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[Intervention Review]

Calcium antagonists for acute ischemic stroke

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ABSTRACT

Background

The sudden loss of blood supply in ischemic stroke is associated with an increase of calcium ions within neurons. Inhibiting this increase could protect neurons and might reduce neurological impairment, disability, and handicap after stroke.

Objectives

To assess the effects of calcium antagonists for reducing the risk of death or dependency after acute ischemic stroke. We investigated the influence of different drugs, dosages, routes of administration, time intervals after stroke, and trial design on the outcomes.

Search methods

The evidence is current to 6 February 2018. We searched the Cochrane Stroke Group Trials Register (6 February 2018), Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 2), MEDLINE Ovid (1950 to 6 February 2018), Embase Ovid (1980 to 6 February 2018), and four Chinese databases (6 February 2018): Chinese Biological Medicine Database (CBM-disc), China National Knowledge Infrastructure (CNKI), Chinese Scientific Periodical Database of VIP information, and Wanfang Data. We also searched the following trials registers: ClinicalTrials.gov, EU Clinical Trials Register, Stroke Trials Registry, ISRCTN registry, WHO International Clinical Trials Registry Platform, and Chinese Clinical Trial Registry, and we contacted trialists and researchers.

Selection criteria

Randomized controlled trials comparing a calcium antagonist versus control in people with acute ischemic stroke.

Data collection and analysis

Two review authors independently selected trials, extracted data, assessed risk of bias, and applied the GRADE approach to assess the quality of the evidence. We used death or dependency at the end of long-term follow-up (at least three months) in activities of daily living as the primary outcome. We used standard Cochrane methodological procedures.

Main results

We included 34 trials involving 7731 participants. All the participants were in the acute stage of ischemic stroke, and their age ranged from 18 to 85 years, with the average age ranging from 52.3 to 74.6 years across different trials. There were more men than women in most trials. Twenty-six trials tested nimodipine, and three trials assessed flunarizine. One trial each used isradipine, nifedipine, PY108-608, fasudil,

and lifarizine. More than half of these trials followed participants for at least three months. Calcium antagonists showed no effects on the primary outcome (risk ratio (RR) 1.05; 95% confidence interval (CI) 0.98 to 1.13; 22 trials; 22 studies; 6684 participants; moderate-quality evidence) or on death at the end of follow-up (RR 1.07, 95% CI 0.98 to 1.17; 31 trials; 7483 participants; moderate-quality evidence). Thirteen trials reported adverse events, finding no significant differences between groups. Most trials did not report the allocation process or how they managed missing data, so we considered these at high risk of selection and attrition bias. Most trials reported double-blind methods but did not state who was blinded, and none of the trial protocols were available.

Authors' conclusions

We found no evidence to support the use of calcium antagonists in people with acute ischemic stroke.

PLAIN LANGUAGE SUMMARY

Calcium antagonists for acute ischemic stroke

Question

Are calcium antagonist drugs beneficial for people who have had an acute ischemic stroke?

Background

Most strokes are due to reduced blood flow with obstruction of large and small arteries. As a result, calcium ions flood into the brain cells and contribute to brain cell death. Calcium antagonists may reduce the damage by preventing the influx of calcium ions. In the past 20 years, there have been many clinical trials focusing on various calcium antagonists for acute ischemic stroke. We reviewed the evidence about the effects of these medicines compared with placebo or control in people with acute ischemic stroke.

Study characteristics

We identified 34 studies to February 6, 2018 that met our inclusion criteria; they involved 7731 participants and investigated different kinds of drugs. Twenty-six trials tested nimodipine, and three trials assessed flunarizine. One trial each used isradipine, nicardipine, PY108-608, fasudil, and lifarizine.

Key results

There was no difference in deaths or dependency between participants who received calcium antagonists or not.

Quality of the evidence

There is no evidence that calcium antagonists after acute ischemic stroke could save lives or reduce disability. The evidence was moderately reliable, which means that further research is unlikely to change our conclusions.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Calcium antagonists versus placebo for acute ischemic stroke

Calcium antagonists versus placebo for acute ischemic stroke

Patient or population: people with acute ischemic stroke

Settings: inpatients

Intervention: calcium antagonists

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo	Calcium antagonists			
Death or dependency at end of follow-up	415 per 1000	466 per 1000	RR 1.05 (0.98 to 1.13)	6684 (22)	⊕⊕⊕⊖ Moderate^a
Death at the end of treatment	127 per 1000	140 per 1000	RR 1.06 (0.93 to 1.20)	6323 (22)	⊕⊕⊕⊖ Moderate^a
Death at the end of follow-up	204 per 1000	217 per 1000	RR 1.07 (0.98 to 1.17)	7483 (31)	⊕⊕⊕⊖ Moderate^a
Recurrence of stroke at the end of follow-up	30 per 1000	28 per 1000	RR 0.93 (0.56 to 1.54)	2460 (9)	⊕⊕⊕⊖ Moderate^a
Adverse events during treatment period	69 per 1000	89 per 1000	RR 1.18 (0.81 to 1.74)	5095 (13)	⊕⊕⊕⊖ Moderate^a
Hypotension during treatment period	12 per 1000	18 per 1000	RR 1.43 (0.61 to 3.38)	1667 (6)	⊕⊕⊕⊖ Moderate^a

Mean systolic blood pressure during or at end of treatment	Mean ranged from 134 mmHg to 141 mmHg	Mean ranged from 132 mmHg to 139 mmHg	MD -1.30 mmHg (-3.92 to 1.32)	630 (3)	⊕⊕⊕⊕ Low ^{a,b}
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*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference; RR: risk ratio

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^aDowngraded one level due to unclear risk of bias.

^bDowngraded one level due to small sample size.

Summary of findings 2. Nimodipine versus placebo for acute ischemic stroke

Nimodipine versus placebo for acute ischemic stroke

Patient or population: people with acute ischemic stroke

Settings: inpatients

Intervention: nimodipine

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo	Nimodipine			
Death or dependency at end of follow-up	410 per 1000	464 per 1000	RR 1.06 (0.97 to 1.14)	6093 (19)	⊕⊕⊕⊕ Moderate ^a
Death at the end of treatment	125 per 1000	137 per 1000	RR 1.02 (0.88 to 1.19)	5163 (16)	⊕⊕⊕⊕ Moderate ^a
Death at the end of follow-up	210 per 1000	218 per 1000	RR 1.05 (0.96 to 1.16)	6312 (24)	⊕⊕⊕⊕

					Moderate^a
Recurrence of stroke at the end of follow-up	32 per 1000	30 per 1000	RR 0.98 (0.96 to 1.11)	1677 (6)	⊕⊕⊕⊖ Moderate^a
Adverse events during treatment period	64 per 1000	73 per 1000	RR 0.93 (0.74 to 1.16)	4604 (11)	⊕⊕⊕⊖ Moderate^a
Hypotension during treatment period	12 per 1000	16 per 1000	RR 1.26 (0.50 to 3.14)	1648 (5)	⊕⊕⊕⊖ Moderate^a
Mean systolic blood pressure during or at end of treatment	Mean ranged from 134 mmHg to 141 mmHg	Mean ranged from 132 mmHg to 139 mmHg	MD -1.30 mmHg (-3.92 to 1.32)	630 (3)	⊕⊕⊖⊖ Low^{a1b}

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference; RR: risk ratio.

GRADE Working Group grades of evidence

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Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^aDowngraded one level due to unclear risk of bias.

^bDowngraded one level due to small sample size.

Summary of findings 3. Flunarizine versus placebo for acute ischemic stroke

Flunarizine versus placebo for acute ischemic stroke

Patient or population: people with acute ischemic stroke

Settings: inpatients

Intervention: flunarizine

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo	Flunarizine			
Death or dependency at end of follow-up	508 per 1000	539 per 1000	RR 0.81 (0.34 to 1.94)	357 (2)	⊕⊕⊕⊕ Low ^{a'b}
Death at the end of treatment	131 per 1000	170 per 1000	RR 1.31 (0.94 to 1.82)	790 (3)	⊕⊕⊕⊕ Low ^{a'b}
Death at the end of follow-up	166 per 1000	221 per 1000	RR 1.34 (1.01 to 1.77)	790 (3)	⊕⊕⊕⊕ Low ^{a'b}
Recurrence of stroke at the end of follow-up	29 per 1000	24 per 1000	RR 0.82 (0.35 to 1.97)	764 (2)	⊕⊕⊕⊕ Low ^{a'b}
Adverse events during treatment period	103 per 1000	325 per 1000	RR 3.16 (1.91 to 5.21)	331 (1)	⊕⊕⊕⊕ Low ^{a'b}
Hypotension during treatment period	No trials reported this outcome.				
Mean systolic blood pressure during or at end of treatment	No trials reported this outcome.				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; RR: risk ratio.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^aDowngraded one level due to unclear risk of bias.

^bDowngraded one level due to small sample size.

Summary of findings 4. Isradipine versus placebo for acute ischemic stroke

Isradipine versus placebo for acute ischemic stroke

Patient or population: people with acute ischemic stroke

Settings: inpatients

Intervention: isradipine

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo	Isradipine			
Death or dependency at end of follow-up	386 per 1000	392 per 1000	RR 1.01 (0.74 to 1.40)	234 (1)	⊕⊕○○ Low ^{a,b}
Death at the end of treatment	No trials reported this outcome.				
Death at the end of follow-up	167 per 1000	175 per 1000	RR 1.05 (0.60 to 1.85)	234 (1)	⊕⊕○○ Low ^{a,b}
Recurrence of stroke at the end of follow-up	No trials reported this outcome.				
Adverse events during treatment period	No trials reported this outcome.				
Hypotension during treatment period	No trials reported this outcome.				
Mean systolic blood pressure during or at end of treatment	No trials reported this outcome.				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

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

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

^aDowngraded one level due to unclear risk of bias.

^bDowngraded one level due to small sample size.

Summary of findings 5. Other calcium antagonists versus placebo for acute ischemic stroke

Other calcium antagonists versus placebo for acute ischemic stroke

Patient or population: people with acute ischemic stroke

Settings: inpatients

Intervention: other calcium antagonists

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo	Other calcium antagonists			
Death or dependency at end of follow-up	No trials reported this outcome.				
Death at the end of treatment	134 per 1000	131 per 1000	RR 0.98 (0.58 to 1.66)	370 (3)	⊕⊕⊕⊕ Low ^{a'b}
Death at the end of follow-up	228 per 1000	191 per 1000	RR 0.84 (0.45 to 1.56)	147 (3)	⊕⊕⊕⊕ Low ^{a'b}
Recurrence of stroke at the end of follow-up	0 per 1000	0 per 1000	—	19 (1)	⊕⊕⊕⊕ Low ^{a'b}
Adverse events during treatment period	114 per 1000	136 per 1000	RR 1.19 (0.52 to 2.72)	160 (1)	⊕⊕⊕⊕ Low ^{a'b}

Hypotension during treatment period	0 per 1000	222 per 1000	RR 5.50 (0.30 to 101.28)	19 (1)	⊕⊕⊕⊖ Low ^{a,b}
Mean systolic blood pressure during or at end of treatment	No trials reported this outcome.				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

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

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^aDowngraded one level due to unclear risk of bias.

^bDowngraded one level due to small sample size.

BACKGROUND

Description of the condition

Stroke is the second most common cause of death and the leading cause of disability worldwide (Liu 2007). In view of the evidence on the existence of an 'ischemic penumbra' (Siesjo 1978), where brain tissue may survive in ischemic periods of variable and as yet not precisely determined duration, a therapeutic effect may be present when people receive prompt treatment, up to several hours after stroke onset. Calcium antagonists may act as neuroprotective drugs by diminishing the influx of calcium ions through the voltage sensitive calcium channels. One Cochrane Review has already demonstrated that calcium antagonists could reduce the risk of death and dependency and secondary ischemia after aneurysmal subarachnoid hemorrhage (SAH) (Dorhout Mees 2008). However, ischemic stroke is quite different from SAH. A number of randomized controlled trials (RCTs) have evaluated various calcium antagonists for acute ischemic stroke, but it is necessary to synthesize this evidence to determine whether this class of drugs can play a neuroprotective role and improve neurological impairment.

Description of the intervention

Approximately 87% of all strokes are ischemic (i.e. due to a blockage of an artery in the brain), which starves the affected area of oxygen (AHA 2007). Massive calcium influx flooding into the cells is a final common pathway that leads to cell death (Siesjo 1989). Therefore, it is necessary to test any promising strategy that could save brain cells by blocking calcium ions. Calcium antagonists may prevent ischemia based on the notion that these drugs counteract the influx of calcium into the vascular smooth-muscle cell. In clinical practice, it has been found that calcium antagonists have neuroprotective properties.

