Calcium Antagonists for Ischemic Stroke
A Systematic Review

J. Horn, MD; M. Limburg, MD, PhD

Background and Purpose—Stroke is a common disease, and many trials with calcium antagonists as possible neuroprotective agents have been conducted. The aim of this review is to determine whether calcium antagonists reduce the risk of death or dependency after acute ischemic stroke.

Methods—Acute stroke trials were identified with help of the Cochrane Collaboration Stroke Group and personal contacts. All randomized trials (published and unpublished) investigating a calcium antagonist (acting on voltage-sensitive calcium channels) were included. Poor outcome, defined as death or dependency in activities of daily living, was used as main outcome. Analyses were, if possible, "intention-to-treat"; pooled relative risks with 95% CIs were calculated.

Results—Forty-seven trials were identified, of which 29 were included (7665 patients). No effect of calcium antagonists on poor outcome at the end of follow-up (relative risk, 1.04; 95% CI, 0.98 to 1.09) or on death at end of follow-up (relative risk, 1.07; 95% CI, 0.98 to 1.17) was found. Sensitivity analyses on route of administration and time interval between stroke and start of treatment showed no effect on outcome. In subgroups of unpublished and methodologically sound trials, a statistically significant negative effect for calcium antagonists was found. This contrasts with results of published trials and trials of moderate or poor methodological quality.

Conclusions—The presented evidence rules out a clinically important effect of calcium antagonists after ischemic stroke. The large amount of data leads to narrow CIs with no significant heterogeneity, and the overall results are therefore likely to be statistically robust. **(*Stroke*. 2001;32:570-576.)**

Key Words: calcium channel blockers ■ cerebrovascular disorders ■ meta-analysis

Acute ischemic stroke is a major cause of death and disability. Despite many experimental studies, there is as yet no effective, generally accepted, specific treatment in the acute phase of stroke. Massive calcium influx into hypoxic cells is a final common pathway, leading to cell death.[1] Animal experiments have indicated that calcium antagonists administered after cerebral ischemia are effective in reducing infarct volume and lead to improvements in neurological outcome.[2,3] Calcium antagonists may act as neuroprotective drugs by diminishing the influx of calcium ions through voltage-sensitive calcium channels.[4]

A clinical trial with the calcium antagonist nimodipine suggested a beneficial effect,[5] but none of the many subsequent trials confirmed these results. However, sample sizes may have been too small to demonstrate a modest but perhaps clinically significant effect. Some meta-analyses with a limited scope (only nimodipine data included) have been performed.[6–8] The aim of this systematic review was to analyze all available clinical evidence to determine whether calcium antagonists reduce the risk of death or poor outcome after ischemic stroke.

Methods

Identification of Trials and Criteria for Inclusion

This review has drawn on the search strategy developed for the Cochrane Collaboration Stroke Group, and relevant trials were identified in the Specialized Register of Controlled Trials.[9] This register was last checked in May 1999. Some unpublished trials were found through contacts with principal investigators and company representatives. Both authors independently selected the trials to be included in the review. Studies were included if they fulfilled the following criteria: true randomization, randomization of patients within 14 days after ischemic stroke, and investigation of the effect of calcium antagonists (defined as agents whose principal mode of action is to inhibit influx of calcium into cells by way of voltage-sensitive calcium channels).

The unblinded trial reports were read and assessed independently by both authors, and information needed on methodological quality was extracted. Disagreement was resolved by discussion. Protocols of studies were sought for methodological information, and data collection forms were sent to all principal investigators.

Types of Outcome Measures

As main outcome we used "poor outcome," defined as all-cause case fatality or dependency from others in activities in daily living, at the end of follow-up. For this purpose the available functional health scale of each study was used in a dichotomized fashion (Table 1).[10–14] Because patients with a Rankin score of 4 or 5 almost

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From the Departments of Neurology (J.H., M.L.) and Medical Informatics (M.L.), Academic Medical Center, University of Amsterdam (Netherlands). Correspondence to J. Horn, AMC J-254, PO Box 22700, 1100 DE, Amsterdam, Netherlands. E-mail jhorn@wxs.nl

