.5 Insulin (iv)	1	25	Mean Difference (IV, Random, 95% CI)	-2.20 [-7.57, 3.17]
8.6 Magnesium (iv)	4	147	Mean Difference (IV, Random, 95% CI)	-2.61 [-10.21, 5.00]
8.7 Naftidrofuryl	2	698	Mean Difference (IV, Random, 95% CI)	-0.50 [-6.23, 5.24]
8.8 Nitric oxide	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8.9 Other vasodilators	1	4	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8.10 Piracetam	2	853	Mean Difference (IV, Random, 95% CI)	-0.69 [-2.47, 1.09]
8.11 Prostacyclin (iv)	3	131	Mean Difference (IV, Random, 95% CI)	-3.86 [-8.12, 0.40]
8.12 Thiazide diuretics (po)	1	37	Mean Difference (IV, Random, 95% CI)	-5.0 [-16.00, 6.00]
9 Heart rate, early	20	1255	Mean Difference (IV, Random, 95% CI)	-0.45 [-3.06, 2.17]
9.1 ACE inhibitors (po)	3	62	Mean Difference (IV, Random, 95% CI)	-1.25 [-7.49, 4.99]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
9.2 Beta blockers (po)	4	301	Mean Difference (IV, Random, 95% CI)	-6.78 [-9.61, -3.96]
9.3 Calcium channel blockers (iv)	3	379	Mean Difference (IV, Random, 95% CI)	0.91 [-1.88, 3.70]
9.4 Calcium channel blockers (po)	3	217	Mean Difference (IV, Random, 95% CI)	-2.17 [-5.58, 1.23]
9.5 Magnesium (iv)	4	146	Mean Difference (IV, Random, 95% CI)	-3.19 [-12.60, 6.21]
9.6 Nitric oxide	5	145	Mean Difference (IV, Random, 95% CI)	6.27 [2.87, 9.66]
9.7 Other vasodilators	1	5	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
10 Heart rate, late	26	2519	Mean Difference (IV, Random, 95% CI)	-2.84 [-4.55, -1.13]
10.1 ACE inhibitors (po)	2	31	Mean Difference (IV, Random, 95% CI)	-11.55 [-30.94, 7.85]
10.2 Beta blockers (po)	4	341	Mean Difference (IV, Random, 95% CI)	-9.32 [-12.00, -6.63]
10.3 Calcium channel blockers (iv)	4	365	Mean Difference (IV, Random, 95% CI)	-0.13 [-5.59, 5.32]
10.4 Calcium channel blockers (po)	10	1422	Mean Difference (IV, Random, 95% CI)	-2.79 [-3.86, -1.73]
10.5 Magnesium (iv)	4	145	Mean Difference (IV, Random, 95% CI)	-4.32 [-11.07, 2.42]
10.6 Naftidrofuryl	1	81	Mean Difference (IV, Random, 95% CI)	0.88 [-5.78, 7.54]
10.7 Nitric oxide	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
10.8 Other vasodilators	1	3	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
10.9 Prostacyclin (iv)	3	131	Mean Difference (IV, Random, 95% CI)	7.61 [-1.92, 17.13]

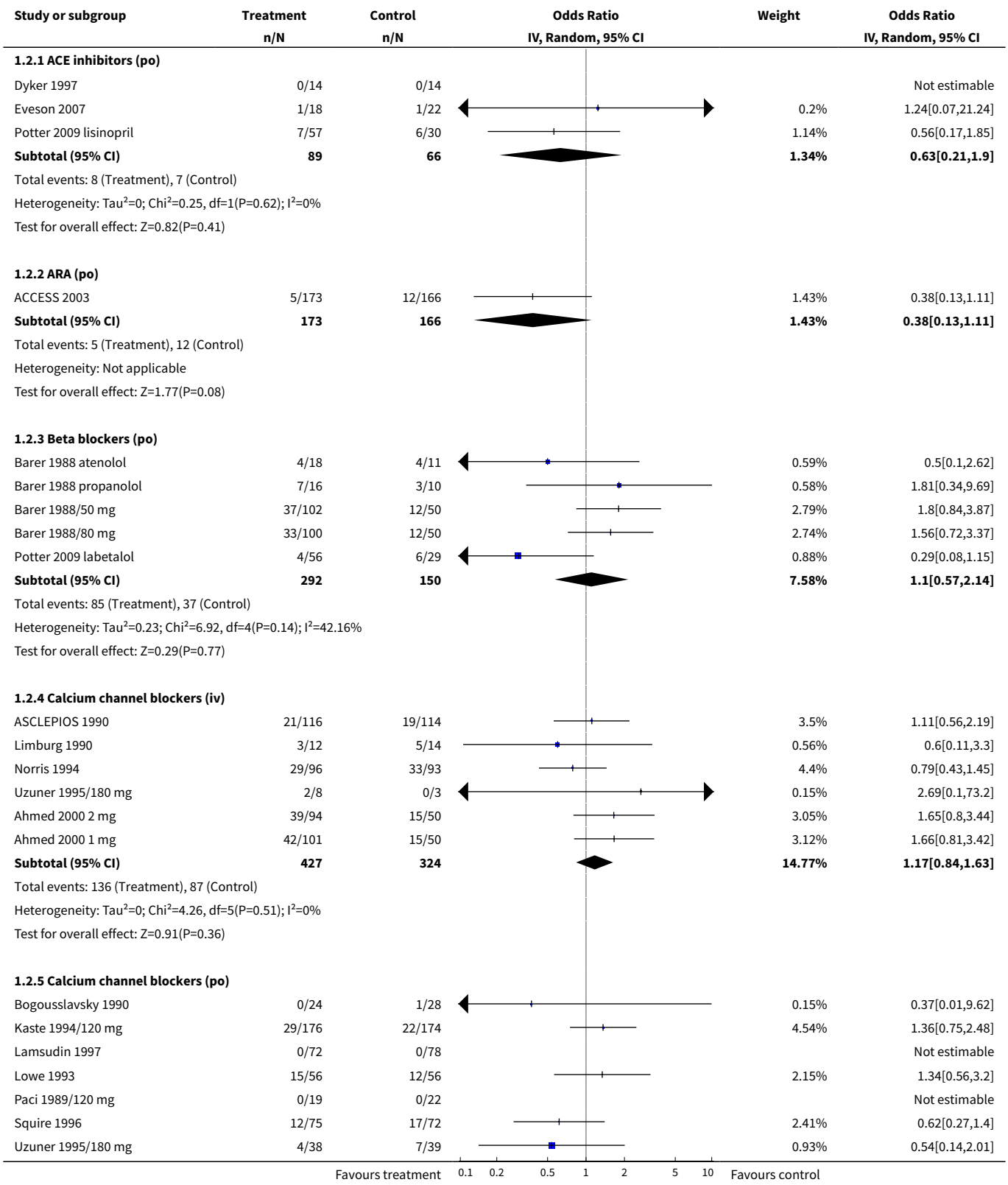
Analysis 1.1. Comparison 1 Drug versus control in stroke: blood pressure lowering therapy, Outcome 1 Early death (≤ 1 month).

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio IV, Random, 95% CI	Weight	Odds Ratio IV, Random, 95% CI
1.1.1 ACE inhibitors (po)					
Dyker 1997	0/14	0/14			Not estimable
Eveson 2007	1/18	1/22		0.34%	1.24[0.07,21.24]
Potter 2009 lisinopril	5/57	4/39		1.45%	0.84[0.21,3.35]
Subtotal (95% CI)	**89**	**75**		**1.79%**	**0.91[0.26,3.14]**
Total events: 6 (Treatment), 5 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.06, df=1(P=0.81); I^2=0%					
Test for overall effect: Z=0.16(P=0.88)					
1.1.2 Beta blockers (po)					
Barer 1988 atenolol	2/18	3/11		0.71%	0.33[0.05,2.41]
Barer 1988 propanolol	5/16	2/10		0.79%	1.82[0.28,11.86]
Barer 1988/50 mg	27/102	7/50		3.33%	2.21[0.89,5.5]
Barer 1988/80 mg	27/101	7/50		3.32%	2.24[0.9,5.58]
Potter 2009 labetalol	1/56	2/20		0.46%	0.16[0.01,1.91]
Subtotal (95% CI)	**293**	**141**		**8.6%**	**1.33[0.58,3.03]**
Total events: 62 (Treatment), 21 (Control)					
Heterogeneity: Tau^2=0.34; Chi^2=6.74, df=4(P=0.15); I^2=40.62%					
Test for overall effect: Z=0.68(P=0.5)					
1.1.3 Calcium channel blockers (iv)					
Ahmed 2000 1 mg	20/101	7/50		3.15%	1.52[0.59,3.87]
Ahmed 2000 2 mg	16/94	7/50		2.98%	1.26[0.48,3.3]
ASCLEPIOS 1990	19/109	16/108		5.25%	1.21[0.59,2.51]
Limburg 1990	2/12	4/14		0.76%	0.5[0.07,3.38]
Norris 1994	19/96	20/93		5.57%	0.9[0.45,1.82]
Uzuner 1995/180 mg	2/8	0/3		0.25%	2.69[0.1,73.2]
Subtotal (95% CI)	**420**	**318**		**17.97%**	**1.13[0.76,1.67]**
Total events: 78 (Treatment), 54 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.83, df=5(P=0.87); I^2=0%					
Test for overall effect: Z=0.6(P=0.55)					
1.1.4 Calcium channel blockers (po)					
Bogousslavsky 1990	0/24	1/28		0.26%	0.37[0.01,9.62]
German-Austrian 120mg	20/239	25/243		7.26%	0.8[0.43,1.48]
Kaste 1994/120 mg	20/176	7/174		3.51%	3.06[1.26,7.43]
Lowe 1993	7/56	9/56		2.44%	0.75[0.26,2.17]
Martinez-Vila 1990	12/81	14/83		3.92%	0.86[0.37,1.99]
Paci 1989/120 mg	0/19	0/22			Not estimable
Squire 1996	8/75	12/72		3%	0.6[0.23,1.56]
VENUS 1995	20/225	23/229		6.98%	0.87[0.47,1.64]
Subtotal (95% CI)	**895**	**907**		**27.37%**	**0.94[0.63,1.4]**
Total events: 87 (Treatment), 91 (Control)					
Heterogeneity: Tau^2=0.08; Chi^2=8.51, df=6(P=0.2); I^2=29.46%					
Test for overall effect: Z=0.28(P=0.78)					
1.1.5 Insulin (iv)					
Walters 2006	1/13	0/12		0.25%	3[0.11,80.95]
Subtotal (95% CI)	**13**	**12**		**0.25%**	**3[0.11,80.95]**