How the intervention might work

Calcium antagonists reduce the influx of calcium into the cell by blocking calcium channels. Thus, a rationale for the use of calcium antagonists for preventing secondary ischemia is based on the notion that these drugs can counteract the influx of calcium into the vascular smooth-muscle cell, thereby decreasing the rate of vasospasm. Animal experiments have indicated that calcium antagonists administered after cerebral ischemia may be effective in reducing infarct volume and lead to improvements in neurological outcome (Germano 1987; Steen 1983). After their introduction into clinical practice, researchers discovered that calcium antagonists also had neuroprotective properties, reducing the risk of poor outcome after SAH (Dorhout Mees 2008). Nimodipine, a typical calcium antagonist, has been shown to be effective in decreasing the occurrence of death and disability (primary outcome) after SAH and traumatic SAH in humans (Di Mascio 1994; Harders 1996; Pickard 1989). We wondered whether calcium antagonists could have the same effects in ischemic stroke patients.

Why it is important to do this review

Some meta-analyses with a more limited scope (restricted to nimodipine and completed before data from some recent trials were available) have been published (Di Mascio 1994; Gelmers 1990; Mohr 1994). These meta-analyses did not demonstrate a beneficial effect of nimodipine except in one subgroup analysis

(participants treated within 12 h of stroke onset), which suggested that early treatment was effective in functional outcome measured by the Barthel score (Mohr 1994). However, any subgroup analysis showing a beneficial effect should be interpreted with caution, since there is always the danger that it might be a chance finding (Counsell 1994).

Calcium antagonists could protect neurons and hence might reduce neurological impairment, disability, and handicap after stroke. Many calcium antagonists have been tested in randomized controlled trials (RCTs) in people with acute ischemic stroke, but none of these trials have demonstrated a convincing beneficial effect. However, the sample size might have been too small to show a significant clinical effect, so a systematic review is necessary. The previous version of this Cochrane Review was published in 2012 (Zhang 2012); we conducted this update to provide more current evidence for clinical practice.

OBJECTIVES

To assess the effects of calcium antagonists for reducing the risk of death or dependency after acute ischemic stroke. We investigated the influence of different drugs, dosages, routes of administration, time intervals after stroke, and trial design on the outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

We included all RCTs of calcium antagonists versus control (placebo or standard medical treatment alone). We also included trials comparing different routes of administration (oral versus intravenous administration) and different doses. We excluded trials that were not truly randomized.

Types of participants

People with presumed or definite acute ischemic stroke who were randomized within 14 days after stroke onset. All were confirmed through computerized tomography (CT) or magnetic resonance imaging (MRI). Two studies included some hemorrhagic stroke patients (255 participants included in total) but, since we could not extract the information for the ischemic stroke patients only, we included all randomized participants (Chandra 1995; Lowe 1989).

Types of interventions

We included all types of calcium antagonists, given in any dose, by the intravenous or oral route. These were defined as agents whose principal mode of action is to inhibit the influx of calcium into cells by way of the voltage-sensitive calcium channels.

We excluded trials that compared calcium antagonists to another active therapy that had not been factored into the randomization.

Types of outcome measures

Primary outcomes

Primary outcome: defined as death (all-cause case fatality) or dependency in activities of daily living at long-term follow-up (at least three months). For assessing dependency, we used the following available functional health scales: the Modified Rankin or Oxford Handicap Scale (dependency > 3) (Bamford 1989),

Glasgow Outcome Scale (dependency < 4) (Jennet 1975), the Barthel Index (dependency < 60) (Mahoney 1965), Toronto Stroke Scale (dependency > 3) (Norris 1982) or the disability item in the Mathew Impairment Scale (dependency = 7) (Mathew 1972). If more than one scale was available, we selected the one with the smallest number of missing values (see the [Characteristics of included studies](#) table for details).

Secondary outcomes

- Death from any cause during the scheduled treatment period
- Death from any cause during long-term follow-up (at least 3 months)
- Recurrent stroke during long-term follow-up
- Adverse effects of the drug (e.g. impairment of kidney function, impairment of liver function, skin irritation, local infusion-related irritation, nausea, etc.) during the scheduled treatment period
- Hypotension: substantial fall in blood pressure during the scheduled treatment period
- Mean systolic blood pressure during the treatment period

We recorded these events if they were reported as such in the original paper, according to the definitions used by the investigators.

Search methods for identification of studies

See the 'Specialized register' information at the [Cochrane Stroke Group's](#) website. We searched for trials in all languages and arranged translation of studies published in languages other than English.

Electronic searches

We searched the Cochrane Stroke Group Trials Register (6 February 2018), Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 2) in the Cochrane Library ([Appendix 1](#)), MEDLINE Ovid (1950 to 6 February 2018; [Appendix 2](#)), and Embase Ovid (1980 to 6 February 2018; [Appendix 3](#)). We also searched the following four Chinese databases: Chinese Biological Medicine Database (CBM-disc; 1978 to 6 February 2018), China National Knowledge Infrastructure (CNKI; 1980 to 6 February 2018), Chinese Scientific Periodical Database of VIP information (1989 to 6 February 2018), and Wanfang Data (www.wanfangdata.com; 1982 to 6 February 2018; [Appendix 4](#)).

We developed the MEDLINE search strategy with the help of the Cochrane Stroke Group Information Specialist and adapted it for the other databases.

To identify further published, unpublished, and ongoing trials, we searched the following trials registers on 6 February 2018 ([Appendix 5](#)).

- ClinicalTrials.gov (www.clinicaltrials.gov).
- EU Clinical Trials Register (www.clinicaltrialsregister.eu).
- Stroke Trials Registry (www.strokecenter.org/trials/).
- ISRCTN registry (www.isrctn.com).
- WHO International Clinical Trials Registry Platform (apps.who.int/trialsearch/).
- Chinese Clinical Trial Registry, ChiCTR (www.chictr.org).

Searching other resources

In an effort to identify further published, ongoing, and unpublished trials we contacted trialists and researchers in the field.

Data collection and analysis

Selection of studies

Two review authors (JZ, JL) read the titles, abstracts, and keywords of all records identified from the searches of the electronic bibliographic databases and excluded studies that were clearly irrelevant. We obtained the full text of the remaining studies, and the same two review authors independently selected trials for inclusion based on our defined criteria. We developed an inclusion/exclusion form to assist with the selection of trials. The two review authors resolved any disagreements by discussion and consulted a third review author (ML) if necessary. If we could not resolve disagreements through discussion, we added the article to those awaiting classification and contacted the study authors for clarification.

Data extraction and management

Two review authors (JZ, JL) independently extracted data on methods, participants, interventions, outcomes, and results, and we recorded the information on a data extraction form. The key information extracted was as follows.

- General information: published/unpublished, title, authors, reference/source, contact address, country, language of publication, year of publication, duplicate publications, sponsor, setting.
- Trial characteristics: design, duration of follow-up, method of randomization, allocation concealment, blinding (participants, people administering treatment, people assessing outcome).
- Interventions: intervention (dose, route, frequency, duration, time interval from the stroke onset), control intervention (dose, route, frequency, duration), comedication(s) (dose, route, frequency, duration).
- Participants: inclusion/exclusion criteria, diagnostic criteria, total number and number in each group, age, baseline characteristics, similarity of groups at baseline (including any comorbidity), assessment of compliance, withdrawals (reasons/description), subgroups.
- Outcomes: outcomes specified above, any other outcomes assessed, other events, length of follow-up, quality of reporting of outcomes.

The same two review authors cross-checked all extracted data and resolved any disagreements by discussion. If they could not reach consensus, the third review author (ML) made the final decision.

Assessment of risk of bias in included studies

Two review authors (JZ, JL) independently assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion among review authors. We assessed the risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment.

- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

We assessed the risk of bias for each domain as high, low, or unclear, providing information from the study report with the description of the sources of bias. We judged a study to be at low risk of bias if all key domains were rated at low risk of bias. If one or more of the domains was rated at unclear risk of bias, we judged the study to be at unclear risk of bias. We judged the study to be at high risk of bias if one or more of the domains was rated at high risk of bias.

Measures of treatment effect

These measures are listed under [Types of outcome measures](#).

Unit of analysis issues

All included trials were randomized and analyzed at the level of the individual patient.

Dealing with missing data

When participants were excluded or lost to follow-up after randomization or if any of the above data were unavailable from the publications, we sought further information by contacting the study authors. If such information remained unavailable, all the review authors decided whether or not to include the trial in the review.

Assessment of heterogeneity

We tested heterogeneity among trial results using the I^2 statistic. We considered a value greater than 50% as indicating substantial heterogeneity.

Assessment of reporting biases

We examined publication and other biases using a funnel plot. We plotted effect size against sample size, resulting in a graphical display that gave some indication of whether or not some studies had not been published or located.

Data synthesis

We performed statistical analysis using Review Manager 5 ([RevMan 2014](#)). We reported the results as risk ratios (RR) with 95% confidence intervals (CI) for dichotomous data, and as mean difference (MD) with 95% CIs for continuous data. We used a random-effects model to combine individual results regardless of whether there was significant heterogeneity or not.

Subgroup analysis and investigation of heterogeneity

For the subgroup analyses we collected information about route of drug administration, dose, and time interval to start of treatment.

Heterogeneity might arise from a wide variety of factors, such as the trial design or participant characteristics. We also examined the influence of excluding trials on heterogeneity.

Sensitivity analysis

According to the *Cochrane Handbook for Systematic Reviews of Interventions*, we did a sensitivity analysis by including only multicenter studies or published trials ([Higgins 2011](#)).

'Summary of findings' table

In a departure from our protocol, we presented five 'Summary of findings' tables, one for each comparison ([Summary of findings for the main comparison](#); [Summary of findings 2](#); [Summary of findings 3](#); [Summary of findings 4](#); [Summary of findings 5](#)). We reported all outcomes in the tables.

We determined the quality of the evidence using the GRADE approach and downgraded evidence in the presence of risk of bias in at least one study, indirectness, unexplained heterogeneity or inconsistency, imprecision, or a high probability of publication bias. We downgraded evidence by one level if we considered the limitation to be serious and by two levels if it was very serious.

RESULTS

Description of studies

Most trials tested nimodipine. Bayer Germany provided results for various trials. The original data sets were often more complete than the published data. For example, in three trials a significant number of participants were excluded after randomization for unclear reasons, and the publications did not present the outcomes ([Martinez-Vila 1990](#); [NEST 1993](#); [Wimalaratna 1994](#)); however, data on these participants were available from the original data set.

On the other hand, the original data set of [Heiss 1990](#), from which we based our calculations, did not account for the number of excluded participants in the published article. Thus, there might be a slight difference between the data reported here and those in the published article.

In this update, we did not find any new trials for inclusion, nor any related ongoing trials that could be included when published or completed.

Results of the search

Our original review included 34 studies. When we re-ran the searches on 6 February 2018, we identified 679 unique records ([Figure 1](#)). We acquired and screened the full text of two articles ([Chen 2016](#); [NICE 2012](#)); these studies did not meet the inclusion criteria due to ineligible participants. The review authors were unanimous in our agreement regarding exclusion. We found no ongoing RCTs.

Figure 1. Study flow diagram.

Included studies

See [Characteristics of included studies](#). Thirty-four trials (including 7731 participants) met the inclusion criteria (ASCLEPIOS 1990; Bogousslavsky 1990; Bridgers 1991; Canwin 1993; Capon 1983; Chandra 1995; FIST 1990; Gelmers 1984; Gelmers 1988; German-Austrian 1994; Heiss 1990; INWEST 1990; Kaste 1994; Kornhuber 1993; Lamsudin 1995; Limburg 1990; Lisk 1993; Lowe 1989; Martinez-Vila 1990; Mohr 1992; Nag 1998; NEST 1993; NIMPAS 1999; Oczkowski 1989; Paci 1989; Sherman 1986; Shibuya 2005; Squire 1996; Sze 1998; TRUST 1990; Uzunur 1995; VENUS 1999; Wimalaratna 1994; Yordanov 1984).

Participants were aged 18 to 85 years, with the average age ranging from 52.3 to 74.6 years across different trials. Most of the trials included more men than women.

Twenty-six trials tested nimodipine, while three trials used flunarizine (FIST 1990; Kornhuber 1993; Limburg 1990), and one each assessed isradipine (ASCLEPIOS 1990), nicardipine (Lisk 1993), PY108-608 (Oczkowski 1989), fasudil (Shibuya 2005), and lifarizine (Squire 1996). Most of these trials used placebo controls, and more than half had a follow-up of three months or more. Calcium antagonists were administered intravenously or orally in different dosages and at different time intervals from stroke onset; we

performed subgroup analyses according to dosages and time intervals from stroke onset.