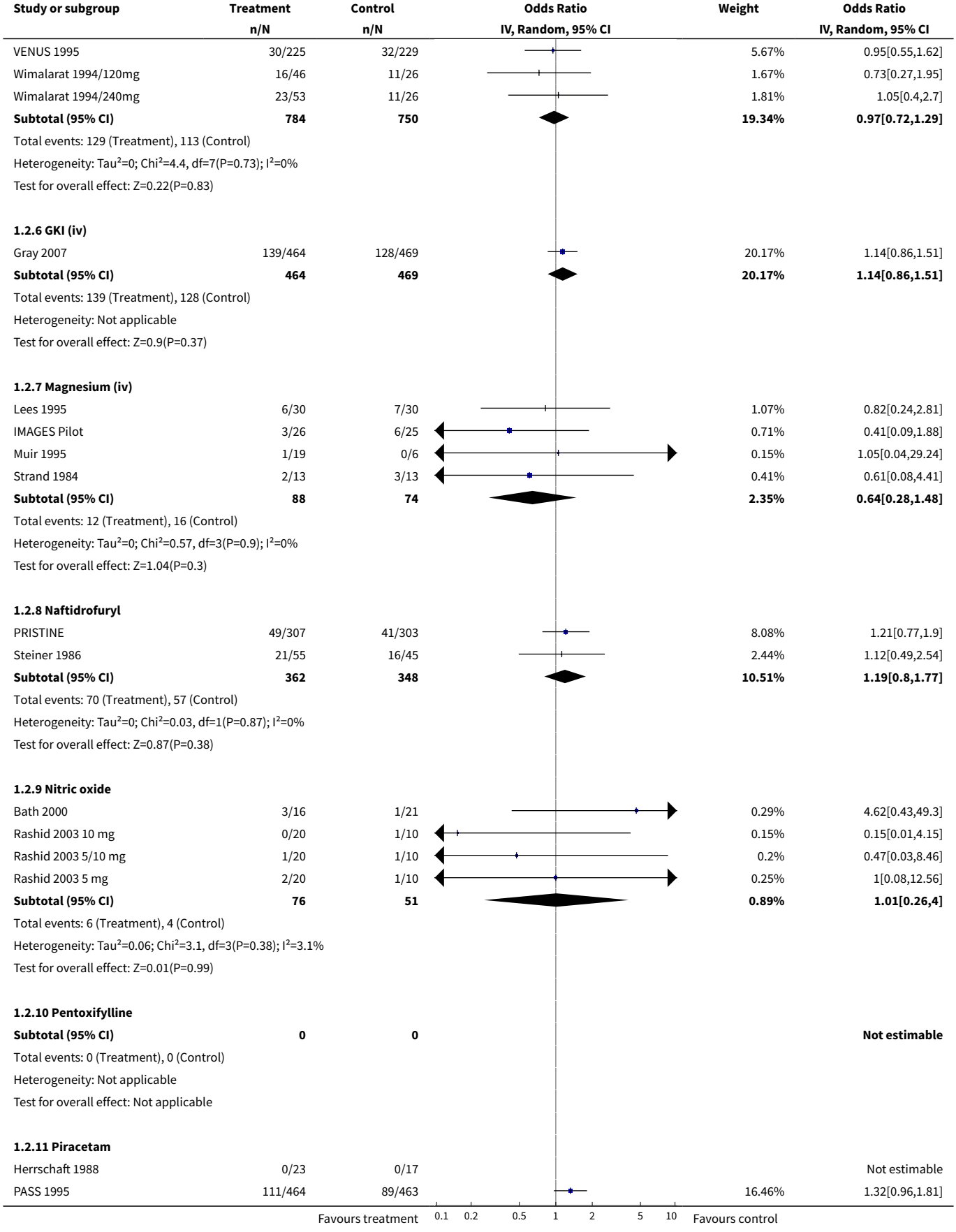


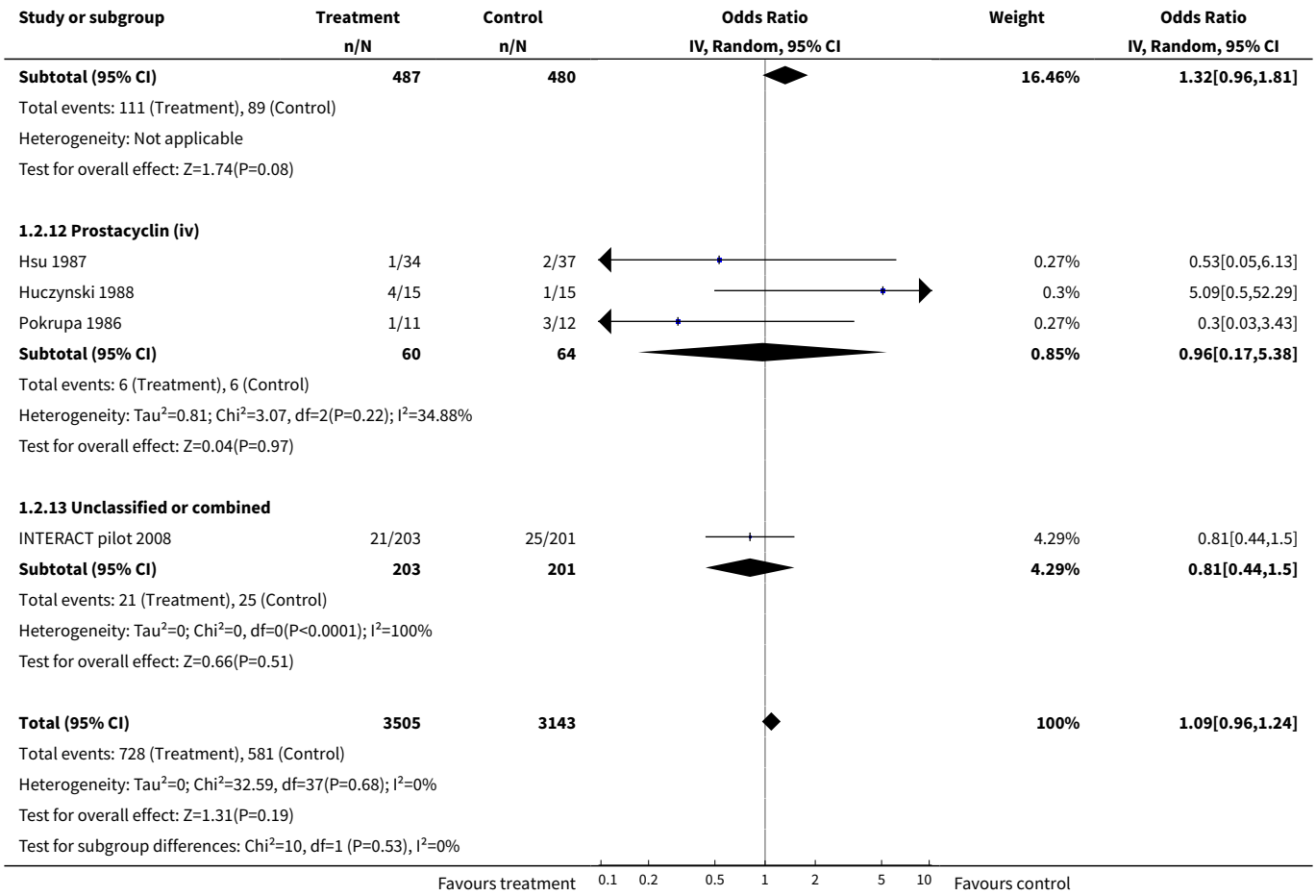


Analysis 1.2. Comparison 1 Drug versus control in stroke: blood pressure lowering therapy, Outcome 2 Death at end of trial.

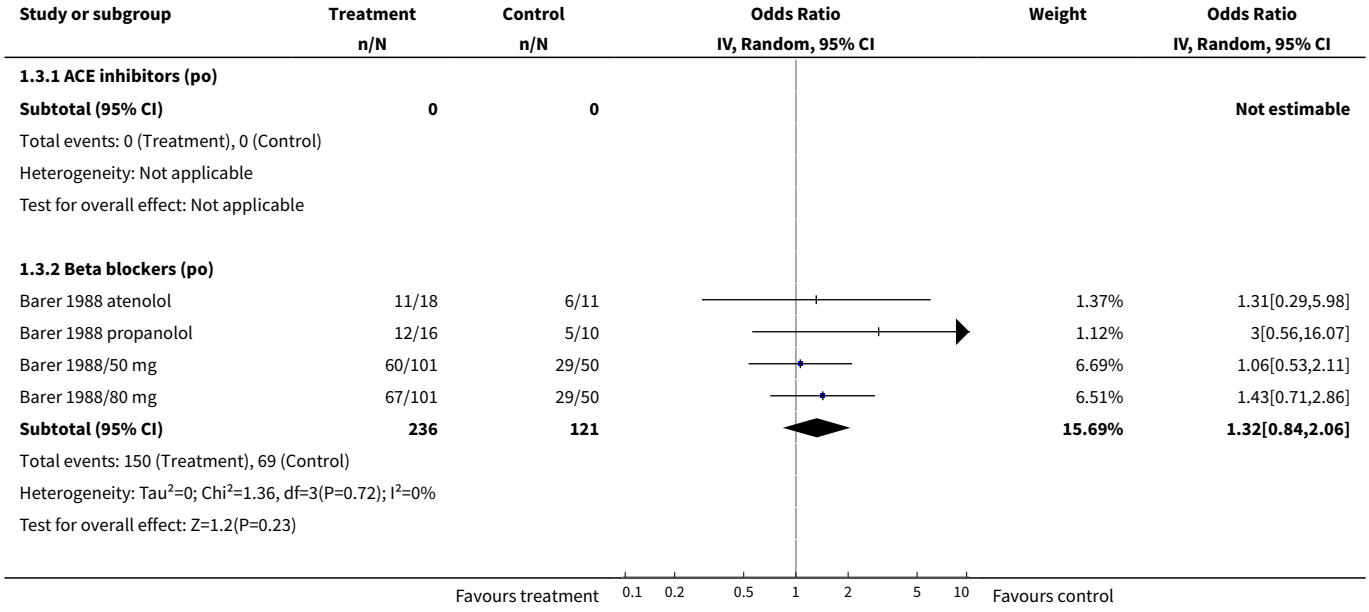


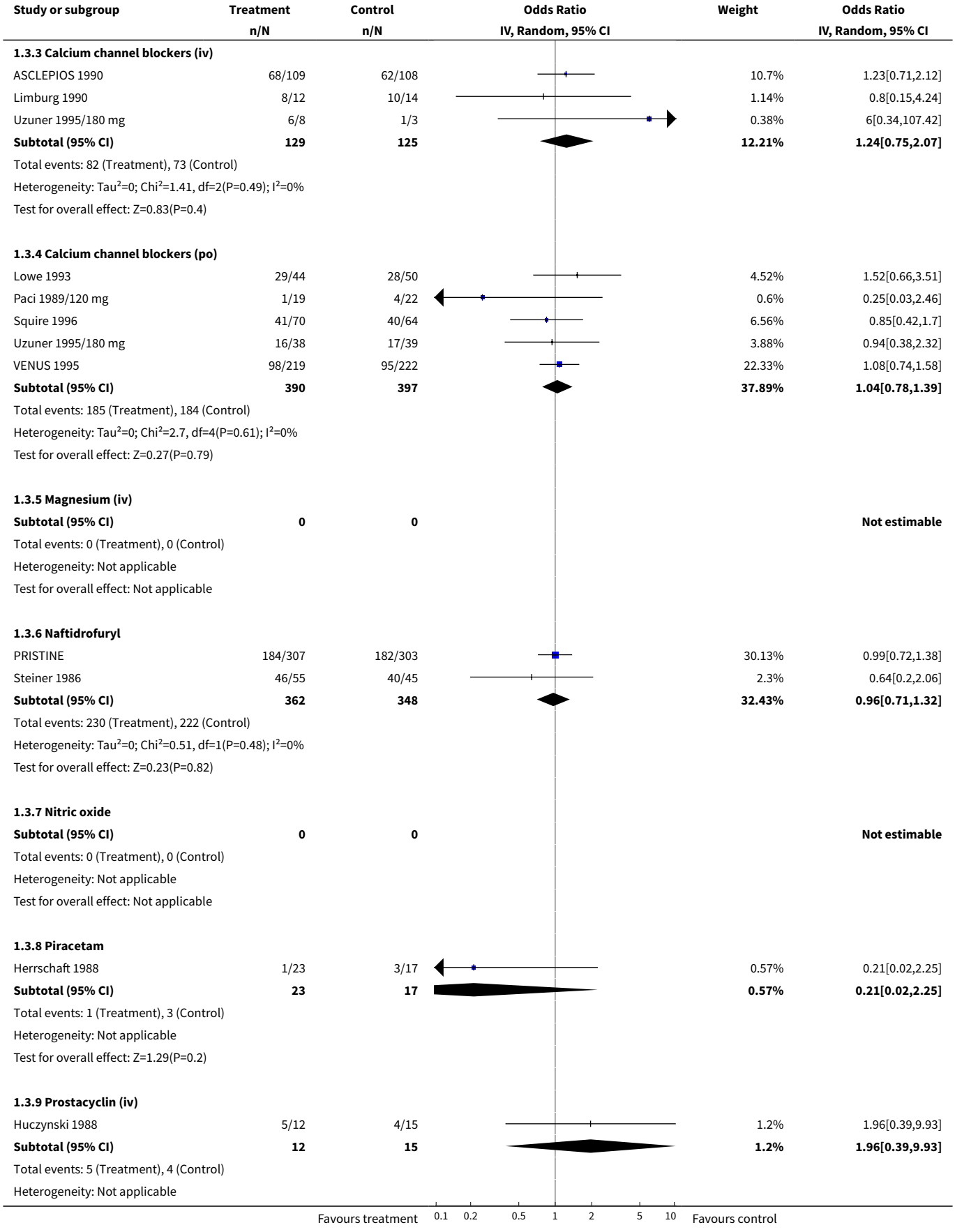
Study or subgroup	Treatment n/N	Control n/N	Odds Ratio IV, Random, 95% CI	Weight	Odds Ratio IV, Random, 95% CI
1.2.1 ACE inhibitors (po)					
Dyker 1997	0/14	0/14			Not estimable
Eveson 2007	1/18	1/22		0.2%	1.24[0.07,21.24]
Potter 2009 lisinopril	7/57	6/30		1.14%	0.56[0.17,1.85]
Subtotal (95% CI)	**89**	**66**		**1.34%**	**0.63[0.21,1.9]**
Total events: 8 (Treatment), 7 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.25, df=1(P=0.62); I^2=0%					
Test for overall effect: Z=0.82(P=0.41)					
1.2.2 ARA (po)					
ACCESS 2003	5/173	12/166		1.43%	0.38[0.13,1.11]
Subtotal (95% CI)	**173**	**166**		**1.43%**	**0.38[0.13,1.11]**
Total events: 5 (Treatment), 12 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.77(P=0.08)					
1.2.3 Beta blockers (po)					
Barer 1988 atenolol	4/18	4/11		0.59%	0.5[0.1,2.62]
Barer 1988 propanolol	7/16	3/10		0.58%	1.81[0.34,9.69]
Barer 1988/50 mg	37/102	12/50		2.79%	1.8[0.84,3.87]
Barer 1988/80 mg	33/100	12/50		2.74%	1.56[0.72,3.37]
Potter 2009 labetalol	4/56	6/29		0.88%	0.29[0.08,1.15]
Subtotal (95% CI)	**292**	**150**		**7.58%**	**1.1[0.57,2.14]**
Total events: 85 (Treatment), 37 (Control)					
Heterogeneity: Tau^2=0.23; Chi^2=6.92, df=4(P=0.14); I^2=42.16%					
Test for overall effect: Z=0.29(P=0.77)					
1.2.4 Calcium channel blockers (iv)					
ASCLEPIOS 1990	21/116	19/114		3.5%	1.11[0.56,2.19]
Limburg 1990	3/12	5/14		0.56%	0.6[0.11,3.3]
Norris 1994	29/96	33/93		4.4%	0.79[0.43,1.45]
Uzuner 1995/180 mg	2/8	0/3		0.15%	2.69[0.1,73.2]
Ahmed 2000 2 mg	39/94	15/50		3.05%	1.65[0.8,3.44]
Ahmed 2000 1 mg	42/101	15/50		3.12%	1.66[0.81,3.42]
Subtotal (95% CI)	**427**	**324**		**14.77%**	**1.17[0.84,1.63]**
Total events: 136 (Treatment), 87 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.26, df=5(P=0.51); I^2=0%					
Test for overall effect: Z=0.91(P=0.36)					
1.2.5 Calcium channel blockers (po)					
Bogousslavsky 1990	0/24	1/28		0.15%	0.37[0.01,9.62]
Kaste 1994/120 mg	29/176	22/174		4.54%	1.36[0.75,2.48]
Lamsudin 1997	0/72	0/78			Not estimable
Lowe 1993	15/56	12/56		2.15%	1.34[0.56,3.2]
Paci 1989/120 mg	0/19	0/22			Not estimable
Squire 1996	12/75	17/72		2.41%	0.62[0.27,1.4]
Uzuner 1995/180 mg	4/38	7/39		0.93%	0.54[0.14,2.01]





Analysis 1.3. Comparison 1 Drug versus control in stroke: blood pressure lowering therapy, Outcome 3 Early death or deterioration (≤ 1month).





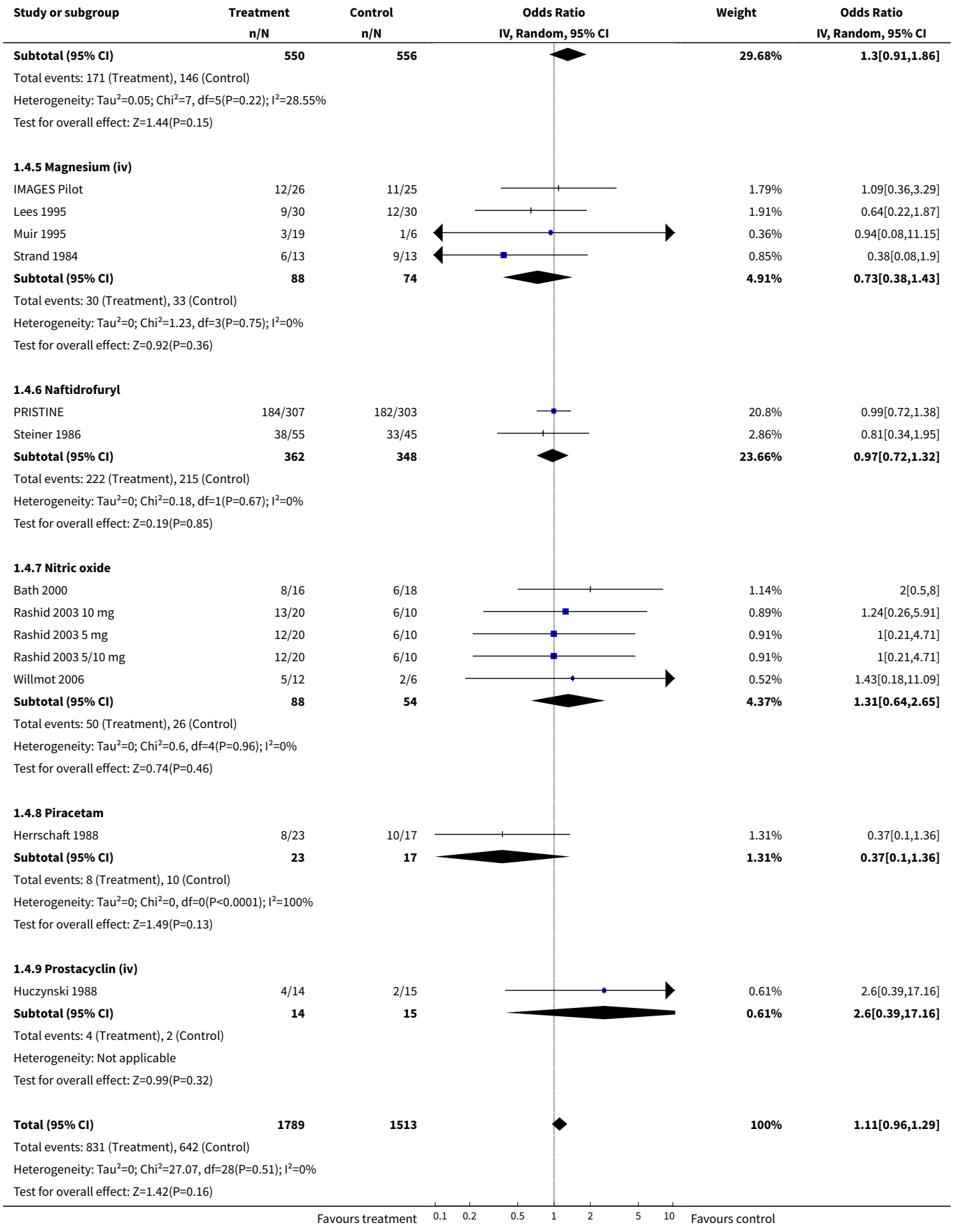
Study or subgroup	Treatment n/N	Control n/N	Odds Ratio IV, Random, 95% CI	Weight	Odds Ratio IV, Random, 95% CI
Test for overall effect: Z=0.82(P=0.41)					
Total (95% CI)	**1152**	**1023**		**100%**	**1.07[0.9,1.28]**
Total events: 653 (Treatment), 555 (Control)					
Heterogeneity: Tau^2=0; Chi^2=9.94, df=15(P=0.82); I^2=0%					
Test for overall effect: Z=0.79(P=0.43)					
Test for subgroup differences: Chi^2=3.95, df=1 (P=0.56), I^2=0%					

Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control

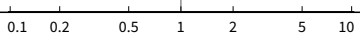
Analysis 1.4. Comparison 1 Drug versus control in stroke: blood pressure lowering therapy, Outcome 4 Death or disability at end of trial.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio IV, Random, 95% CI	Weight	Odds Ratio IV, Random, 95% CI
1.4.1 ACE inhibitors (po)					
Eveson 2007	7/18	8/22		1.32%	1.11[0.31,4.03]
Subtotal (95% CI)	**18**	**22**		**1.32%**	**1.11[0.31,4.03]**
Total events: 7 (Treatment), 8 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.16(P=0.87)					
1.4.2 Beta blockers (po)					
Barer 1988 atenolol	8/16	5/10		0.87%	1[0.21,4.86]
Barer 1988 propanolol	11/16	5/10		0.82%	2.2[0.43,11.22]
Barer 1988/50 mg	45/101	21/50		4.65%	1.11[0.56,2.2]
Barer 1988/80 mg	48/100	22/50		4.69%	1.17[0.59,2.32]
Subtotal (95% CI)	**233**	**120**		**11.04%**	**1.19[0.76,1.85]**
Total events: 112 (Treatment), 53 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.63, df=3(P=0.89); I^2=0%					
Test for overall effect: Z=0.75(P=0.45)					
1.4.3 Calcium channel blockers (iv)					
Ahmed 2000 1 mg	66/101	28/50		4.55%	1.48[0.74,2.96]
Ahmed 2000 2 mg	72/94	28/50		4.05%	2.57[1.23,5.36]
ASCLEPIOS 1990	47/116	44/114		7.81%	1.08[0.64,1.84]
Limburg 1990	3/12	7/14		0.78%	0.33[0.06,1.78]
Norris 1994	39/90	42/79		5.92%	0.67[0.37,1.24]
Subtotal (95% CI)	**413**	**307**		**23.1%**	**1.13[0.67,1.91]**
Total events: 227 (Treatment), 149 (Control)					
Heterogeneity: Tau^2=0.21; Chi^2=10.25, df=4(P=0.04); I^2=60.96%					
Test for overall effect: Z=0.46(P=0.64)					
1.4.4 Calcium channel blockers (po)					
Bogousslavsky 1990	6/24	4/28		1.11%	2[0.49,8.15]
Kaste 1994/120 mg	44/175	31/172		8.15%	1.53[0.91,2.56]
Lowe 1993	25/40	18/46		2.87%	2.59[1.08,6.2]
Paci 1989/120 mg	1/19	4/22		0.42%	0.25[0.03,2.46]
Squire 1996	32/69	32/63		4.67%	0.84[0.42,1.66]
VENUS 1995	63/223	57/225		12.46%	1.16[0.76,1.76]

Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control

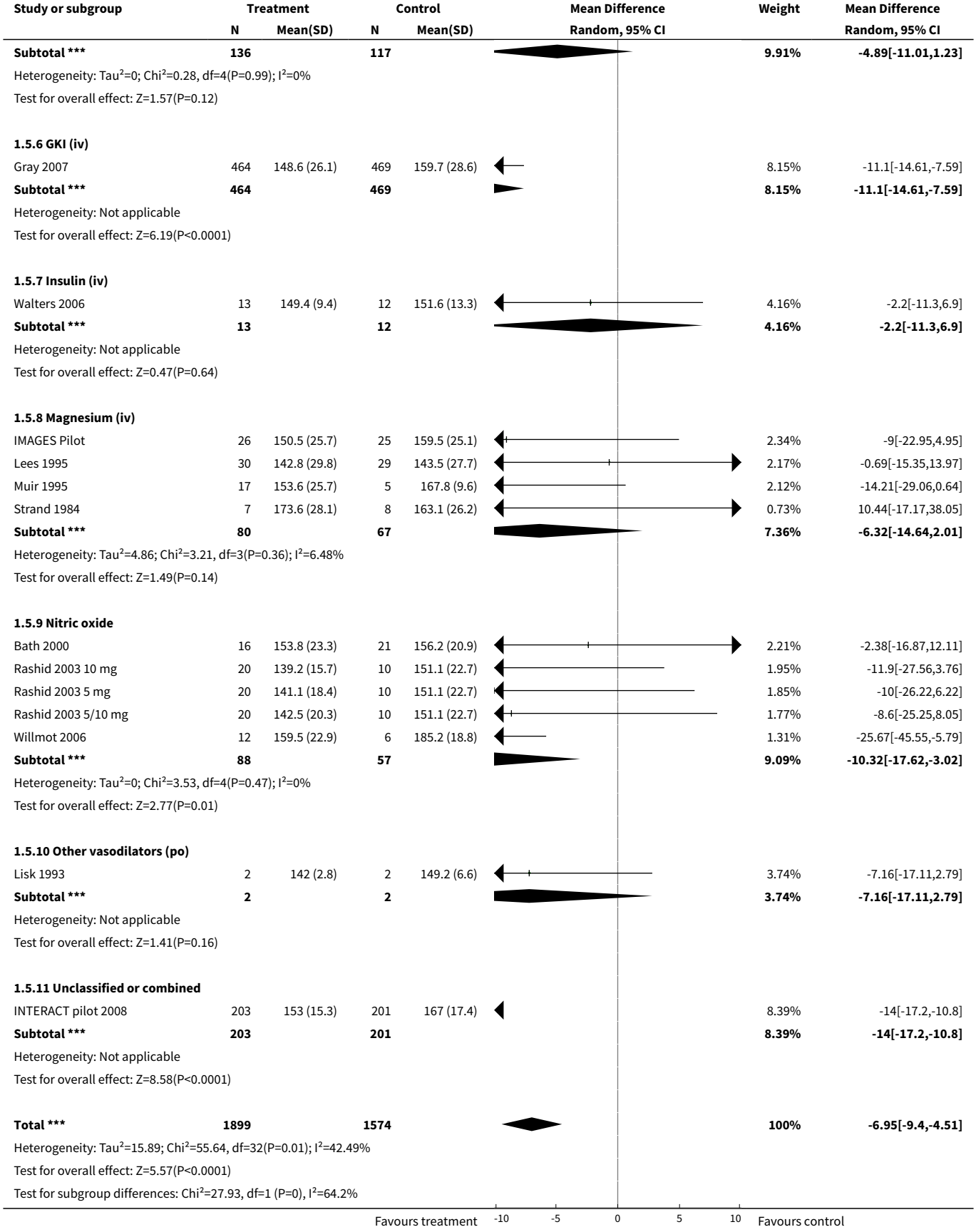


Study or subgroup	Treatment n/N	Control n/N	Odds Ratio IV, Random, 95% CI	Weight	Odds Ratio IV, Random, 95% CI
Test for subgroup differences: Chi²=7.18, df=1 (P=0.52), I²=0%					



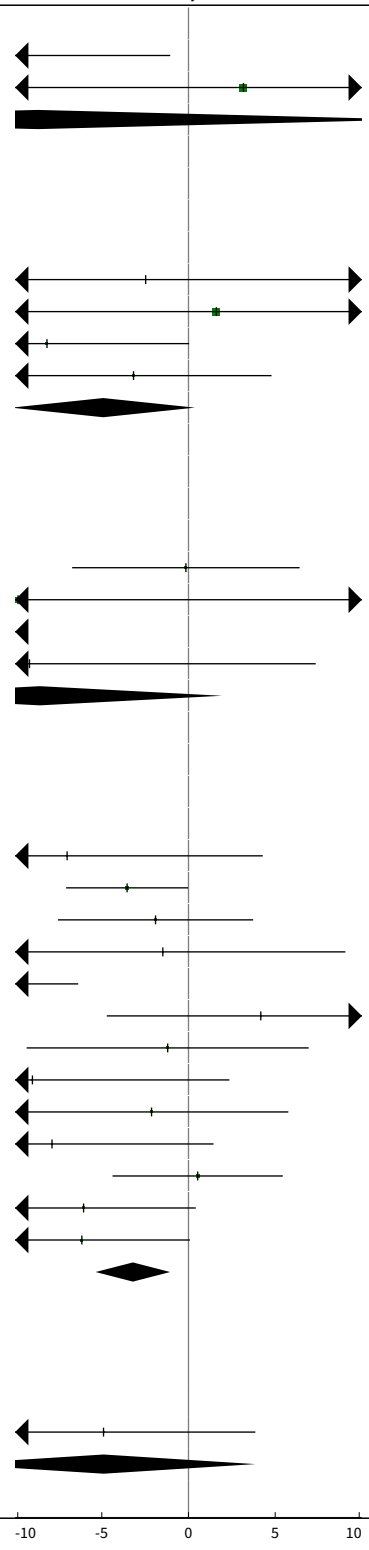
Analysis 1.5. Comparison 1 Drug versus control in stroke: blood pressure lowering therapy, Outcome 5 Systolic blood pressure, early.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.5.1 ACE inhibitors (po)							
Dyker 1997	12	158.3 (20.9)	11	175.8 (23.3)		1.53%	-17.53[-35.67,0.61]
Eveson 2007	17	163.2 (20.4)	18	163.7 (18)		2.67%	-0.5[-13.27,12.27]
Lisk 1993	3	180 (31.6)	2	149.2 (6.7)		0.42%	30.83[-6.11,67.77]
Potter 2009 lisinopril	57	158 (28)	30	170 (21)		3.51%	-12[-22.45,-1.55]
Subtotal ***	**89**		**61**			**8.13%**	**-5.68[-18.32,6.96]**
Heterogeneity: Tau²=89.32; Chi²=7.18, df=3(P=0.07); I²=58.19%							
Test for overall effect: Z=0.88(P=0.38)							
1.5.2 ARA (po)							
ACCESS 2003	173	165.8 (20.9)	166	168.4 (19.7)		7.5%	-2.6[-6.92,1.72]
Subtotal ***	**173**		**166**			**7.5%**	**-2.6[-6.92,1.72]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.18(P=0.24)							
1.5.3 Beta blockers (po)							
Barer 1988 atenolol	15	142 (25.7)	10	146.2 (27.3)		1.16%	-4.21[-25.56,17.14]
Barer 1988 propanolol	14	145.7 (17.9)	9	146.2 (27.3)		1.28%	-0.5[-20.66,19.66]
Barer 1988/50 mg	91	142.8 (23.2)	43	152.7 (28.2)		3.87%	-9.85[-19.53,-0.17]
Barer 1988/80 mg	87	149.7 (26.8)	43	152.7 (28.2)		3.66%	-2.99[-13.12,7.14]
Potter 2009 labetalol	56	163 (22)	29	170 (21)		3.92%	-7[-16.57,2.57]
Subtotal ***	**263**		**134**			**13.88%**	**-6.14[-11.42,-0.87]**
Heterogeneity: Tau²=0; Chi²=1.3, df=4(P=0.86); I²=0%							
Test for overall effect: Z=2.28(P=0.02)							
1.5.4 Calcium channel blockers (iv)							
Ahmed 2000 1 mg	97	153.6 (25.2)	46	148.4 (26.8)		4.09%	5.21[-4.02,14.44]
Ahmed 2000 2 mg	87	140.9 (23.3)	46	148.4 (26.8)		4.12%	-7.47[-16.64,1.7]
ASCLEPIOS 1990	118	151.8 (22.5)	111	153.6 (28)		5.72%	-1.81[-8.41,4.79]
Norris 1994	78	138 (21.8)	82	152.3 (26.8)		5.06%	-14.23[-21.79,-6.67]
Uzuner 1995/180 mg	8	141.9 (33.6)	3	158.3 (14.4)		0.69%	-16.45[-44.88,11.98]
Subtotal ***	**388**		**288**			**19.68%**	**-5.4[-12.86,2.07]**
Heterogeneity: Tau²=44.33; Chi²=12.22, df=4(P=0.02); I²=67.27%							
Test for overall effect: Z=1.42(P=0.16)							
1.5.5 Calcium channel blockers (po)							
Fagan 1988/120 mg	10	136 (21)	5	143 (33)		0.56%	-7[-38.72,24.72]
Fagan 1988/240 mg	10	133 (19)	4	143 (33)		0.48%	-10[-44.42,24.42]
Lisk 1993	5	145.2 (26.5)	2	149.2 (6.7)		0.87%	-3.97[-28.98,21.04]
Squire 1996	73	148.1 (24.1)	67	153.8 (25.6)		4.63%	-5.74[-14,2.52]
Uzuner 1995/180 mg	38	138 (22)	39	140.9 (26.2)		3.37%	-2.87[-13.66,7.92]