Most trials reported that both treatment and control groups received antiplatelet and anticoagulation therapy.

Thirty-one trials reported death, but only six reported details of the causes of death (Capon 1983; Gelmers 1988; Kaste 1994; Kornhuber 1993; Martinez-Vila 1990; Sze 1998). The main causes of death in these six trials were stroke recurrence, myocardial infarction, cardiac failure, and pneumonia. Thirteen trials reported adverse events.

One included study was funded by the Canadian Heart Foundation, while around 20 out of the 34 studies were funded by drug manufacturers. All studies in this systematic review were old, and we could not find the funding sources that supported the rest.

Excluded studies

We excluded 15 studies. For details see [Characteristics of excluded studies](#).

Risk of bias in included studies

Information regarding risk of bias is provided in [Figure 2](#) and [Figure 3](#).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)
ASCLEPIOS 1990	?	?	-	?	+	+
Bogousslavsky 1990	+	?	-	?	+	+
Bridgers 1991	?	?	-	?	+	+
Canwin 1993	?	?	-	?	?	?
Capon 1983	?	?	?	?	?	?
Chandra 1995	?	?	?	?	+	+
FIST 1990	?	?	-	?	+	+
Gelmers 1984	?	?	+	?	+	?
Gelmers 1988	+	+	-	?	+	+
German-Austrian 1994	?	?	-	?	+	+
Heiss 1990	+	+	-	?	+	+
INWEST 1990	?	?	+	?	+	+
Kaste 1994	?	+	-	?	+	+
Kornhuber 1993	+	?	-	?	+	+
Lamsudin 1995	?	?	-	?	+	+
Limburg 1990	+	?	+	?	+	+
Lisk 1993	?	?	+	?	+	+
Lowe 1989	+	?	?	?	?	?
Martinez-Vila 1990	?	?	-	?	+	+
Mohr 1992	?	+	+	?	+	+

Figure 3. (Continued)

Mohr 1992	?	+	+	?	+	+
Nag 1998	?	?	-	?	+	+
NEST 1993	?	?	-	?	+	+
NIMPAS 1999	?	?	-	?	+	+
Oczkowski 1989	?	?	+	?	+	+
Paci 1989	?	?	-	?	+	+
Sherman 1986	?	?	?	?	+	+
Shibuya 2005	+	?	+	?	?	+
Squire 1996	?	?	-	?	+	+
Sze 1998	?	+	-	?	?	+
TRUST 1990	?	?	-	?	+	+
Uzunur 1995	?	?	?	?	?	?
VENUS 1999	+	+	+	?	+	+
Wimalaratna 1994	?	?	-	?	+	+
Yordanov 1984	?	?	?	?	?	?

Allocation

Eight trials allocated participants by clear methods with low risk of bias for random sequence generation (Bogousslavsky 1990; Gelmers 1988; Heiss 1990; Kornhuber 1993; Limburg 1990; Lowe 1989; Shibuya 2005; VENUS 1999).

With regard to allocation concealment, six trials used numbered boxes as the method (Gelmers 1988; Heiss 1990; Kaste 1994; Mohr 1992; Sze 1998; VENUS 1999). The remaining trials did not report the method of random sequence generation or allocation concealment, so we assessed these domains as being at unclear risk of bias.

Blinding

Five trials did not report the method of blinding, so we judged them to be at unclear risk (Canwin 1993; Capon 1983; Lowe 1989; Uzunur 1995; Yordanov 1984). One trial did not report that the assessors were blinded (Gelmers 1984). Therefore, we regarded performance bias and detection bias as 'unclear risk'.

Incomplete outcome data

Only seven trials reported losing no participants to follow-up (low risk) (Gelmers 1984; Lisk 1993; Lowe 1989; Mohr 1992; Oczkowski 1989; Shibuya 2005; VENUS 1999). One trial reported some loss to follow-up, but there was no difference after an intention-to-treat (ITT) analysis of the results (low risk) (INWEST 1990). We could not obtain any information about incomplete outcome data in six trials (Capon 1983; Chandra 1995; Lowe 1989; Sherman 1986; Uzunur 1995; Yordanov 1984) (unclear risk); we categorized the remaining

20 trials as being at high risk for attrition bias since they all had data loss and no ITT analysis.

Selective reporting

The protocols for the included trials were unavailable. Therefore, there was insufficient information for us to make a judgement on selective reporting (unclear risk).

Other potential sources of bias

None known.

Effects of interventions

See: [Summary of findings for the main comparison Calcium antagonists versus placebo for acute ischemic stroke](#); [Summary of findings 2 Nimodipine versus placebo for acute ischemic stroke](#); [Summary of findings 3 Flunarizine versus placebo for acute ischemic stroke](#); [Summary of findings 4 Isradipine versus placebo for acute ischemic stroke](#); [Summary of findings 5 Other calcium antagonists versus placebo for acute ischemic stroke](#)

Primary outcome

Death or dependency at end of follow-up

Data from 22 trials with 6684 participants were available, but they showed no difference between participants using calcium antagonists or not. If anything, there may be a small but detrimental effect (RR 1.05, 95% CI 0.98 to 1.13; moderate-quality evidence). These 22 trials tested three drugs: nimodipine (19 trials), flunarizine

(2 trials), and isradipine (1 trial). The indirect comparisons between drugs did not show clear evidence of differences ([Analysis 1.1](#)).

Heterogeneity was present in the analysis of 'Flunarizine versus control' ($P = 0.09$, $I^2 = 64\%$, $df = 1$), which included only two trials

([FIST 1990](#); [Limburg 1990](#)). In [FIST 1990](#), there were 331 participants involved, while [Limburg 1990](#) included only 26 participants; this may have been the most substantial cause of the heterogeneity.

A funnel plot showed obvious publication bias existed ([Figure 4](#)).

Figure 4. Funnel plot of comparison: primary outcome at end of follow-up.

Secondary outcomes

Death at end of treatment period

Data were available from 22 trials with 6323 participants. There was no difference between groups for death at the end of treatment period (RR 1.06, 95% CI 0.93 to 1.20; moderate-quality evidence).

In participants treated with intravenous flunarizine, we also found there was no statistically significant increase in mortality (RR 1.31, 95% CI 0.94 to 1.82; [Analysis 1.2](#)).

A funnel plot showed there was obvious publication bias ([Figure 5](#)).

Figure 5. Funnel plot of comparison: death at end of treatment period.

Death at end of follow-up

Data were available from 31 trials with 7483 participants. There was no difference between groups for death (RR 1.07, 95% CI 0.98 to 1.17; moderate-quality evidence). In participants treated with intravenous flunarizine, there was a statistically significant increase

in mortality (RR 1.34, 95% CI 1.01 to 1.77). As for the other calcium antagonists, such as nimodipine, isradipine, lifarizine, PY106-608, and nicardipine, the analysis showed no difference ([Analysis 1.3](#)).

A funnel plot showed there was obvious publication bias ([Figure 6](#)).

Figure 6. Funnel plot of comparison: death at end of follow-up.

Recurrence of stroke at end of follow-up

Only a limited number of reports mentioned stroke recurrences (nine trials with 2460 participants). There was no difference in the number of events between treatment and control groups (RR 0.93, 95% CI 0.56 to 1.54; moderate-quality evidence). However, the confidence intervals were wide, probably because of small sample sizes in the trials ([Analysis 1.4](#)).

All adverse events during treatment period

Adverse events were more frequent in the intervention groups (8.9% versus 6.9%). About half of the excess adverse events in the treatment groups (after correction for differences in the group sizes) were caused by thrombophlebitis due to intravenous administration of flunarizine. The occurrence of hypotension (defined as episodes leading to cessation of drug treatment) was

reported in only five trials and was more frequent in the treatment group (1.8% versus 1.2%).

In the largest flunarizine trial there was a clear increase of adverse events in the treated group (33% versus 10%, RR 3.16, 95% CI 1.91 to 5.21). This was mainly due to an excess of superficial thrombophlebitis in the flunarizine group. In the rest of the studies there was no difference in adverse events. The overall result was an RR of 1.18 (95% CI 0.81 to 1.74; 5095 participants; 13 trials; moderate-quality evidence; [Analysis 1.5](#)).

Heterogeneity was strongly present in this analysis, caused by the results of the intravenous flunarizine trial [FIST 1990](#); the considerable heterogeneity could be completely reversed by removing it.

A funnel plot showed there was obvious publication bias ([Figure 7](#)).

Figure 7. Funnel plot of comparison: adverse events (all) during treatment period.

Hypotension during treatment period

Six trials with 1667 participants reported episodes of hypotension (sufficient to stop treatment). Hypotensive episodes were more frequent in the treatment groups, but there was no statistically significant difference (1.8% versus 1.2%, RR 1.43, 95% CI 0.61 to 3.38; moderate-quality evidence; [Analysis 1.6](#)).

Mean systolic blood pressure during or at end of treatment

Data were available in three trials with 630 participants. The mean blood pressure in the treated groups was on average 1.3 mmHg lower. This was a very small difference. The result was not statistically significant (MD -1.3 mmHg, 95% CI -3.92 to 1.32; low-quality evidence; [Analysis 1.7](#)).

There was considerable heterogeneity, which could be completely reversed by removing [Martinez-Vila 1990](#).

Subgroup analyses

Primary outcome by route of administration

Data were available for 23 trials: 14 trials with 5131 participants used oral administration, 8 trials with 1544 participants used intravenous administration, and 1 trial with 143 participants compared oral and intravenous administration directly. Intravenous administration was associated with a worse outcome in treated groups compared with placebo controls (RR

1.11, 95% CI 1.01 to 1.22). In the orally treated groups no difference was present (RR 1.03, 95% CI 0.93 to 1.14; [Analysis 2.1](#)).

[Chandra 1995](#) performed the only direct comparison between oral and intravenous administration of nimodipine, but results did not support the notion that intravenous administration was associated with poorer outcome (RR 7.10, 95% CI 0.37 to 134.96; [Analysis 2.1](#)).

Readers should interpret these observations with caution, as there was no significant difference between the subgroups.

Primary outcome by dose: indirect comparisons (calcium antagonists versus control)

Data were available for 18 trials: 1 trial with 529 participants used 60 mg/d oral nimodipine, 14 trials with 4526 participants used 120 mg/d oral nimodipine, 2 trials with 637 participants used 240 mg/d oral nimodipine, 4 trials with 552 participants used 2 mg/h intravenous nimodipine per day (3 trials for 5 days and 1 trial for 10 days), and 2 trials with 329 participants used 1 mg/h intravenous nimodipine per day for 5 days. The indirect comparisons did not show a clear dose-dependent treatment effect. Nimodipine, given orally at 60 mg, 120 mg, and 240 mg versus control yielded the following risk ratios: 1.08, 0.99 and 1.07 (they did not show a difference between groups). Intravenous nimodipine of 2 mg/h showed a non-significant increase in the risk of the primary outcome (RR 1.34, 95% CI 0.93 to 1.93), while there was no clear difference between control

and the group treated intravenously with 1 mg/h (RR 1.09, 95% CI 0.91 to 1.29; [Analysis 2.2](#)).

Heterogeneity existed in the analysis of nimodipine 2 mg/h versus control in the primary outcome by dose, and it was largely caused by [Bridgers 1991](#). Removing this trial decreased the heterogeneity but did not eliminate it.

Readers should interpret these observations with caution, as there was no significant difference between the subgroups.

Primary outcome by dose: direct comparisons (calcium antagonists with different doses)

These direct comparisons were possible in very few trials: data were available in six trials, including one trial with 533 participants comparing 60 mg versus 120 mg oral nimodipine per day, one trial with 532 participants comparing 60 mg versus 240 mg oral nimodipine per day, two trials with 681 participants comparing 120 mg versus 240 mg oral nimodipine per day, two trials with 333 participants comparing 1 mg/h versus 2 mg/h intravenous nimodipine. This direct comparison showed no significant difference between 120 mg and 60 mg (RR 1.08, 95% CI 0.94 to 1.24) or between 120 mg and 240 mg (RR 1.00, 95% CI 0.88 to 1.13). A dose-dependent relationship appeared to exist for intravenous nimodipine without a significant difference (RR 0.82, 95% CI 0.71 to 0.95, $P = 0.57$; [Analysis 2.3](#)).

Readers should interpret these observations with caution, as there was no significant difference between the subgroups.

Primary outcome by time start of treatment

Data were available for 32 trials, including 18 trials with 1879 participants whose treatment started within 12 h after stroke onset, and 14 trials with 4071 participants whose treatment started after 12 h from stroke onset. There was no significant difference in the odds of the primary outcome, comparing early treatment (within 12 h after stroke onset) with calcium antagonists to placebo (RR 1.08, 95% CI 0.96 to 1.21). Treatment after 12 h showed no effect whatsoever (RR 1.01, 95% CI 0.90 to 1.13). This analysis might be confounded by route of administration ([Analysis 2.4](#)).

Readers should interpret these observations with caution, as there was no significant difference between the subgroups.

Sensitivity analyses

Primary outcome in multicenter placebo-controlled trials

Of the 34 included trials, 10 trials including 4012 participants reported that their data were from multicenter placebo-controlled trials. We did the primary outcome analysis on these 10 trials and found there was no clear difference (RR 1.04, 95% CI 0.95 to 1.14; [Analysis 3.1](#)).

Publication status

Data were from 22 trials, including 18 trials with 5887 participants from which we could extract the primary outcome from the published papers, and 4 trials with 788 participants with unpublished data. The published trials did not show an overall effect of active treatment on the primary outcome (RR 1.03, 95% CI 0.94 to 1.12). On the contrary, the unpublished trials were associated with a deleterious effect of calcium antagonist treatment (RR 1.14, 95% CI 1.00 to 1.30; [Analysis 3.2](#)). However,

these observations must be viewed with caution as there was no significant difference between the subgroups.

DISCUSSION

Summary of main results

This systematic review of all available randomized data failed to demonstrate a reduction in mortality and dependency after treatment with calcium antagonists in people with acute ischemic stroke. Due to the large amount of data (34 trials with 7731 patients), confidence intervals were narrow and the overall result was therefore subject to limited statistical uncertainty.

Intravenous administration of calcium antagonists was not associated with a significantly increased risk of the primary outcome. For nimodipine, the direct comparison showed no significant difference between 120 mg and 60 mg or between 120 mg and 240 mg. A dose-dependent relationship appeared to exist for intravenous nimodipine without a significant difference.

Overall completeness and applicability of evidence

We did two sensitivity analyses: one based on the primary outcome in multicenter placebo-controlled trials, and the other on published trials, while drawing the same conclusions.

Quality of the evidence

The quality of the included trials of calcium antagonists for ischemic stroke was generally acceptable. All trials included were placebo-controlled trials except [Chandra 1995](#), [Gelmers 1984](#), and [Uzunur 1995](#), and all but five trials used a blinding method. However, there were still two main drawbacks: first, only seven trials reported the methods of random sequence generation, and only five trials reported the method of allocation concealment, which might lead to selection bias; secondly, we categorized incomplete outcome as 'low risk' in only eight trials. As most participants were excluded in the treatment period and lost at follow-up, this might lead to reporting bias.

Potential biases in the review process

Our sensitivity analysis provides a strong argument in favor of the presence of publication bias with regard to treatment effect. While the published trials showed no effect on the primary outcome, unpublished trials without exception were associated with a significantly worse outcome in the treatment group. It was quite conceivable that more trials remained unpublished, with perhaps similarly negative results.

Agreements and disagreements with other studies or reviews

The findings were intriguing regarding the time interval between stroke onset and the start of treatment. Based on the previous meta-analysis by [Mohr 1994](#), we expected to find an improved outcome in the promptly treated group (defined as those treated within 12 h after stroke onset). However, this was not the case. On the contrary, early treatment was associated with a non-significant increase in the risk of primary outcome or death. When participants were treated late (more than 12 h after stroke onset), we saw no effect of nimodipine on either the primary outcome or death alone. Our results do not confirm the positive effect reported in the meta-analysis by [Mohr 1994](#). For the primary outcome and mortality

alone, we found no effect of nimodipine. Because more studies have become available, our study contains data from a larger number of participants. Direct comparison of the results of the two meta-analyses was hampered by the absence of exact participant numbers in the various outcome categories in [Mohr 1994](#).

There has been some debate about the antithrombotic properties of some calcium antagonists ([Heininger 1996](#); [Legault 1996](#)). We found no influence of calcium antagonists on stroke recurrence or myocardial infarction. However, the number of trials reporting these data adequately was small. This might be a result of inadequate monitoring and reporting.

AUTHORS' CONCLUSIONS

Implications for practice

This review does not provide any evidence to justify the routine use of calcium antagonists in people with acute ischemic stroke for reducing the risk of mortality and dependence, adverse events, or other adverse clinical outcomes.

Implications for research

In view of the consistent results with relatively narrow confidence intervals, we do not believe there is any need to perform further studies to explore the effect of calcium antagonists in people with ischemic stroke.

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If anyone is aware of any trials that we have omitted, please contact Pro

Ming Liu.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

ASCLEPIOS 1990

Methods	Publication status: unpublished
	Multicenter placebo-controlled trial

ASCLEPIOS 1990 (Continued)

	Double-blind
	Exclusions during trial: unclear
	Losses to follow-up: 4
Participants	Inclusion criteria: age: 45 to 85 years, start within 12 h, probable MCA infarction, CT scan within 72 h Exclusion: massive hemispherical infarction, Orgogozo score > 65, clinical resolution within 24 h
Interventions	Treatment: intravenous isradipine, 28 days, 80 µg/h for 72 h, followed orally with 2.5 mg twice daily Placebo: identical regimen
Outcomes	Barthel Index Death Last follow-up: 3 months Dependency measurement used in review: Barthel Index Missing: 4 participants in isradipine group
Notes	Data available from principal investigator (JM Orgogozo) Funding sources: unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing 4 participants in isradipine group without ITT analysis
Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Bogousslavsky 1990

Methods	Publication status: published Single-center placebo-controlled trial
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Calcium antagonists for acute ischemic stroke (Review)

Bogousslavsky 1990 (Continued)

	Double-blind
	Exclusions during trial: 8
	Losses to follow-up: 1
Participants	<p>Inclusion criteria: age 40 to 85 years, start within 48 h, acute ischemic stroke of mild-to-moderate severity (Mathew Scale score 50 to 75), diagnosis on CT scan and clinical evaluation</p> <p>Exclusion criteria: rapid improvement < 24 h, loss of consciousness, brainstem infarction, pregnancy, cerebral neoplasm, cause of brain infarction other than atherothrombosis, other severe diseases, medication (concomitant use of calcium channel antagonists, piracetam, pentoxifylline, naftidrofuryl dehydrogenoxalate, dihydroergetoxine, alpha-methyl dopa)</p>
Interventions	<p>Treatment: oral nimodipine, 30 mg 4 times daily for 2 weeks</p> <p>Placebo: identical regimen</p>
Outcomes	<p>Mathew Scale score</p> <p>Death</p> <p>Last follow-up: 4 months</p> <p>Dependency measurement used in review: functional item Mathew Scale scale</p> <p>Missing: 1 participant in placebo group</p>
Notes	<p>Data available from publication and database of Bayer AG, Wuppertal, Germany</p> <p>Funding sources: Bayer AG</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The participants received nimodipine or placebo according to a random list
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	60 participants recruited but only 52 participants had been analyzed; there was no ITT analysis
Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Bridgers 1991

Methods	Publication status: published as abstract Multicenter placebo-controlled trial Double-blind Exclusions during trial: unclear Losses to follow-up: 1
Participants	Inclusion criteria: acute stroke, moderate to severe, < 24 h after stroke onset Exclusion criteria: unknown
Interventions	Treatment: intravenous nimodipine, 2 active groups: 1 mg/h or 2 mg/h for 5 days, followed by oral nimodipine 120 mg/d days 5 to 21 Placebo: identical regimen
Outcomes	Barthel Index, Glasgow Outcome Scale and Mathew Scale Death Last follow-up: 21 days (not completely clear) Dependency measurement used in review: Glasgow Outcome Scale Missing: 1 missing in placebo group
Notes	Data available from published abstract and Bayer AG, Wuppertal Trial was stopped after inclusion of 204 of planned 720 participants because of deleterious effect in high dosage group Funding sources: unknown, it was likely funded by Bayer AG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	1 missing in the placebo group and there was no ITT analysis
Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Calcium antagonists for acute ischemic stroke (Review)

Canwin 1993

Methods	Publication status: published Placebo-controlled trial Blinding: unclear Exclusions during trial: 25 Losses to follow-up: 16
Participants	Inclusion criteria: age 45 to 85 years, start within 48 h, hemiplegia, CT-confirmed hemispheric cerebral infarction, Toronto Stroke Scale scores > 20 Exclusion: coma, no motor weakness, brainstem strokes or previous strokes, CT scan not compatible with ischemic stroke, use of calcium antagonists, concurrent terminal illness
Interventions	Treatment: intravenous nimodipine; days 1 to 10 at 2 mg/h, days 11 to 6 months at 180 mg/d orally Placebo: identical regimen
Outcomes	Toronto Stroke Scale Functional disability using 3 categories: minor or no disability, moderate disability, severely disabled or bedridden Death Last follow-up: 1 year Dependency measurement used in review: Toronto Stroke Scale Missing: 5 in active treatment group, 11 in control group
Notes	Data available from publication, principal investigator, Bayer Canada and Bayer AG, Wuppertal, Germany Funding sources: unknown, it was likely funded by Bayer AG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	189 participants randomized into the study but 164 were suitable for statistical evaluation, however, they did not do the ITT analysis
Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported

Calcium antagonists for acute ischemic stroke (Review)

Canwin 1993 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
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Capon 1983

Methods	Publication status: unpublished Placebo-controlled trial Blinding: unclear Exclusions during trial: unclear Losses to follow-up: unclear
Participants	Stroke participants, criteria unknown
Interventions	Treatment: nimodipine oral, 30 mg 4 times daily for 56 days Placebo: identical regimen
Outcomes	Death Last follow-up: at end of treatment No dependency measurement available
Notes	Very limited data available from Bayer AG, Wuppertal, Germany. Unpublished data Funding sources: unknown, it was likely funded by Bayer AG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported

Chandra 1995

Methods	Publication status: published Blinded comparison of oral versus intravenous administration of nimodipine Double-blind Exclusions during trial: unclear Losses to follow-up: 0 Placebo-controlled
Participants	Inclusion criteria: sudden focal neurologic deficit, admission within 6 h Exclusion: transient signs, large (> 60 mL on CT) cerebral hemorrhage; no informed consent; recent myocardial infarction; congestive heart failure; abnormal renal, pulmonary or hepatic function
Interventions	Treatment: oral versus intravenous treatment: arm 1: oral nimodipine 30 mg 4 times daily and intravenous placebo; arm 2: nimodipine 2.5 mg/h intravenous and oral placebo Treatment period 10 days, followed by oral nimodipine for all
Outcomes	Unmodified Mathew Scale, Barthel Index Death Last follow-up: day 14 Dependency: data reported in unusable way Missing: none
Notes	Data from original publication, only average scores on functional items available, hence not used in meta-analysis This trial is only used for direct comparison of route of administration Funding sources: unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind

Calcium antagonists for acute ischemic stroke (Review)

Chandra 1995 (Continued)

Blinding of outcome assessment (detection bias)	Low risk	Double-blind
All outcomes		

FIST 1990

Methods	Publication status: published Multicenter placebo-controlled trial Double-blind Exclusions during trial: 32 Losses to follow-up: 5
Participants	Inclusion criteria: clinical diagnosis of ischemic stroke in MCA territory, disabling motor deficit, total Glasgow Coma Score > 3, < 24 h of stroke onset Exclusion criteria: brain tumor, intracranial hemorrhage or lacunar infarction on CT scan, previous disabling stroke, other severe disorder, poor physical or mental condition
Interventions	Treatment: intravenous flunarizine: days 1 to 7 at 25 mg twice daily followed by oral flunarizine: days 8 to 14 at 21 mg/d; days 15 to 28 at 7 mg/d Placebo: identical regimen
Outcomes	Modified Rankin scale, Orgogozo scale, Modified Barthel Index Death Last follow-up: 24 weeks Dependency measurement used in review: Modified Rankin scale Missing: 4 in active treatment, 1 in placebo group
Notes	Other 'stroke therapies' were not allowed Data were available from publication and from Janssen Pharmaceutica BV, Tilburg, Netherlands Funding sources: Janssen Pharmaceutica, Tilburg

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	331 participants recruited, but only 290 analyzed, ITT analysis performed but results not reported

FIST 1990 (Continued)

Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Gelmers 1984

Methods	Publication status: published Placebo-controlled trial Single-blind Exclusions during trial: 0 Losses to follow-up: 0
Participants	Inclusion criteria: acute ischemic stroke, age > 40 years, CT scan compatible with diagnosis Exclusion criteria: not described
Interventions	Treatment: oral nimodipine, 30 mg 4 times daily, 28 days Placebo: none
Outcomes	Mathew Stroke Scale Death Last follow-up: 28 days Dependency measurement used in review: functional item in Mathew Scale Missing: none
Notes	All participants standard treatment with 10% depolymerized dextran for 12 h/d for 5 days Data available from publication and Bayer AG, Wuppertal, Germany Funding sources: unknown, it was likely founded by Bayer AG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

Gelmers 1984 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	60 participants recruited and no data loss
Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Single-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported

Gelmers 1988

Methods	Publication status: published Multicenter placebo-controlled trial Double-blind Exclusions during trial: 22 Losses to follow-up: 38
Participants	Inclusion criteria: age > 45 years, clinical diagnosis of complete acute ischemic stroke < 24 h after stroke onset Exclusion criteria: other causes than atherothrombosis (subarachnoid and intracerebral hemorrhage), complicated migraine, severe systemic diseases
Interventions	Treatment: oral nimodipine, 30 mg 4 times daily, 28 days Placebo: identical regimen
Outcomes	Mathew Scale Death Last follow-up: 6 months Dependency measurement used in review: functional-item Mathew Scale (at end of treatment) Missing: 18 participants in active treatment and 20 participants in placebo group
Notes	All participants received a standard regimen of 10% depolymerized low-molecular-weight dextran for 12 h per day during 5 days Data available from publication and Bayer AG, Wuppertal, Germany Funding sources: Bayer AG

Risk of bias

Bias	Authors' judgement	Support for judgement
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Gelmers 1988 (Continued)

Random sequence generation (selection bias)	Low risk	Medication was randomized in equal blocks of 10, according to computer-generated lists
Allocation concealment (selection bias)	Low risk	Numbered boxes contained 1 complete treatment or identical placebo course and were sequentially distributed among participating general practitioners and neurologists
Incomplete outcome data (attrition bias) All outcomes	High risk	They excluded 22 participants that had been recruited into either group and gave the reason for the exclusion but did not do ITT analysis
Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

German-Austrian 1994

Methods	Publication status: published Multicenter placebo-controlled trial Double-blind Exclusions during trial: 126 Losses to follow-up: unclear
Participants	Inclusion criteria: age 40 to 80 years, start within 48 h, infarcts in anterior circulation (CT-confirmed), no clinical or CT scan (within 1 week) evidence of non-ischemic disorder, Mathew sum score < 66 Exclusion criteria: TIA, progressive stroke, vertebrobasilar ischemia, coma, intracerebral bleeding or tumor, SAH, pregnancy, cardiac surgery within last 3 months and severe systemic illnesses, use of other 'stroke treatment'
Interventions	Treatment: oral nimodipine, 30 mg 4 times daily, 21 days Placebo: identical regimen
Outcomes	Modified Mathew Scale, Barthel Index Death Last follow-up: 6 months Dependency measurement used in review: functional item in Mathew Scale Missing: 89 participants in active treatment, 83 in placebo group
Notes	Data available from publication, abstracts and Bayer AG, Wuppertal, Germany

German-Austrian 1994 (Continued)

Funding sources: unknown, it was likely founded by Bayer AG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	482 participants were included. Only 356 participants were eligible for analysis and ITT analysis was not performed
Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Heiss 1990

Methods	Publication status: published Multicenter placebo-controlled trial Double-blind Exclusions during trial: 4 Losses to follow-up: unclear
Participants	Inclusion criteria: age > 45 years, acute completed ischemic stroke; admission < 48 h, Mathew Scale Score < 66 Exclusion criteria: other causes than atherothrombosis, overt systemic disease, coma, previous cerebral infarction
Interventions	Treatment: intravenous nimodipine, 1 mg/h in first 2 h, 2 mg/h next 5 days, followed by 30 mg oral 4 times daily days 6 to 21 Placebo: identical regimen
Outcomes	Mathew Scale Score, Barthel Index Death Last follow-up: 6 months Dependency measurement used in review: Barthel Index

Heiss 1990 (Continued)

Missing: in publication 27 participants were said to be randomized, in original data set 24: numbers reported in publication used

Notes

All participants were treated with low-molecular-weight dextran (500 mL/d for 15 days) and glycerol (10% for 5 days)

Data available from publication and Bayer AG, Wuppertal, Germany

Funding sources: unknown, it was likely founded by Bayer AG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number
Allocation concealment (selection bias)	Low risk	Nimodipine or placebo was packed in a box identified only by a random number
Incomplete outcome data (attrition bias) All outcomes	High risk	27 participants were randomly assigned, but 4 of them could not be evaluated
Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

INWEST 1990

Methods	<p>Publication status: published</p> <p>Multicenter placebo-controlled trial</p> <p>Double-blind</p> <p>Exclusions during trial: 67</p> <p>Losses to follow-up: 4</p>
Participants	<p>Inclusion criteria: age > 40 years, start < 24 h, clinical diagnosis of ischemic stroke carotid territory, functionally independent before stroke, conscious, Mathew Scale Score < 66 or Orgogozo score 5 to 50</p> <p>Exclusion criteria: cardiac disease, any disorder interfering with assessment, life-threatening concurrent illness</p>
Interventions	<p>Treatment: intravenous nimodipine 1 mg/h or 2 mg/h for 5 days, followed by oral nimodipine 120 mg/d days 5 to 21</p> <p>Placebo: identical regimen</p>

INWEST 1990 (Continued)

Outcomes	Barthel Index, Orgogozo and Mathew Scales Death Last follow-up: 24 weeks Dependency measurement used in review: Barthel Index Missing: 4 participants in nimodipine group
Notes	Trial was terminated early after including 295 participants (planned 600) because of safety concerns Data available from author's manuscript, abstract and Bayer AG, Wuppertal, Germany Funding sources: Bayer AG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	295 participants were recruited and entered into the treatment and control groups but only 228 participants were valid for the primary analysis ITT analysis performed and there were no statistically significant differences between these groups
Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Kaste 1994

Methods	Publication status: published Multicenter placebo-controlled trial Double-blind Exclusions during trial: 4 Losses to follow-up: unclear
Participants	Inclusion criteria: age 16 to 69 years, start within 48 h, acute ischemic hemispheric stroke, CT scan compatible with clinical diagnosis

Kaste 1994 (Continued)

Exclusion criteria: unconsciousness, inability to swallow, rapidly improving, dependence before stroke, brainstem infarction, complicated migraine, pregnancy, overt renal, hepatic or cardiac failure, severe systemic infection, serious psychiatric disturbance, terminal malignancy

Interventions	Treatment: oral nimodipine, 30 mg 4 times daily, 21 days Placebo: identical regime
Outcomes	Neurological examination Rankin scale Death Last follow-up: 12 months Dependency measurement used in review: Rankin scale Missing: 2 living participants in placebo, 1 living participant in active treatment group
Notes	Data available from authors and publication Funding sources: unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Sealed envelope
Incomplete outcome data (attrition bias) All outcomes	High risk	Data for 1 participant was lost
Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Kornhuber 1993

Methods	Publication status: published Multicenter placebo-controlled trial Double-blind
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Kornhuber 1993 (Continued)

Exclusions during trial: 4

Participants	<p>Inclusion criteria: age 50 to 85 years, start within 36 h, clinical diagnosis of anterior or MCA stroke</p> <p>Exclusion criteria: transient signs, coma, previous cerebral infarction, severe cardiac insufficiency, acute myocardial infarction, acute pulmonary embolism, connective tissue disease, cytostatic therapy, use of calcium antagonists or oral anticoagulation, dialysis, dementia, intracranial hemorrhage, brain tumor, brainstem infarction, complicated migraine, flunarizine treatment within previous 4 weeks</p>
Interventions	<p>Treatment: intravenous flunarizine, 25 mg twice daily, 7 days, followed by oral 10 mg/d and 20 mg/d, days 8 to 28</p> <p>Placebo: identical regimen</p>
Outcomes	<p>Modified Mathew Scale</p> <p>Death</p> <p>Last follow-up: 28 days</p> <p>Data on dependency: not available from all participants randomized, since data from 1 center were excluded from analysis</p>
Notes	<p>All participants received aspirin, subcutaneous aspirin and hydroxyethyl starch for 7 days</p> <p>Data available from publication and abstract</p> <p>Mortality data were available from all centers</p> <p>Funding sources: unknown</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The study was double-blind and randomized in 32 blocks: each block contained 4 sub-blocks of 8 participants randomized at a ratio of 1:1 and given either flunarizine or placebo; each of these sub-blocks was allocated to 1 of the 4 groups
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	443 participants recruited but 11 participants were withdrawn - reason given but ITT analysis not performed
Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Lamsudin 1995

Methods	Publication status: published Multicenter placebo-controlled trial Double-blind Exclusions during trial: 15 Losses to follow-up: unclear
Participants	Inclusion criteria: acute ischemic stroke within the preceding 24 h, either sex, all ages, diagnosis by CT Exclusion criteria: coma, intracranial hemorrhage, tumor, infection, trauma, serious organic brain disease
Interventions	Treatment: oral nimodipine, 30 mg 4 times daily, 28 days Placebo: identical regimen
Outcomes	Canadian Scale score, Barthel Index score Death during study period Missing: 15 participants
Notes	Data provided by Professor Thomas Funding sources: unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	15 participants excluded but did not analyze whether they were related to the outcome
Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Limburg 1990

Methods	Publication status: published Single-center placebo-controlled trial Double-blind Exclusions during trial: 0 Losses to follow-up: 0
Participants	Inclusion criteria: start within 24 h, supratentorial ischemic stroke with hemiparesis, CT scan exclusion of other relevant pathology Exclusion criteria: lacunar syndromes, serious underlying diseases, previous disabling strokes, use of calcium antagonists
Interventions	Treatment: intravenous flunarizine; bolus of 0.1 mg/kg body weight, followed after 3 h by continuous intravenous infusion 0.3 mg/kg/24 h during 72 h, subsequently oral administration of 10 mg/d for 11 days Placebo: identical regimen
Outcomes	Motricity Index, Rankin scale, Barthel Index Death Last follow-up: 6 months Dependency measurement used in review: Rankin scale Missing: none
Notes	Data available from authors and publication Funding sources: Janssen Pharmaceuticals, Tilburg

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random table
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reported all the participants recruited
Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias)	Low risk	Double-blind

Calcium antagonists for acute ischemic stroke (Review)

Limburg 1990 (Continued)

All outcomes

Lisk 1993

Methods	Publication status: published Placebo-controlled trial Double-blind Exclusions during trial: 0 Losses to follow-up: 0
Participants	Inclusion criteria: age 40 to 90 years, start within 72 h, clinical diagnosis of ischemic stroke in MCA territory, systolic BP > 170 mmHg, diastolic BP > 119 mmHg or MABP > 139 mmHg, history of hypertension Exclusion criteria: coma, previous serious stroke, unstable cardiac disease, history of angioedema or collagen vascular disease, liver dysfunction, brainstem strokes
Interventions	Treatment: oral nicardipine, 20 mg 3 times daily for 3 days Placebo: identical regimen
Outcomes	National Institutes of Health Stroke Scale Death Last follow-up: 3 days Data on dependency: not available Missing: none
Notes	Data from publication Trial compared treatment with nicardipine or captopril versus placebo, in this analysis the captopril group was excluded Trial designed to find differences in cerebral blood flow as measured with SPECT in hypertensive participants with a stroke Funding sources: unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	They reported all the participants recruited

Lisk 1993 (Continued)

Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Lowe 1989

Methods	Publication status: unpublished Placebo-controlled trial Exclusions during trial: unclear Losses to follow-up: 0
Participants	Inclusion criteria: age 45 to 85 years, start within 48 h, clinical diagnosis of acute cerebral hemispheric infarction, Barthel Index < 66 Exclusion criteria: other cause for neurological deficits, CT scan within 7 days of ictus, not expected to survive, women capable of childbearing, severe liver or renal failure, recent myocardial infarction, de-compensated heart failure, disability due to other causes not separable from present illness
Interventions	Treatment: oral nimodipine, 40 mg 3 times daily for 16 weeks Placebo: identical regimen
Outcomes	Neurological score (MRC 10-item), Barthel Index Death Last follow-up: 24 weeks Dependency measurement used in review: Barthel Index Missing: none
Notes	Data available from investigators and Bayer AG, Wuppertal, Germany For analysis on time interval after stroke onset 12 participants with missing data in nimodipine group, and 8 in placebo group For all other analyses data from the investigators were used, without missing data Funding sources: unknown, it was likely funded by Bayer AG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number

Lowe 1989 (Continued)

Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported

Martinez-Vila 1990

Methods	Publication status: published Multicenter placebo-controlled trial Double-blind Exclusions during trial: 41 Losses to follow-up: 81
Participants	Inclusion criteria: age > 44 years, start within 48 h, clinical diagnosis of ICA territory ischemic stroke, CT scan within 3 days Exclusion criteria: complete recovery within 24 h, acute myocardial infarction, renal or liver failure, severe systemic infections, poorly controlled diabetes mellitus, systolic arterial BP < 100 mmHg, terminal malignancy
Interventions	Treatment: oral nimodipine, 30 mg 4 times daily for 28 days Placebo: identical regimen
Outcomes	Mathew Scale, Toronto Stroke Scale Death Last follow-up: 28 days Dependency measurement used in review: Toronto Stroke Scale Missing: 40 in active treatment group, 41 in placebo group
Notes	Data available from publication and Bayer AG, Wuppertal, Germany Funding sources: Bayer AG

Risk of bias

Martinez-Vila 1990 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	164 participants in total were recruited (81 to the treatment group and 83 to the placebo group), but 41 participants were subsequently excluded (23 from the treatment group and 18 from the placebo group). There were no significant differences in severity of the remaining 123 participants (58 in the treatment group and 65 in the placebo group)
Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Mohr 1992

Methods	Publication status: published Multicenter placebo-controlled trial Double-blind Exclusions during trial: 102 Losses to follow-up: unclear
Participants	Inclusion criteria: age 20 to 90 years, start within 48 h, clinical diagnosis of acute ischemic stroke, CT scan without evidence of cerebral hemorrhage Exclusion criteria: coma, intracranial hemorrhage, tumor, infection, trauma, serious other organic brain disease, need for mechanical ventilation, calcium antagonist therapy, pregnancy, hypotension, bradycardia, heart block, hepatic or renal dysfunction, congestive heart failure, pneumonia
Interventions	Treatment: oral nimodipine 20 mg, 40 mg or 80 mg 3 times daily for 2 weeks Placebo: identical regimen (4 groups: 60 mg/d, 120 mg/d and 240 mg/d and placebo)
Outcomes	Motor strength from Stroke Data Bank, Toronto Stroke Scale, Barthel Index, Mathew Scale Dependency measurement used in review: Barthel Index at 21 days Death Last follow-up: 6 months (only deaths)

Calcium antagonists for acute ischemic stroke (Review)

Mohr 1992 (Continued)

Notes Data available from publication and Bayer AG, Wuppertal, Germany

Funding sources: Bayer AG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Study centers were provided with numbered boxes containing tablets in blister packs of 4 each The appearance of placebo and each drug dose was identical
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants randomized were analyzed, the analysis followed the ITT principle
Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Nag 1998

Methods	Publication status: published Placebo-controlled trial Double-blind Exclusions during trial: 18 Losses to follow-up: unclear
Participants	Inclusion criteria: acute ischemic stroke within preceding 48 h, acute onset of hemiplegia of either side with or without aphasia, diagnosis was confirmed by CT that showed a hypodense lesion in the territory of either MCA Exclusion criteria: only transient neurological deficiency (persisting < 24 h), coma (Glasgow Coma Scale score < 10), intracranial hemorrhage, tumor, infection, trauma, need for assisted ventilation, pregnancy, severe hypertension (diastolic BP > 120 mmHg), hepatic or renal dysfunction
Interventions	Treatment: oral nimodipine 120 mg/d for 28 days Placebo: identical regimen
Outcomes	Mathew Scale

Nag 1998 (Continued)

Mortality at the end of follow-up

Adverse effects

BP

Notes	Other routine management (antihypertensive drugs, hyperlipidemic drugs, platelet antiaggregants, hemorrheological drugs, edema-reducing measures, etc.) were given in both the groups
	Data provided by Professor Thomas
	Funding sources: Ranbaxy Company

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	80 participants recruited but reports of only 62 participants
Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

NEST 1993

Methods	Publication status: published Multicenter placebo-controlled trial Double-blind Exclusions during trial: unclear Losses to follow-up: 49
Participants	Inclusion criteria: age 39 to 81 years, start within 48 h, clinical diagnosis of ischemic stroke in MCA territory, Barthel Index ≤ 60 , N-score ≤ 50 , CT scan within 7 days Exclusion criteria: stupor and coma, stroke progression before randomization, disorders interfering with assessment, serious infection, cardiac disease, life-threatening concomitant illness
Interventions	Treatment: oral nimodipine, 30 mg 4 times daily for 21 days

NEST 1993 (Continued)

Placebo: identical regimen

Outcomes	Neurological score Barthel Index Death Last follow-up: 3 months Dependency measurement used in review: Barthel Index Missing: 27 participants in active treatment group, 22 in placebo group
Notes	Standard hospital regimens (hemodilution and heparin) were allowed Data available from publication and Bayer AG, Wuppertal, Germany In paper, 195 participants were excluded from the analysis; however, data set from Bayer included 879 participants Funding sources: unknown, it was likely funded by Bayer AG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	27 participants in active treatment group and 22 in placebo group missed
Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

NIMPAS 1999

Methods	Publication status: published Placebo-controlled trial Double-blind Exclusions during trial: 4 Losses to follow-up: unclear
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NIMPAS 1999 (Continued)

Participants	<p>Inclusion criteria: start within 12 h, cortical infarction in MCA territory (confirmed by CT or clinical findings), participant able to have acute SPECT and CT</p> <p>Exclusion criteria: concurrent use of dihydropyridine calcium antagonists, contraindications to calcium antagonist use, other severe disease, previous stroke, cerebral hemorrhage or non-cerebrovascular pathology on CT scan</p>
Interventions	<p>Treatment: oral nimodipine 30 mg 4 times daily for 14 days</p> <p>Placebo: identical regimen</p>
Outcomes	<p>Canadian Neurological Scale, Barthel Index</p> <p>Death</p> <p>Last follow-up: 3 months</p> <p>Dependency measurement used in review: Barthel Index</p> <p>Missing: none</p>
Notes	<p>Data available from investigators</p> <p>Trial designed to measure the effect of nimodipine on perfusion changes after acute stroke with SPECT</p> <p>Funding sources: unknown</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	50 participant included and 4 excluded. There was no ITT analysis
Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Oczkowski 1989

Methods	<p>Publication status: published</p> <p>Placebo-controlled trial</p>
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Oczkowski 1989 (Continued)

	Double-blind
	Exclusions during trial: 0
	Losses to follow-up: 0
Participants	<p>Inclusion criteria: age 45 to 80 years, start within < 48 h, acute ischemic cerebral infarction in MCA territory, chief symptom hemiparesis</p> <p>Exclusion criteria: previous stroke, brain hemorrhage, brainstem infarction, coma, recurrent seizures, organ failure, lacunar infarction, systolic BP > 165 mmHg or < 110 mmHg</p>
Interventions	<p>Treatment: oral PY108-608 100 mg day 1, 112.5 mg day 2, 125 mg day 3, 150 mg days 4 to 21, divided in 4 daily doses</p> <p>Placebo: identical regime</p>
Outcomes	<p>Toronto Stroke Scale, Barthel Index</p> <p>Deaths</p> <p>Last follow-up: 12 weeks</p> <p>Data on dependency presented in an unusable way</p> <p>Missing: none</p>
Notes	<p>Only data from publication, no additional data from authors available</p> <p>Funding sources: funded by Pharmaceutical Division of Sandoz Canada, a fellow of the Canadian Heart Foundation</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reported all participants included
Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Paci 1989

Methods	Publication status: published Placebo-controlled trial Double-blind Exclusions during trial: unclear Losses to follow-up: 1
Participants	Inclusion criteria: start within < 12 h, sudden and persistent focal event in carotid artery distribution Exclusion criteria: TIA, progressing stroke, cerebral hemorrhage (confirmed by CT scan), severe systemic disorders, recent myocardial infarction, congestive heart failure, evidence of abnormal hepatic, pulmonary or renal functions, previous complete stroke
Interventions	Treatment: oral nimodipine 40 mg 3 times daily for 28 days Placebo: identical regimen
Outcomes	Mathew Neurological score, global assessment of outcome: good/fair/poor Death Dependency measurement used in review: functional item from Mathew score Last follow-up: 28 days Missing: 1 participant in active treatment and 1 participant in control group
Notes	Data available from publication and Bayer AG, Wuppertal, Germany Funding sources: Bayer AG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	1 participant in active treatment and 1 participant in control group missed. No ITT analysis
Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Sherman 1986

Methods	Publication status: published Placebo-controlled trial Double-blind Exclusions during trial: unclear Losses to follow-up: 0
Participants	Inclusion criteria: start within 48 h, clinical evidence of cerebral hemisphere ischemic event Exclusion criteria: TIA, brainstem infarction, progressing stroke, cerebral hemorrhage, severe cardiac, renal or hepatic disease
Interventions	Treatment: oral nimodipine 30 mg 4 times daily for 21 days Placebo: identical regimen
Outcomes	Neurological examination, mobility, functional status Death Last follow-up: 60 days No data available on functional outcome Missing: none
Notes	Data only from limited publication in book Funding sources: unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Shibuya 2005

Methods	Publication status: published Multicenter placebo-controlled trial Double-blind Exclusions during trial: 0 Losses to follow-up: 0
Participants	Inclusion criteria: age > 20 years, informed consent, acute ischemic stroke due to thrombosis, treatment onset < 48 h after stroke onset, Japan Coma Scale score of 0 to 3, motor deficit (from moderate to severe) of the arms, legs, or both Exclusion criteria: history of severe cardiopulmonary, hepato-renal or metabolic diseases, women of childbearing potential, cerebral hemorrhage on CT scan, systolic BP < 90 mmHg
Interventions	Treatment: intravenous fasudil 60 mg twice daily for 14 days Placebo: identical regimen
Outcomes	Neurological status was assessed by the Motor System of Japan Stroke Scale (JSS), modified Rankin Scale (mRS), adverse events
Notes	This article did not provide the result of poor outcome or death at the end of treatment or follow-up, but it did provide adverse events and neurological improvement as the result Data were available from publication and from the database of Sichuan University, Chengdu, China Funding sources: unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A random list was prepared by an independent statistical center Participants were randomized to fasudil or placebo with the use of separate randomization lists balanced for each participating center by personnel unrelated to the study
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reported all the participants included
Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias)	Low risk	Quote: "All assessments were blinded"

Shibuya 2005 (Continued)

All outcomes

Squire 1996

Methods	Publication status: published Placebo-controlled trial Double-blind Exclusions during trial: 30 Losses to follow-up: 0
Participants	Inclusion criteria: first-ever ischemic stroke < 6 h or 6 h to 12 h from onset of symptoms, age 21 to 74 years, stable clinical signs, had written informed consent, pretreatment motor arm or motor leg (NIH scale) of 2 or 3, treatment could be started within 12 h of onset of symptoms, normal plasma electrolytes prior to start of treatment Exclusion criteria: NIH scale level of consciousness 2 or 3; previous stroke; unable to initiate treatment within 12 h from onset; myocardial infarction within previous 4 months; BP < 120/80 mmHg; history of ventricular arrhythmia, AV block or IVCD; not likely to be available for 3-month assessment; premenopausal female not surgically sterilized; pre-existing life-threatening disease or systematic illness
Interventions	Treatment: lifarizine 250 µg/kg intravenous stat plus 60 mg twice daily orally for 5 days within 6 h or 6 h to 12 h since stroke onset Placebo: identical regimen
Outcomes	Mortality at the end of treatment and follow-up Rankin Scale, Barthel Index
Notes	Data available via Professor Thomas Funding sources: unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	147 participants involved but only 117 participants evaluated
Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind

Calcium antagonists for acute ischemic stroke (Review)

Squire 1996 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
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Sze 1998

Methods	Publication status: published Placebo-controlled trial Double-blind Exclusions during trial: 14 Losses to follow-up: unclear
Participants	Inclusion criteria: based on brain CT scan within 14 days, clinical assessment according to WHO definition on stroke Exclusion criteria: cerebral hemorrhage, participant refused, acute cardiopulmonary instability, sepsis, clinical depression, Glasgow Coma Scale score < 15 and participants who did not complete the full course of treatment
Interventions	Treatment: oral nimodipine 30 mg 3 times daily between days 7 to 14 after the onset of the stroke for 12 weeks Placebo: identical regimen
Outcomes	Death, Mini-Mental State Examination and Fuld Object-Memory Evaluation
Notes	Data were available from publication and from the database of Sichuan University, Chengdu, China Funding sources: unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Participants were separately randomized to the groups according to random permuted blocks
Incomplete outcome data (attrition bias) All outcomes	High risk	14 participants excluded
Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias)	Low risk	They described that the assessors were blinded

Calcium antagonists for acute ischemic stroke (Review)