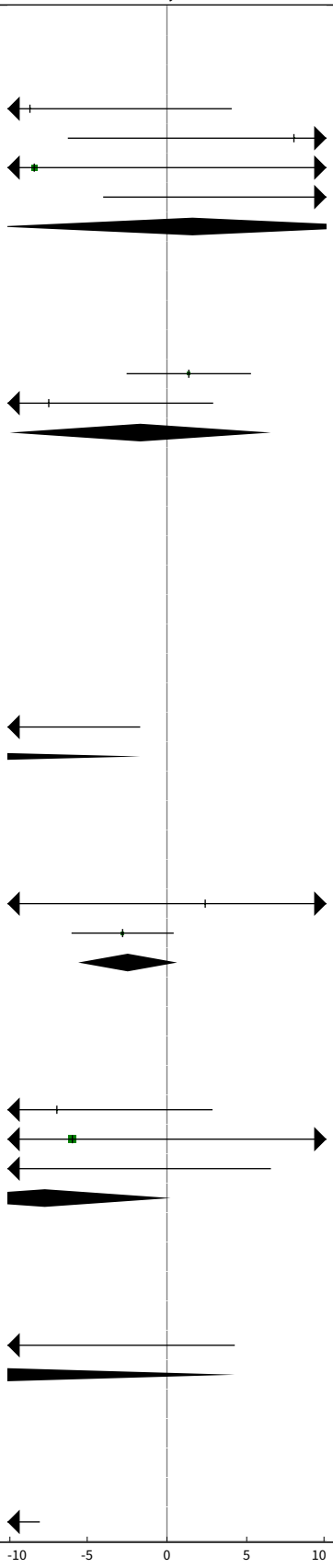


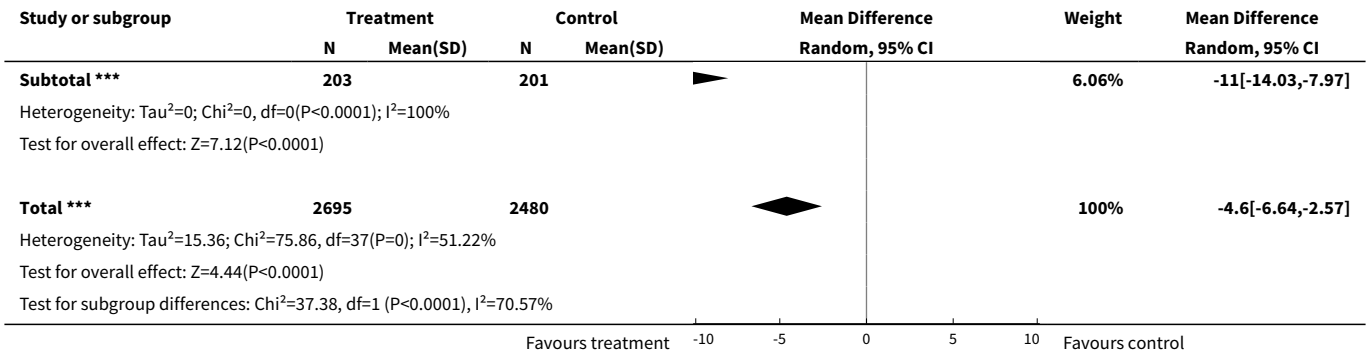
Analysis 1.6. Comparison 1 Drug versus control in stroke: blood pressure lowering therapy, Outcome 6 Systolic blood pressure, late.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.6.1 ACE inhibitors (po)							
Dyker 1997	12	156.5 (21.1)	12	175.5 (23.7)		1.09%	-19[-36.95,-1.05]
Lisk 1993	3	171.7 (7.6)	2	168.5 (14.1)		0.8%	3.17[-18.16,24.5]
Subtotal ***	**15**		**14**			**1.89%**	**-8.7[-30.37,12.98]**
Heterogeneity: Tau²=144.61; Chi²=2.43, df=1(P=0.12); I²=58.84%							
Test for overall effect: Z=0.79(P=0.43)							
1.6.2 Beta blockers (po)							
Barer 1988 atenolol	18	138.1 (24.7)	10	140.5 (23.3)		1.04%	-2.47[-20.85,15.91]
Barer 1988 propanolol	14	142.1 (30.9)	9	140.5 (23.3)		0.75%	1.61[-20.61,23.83]
Barer 1988/50 mg	95	137.3 (25.1)	47	145.5 (22.6)		3.28%	-8.16[-16.36,0.04]
Barer 1988/80 mg	97	142.3 (23.9)	48	145.5 (22.6)		3.38%	-3.17[-11.13,4.79]
Subtotal ***	**224**		**114**			**8.45%**	**-4.92[-10.22,0.37]**
Heterogeneity: Tau²=0; Chi²=1.19, df=3(P=0.76); I²=0%							
Test for overall effect: Z=1.82(P=0.07)							
1.6.3 Calcium channel blockers (iv)							
ASCLEPIOS 1990	107	144.7 (23.8)	97	144.9 (24)		4.05%	-0.15[-6.71,6.41]
Limburg 1990	10	141 (26.7)	6	150.8 (24.6)		0.58%	-9.83[-35.51,15.85]
Norris 1994	83	133.6 (16.3)	75	149.9 (25.1)		3.99%	-16.25[-22.93,-9.57]
Uzuner 1995/180 mg	8	147.5 (21.9)	3	156.7 (5.8)		1.25%	-9.17[-25.68,7.34]
Subtotal ***	**208**		**181**			**9.87%**	**-8.57[-19.08,1.93]**
Heterogeneity: Tau²=72.8; Chi²=11.4, df=3(P=0.01); I²=73.69%							
Test for overall effect: Z=1.6(P=0.11)							
1.6.4 Calcium channel blockers (po)							
Bogousslavsky 1990	24	134 (24)	28	141 (16)		2.22%	-7[-18.28,4.28]
German-Austrian 120mg	239	139.7 (20.7)	243	143.2 (18.6)		5.79%	-3.54[-7.06,-0.02]
Kaste 1994/120 mg	160	146.6 (25.8)	163	148.5 (25.8)		4.56%	-1.9[-7.53,3.73]
Lamsudin 1997	72	161.3 (30.2)	78	162.8 (35.5)		2.43%	-1.48[-12.01,9.05]
Lisk 1993	5	130 (29.2)	2	168.5 (14.1)		0.38%	-38.5[-70.64,-6.36]
Lowe 1993	54	145.2 (24.7)	54	141 (22.4)		3%	4.17[-4.71,13.05]
Martinez-Vila 1990	58	141 (22.7)	65	142.2 (23.3)		3.3%	-1.2[-9.33,6.93]
Paci 1989/120 mg	19	136.7 (17.4)	22	145.7 (19.7)		2.2%	-9[-20.36,2.36]
Squire 1996	68	145.7 (22.7)	55	147.9 (21.8)		3.41%	-2.13[-10.02,5.76]
Uzuner 1995/180 mg	38	128.2 (16.7)	39	136 (24.4)		2.84%	-7.87[-17.19,1.45]
VENUS 1995	215	152.7 (25.3)	213	152.2 (26.5)		4.97%	0.53[-4.38,5.44]
Wimalarat 1994/120mg	69	144.5 (13.1)	33	150.5 (16.7)		4.1%	-6.05[-12.52,0.42]
Wimalarat 1994/240mg	69	144.4 (11.5)	34	150.5 (16.7)		4.23%	-6.15[-12.38,0.08]
Subtotal ***	**1090**		**1029**			**43.44%**	**-3.21[-5.36,-1.06]**
Heterogeneity: Tau²=2.29; Chi²=14.15, df=12(P=0.29); I²=15.18%							
Test for overall effect: Z=2.92(P=0)							
1.6.5 Insulin (iv)							
Walters 2006	13	147.2 (8.9)	12	152.1 (12.9)		3.05%	-4.9[-13.66,3.86]
Subtotal ***	**13**		**12**			**3.05%**	**-4.9[-13.66,3.86]**
Heterogeneity: Not applicable							

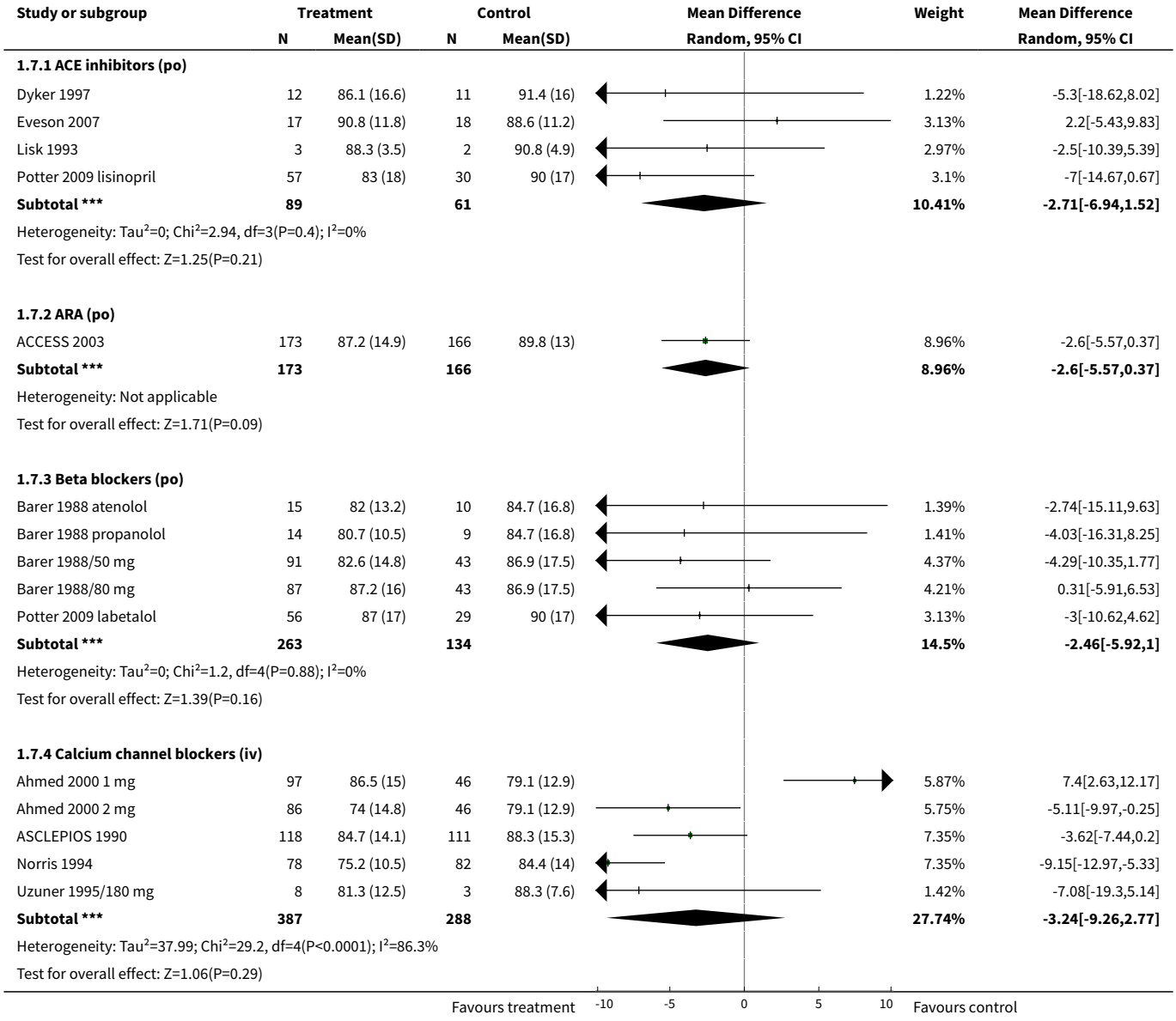


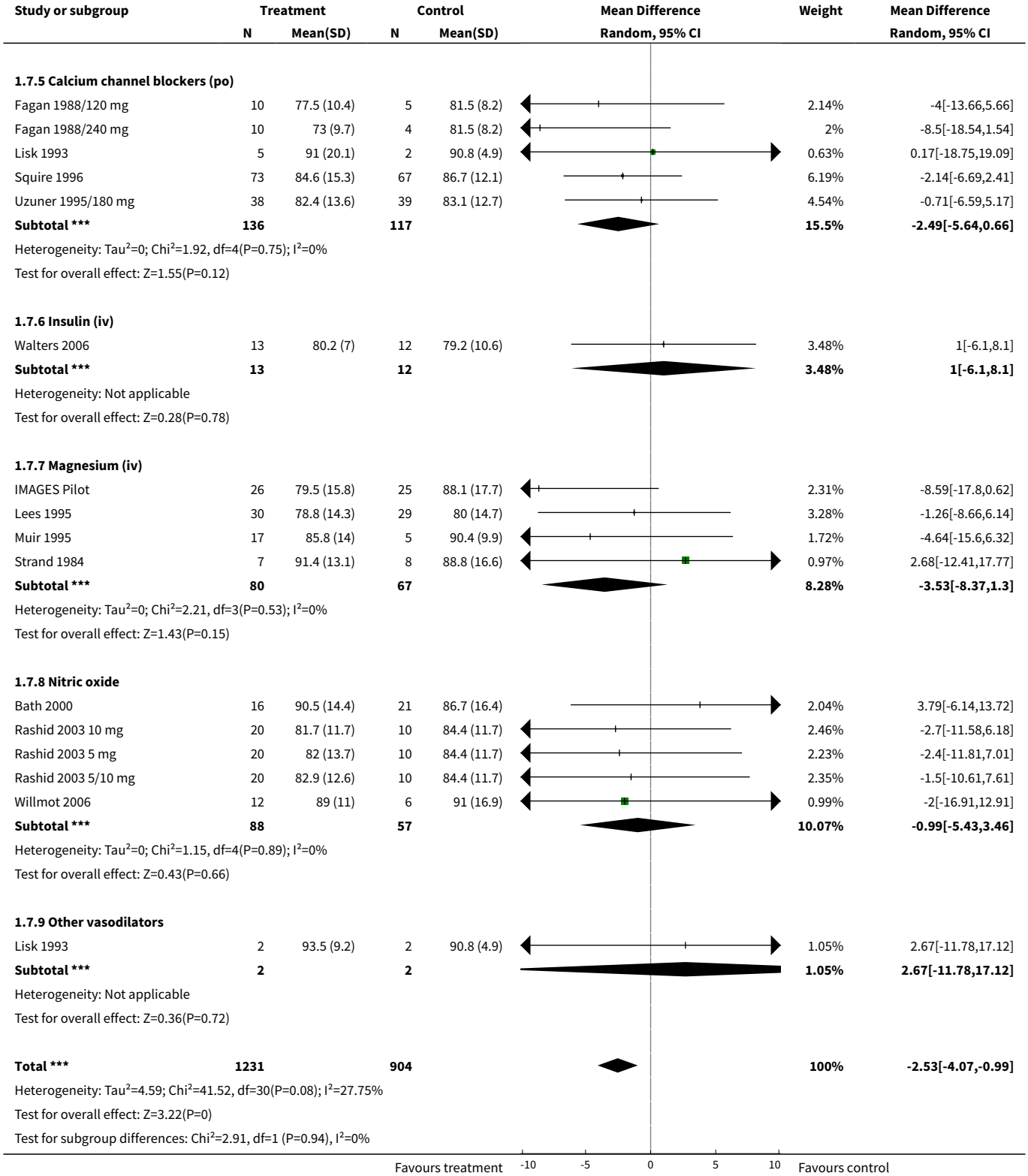
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for overall effect: Z=1.1(P=0.27)							
1.6.6 Magnesium (iv)							
IMAGES Pilot	26	147.4 (17.5)	25	155.9 (27.3)		1.89%	-8.59[-21.24,4.06]
Lees 1995	27	147.5 (28.3)	25	139.5 (23.8)		1.59%	7.96[-6.21,22.13]
Muir 1995	15	150.9 (20.3)	4	159.3 (22)		0.66%	-8.32[-32.23,15.59]
Strand 1984	13	168.5 (35.7)	12	150.4 (18.4)		0.76%	18.04[-4,40.08]
Subtotal ***	**81**		**66**			**4.89%**	**1.6[-10.62,13.83]**
Heterogeneity: Tau²=75.88; Chi²=6, df=3(P=0.11); I²=50.03%							
Test for overall effect: Z=0.26(P=0.8)							
1.6.7 Naftidrofuryl							
PRISTINE	310	155.7 (24.5)	307	154.3 (25)		5.57%	1.37[-2.53,5.27]
Steiner 1986	44	139.9 (20)	37	147.3 (26.2)		2.5%	-7.41[-17.72,2.9]
Subtotal ***	**354**		**344**			**8.07%**	**-1.67[-9.86,6.52]**
Heterogeneity: Tau²=22.73; Chi²=2.44, df=1(P=0.12); I²=58.98%							
Test for overall effect: Z=0.4(P=0.69)							
1.6.8 Nitric oxide							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.6.9 Other vasodilators							
Lisk 1993	2	145 (7.1)	2	168.5 (14.1)		0.77%	-23.5[-45.32,-1.68]
Subtotal ***	**2**		**2**			**0.77%**	**-23.5[-45.32,-1.68]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.11(P=0.03)							
1.6.10 Piracetam							
Herrschaft 1988	23	176.6 (19.6)	17	174.2 (20.2)		1.92%	2.4[-10.1,14.9]
PASS 1995	396	145.6 (24)	418	148.4 (22.6)		5.97%	-2.78[-5.98,0.42]
Subtotal ***	**419**		**435**			**7.89%**	**-2.46[-5.56,0.64]**
Heterogeneity: Tau²=0; Chi²=0.62, df=1(P=0.43); I²=0%							
Test for overall effect: Z=1.55(P=0.12)							
1.6.11 Prostacyclin (iv)							
Hsu 1987	42	142.2 (21.1)	36	149.1 (22.6)		2.68%	-6.9[-16.66,2.86]
Huczynski 1988	15	140.4 (27.8)	15	146.3 (26.9)		0.93%	-5.93[-25.54,13.68]
Pokrupa 1986	11	132.3 (22.3)	12	144.2 (22.8)		1.04%	-11.9[-30.32,6.52]
Subtotal ***	**68**		**63**			**4.65%**	**-7.66[-15.55,0.23]**
Heterogeneity: Tau²=0; Chi²=0.26, df=2(P=0.88); I²=0%							
Test for overall effect: Z=1.9(P=0.06)							
1.6.12 Thiazide diuretics (po)							
Eames 2005	18	158 (24)	19	173 (35)		0.96%	-15[-34.25,4.25]
Subtotal ***	**18**		**19**			**0.96%**	**-15[-34.25,4.25]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.53(P=0.13)							
1.6.13 Unclassified or combined							
INTERACT pilot 2008	203	146 (14.6)	201	157 (16.4)		6.06%	-11[-14.03,-7.97]





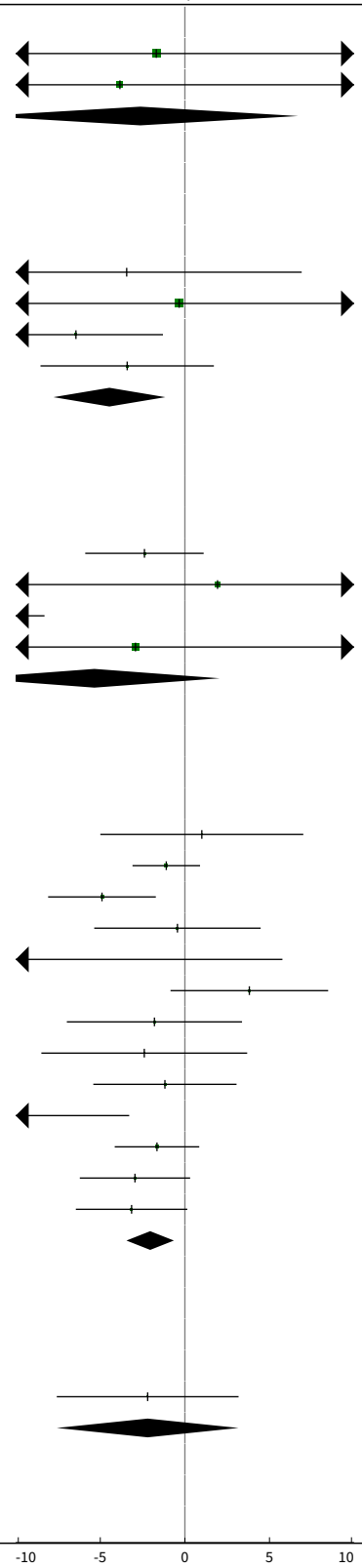
Analysis 1.7. Comparison 1 Drug versus control in stroke: blood pressure lowering therapy, Outcome 7 Diastolic blood pressure, early.

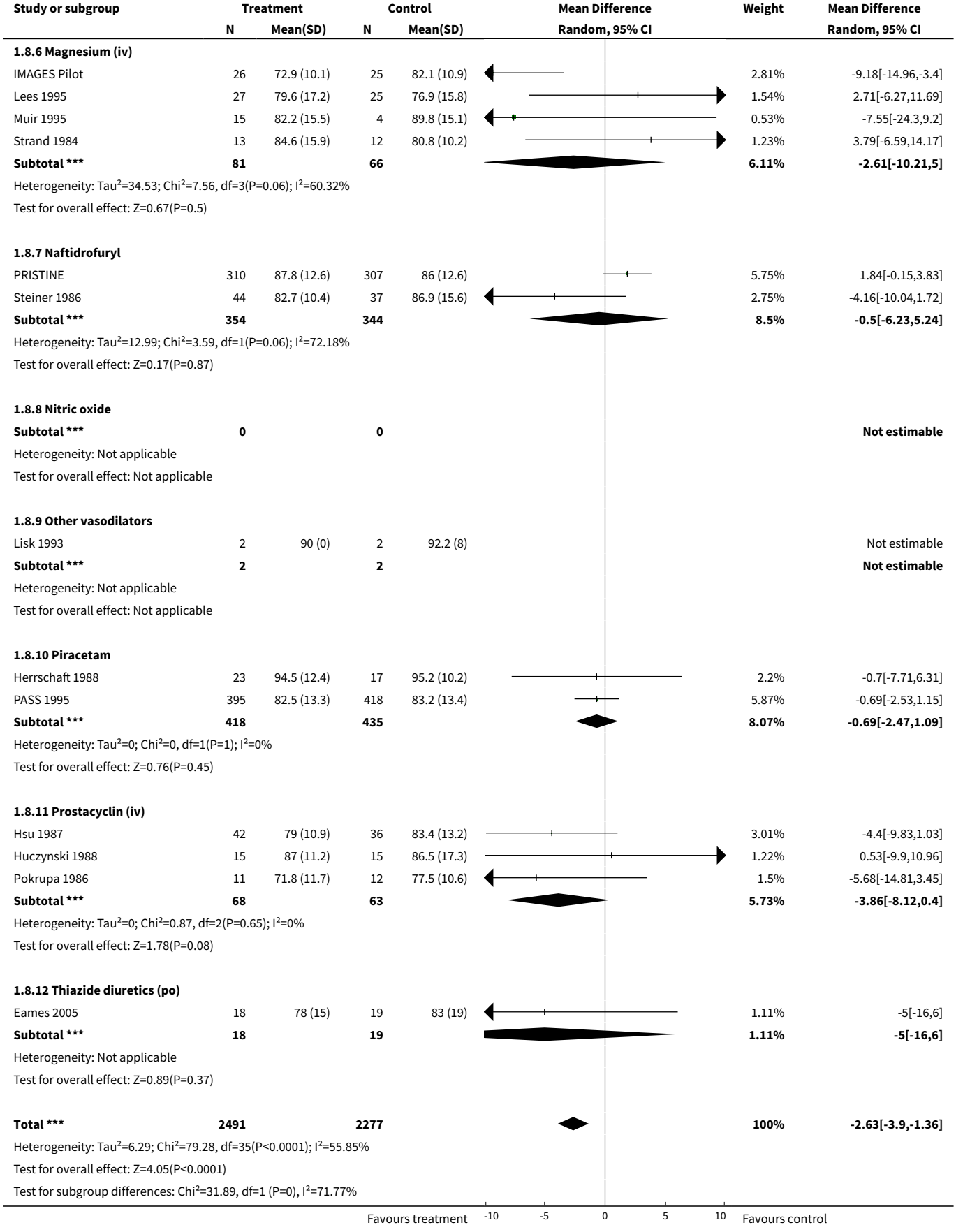




Analysis 1.8. Comparison 1 Drug versus control in stroke: blood pressure lowering therapy, Outcome 8 Diastolic blood pressure, late.

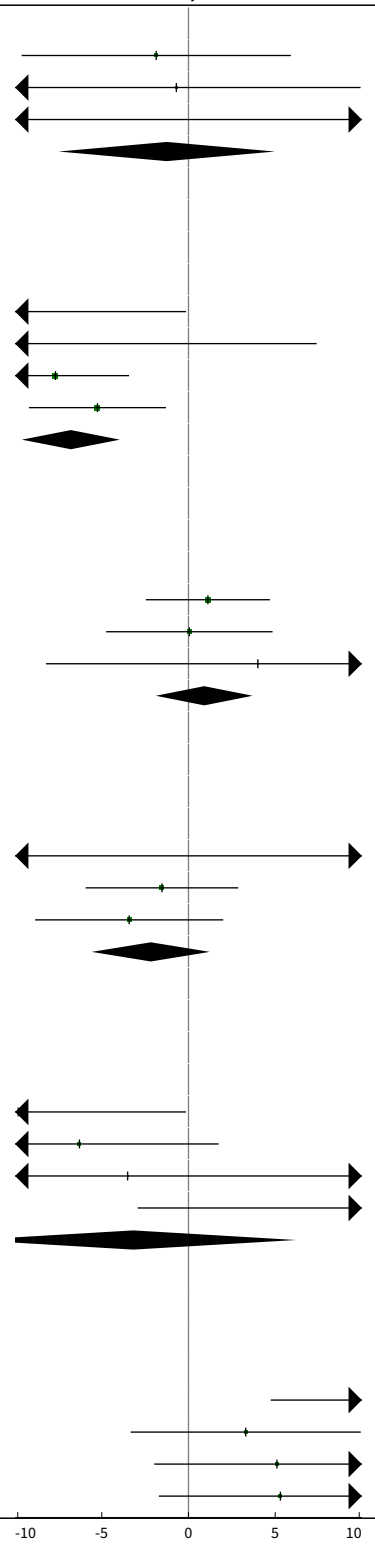
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.8.1 ACE inhibitors (po)							
Dyker 1997	12	88.2 (13.9)	12	89.9 (17.1)		0.9%	-1.69[-14.15,10.77]
Lisk 1993	3	88.3 (7.6)	2	92.2 (8)		0.73%	-3.84[-17.91,10.23]
Subtotal ***	**15**		**14**			**1.63%**	**-2.64[-11.96,6.69]**
Heterogeneity: Tau^2=0; Chi^2=0.05, df=1(P=0.82); I^2=0%							
Test for overall effect: Z=0.55(P=0.58)							
1.8.2 Beta blockers (po)							
Barer 1988 atenolol	18	77.6 (11.3)	10	81.1 (14.4)		1.23%	-3.44[-13.78,6.9]
Barer 1988 propanolol	14	80.7 (16.5)	9	81.1 (14.4)		0.86%	-0.34[-13.11,12.43]
Barer 1988/50 mg	95	79.6 (13.6)	47	86.1 (15.2)		3.19%	-6.44[-11.58,-1.3]
Barer 1988/80 mg	97	82.7 (13.9)	48	86.1 (15.2)		3.21%	-3.41[-8.53,1.71]
Subtotal ***	**224**		**114**			**8.49%**	**-4.46[-7.77,-1.15]**
Heterogeneity: Tau^2=0; Chi^2=1.17, df=3(P=0.76); I^2=0%							
Test for overall effect: Z=2.64(P=0.01)							
1.8.3 Calcium channel blockers (iv)							
ASCLEPIOS 1990	107	81 (11.8)	97	83.4 (13.5)		4.44%	-2.39[-5.89,1.11]
Limburg 1990	10	86.1 (18.5)	6	84.2 (13.6)		0.59%	1.93[-13.88,17.74]
Norris 1994	83	71.4 (10.3)	75	83.3 (12.4)		4.37%	-11.88[-15.46,-8.3]
Uzuner 1995/180 mg	8	83.8 (9.2)	3	86.7 (15.3)		0.44%	-2.92[-21.34,15.5]
Subtotal ***	**208**		**181**			**9.84%**	**-5.35[-12.76,2.06]**
Heterogeneity: Tau^2=35.23; Chi^2=15.16, df=3(P=0); I^2=80.22%							
Test for overall effect: Z=1.42(P=0.16)							
1.8.4 Calcium channel blockers (po)							
Bogousslavsky 1990	24	81 (11)	28	80 (11)		2.69%	1[-5,7]
German-Austrian 120mg	239	80.6 (11)	243	81.7 (11.4)		5.74%	-1.1[-3.1,0.9]
Kaste 1994/120 mg	160	84.3 (14.8)	161	89.2 (14.2)		4.71%	-4.9[-8.08,-1.72]
Lamsudin 1997	72	95.8 (14.9)	78	96.3 (15.8)		3.34%	-0.44[-5.36,4.48]
Lisk 1993	5	82 (13)	2	92.2 (8)		0.58%	-10.17[-26.1,5.76]
Lowe 1993	54	85.1 (13.3)	54	81.3 (11.3)		3.52%	3.81[-0.85,8.47]
Martinez-Vila 1990	58	78.1 (11.9)	65	79.9 (17.2)		3.17%	-1.8[-6.98,3.38]
Paci 1989/120 mg	19	82.8 (10)	22	85.2 (9.8)		2.64%	-2.4[-8.48,3.68]
Squire 1996	68	81.4 (12.7)	55	82.5 (11.3)		3.84%	-1.18[-5.41,3.05]
Uzuner 1995/180 mg	38	74.3 (10.3)	39	83.7 (16.4)		2.64%	-9.38[-15.47,-3.29]
VENUS 1995	215	84.2 (12.8)	213	85.8 (13.5)		5.32%	-1.65[-4.15,0.85]
Wimalarat 1994/120mg	69	83.9 (5.4)	33	86.8 (8.8)		4.65%	-2.95[-6.21,0.31]
Wimalarat 1994/240mg	69	83.7 (6.1)	34	86.8 (8.8)		4.62%	-3.15[-6.44,0.14]
Subtotal ***	**1090**		**1027**			**47.46%**	**-2.05[-3.45,-0.65]**
Heterogeneity: Tau^2=2.19; Chi^2=18.98, df=12(P=0.09); I^2=36.78%							
Test for overall effect: Z=2.87(P=0)							
1.8.5 Insulin (iv)							
Walters 2006	13	78.8 (4.4)	12	81 (8.5)		3.05%	-2.2[-7.57,3.17]
Subtotal ***	**13**		**12**			**3.05%**	**-2.2[-7.57,3.17]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.8(P=0.42)							