Sze 1998 (Continued)

All outcomes

TRUST 1990

Methods	Publication status: published Multicenter placebo-controlled trial Double-blind Exclusions during trial: 26 Losses to follow-up: 12
Participants	Inclusion criteria: age > 40 years, start within 48 h, clinical evidence of hemiparetic stroke, independent before stroke, conscious, able to swallow Exclusion criteria: intracranial hemorrhage or tumor on CT scan between days 7 to 14 (whenever possible)
Interventions	Treatment: oral nimodipine 40 mg 3 times daily for 21 days Placebo: identical regimen
Outcomes	Neurological examination, Orgogozo Stroke scale, Nottingham Activities of Daily Living scale, Barthel Index Death Last follow-up: 24 weeks Dependency measurement used in review: Barthel Index Missing: 4 participants in active treatment group, 8 participants in placebo group
Notes	Data available from publication and Bayer AG, Wuppertal, Germany Some minor differences between original data set and publication - we used original data set for analysis on time after stroke onset Funding sources: Bayer AG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Many participants were withdrawn and 12 participants were lost to follow-up; the article did not provide the results of these participants and there was no ITT analysis
Selective reporting (reporting bias)	Unclear risk	Not reported

TRUST 1990 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Uzunur 1995

Methods	Publication status: published as an abstract Open controlled trial Exclusions during trial: unclear Losses to follow-up: unclear
Participants	Inclusion criteria: acute stroke (hemorrhage and ischemic), start within 24 h
Interventions	Treatment: oral nimodipine 180 mg/d. If CT demonstrated intracranial or intracerebral hemorrhage, intravenous nimodipine 2 mg/h Control: no nimodipine
Outcomes	Death BP at various time intervals Last follow-up: discharge from hospital, maximum 40 days Data on dependency: not available Missing: 2 participants in active treatment, 8 participants in control group withdrawn because of "malignant" hypertension
Notes	Data available from manuscript and abstract, received from principal investigator Funding sources: unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Not reported

Uzunur 1995 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported

VENUS 1999

Methods	Publication status: published Multicenter placebo-controlled trial Double-blind Exclusions during trial: 0 Losses to follow-up: 0
Participants	Inclusion criteria: age 18 to 85 years, start within < 6 h, acute stroke, hemiparesis Exclusion criteria: unconsciousness, rapidly improving, symptoms indicative for intracranial hemorrhage (Panzer criteria), dependence before stroke, pregnancy, other severe disease, hypotension, bradycardia, inability to swallow
Interventions	Treatment: oral nimodipine 30 mg 4 times daily for 10 days Placebo: identical regimen
Outcomes	Neurological examination, Rankin scale Death Last follow-up: 3 months Dependency measurement used in review: Rankin scale Missing: 3 living participants in placebo, 3 living participant in active treatment group 261 participants with ischemic stroke were randomized; 133 received nimodipine and 128 received placebo Missing: none
Notes	All data (assessed in trial) available Inclusion by general practitioners Data available from publication Funding sources: unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Medication was randomized in equal blocks of 10, according to computer-generated lists

Calcium antagonists for acute ischemic stroke (Review)

VENUS 1999 (Continued)

Allocation concealment (selection bias)	Low risk	Numbered boxes contained 1 complete treatment or identical placebo and were distributed among participating general practitioners and neurologists
Incomplete outcome data (attrition bias) All outcomes	Low risk	261 participants with ischemia recruited and all of them reported
Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Wimalaratna 1994

Methods	Publication status: published Placebo-controlled trial Double-blind Exclusions during trial: 0 Losses to follow-up: 45
Participants	Inclusion criteria: age 45 to 85 years, start within 24 h, Barthel Index < 65 Exclusion criteria: hemorrhage on CT scan
Interventions	Treatment: oral nimodipine 120 mg/d or 240 mg/d for 16 weeks Placebo: identical regimen
Outcomes	MRC-based rating system for motor scoring, Barthel Index Death Last follow-up: 24 weeks Dependency measurement used in review: Barthel Index Missing: 32 participants in active treatment group, 13 participants in placebo group
Notes	Data available from publication, manuscript, abstracts and Bayer AG, Wuppertal, Germany Funding sources: unknown, it was likely funded by Bayer AG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported

Calcium antagonists for acute ischemic stroke (Review)

Wimalaratna 1994 (Continued)

Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	32 participants in active treatment group and 13 in placebo group were missed
Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Yordanov 1984

Methods	Publication status: published Placebo-controlled trial? Exclusions during trial: unclear Losses to follow-up: unclear
Participants	Stroke participants, inclusion within 5 days after onset of symptoms
Interventions	Treatment: nimodipine 0.5 mg/h intravenously for 7 days, followed by 30 mg 4 times daily for 21 days Placebo: identical regimen (?)
Outcomes	Toronto Stroke Scale Death Last follow-up: 6 months Dependency measurement used in review: Toronto Stroke Scale Missing: none
Notes	Only limited data available from Bayer AG, Wuppertal, Germany Funding sources: unknown, it was likely funded by Bayer AG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported

Yordanov 1984 (Continued)

Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported

AV block: atrioventricular block; **BP:** blood pressure; **CT:** computerized tomography; **ICA:** internal carotid artery; **ITT:** intention-to-treat; **IVCD:** interior vena cava diameter; **MABP:** mean arterial blood pressure; **MCA:** middle cerebral artery; **MRC:** Medical Research Council; **SAH:** subarachnoid hemorrhage; **SPECT:** single-photon emission computed tomography; **TIA:** transient ischemic attack; **WHO:** World Health Organization.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Ameriso 1992	Nimodipine trial Appears to be part of the another larger trial, but which one is unknown In this report the hemorrhological data of few participants are reported
Borhani 1990	Isradipine trial Participants in this trial had ischemic stroke but not in the acute phase
Chen 2016	Ginsenoside trial Intervention was ineligible
CHERISH 2006	Cilnidipine trial Lack of comparison
Csiba 2001	Nimodipine trial performed in Hungary Investigators and company are unable to retrieve data
Dalal 1995	Nimodipine trial The treatment group received intravenous nimodipine followed by oral nimodipine, while the control group is antithrombotic agents, anticoagulant drugs and other supportive measures
Fagan 1988	Nimodipine trial Outcomes are BP recorded before and 30 min and 60 min after a dose for the first 8 days, which is not related to this systematic review's outcome measures
Gu 1998	Nimodipine trial

Calcium antagonists for acute ischemic stroke (Review)

Study	Reason for exclusion
	Treatment and control group were both given nimodipine
Marín Gámez 1988	Nicardipine trial Spanish article: in the study 75 participants were included; unknown how many participants in which treatment group; more than 30% of participants (24/75) were excluded after randomization, no follow-up data are provided
Matias Guiu 1992	Nicardipine trial Aim of the study was to assess the effect on cognitive impairment after minor stroke
Molto 1994	Nicardipine trial Included participants with TIA, Spanish article
NICE 2012	Nicardipine trial Only a protocol without any data
OSF Healthcare System 2006	Nicardipine trial Principal investigator could not supply data from this unpublished trial
Petrogiannopoulos 1996	Nimodipine trial Participants were included 1 to 2 months after acute ischemic stroke
Popa 1992	Nimodipine trial This trial was not an RCT
Rosenbaum 1990	Nicardipine trial Safety study without a control group
Rosselli 1992	Nimodipine trial (Italy) Outcomes are not included in this review Data extraction provided Dr Chiara Menichetti
Shi 2001	Nimodipine trial The participants in the treatment group were quite different from those in the control group; one of them was not an ischemic stroke patient
Szczechowski 1994	Nimodipine trial Treatment group given intravenous nimodipine, control group given standard treatment with dextran
Teasdale 1990	Nimodipine trial Participants in both groups also included hemorrhage stroke and we could not extract the ischemic-only data
Vorstrup 1986	There was no control group
Wang 1990	Nimodipine trial

Study	Reason for exclusion
	Treatment group given intravenous nimodipine, control group given standard treatment with Vitamin B1
Yao 1991	Nimodipine trial Chinese report of 'preliminary study', no outcome data available

BP: blood pressure; **RCT:** randomized controlled trial; **TIA:** transient ischemic attack.

DATA AND ANALYSES

Comparison 1. Calcium antagonists versus control in acute ischemic stroke

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or dependency at end of follow-up	22	6684	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.98, 1.13]
1.1 Nimodipine versus control	19	6093	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.97, 1.14]
1.2 Flunarizine versus control	2	357	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.34, 1.94]
1.3 Isradipine versus control	1	234	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.74, 1.40]
2 Death at end of treatment period	22	6323	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.93, 1.20]
2.1 Nimodipine versus control	16	5163	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.88, 1.19]
2.2 Flunarizine versus control	3	790	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.94, 1.82]
2.3 Any other agent versus control	3	370	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.58, 1.66]
3 Death at end of follow-up	31	7483	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.98, 1.17]
3.1 Nimodipine versus control	24	6312	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.96, 1.16]
3.2 Flunarizine versus control	3	790	Risk Ratio (M-H, Random, 95% CI)	1.34 [1.01, 1.77]
3.3 Isradipine versus control	1	234	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.60, 1.85]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.4 Any other agent versus control	3	147	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.45, 1.56]
4 Recurrence of stroke at end of follow-up	9	2460	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.56, 1.54]
4.1 Nimodipine versus control	6	1677	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.45, 2.10]
4.2 Flunarizine versus control	2	764	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.35, 1.97]
4.3 Any other agent versus control	1	19	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Any adverse event during treatment period	13	5095	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.81, 1.74]
5.1 Nimodipine versus control	11	4604	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.74, 1.16]
5.2 Flunarizine versus control	1	331	Risk Ratio (M-H, Random, 95% CI)	3.16 [1.91, 5.21]
5.3 Any other agent versus control	1	160	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.52, 2.72]
6 Hypotension during treatment period (reason to stop treatment)	6	1667	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.61, 3.38]
6.1 Nimodipine versus control	5	1648	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.50, 3.14]
6.2 Any other agent versus control	1	19	Risk Ratio (M-H, Random, 95% CI)	5.50 [0.30, 101.28]
7 Mean systolic blood pressure during or at end of treatment	3	630	Mean Difference (IV, Random, 95% CI)	-1.30 [-3.92, 1.32]
7.1 Nimodipine versus control	3	630	Mean Difference (IV, Random, 95% CI)	-1.30 [-3.92, 1.32]

Analysis 1.1. Comparison 1 Calcium antagonists versus control in acute ischemic stroke, Outcome 1 Death or dependency at end of follow-up.

Analysis 1.2. Comparison 1 Calcium antagonists versus control in acute ischemic stroke, Outcome 2 Death at end of treatment period.

Analysis 1.3. Comparison 1 Calcium antagonists versus control in acute ischemic stroke, Outcome 3 Death at end of follow-up.

Analysis 1.4. Comparison 1 Calcium antagonists versus control in acute ischemic stroke, Outcome 4 Recurrence of stroke at end of follow-up.

Analysis 1.5. Comparison 1 Calcium antagonists versus control in acute ischemic stroke, Outcome 5 Any adverse event during treatment period.

Analysis 1.6. Comparison 1 Calcium antagonists versus control in acute ischemic stroke, Outcome 6 Hypotension during treatment period (reason to stop treatment).

Analysis 1.7. Comparison 1 Calcium antagonists versus control in acute ischemic stroke, Outcome 7 Mean systolic blood pressure during or at end of treatment.

Comparison 2. Calcium antagonists versus control: subgroup analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or dependency at end of follow-up by route of administration	23		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Oral administration	14	5131	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.93, 1.14]
1.2 Intravenous administration	8	1544	Risk Ratio (M-H, Random, 95% CI)	1.11 [1.01, 1.22]
1.3 Oral versus intravenous administration (outcome death)	1	143	Risk Ratio (M-H, Random, 95% CI)	7.10 [0.37, 134.96]
2 Death or dependency at end of follow-up by dose: indirect comparisons	18		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Nimodipine 60 mg versus control oral	1	529	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.94, 1.24]
2.2 Nimodipine 120 mg versus control oral	14	4526	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.88, 1.11]
2.3 Nimodipine 240 mg versus control oral	2	673	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.94, 1.22]
2.4 Nimodipine 2 mg/h versus control intravenous	4	552	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.93, 1.93]
2.5 Nimodipine 1 mg/h versus control intravenous	2	329	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.91, 1.29]
3 Death or dependency at end of follow-up by dose: direct comparisons	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Nimodipine 60 mg versus 120 mg oral	1	533	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.94, 1.24]
3.2 Nimodipine 60 mg versus 240 mg oral	1	532	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.88, 1.13]
3.3 Nimodipine 120 mg versus 240 mg oral	2	681	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.82, 1.06]
3.4 Nimodipine 1 mg/h versus 2 mg/h intravenous	2	333	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.71, 0.95]
4 Death or dependency at end of follow-up by time of start of treatment	18	5950	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.96, 1.13]
4.1 Treatment started ≤ 12 h	18	1879	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.96, 1.21]
4.2 Treatment started > 12 h	14	4071	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.90, 1.13]

Analysis 2.1. Comparison 2 Calcium antagonists versus control: subgroup analysis, Outcome 1 Death or dependency at end of follow-up by route of administration.