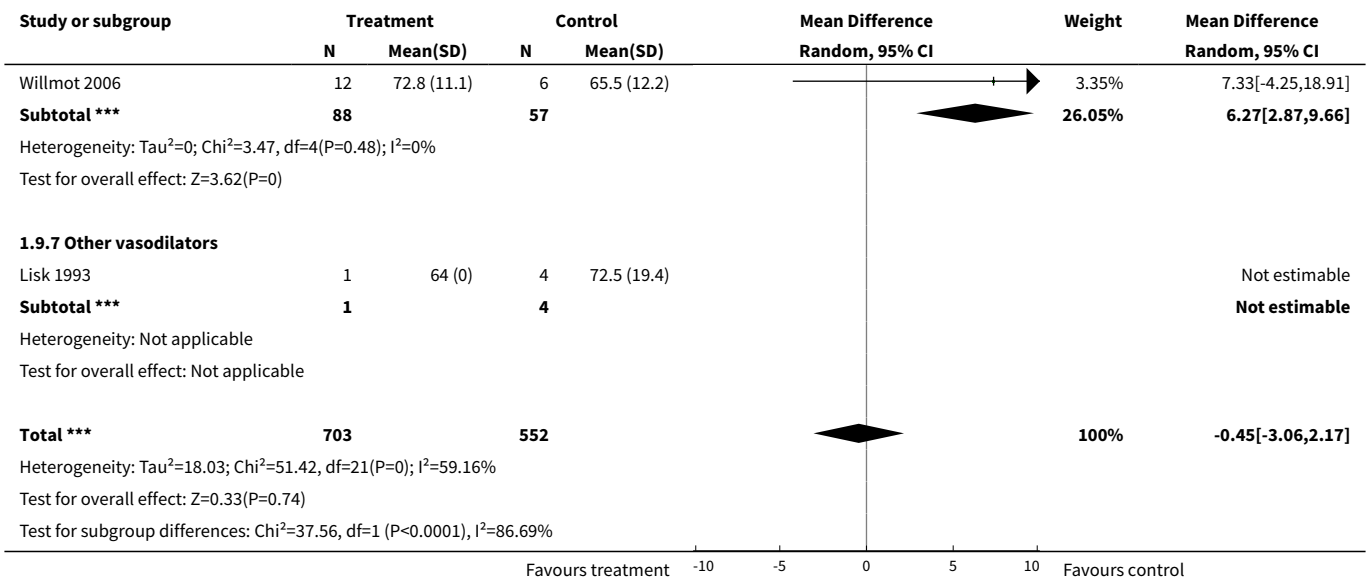




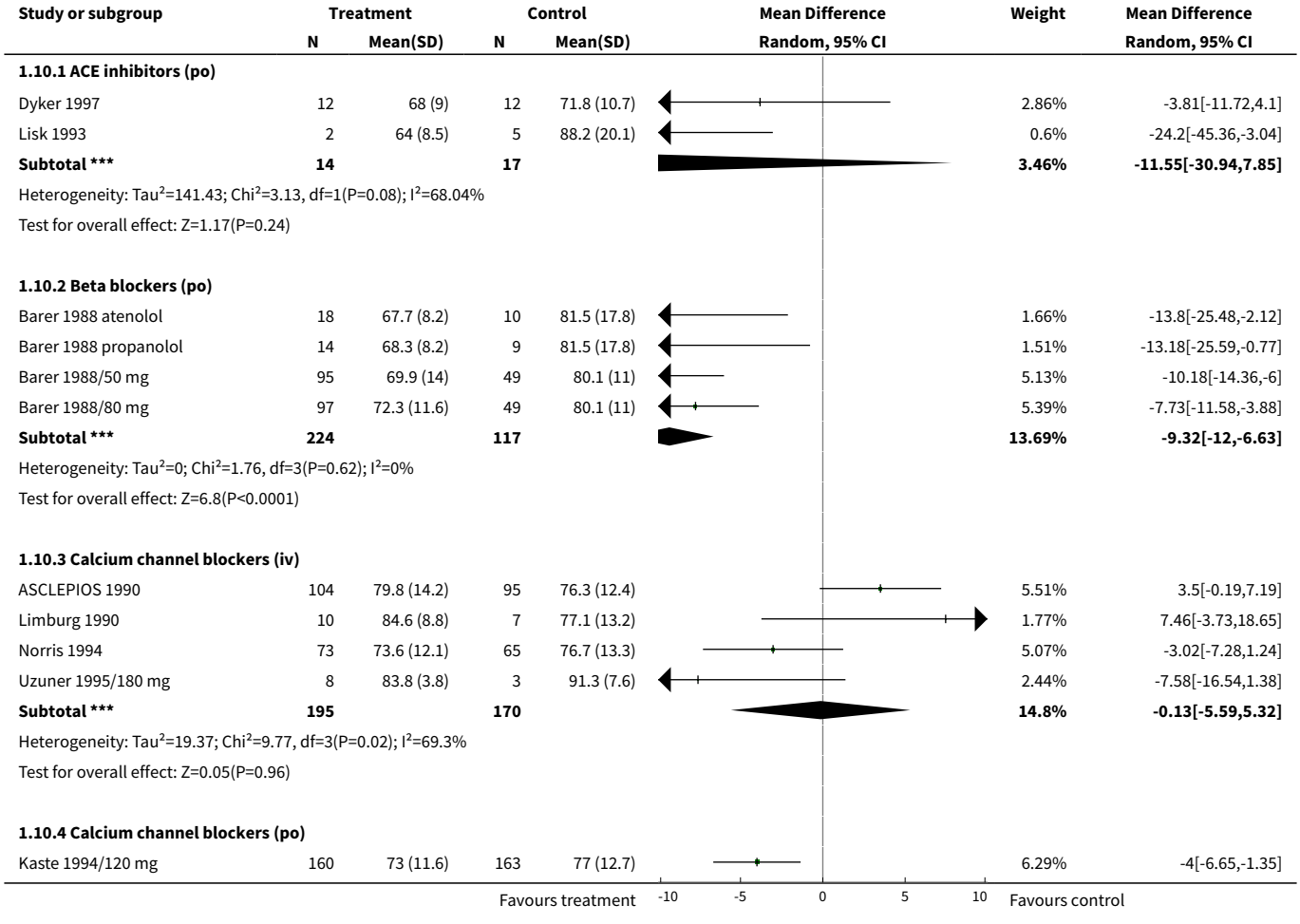
Analysis 1.9. Comparison 1 Drug versus control in stroke: blood pressure lowering therapy, Outcome 9 Heart rate, early.

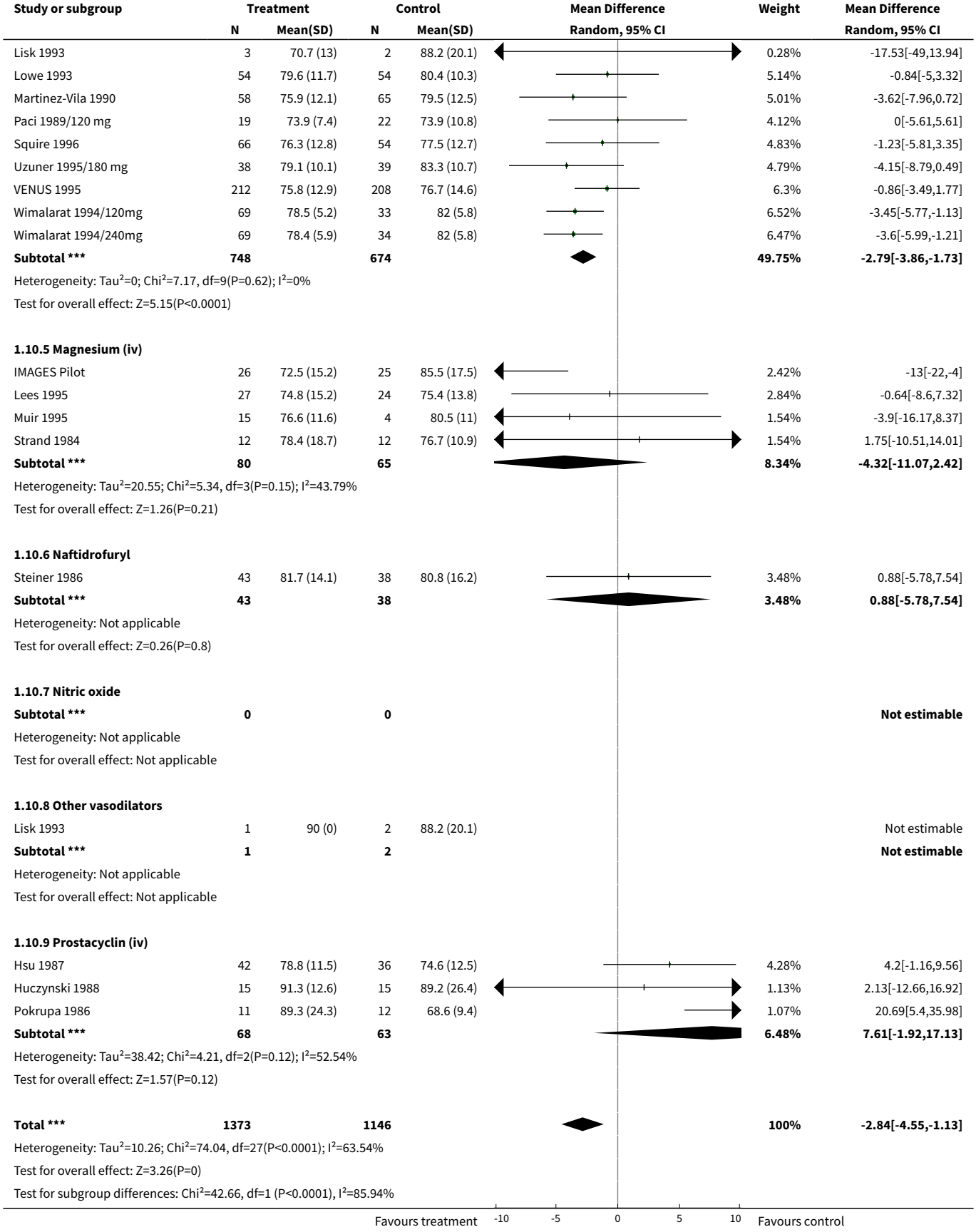
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.9.1 ACE inhibitors (po)							
Dyker 1997	12	70.9 (7)	11	72.7 (11.3)		5.26%	-1.86[-9.62,5.9]
Eveson 2007	17	73.9 (13.4)	18	74.6 (18.4)		3.74%	-0.7[-11.32,9.92]
Lisk 1993	2	94 (43.8)	2	72.5 (19.4)		0.15%	21.5[-44.92,87.92]
Subtotal ***	**31**		**31**			**9.16%**	**-1.25[-7.49,4.99]**
Heterogeneity: Tau²=0; Chi²=0.48, df=2(P=0.78); I²=0%							
Test for overall effect: Z=0.39(P=0.69)							
1.9.2 Beta blockers (po)							
Barer 1988 atenolol	14	68.6 (10.7)	10	86.9 (27.8)		1.72%	-18.25[-36.36,-0.14]
Barer 1988 propanolol	14	74.9 (12.9)	9	86.9 (27.8)		1.54%	-11.96[-31.31,7.39]
Barer 1988/50 mg	88	73.4 (13.2)	41	81.1 (10.5)		7.81%	-7.67[-11.91,-3.43]
Barer 1988/80 mg	83	75.8 (10.9)	42	81.1 (10.5)		8.03%	-5.25[-9.2,-1.3]
Subtotal ***	**199**		**102**			**19.1%**	**-6.78[-9.61,-3.96]**
Heterogeneity: Tau²=0; Chi²=2.56, df=3(P=0.46); I²=0%							
Test for overall effect: Z=4.7(P<0.0001)							
1.9.3 Calcium channel blockers (iv)							
ASCLEPIOS 1990	117	80.6 (13.9)	108	79.5 (13.4)		8.31%	1.12[-2.46,4.7]
Norris 1994	70	76.7 (12)	73	76.6 (17)		7.39%	0.05[-4.75,4.85]
Uzuner 1995/180 mg	8	92 (13.5)	3	88 (6.9)		3.12%	4[-8.22,16.22]
Subtotal ***	**195**		**184**			**18.81%**	**0.91[-1.88,3.7]**
Heterogeneity: Tau²=0; Chi²=0.38, df=2(P=0.83); I²=0%							
Test for overall effect: Z=0.64(P=0.52)							
1.9.4 Calcium channel blockers (po)							
Lisk 1993	2	87 (24)	2	72.5 (19.4)		0.36%	14.5[-28.28,57.28]
Squire 1996	70	79.2 (14.3)	66	80.7 (11.8)		7.69%	-1.53[-5.93,2.87]
Uzuner 1995/180 mg	38	82.8 (10.4)	39	86.3 (13.7)		6.91%	-3.42[-8.84,2]
Subtotal ***	**110**		**107**			**14.96%**	**-2.17[-5.58,1.23]**
Heterogeneity: Tau²=0; Chi²=0.87, df=2(P=0.65); I²=0%							
Test for overall effect: Z=1.25(P=0.21)							
1.9.5 Magnesium (iv)							
IMAGES Pilot	26	77.6 (19.2)	25	87.5 (15.9)		4.19%	-9.82[-19.49,-0.15]
Lees 1995	30	75.4 (14)	29	81.7 (17.2)		5.1%	-6.29[-14.32,1.74]
Muir 1995	17	75.3 (14.4)	5	78.8 (85.7)		0.12%	-3.51[-78.96,71.94]
Strand 1984	6	86.2 (15.2)	8	74.9 (10.7)		2.51%	11.29[-2.93,25.51]
Subtotal ***	**79**		**67**			**11.91%**	**-3.19[-12.6,6.21]**
Heterogeneity: Tau²=41.8; Chi²=6.09, df=3(P=0.11); I²=50.7%							
Test for overall effect: Z=0.66(P=0.51)							
1.9.6 Nitric oxide							
Bath 2000	16	82.7 (12.1)	21	70.1 (12)		5.21%	12.59[4.74,20.44]
Rashid 2003 10 mg	20	78.8 (10.5)	10	75.5 (7.7)		6.02%	3.3[-3.33,9.93]
Rashid 2003 5 mg	20	80.6 (11.9)	10	75.5 (7.7)		5.71%	5.1[-1.97,12.17]
Rashid 2003 5/10 mg	20	80.8 (11.7)	10	75.5 (7.7)		5.76%	5.3[-1.71,12.31]





Analysis 1.10. Comparison 1 Drug versus control in stroke: blood pressure lowering therapy, Outcome 10 Heart rate, late.





Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Lisk 1993	3	70.7 (13)	2	88.2 (20.1)		0.28%	-17.53[-49,13.94]
Lowe 1993	54	79.6 (11.7)	54	80.4 (10.3)		5.14%	-0.84[-5,3.32]
Martinez-Vila 1990	58	75.9 (12.1)	65	79.5 (12.5)		5.01%	-3.62[-7.96,0.72]
Paci 1989/120 mg	19	73.9 (7.4)	22	73.9 (10.8)		4.12%	0[-5.61,5.61]
Squire 1996	66	76.3 (12.8)	54	77.5 (12.7)		4.83%	-1.23[-5.81,3.35]
Uzuner 1995/180 mg	38	79.1 (10.1)	39	83.3 (10.7)		4.79%	-4.15[-8.79,0.49]
VENUS 1995	212	75.8 (12.9)	208	76.7 (14.6)		6.3%	-0.86[-3.49,1.77]
Wimalarat 1994/120mg	69	78.5 (5.2)	33	82 (5.8)		6.52%	-3.45[-5.77,-1.13]
Wimalarat 1994/240mg	69	78.4 (5.9)	34	82 (5.8)		6.47%	-3.6[-5.99,-1.21]
Subtotal ***	**748**		**674**			**49.75%**	**-2.79[-3.86,-1.73]**
Heterogeneity: Tau²=0; Chi²=7.17, df=9(P=0.62); I²=0%							
Test for overall effect: Z=5.15(P<0.0001)							
1.10.5 Magnesium (iv)							
IMAGES Pilot	26	72.5 (15.2)	25	85.5 (17.5)		2.42%	-13[-22,-4]
Lees 1995	27	74.8 (15.2)	24	75.4 (13.8)		2.84%	-0.64[-8.6,7.32]
Muir 1995	15	76.6 (11.6)	4	80.5 (11)		1.54%	-3.9[-16.17,8.37]
Strand 1984	12	78.4 (18.7)	12	76.7 (10.9)		1.54%	1.75[-10.51,14.01]
Subtotal ***	**80**		**65**			**8.34%**	**-4.32[-11.07,2.42]**
Heterogeneity: Tau²=20.55; Chi²=5.34, df=3(P=0.15); I²=43.79%							
Test for overall effect: Z=1.26(P=0.21)							
1.10.6 Naftidrofuryl							
Steiner 1986	43	81.7 (14.1)	38	80.8 (16.2)		3.48%	0.88[-5.78,7.54]
Subtotal ***	**43**		**38**			**3.48%**	**0.88[-5.78,7.54]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.26(P=0.8)							
1.10.7 Nitric oxide							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.10.8 Other vasodilators							
Lisk 1993	1	90 (0)	2	88.2 (20.1)			Not estimable
Subtotal ***	**1**		**2**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.10.9 Prostacyclin (iv)							
Hsu 1987	42	78.8 (11.5)	36	74.6 (12.5)		4.28%	4.2[-1.16,9.56]
Huczynski 1988	15	91.3 (12.6)	15	89.2 (26.4)		1.13%	2.13[-12.66,16.92]
Pokrupa 1986	11	89.3 (24.3)	12	68.6 (9.4)		1.07%	20.69[5.4,35.98]
Subtotal ***	**68**		**63**			**6.48%**	**7.61[-1.92,17.13]**
Heterogeneity: Tau²=38.42; Chi²=4.21, df=2(P=0.12); I²=52.54%							
Test for overall effect: Z=1.57(P=0.12)							
Total ***	**1373**		**1146**			**100%**	**-2.84[-4.55,-1.13]**
Heterogeneity: Tau²=10.26; Chi²=74.04, df=27(P<0.0001); I²=63.54%							
Test for overall effect: Z=3.26(P=0)							
Test for subgroup differences: Chi²=42.66, df=1 (P<0.0001), I²=85.94%							

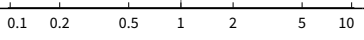
Comparison 2. Drug versus control in stroke: blood pressure elevation therapy

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Early death (≤ 1 month)	1	15	Odds Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.1 DCLHb (iv)	0	0	Odds Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Phenylephrine (iv)	1	15	Odds Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Death at end of trial	4	100	Odds Ratio (IV, Random, 95% CI)	2.96 [0.82, 10.72]
2.1 DCLHb (iv)	3	85	Odds Ratio (IV, Random, 95% CI)	2.96 [0.82, 10.72]
2.2 Phenylephrine (iv)	1	15	Odds Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Death or disability at end of trial	3	85	Odds Ratio (IV, Random, 95% CI)	5.41 [1.87, 15.64]
3.1 DCLHb (iv)	3	85	Odds Ratio (IV, Random, 95% CI)	5.41 [1.87, 15.64]
3.2 Phenylephrine (iv)	0	0	Odds Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 Systolic blood pressure, early	4	100	Mean Difference (IV, Random, 95% CI)	15.82 [5.10, 26.54]
4.1 DCLHb (iv)	3	85	Mean Difference (IV, Random, 95% CI)	15.29 [3.99, 26.58]
4.2 Phenylephrine (iv)	1	15	Mean Difference (IV, Random, 95% CI)	20.60 [-13.31, 54.51]
5 Systolic blood pressure, late	3	85	Mean Difference (IV, Random, 95% CI)	15.90 [1.84, 29.96]
5.1 DCLHb (iv)	3	85	Mean Difference (IV, Random, 95% CI)	15.90 [1.84, 29.96]
5.2 Phenylephrine (iv)	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6 Diastolic blood pressure, early	4	100	Mean Difference (IV, Random, 95% CI)	5.11 [-3.18, 13.39]
6.1 DCLHb (iv)	3	85	Mean Difference (IV, Random, 95% CI)	6.01 [-4.35, 16.38]
6.2 Phenylephrine (iv)	1	15	Mean Difference (IV, Random, 95% CI)	0.5 [-14.86, 15.86]
7 Diastolic blood pressure, late	3	85	Mean Difference (IV, Random, 95% CI)	1.94 [-8.96, 12.83]
7.1 DCLHb (iv)	3	85	Mean Difference (IV, Random, 95% CI)	1.94 [-8.96, 12.83]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
7.2 Phenylephrine (iv)	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8 Heart rate, early	3	85	Mean Difference (IV, Random, 95% CI)	0.43 [-6.36, 7.22]
8.1 DCLHb (iv)	3	85	Mean Difference (IV, Random, 95% CI)	0.43 [-6.36, 7.22]
8.2 Phenylephrine (iv)	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

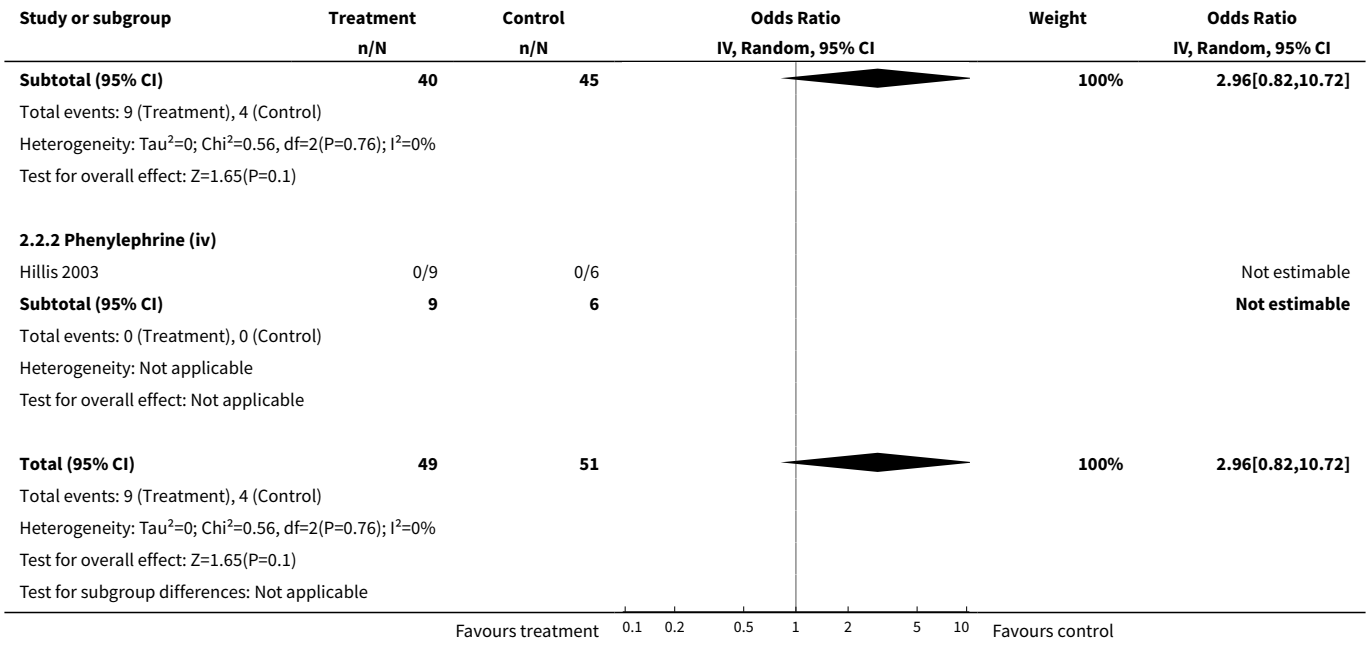
Analysis 2.1. Comparison 2 Drug versus control in stroke: blood pressure elevation therapy, Outcome 1 Early death (≤ 1 month).

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio IV, Random, 95% CI	Weight	Odds Ratio IV, Random, 95% CI
2.1.1 DCLHb (iv)					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
2.1.2 Phenylephrine (iv)					
Hillis 2003	0/9	0/6			Not estimable
Subtotal (95% CI)	**9**	**6**			**Not estimable**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**9**	**6**			**Not estimable**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Not applicable					

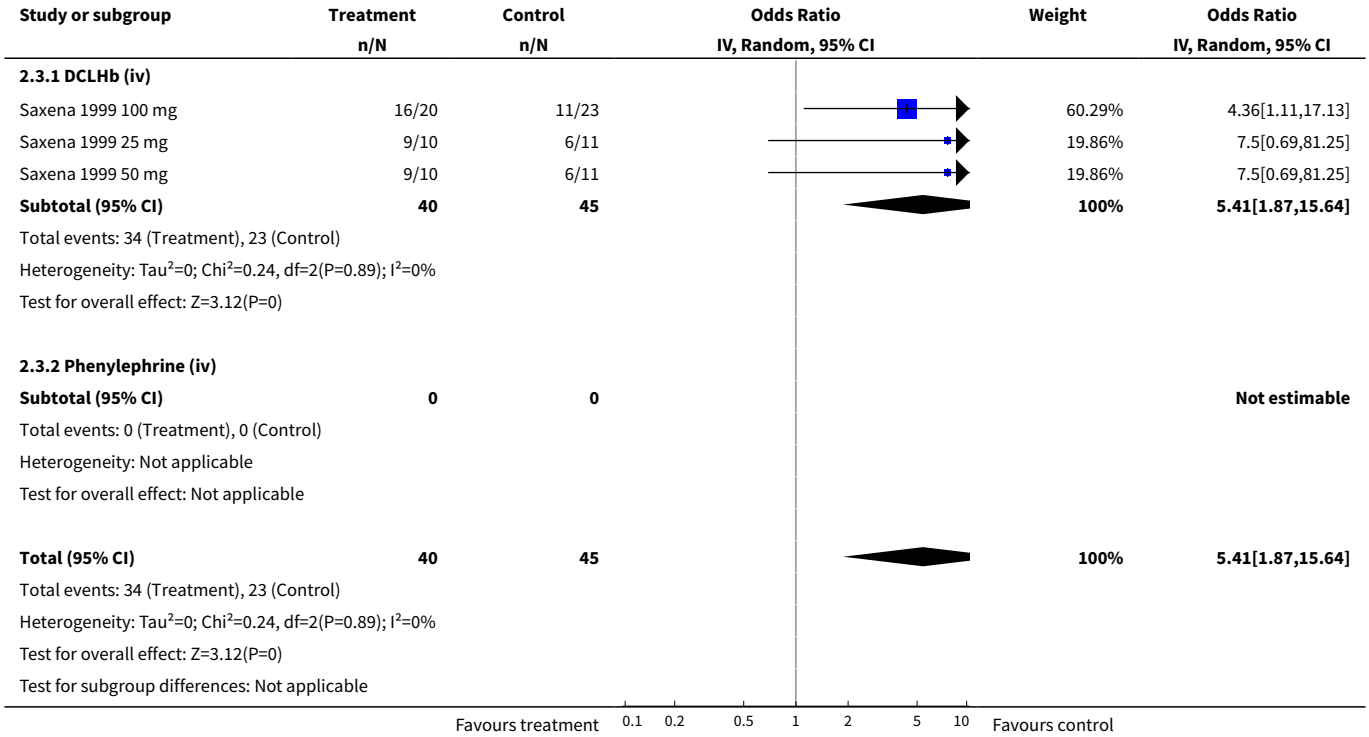


Analysis 2.2. Comparison 2 Drug versus control in stroke: blood pressure elevation therapy, Outcome 2 Death at end of trial.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio IV, Random, 95% CI	Weight	Odds Ratio IV, Random, 95% CI
2.2.1 DCLHb (iv)					
Saxena 1999 100 mg	5/20	2/23		53.05%	3.5[0.6,20.52]
Saxena 1999 25 mg	3/10	1/11		27.41%	4.29[0.37,50.2]
Saxena 1999 50 mg	1/10	1/11		19.54%	1.11[0.06,20.49]

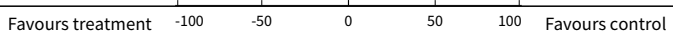


Analysis 2.3. Comparison 2 Drug versus control in stroke: blood pressure elevation therapy, Outcome 3 Death or disability at end of trial.



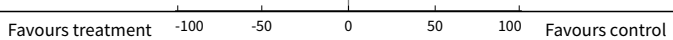
Analysis 2.4. Comparison 2 Drug versus control in stroke: blood pressure elevation therapy, Outcome 4 Systolic blood pressure, early.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.4.1 DCLHb (iv)							
Saxena 1999 100 mg	20	172 (32)	23	150 (26)		37.1%	22[4.4,39.6]
Saxena 1999 25 mg	10	160 (27)	11	150 (26)		22.26%	10[-12.72,32.72]
Saxena 1999 50 mg	10	161 (19)	11	150 (26)		30.65%	11[-8.36,30.36]
Subtotal ***	**40**		**45**			**90.01%**	**15.29[3.99,26.58]**
Heterogeneity: Tau^2=0; Chi^2=0.96, df=2(P=0.62); I^2=0%							
Test for overall effect: Z=2.65(P=0.01)							
2.4.2 Phenylephrine (iv)							
Hillis 2003	9	185.4 (15.3)	6	164.8 (40.5)		9.99%	20.6[-13.31,54.51]
Subtotal ***	**9**		**6**			**9.99%**	**20.6[-13.31,54.51]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.19(P=0.23)							
Total ***	**49**		**51**			**100%**	**15.82[5.1,26.54]**
Heterogeneity: Tau^2=0; Chi^2=1.04, df=3(P=0.79); I^2=0%							
Test for overall effect: Z=2.89(P=0)							
Test for subgroup differences: Chi^2=0.08, df=1 (P=0.77), I^2=0%							



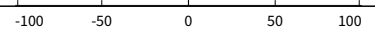
Analysis 2.5. Comparison 2 Drug versus control in stroke: blood pressure elevation therapy, Outcome 5 Systolic blood pressure, late.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.5.1 DCLHb (iv)							
Saxena 1999 100 mg	20	164 (18)	23	140 (20)		42.11%	24[12.64,35.36]
Saxena 1999 25 mg	10	141 (21)	11	140 (20)		30.44%	1[-16.58,18.58]
Saxena 1999 50 mg	10	160 (25)	11	140 (20)		27.45%	20[0.51,39.49]
Subtotal ***	**40**		**45**			**100%**	**15.9[1.84,29.96]**
Heterogeneity: Tau^2=88.66; Chi^2=4.7, df=2(P=0.1); I^2=57.45%							
Test for overall effect: Z=2.22(P=0.03)							
2.5.2 Phenylephrine (iv)							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**40**		**45**			**100%**	**15.9[1.84,29.96]**
Heterogeneity: Tau^2=88.66; Chi^2=4.7, df=2(P=0.1); I^2=57.45%							
Test for overall effect: Z=2.22(P=0.03)							
Test for subgroup differences: Not applicable							



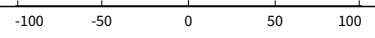
Analysis 2.6. Comparison 2 Drug versus control in stroke: blood pressure elevation therapy, Outcome 6 Diastolic blood pressure, early.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.6.1 DCLHb (iv)							
Saxena 1999 100 mg	20	99 (15)	23	84 (17)		31.99%	15[5.44,24.56]
Saxena 1999 25 mg	10	85 (16)	11	84 (17)		21.29%	1[-13.12,15.12]
Saxena 1999 50 mg	10	84 (8)	11	84 (17)		27.61%	0[-11.2,11.2]
Subtotal ***	**40**		**45**			**80.89%**	**6.01[-4.35,16.38]**
Heterogeneity: Tau²=49.29; Chi²=4.88, df=2(P=0.09); I²=59.02%							
Test for overall effect: Z=1.14(P=0.26)							
2.6.2 Phenylephrine (iv)							
Hillis 2003	9	81.9 (10.2)	6	81.4 (17.3)		19.11%	0.5[-14.86,15.86]
Subtotal ***	**9**		**6**			**19.11%**	**0.5[-14.86,15.86]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.06(P=0.95)							
Total ***	**49**		**51**			**100%**	**5.11[-3.18,13.39]**
Heterogeneity: Tau²=32.04; Chi²=5.48, df=3(P=0.14); I²=45.22%							
Test for overall effect: Z=1.21(P=0.23)							
Test for subgroup differences: Chi²=0.6, df=1 (P=0.44), I²=0%							



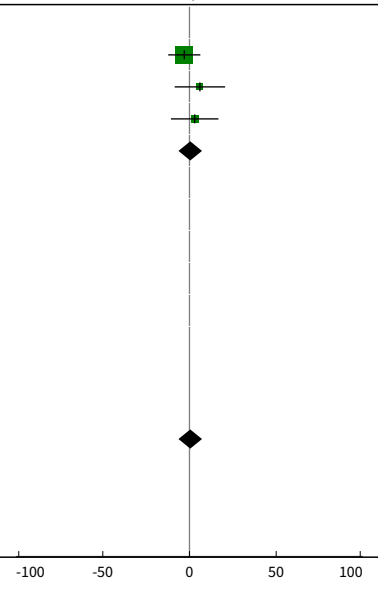
Analysis 2.7. Comparison 2 Drug versus control in stroke: blood pressure elevation therapy, Outcome 7 Diastolic blood pressure, late.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.7.1 DCLHb (iv)							
Saxena 1999 100 mg	20	91 (10)	23	80 (13)		37.15%	11[4.11,17.89]
Saxena 1999 25 mg	10	73 (12)	11	80 (13)		30.72%	-7[-17.69,3.69]
Saxena 1999 50 mg	10	80 (10)	11	80 (13)		32.13%	0[-9.87,9.87]
Subtotal ***	**40**		**45**			**100%**	**1.94[-8.96,12.83]**
Heterogeneity: Tau²=70.79; Chi²=8.65, df=2(P=0.01); I²=76.89%							
Test for overall effect: Z=0.35(P=0.73)							
2.7.2 Phenylephrine (iv)							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**40**		**45**			**100%**	**1.94[-8.96,12.83]**
Heterogeneity: Tau²=70.79; Chi²=8.65, df=2(P=0.01); I²=76.89%							
Test for overall effect: Z=0.35(P=0.73)							
Test for subgroup differences: Not applicable							



Analysis 2.8. Comparison 2 Drug versus control in stroke: blood pressure elevation therapy, Outcome 8 Heart rate, early.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.8.1 DCLHb (iv)							
Saxena 1999 100 mg	20	72 (14)	23	75 (17)		53.65%	-3[-12.27,6.27]
Saxena 1999 25 mg	10	81 (17)	11	75 (17)		21.75%	6[-8.56,20.56]
Saxena 1999 50 mg	10	78 (15)	11	75 (17)		24.6%	3[-10.69,16.69]
Subtotal ***	**40**		**45**			**100%**	**0.43[-6.36,7.22]**
Heterogeneity: Tau^2=0; Chi^2=1.22, df=2(P=0.54); I^2=0%							
Test for overall effect: Z=0.13(P=0.9)							
2.8.2 Phenylephrine (iv)							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**40**		**45**			**100%**	**0.43[-6.36,7.22]**
Heterogeneity: Tau^2=0; Chi^2=1.22, df=2(P=0.54); I^2=0%							
Test for overall effect: Z=0.13(P=0.9)							
Test for subgroup differences: Not applicable							



APPENDICES

Appendix 1. MEDLINE search strategy

01. stroke.mp.
02. infarction.mp.
03. exp brain Infarction/
04. exp infarction, anterior cerebral artery/
05. exp infarction, middle cerebral artery/
06. exp infarction, posterior cerebral artery/
07. exp brain ischemia/
08. brain ischaemia.mp.
09. cerebral ischaemia.mp.
10. hemorrhage.mp.
11. exp cerebral hemorrhage/
12. cerebral haemorrhage.mp.
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. (nitrate or L-arginine or thiazide or diuretics or beta blockers or calcium channel blockers or angiotensin-converting enzyme inhibitors or ACE inhibitors or angiotensin receptor antagonists or rennin inhibitors or neuroprotective agents or alpha receptor antagonists or vasoconstrictors or adrenoceptor agonists or centrally acting antihyperten$ or vasodilators or hemodilution or haemodilution).mp.
15. (bendrofluazide or bendroflumethiazide or hydrochrlothiazide or atenolol or propanalol or bisoprolol or labetalol or nimodipine or nicardipine or amilodipine or felodipine or clinidipine or isradipine or nifedipine or nisolodipine or tirilazad or flunarazine or captopril or enalapril or lisinopril or perindopril or ramipril or candesartan or losartan or telmisartan or valsartan or clonidine or pentoxifylline or pentifylline or naftidrofuryl or prostacyclin or PGI2 or magnesium or papaverine or vinpocetin or piracetam or dopamine or dobutamine or adrenaline or noradrenaline or phenylephrine or amphetamine or caffeinol or caffeine or theophylline or diaspirin cross linked haemoglobin or DCLHb).mp.
16. 14 or 15
17. 13 and 16
18. (randomized controlled trial.pt. or controlled clinical trial.pt.or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) and humans.sh.
19. 17 and 18

Appendix 2. EMBASE search strategy

01. stroke.mp.
02. infarction.mp.
03. exp brain Infarction/
04. exp brain infarction size/
05. brain stem infarction
06. cerebellum infarction
07. brain ischemia.mp.
08. brain ischaemia.mp.
09. exp brain ischemia/
10. cerebral ischaemia.mp.
11. hemorrhage.mp.
12. exp cerebral hemorrhage/
13. cerebral haemorrhage.mp.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
15. (nitrate or L-arginine or thiazide or diuretics or beta blockers or calcium channel blockers or angiotensin-converting enzyme inhibitors or ACE inhibitors or angiotensin receptor antagonists or rennin inhibitors or neuroprotective agents or alpha receptor antagonists or vasoconstrictors or adrenoceptor agonists or centrally acting antihyperten$ or vasodilators or hemodilution or haemodilution).mp.
16. (bendrofluazide or bendroflumethiazide or hydrochrlothiazide or atenolol or propanalol or bisoprolol or labetalol or nimodipine or nicardipine or amilodipine or felodipine or clinidipine or isradipine or nifedipine or nisolodipine or tirilazad or flunarazine or captopril or enalapril or lisinopril or perindopril or ramipril or candesartan or losartan or telmisartan or valsartan or clonidine or pentoxifylline or pentifylline or naftidrofuryl or prostacyclin or PGI2 or magnesium or papaverine or vinpocetin or piracetam or dopamine or dobutamine or adrenaline or noradrenaline or phenylephrine or amphetamine or caffeinol or caffeine or theophylline or diaspirin cross linked haemoglobin or DCLHb).mp.
17. 15 or 16
18. 14 and 17
19. ((RANDOMIZED-CONTROLLED-TRIAL/ or RANDOMIZATION/ or CONTROLLED-STUDY/ or MULTICENTER-STUDY/ or PHASE-3-CLINICAL-TRIAL/ or PHASE-4-CLINICAL-TRIAL/ or DOUBLE-BLIND-PROCEDURE/ or SINGLE-BLIND-PROCEDURE/) or ((RANDOM* or CROSS?OVER* or FACTORIAL* or PLACEBO* or VOLUNTEER*) or ((SINGL* or DOUBL* or TREBL* or TRIPL*) adj3 (BLIND* or MASK*))).ti,ab) and human*.ec,hw,fs.
20. 18 and 19

Appendix 3. Science Citation Index search strategy

01. stroke.TS./TI
02. acute stroke.TS./TI.
03. cerebral infarction.TS./TI.
04. brain Infarction.TS./TI.
05. brain ischemia.TS./TI.
06. brain ischaemia.TS./TI.
07. brain ischemia.TS./TI.
08. cerebral ischaemia.TS./TI.
09. cerebral hemorrhage.TS./TI.
10. cerebral haemorrhage.TS./TI.
11. cerebral bleeding.TS./TI.
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
13. (nitrate or L-arginine or thiazide or diuretics or beta blockers or calcium channel blockers or angiotensin-converting enzyme inhibitors or ACE inhibitors or angiotensin receptor antagonists or rennin inhibitors or neuroprotective agents or alpha receptor antagonists or vasoconstrictors or adrenoceptor agonists or centrally acting antihyperten$ or vasodilators or hemodilution or haemodilution.TS./TI.
14. (bendrofluazide or bendroflumethiazide or hydrochrlothiazide or atenolol or propanalol or bisoprolol or labetalol or nimodipine or nicardipine or amilodipine or
felodipine or clinidipine or isradipine or nifedipine or nisolodipine or tirilazad or flunarazine or captopril or enalapril or lisinopril or perindopril or ramipril or candesartan or losartan or telmisartan or valsartan or clonidine or pentoxifylline or pentifylline or naftidrofuryl or prostacyclin or PGI2 or magnesium or papaverine or vinpocetin or piracetam or dopamine or dobutamine or adrenaline or noradrenaline or phenylephrine or amphetamine or caffeinol or caffeine or theophylline or diaspirin cross linked haemoglobin or DCLHb).TS./TI.
15. 13 or 14
16. 12 and 15
17. (randomized controlled trial.TI. or controlled clinical trial.TI.or randomized.TI. or placebo.TI. or clinical trials TI. or randomly.TI. or trial.TI.) and humans.TI.
18. 16 and 17

Appendix 4. Baseline haemodynamic measures for included studies

Drug class	Baseline SBP	N	Baseline DBP	N	Baseline HR	N
	MD (95% CI)		MD (95% CI)		MD (95% CI)	
BP lowering therapy						
ACE inhibitors (po)	1.79 (-3.84 to 7.43)	4	-0.22 (-4.34 to 3.89)	4	0.22 (-5.31 to 5.75)	3
ARA (po)	-2.00 (-6.32 to 2.32)	1	0.00 (-2.97 to 2.97)	1		
Beta blockers (po)	0.34 (-4.27 to 4.96)	5	0.03 (-3.75 to 3.80)	5	-0.36 (-3.73 to 3.02)	4
Calcium channel blockers (iv)	**-6.60 (-13.37 to 0.16)**	6	-1.72 (-5.99 to 2.55)	6	-0.24 (-3.18 to 2.71)	4
Calcium channel blockers (po)	0.44 (-2.82 to 1.94)	14	-0.11 (-1.54 to 1.33)	14	-1.32 (-2.77 to 0.13)	9
Glucose potassium insulin (iv)	-2.51 (-6.29 to 1.29)					
Insulin (iv)	-7.00 (-20.73 to 6.73)	1	0.00 (-9.08 to 9.08)	1		
Magnesium (iv)	1.42 (-7.13 to 9.98)	4	0.99 (-4.37 to 6.35)	4	-1.79 (-7.95 to 4.37)	4
Naftidrofuryl	-1.46 (-7.95 to 5.02)	2	-0.18 (-4.70 to 4.35)	2	1.27(-4.30 to 6.83)	2

(Continued)

Nitric oxide	0.985 (-6.13 to 8.08)	3.9 (-0.22 to 8.03)	5	3.44 (-2.29 to 9.17)	5
Other vasodilators (po)	**-24.83 (-48.89 to -0.77)**	8.33 (-1.66 to 18.32)	1		
Piracetam	-2.112 (-6.39 to 2.16)	-0.39 (-2.34 to 1.56)	2		
Prostacyclin	-2.753 (-10.87 to 5.36)	-4.84 (-9.72 to 0.04)	3	-0.71 (-5.52 to 4.11)	3
Thiazide diuretics (po)	**-20.00(-39.44 to -0.56)**	**-15.00 (-29.51 to -0.49)**	1		
Unclassified or combined	-2.001 (-5.61 to 1.61)	**-4.00 (-6.83 to -1.17)**	1		
Total	**-1.591 (-2.83 to -0.35)**	-0.41 (-1.37 to 0.55)	50		
BP elevation therapy					
DCLHb	5.373 (-3.59 to 14.34)	-2.56 (-8.78 to 3.65)	3	3.37 (-2.43 to 9.17)	3
Phenylephrine	-27.51 (-50.83 to -4.17)	-8.30 (-19.13 to 2.53)	1		
Total	-1.534 (-15.15 to 12.09)	-3.73 (-8.99 to 1.54)	4	3.37 (-2.43 to 9.17)	3

Significant results are in bold type

CI: confidence interval
DBP: diastolic blood pressure

DCLHb: diaspirin cross-linked haemoglobin
HR: heart rate
iv: intravenous
MD: mean difference
N: number of studies
po: oral
SBP: systolic blood pressure

WHAT'S NEW

Date	Event	Description
1 October 2009	New search has been performed	This review was updated in October 2009 and includes the following: (1) the addition of 11 completed trials involving 2281 patients; (2) the addition of 13 ongoing or planned trials. The previous version of the review included 32 trials involving 5368 patients. The conclusions of this review have not changed with the addition of the new data.
1 October 2009	New citation required but conclusions have not changed	Change of authors.

HISTORY

Protocol first published: Issue 4, 2000
Review first published: Issue 4, 2000

Date	Event	Description
29 May 2008	Amended	Converted to new review format.
21 February 2007	Amended	Substantive amendment.

CONTRIBUTIONS OF AUTHORS

Philip Bath was involved with the design, development of search strategies, analysis and writing. He is the study guarantor.
Chamila Geeganage was involved with searches for studies, input of data into the latest version, analysis of the latest version, and writing.

DECLARATIONS OF INTEREST

PMW Bath was involved in three completed studies included in this review. He is the principal investigator of the ongoing Efficacy of Nitric Oxide in Stroke (ENOS) trial.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Trent NHS Executive (1998 to 2000), UK.
- The Stroke Association (1998 ongoing), UK.
- South Thames NHS Executive (1995 to 1997), UK.
- Wolfson Foundation (1993 to 1998), UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Antihypertensive Agents [*therapeutic use]; Aspirin [adverse effects] [analogs & derivatives]; Blood Pressure [*drug effects] [physiology]; Hemoglobins [adverse effects]; Hypertension [*drug therapy]; Hypotension [*drug therapy]; Injections, Intravenous; Randomized Controlled Trials as Topic; Stroke [*drug therapy] [physiopathology]; Vasoconstrictor Agents [therapeutic use]; Vasodilator Agents [therapeutic use]

MeSH check words

Adult; Humans