Analysis 2.2. Comparison 2 Calcium antagonists versus control: subgroup analysis, Outcome 2 Death or dependency at end of follow-up by dose: indirect comparisons.

Analysis 2.3. Comparison 2 Calcium antagonists versus control: subgroup analysis, Outcome 3 Death or dependency at end of follow-up by dose: direct comparisons.

Analysis 2.4. Comparison 2 Calcium antagonists versus control: subgroup analysis, Outcome 4 Death or dependency at end of follow-up by time of start of treatment.

Comparison 3. Calcium antagonists versus control: sensitivity analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or dependency at end of follow-up in multicenter placebo controlled trials	10	4012	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.95, 1.14]
2 Publication status	22	6675	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.98, 1.14]
2.1 Death or dependency at end of follow-up in published trials	18	5887	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.94, 1.12]
2.2 Death or dependency at end of follow-up in unpublished trials	4	788	Risk Ratio (M-H, Random, 95% CI)	1.14 [1.00, 1.30]

Analysis 3.1. Comparison 3 Calcium antagonists versus control: sensitivity analysis, Outcome 1 Death or dependency at end of follow-up in multicenter placebo controlled trials.

Analysis 3.2. Comparison 3 Calcium antagonists versus control: sensitivity analysis, Outcome 2 Publication status. **APPENDICES****Appendix 1. Cochrane Central Register of Controlled Trials (CENTRAL)**

#1[mh "cerebrovascular disorders"] or [mh "basal ganglia cerebrovascular disease"] or [mh "brain ischemia"] or [mh "brain infarction"] or [mh "hypoxia-ischemia, brain"] or [mh "carotid artery diseases"] or [mh "carotid artery thrombosis"] or [mh "carotid artery, internal, dissection"] or [mh "intracranial arterial diseases"] or [mh "cerebral arterial diseases"] or [mh "infarction, anterior cerebral artery"] or

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[mh ^"infarction, middle cerebral artery"] or [mh ^"infarction, posterior cerebral artery"] or [mh "intracranial embolism and thrombosis"]
or [mh stroke] or [mh ^"vertebral artery dissection"]
#2isch*mi* near/5 (stroke* or apoplex* or cerebral next vasc* or cerebrovasc* or cva):ti,ab
#3(brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or middle
next cerebr* or mca* or "anterior circulation" or "basilar artery" or "vertebral artery") near/5 (isch*mi* or infarct* or thrombo* or emboli*
or occlus* or hypoxi*):ti,ab
#4#1 or #2 or #3
#5[mh "Calcium Channel Blockers"]
#6[mh ^Calcium/AI]
#7(calcium near/5 (antagonist* or block* or inhibitor*)):ti,ab
#8(amlodipine or amrinone or azelnidipine or bencyclan$ or bepridil or AT877 or "AT 877" or cilnidipine or cinnarizine or conotoxin* or
daropidine or diltiazem or efonidipine or felodipine or fendiline or flunarizine or gallopamil or isradipine or lacidopine or lidoflazine or
magnesium next sul* or mibefradil or nicardipine or nifedipine or nimodipine or nisoldipine or nitrendipine or perhexiline or prenylamine
or verapamil):ti,ab
#9#5 or #6 or #7 or #8
#10#4 and #9
```

Appendix 2. MEDLINE (Ovid) search strategy

1. cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or brain ischemia/ or exp brain infarction/ or hypoxia-ischemia, brain/ or carotid artery diseases/ or carotid artery thrombosis/ or carotid artery, internal, dissection/ or intracranial arterial diseases/ or cerebral arterial diseases/ or infarction, anterior cerebral artery/ or infarction, middle cerebral artery/ or infarction, posterior cerebral artery/ or exp "intracranial embolism and thrombosis"/ or exp stroke/ or vertebral artery dissection/
2. (isch?emi\$ adj5 (stroke\$ or apoplex\$ or cerebral vasc\$ or cerebrovasc\$ or cva)).tw.
3. ((brain or cerebr\$ or cerebell\$ or vertebrobasil\$ or hemispher\$ or intracran\$ or intracerebral or infratentorial or supratentorial or middle cerebr\$ or mca\$ or anterior circulation or basilar artery or vertebral artery) adj5 (isch?emi\$ or infarct\$ or thrombo\$ or emboli\$ or occlus\$ or hypoxi\$)).tw.
4. 1 or 2 or 3
5. exp Calcium Channel Blockers/
6. Calcium/ai
7. (calcium adj3 (antagonist\$ or block\$ or inhibitor\$)).tw.
8. (amlodipine or amrinone or azelnidipine or bencyclan\$ or bepridil or AT877 or AT 877 or cilnidipine or cinnarizine or conotoxin\$ or daropidine or diltiazem or efonidipine or felodipine or fendiline or flunarizine or gallopamil or isradipine or lacidopine or lidoflazine or magnesium sul\$ or mibefradil or nicardipine or nifedipine or nimodipine or nisoldipine or nitrendipine or perhexiline or prenylamine or verapamil).tw.
9. 5 or 6 or 7 or 8
10. Randomized Controlled Trials as Topic/
11. random allocation/
12. Controlled Clinical Trials as Topic/
13. control groups/
14. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/
15. double-blind method/
16. single-blind method/
17. Placebos/
18. placebo effect/
19. Drug Evaluation/
20. Research Design/
21. randomized controlled trial.pt.
22. controlled clinical trial.pt.
23. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.
24. (random\$ or RCT or RCTs).tw.
25. (controlled adj5 (trial\$ or stud\$)).tw.
26. (clinical\$ adj5 trial\$).tw.
27. ((control or treatment or experiment\$ or intervention) adj5 (group\$ or subject\$ or patient\$)).tw.
28. (quasi-random\$ or quasi random\$ or pseudo-random\$ or pseudo random\$).tw.
29. ((control or experiment\$ or conservative) adj5 (treatment or therapy or procedure or manage\$)).tw.
30. ((singl\$ or doubl\$ or tripl\$ or trebl\$) adj5 (blind\$ or mask\$)).tw.
31. (placebo\$ or sham).tw.
32. trial.ti.
33. (assign\$ or allocate\$).tw.
34. controls.tw.

35. or/10-34
36. 4 and 9 and 35
37. exp animals/ not humans.sh.
38. 36 not 37

Appendix 3. Embase (Ovid) search strategy

1. cerebrovascular disease/ or brain infarction/ or brain stem infarction/ or cerebellum infarction/ or exp brain ischemia/ or carotid artery disease/ or exp carotid artery obstruction/ or cerebral artery disease/ or exp cerebrovascular accident/ or exp occlusive cerebrovascular disease/ or stroke patient/
2. (isch?emi\$ adj5 (stroke\$ or apoplex\$ or cerebral vasc\$ or cerebrovasc\$ or cva)).tw.
3. ((brain or cerebr\$ or cerebell\$ or vertebrobasil\$ or hemispher\$ or intracran\$ or intracerebral or infratentorial or supratentorial or middle cerebr\$ or mca\$ or anterior circulation or basilar artery or vertebral artery) adj5 (isch?emi\$ or infarct\$ or thrombo\$ or emboli\$ or occlus\$ or hypoxi\$)).tw.
4. 1 or 2 or 3
5. exp calcium antagonist/
6. (calcium adj3 (antagonist\$ or block\$ or inhibitor\$)).tw.
7. (amlodipine or amrinone or azelnidipine or bencyclan\$ or bepridil or AT877 or AT 877 or cilnidipine or cinnarizine or conotoxin\$ or daropidine or diltiazem or efonidipine or felodipine or fendiline or flunarizine or gallopamil or isradipine or lacidopine or lidoflazine or magnesium sul\$ or mibefradil or nicardipine or nifedipine or nimodipine or nisoldipine or nitrendipine or perhexiline or prenylamine or verapamil).tw.
8. 5 or 6 or 7
9. Randomized Controlled Trial/ or "randomized controlled trial (topic)"/
10. Randomization/
11. Controlled clinical trial/ or "controlled clinical trial (topic)"/
12. control group/ or controlled study/
13. clinical trial/ or "clinical trial (topic)"/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or controlled clinical trial/
14. Double Blind Procedure/
15. Single Blind Procedure/ or triple blind procedure/
16. placebo/ or placebo effect/
17. (random\$ or RCT or RCTs).tw.
18. (controlled adj5 (trial\$ or stud\$)).tw.
19. (clinical\$ adj5 trial\$).tw.
20. ((control or treatment or experiment\$ or intervention) adj5 (group\$ or subject\$ or patient\$)).tw.
21. (quasi-random\$ or quasi random\$ or pseudo-random\$ or pseudo random\$).tw.
22. ((control or experiment\$ or conservative) adj5 (treatment or therapy or procedure or manage\$)).tw.
23. ((singl\$ or doubl\$ or tripl\$ or trebl\$) adj5 (blind\$ or mask\$)).tw.
24. (placebo\$ or sham).tw.
25. trial.ti.
26. (assign\$ or allocat\$).tw.
27. controls.tw.
28. or/9-27
29. 4 and 8 and 28
30. (exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/) not (human/ or normal human/ or human cell/)
31. 29 not 30

Appendix 4. Chinese databases search strategy

1. 脑卒中 OR 脑血管病 OR 缺血性卒中 OR 脑梗塞 OR 脑梗死
2. 主题词="脑梗死"[不加权:扩展] OR "脑血管障碍"[不加权:扩展]
3. 中风 OR CVD OR 脑血管意外 4. 钙离子拮抗剂 OR 钙离子通道阻滞剂
5. (#3) OR (#2) OR (#1)
6. (#5) AND (#4) AND (临床试验[文献类型] OR 随机对照试验[文献类型])

Appendix 5. Trials registers search strategy

1. "Acute ischemic stroke" AND "Calcium antagonists" ("急性缺血性脑卒中" , "钙离子拮抗剂")

2. "Acute cerebral infarction" ("急性脑梗死", "钙离子拮抗剂")

WHAT'S NEW

Date	Event	Description
16 June 2018	New citation required but conclusions have not changed	Conclusions are unchanged.
6 February 2018	New search has been performed	The searches were updated on 6 February 2018. No new trials have been included in this update, which still includes 34 studies with 7731 participants.

HISTORY

Protocol first published: Issue 1, 1997

Review first published: Issue 1, 2000

Date	Event	Description
25 January 2012	New search has been performed	The searches were updated in January 2012. We have added four new included trials in this update. These four trials included approximately 423 patients. This review now has 34 included trials with a total of 7731 participants. We have also added 'Risk of bias' tables for nearly all the trials included in this review. Specifically, we have added new information to this update, but the conclusions have not changed.
25 January 2012	New citation required but conclusions have not changed	The authorship of this review has changed. The basic conclusion is unchanged.
22 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Jing Zhang and Jia Liu were involved in all aspects of the development of this review. They assessed all the trials, discussed and resolved any problems, and wrote the review. Dan Li and Canfei Zhang helped in the related trials selection and looked for the full text of the related trials. Ming Liu was in charge of the judgement of the selection, did the evaluation for methodological quality of trials, and was in charge of the final draft of this review.

DECLARATIONS OF INTEREST

Jing Zhang: none known.

Jia Liu: none known.

Dan Li: none known.

Canfei Zhang: none known.

Ming Liu: none known.

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Internal sources

- No sources of support supplied

External sources

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- Stichting De Drie Lichten, Netherlands.

INDEX TERMS**Medical Subject Headings (MeSH)**

Acute Disease; Brain Ischemia [*drug therapy] [mortality]; Calcium [metabolism]; Calcium Channel Blockers [administration & dosage] [adverse effects] [*therapeutic use]; Flunarizine [administration & dosage] [adverse effects] [therapeutic use]; Isradipine [administration & dosage] [adverse effects] [therapeutic use]; Nimodipine [administration & dosage] [adverse effects] [therapeutic use]; Randomized Controlled Trials as Topic; Stroke [*drug therapy]; Vasodilator Agents [administration & dosage] [*therapeutic use]

MeSH check words

Adult; Aged; Aged, 80 and over; Female; Humans; Male; Middle Aged; Young Adult