Stroke **is available at http://www.strokeaha.org**

TABLE 1. Dichotomized Functional Outcome Scales

Name of Scale	Good Outcome	Poor Outcome
Modified Rankin Scale[10]	1–3	4–6
Barthel ADL Index[11]	60–100	<60
Glasgow Outcome Scale[12]	4, 5	<4
Toronto Stroke Scale[13]	1–3	4, 5
Mathew Impairment Scale[14]	14, 21, 28	7, 0

ADL indicates activities of daily living.

certainly cannot live independently,[15] this cutoff point for the Modified Rankin Scale was chosen. The cutoff points for the other scales were derived from this cutoff point. These cutoff points were established before the analysis of data started. If more than one scale was available, the one with the smallest number of missing values was selected.

Mortality at end of treatment and at the end of follow-up and adverse events were assessed as secondary outcome. Adverse events were recorded if they were mentioned as such in the original article, and therefore the definitions of the investigators were used.

Analyses

The primary analysis concerned the main end point of poor outcome. Several trials only reported data on mortality.

Sensitivity analyses were performed for the following: (1) Route of drug administration (intravenous or oral) was analyzed. In contrast to oral administration, intravenous administration of nimodipine seemed to cause serious hypotension.[16] (2) Time interval between stroke and start of treatment, in view of evidence that time elapsed between stroke onset and initiation of treatment is important for therapeutic success, was analyzed. Treatment started within 12 hours after stroke onset was considered early treatment. In view of previous meta-analyses we separately addressed nimodipine trials (120 mg/d, oral administration, started within 12 hours after stroke onset) in this analysis. (3) Trial methodology was analyzed. We determined methodological quality of the studies[17]: 1 credit was given if the word *randomized* was mentioned, and 1 credit was given if the method of randomization was properly described and sufficient. If the title or article contained phrases such as *double-blind* or *concealed*, this yielded another credit; proper description of the method of treatment concealment led to another credit. The last credit was given when all included patients were accounted for in the article. Trials scoring 5 points were considered good quality trials, trials scoring 3 or 4 points were considered moderate quality trials, and trials scoring <3 points were considered poor quality trials. (4) Publication status was analyzed to investigate the effect of publication bias. In all these sensitivity analyses, poor outcome was assessed.

In several cases both the original data set and the published article were available. The numbers in the data sets were usually slightly different, and in some cases differences were extensive. Many authors report data of patients valid for efficacy analysis instead of reporting intention-to-treat analyses. In Table 2[18–41] we indicate which data set is used for each trial. Thus, the numbers used in this review may differ from those in original publications. In case of incomplete follow-up data on functional status, the last known value was carried forward. If only functional status at trial inclusion was available, these data were not used. The present analysis can be considered a "best case" analysis: missing values are handled as if they represent good outcomes. Most missing values regarded dependency. We performed a "worst case" sensitivity analysis by considering all missing values to represent poor outcomes.

Results of analyses are presented as relative risks (RRs) with 95% CIs. Relative risks were computed with the Mantel-Haenszel method (fixed effects model).

All analyses were performed by the authors with Revman software, developed and provided by the Cochrane Collaboration.

Heterogeneity

We tested for statistical heterogeneity between trial results using a standard χ^2 test. $P<0.05$ indicated presence of statistical heterogeneity.

Full details of the methods can be found in the full Cochrane Library electronic publication, on which this article is based.[42]

Results

Description of Studies

We identified 47 studies using calcium antagonists in patients with acute ischemic stroke. Eighteen studies were excluded, of which 9 did not fulfill inclusion criteria and 9 lacked crucial information (Table 3).[43–56] Characteristics of the 29 included studies (with data of 7665 patients) are presented in Table 2. In 25 studies treatment was started within 48 hours after stroke onset. Length of follow up was <3 months in 10 included trials, approximately 3 months (12 weeks) in 5 trials, and >3 months (6 months to 1 year) in 14 trials.

Main Analyses

Results are presented in the Figure. Data of 22 trials could be used (6877 patients) for the analysis of poor outcome. No overall effect was found, and none of the separate drugs showed any statistically significant effect. No major differences arose in the analysis in which patients with missing functional outcome were considered to have a poor outcome. Data of 7522 patients were included in the mortality at end of follow-up analysis; no effect of any calcium antagonist was found. In this analysis the 3 flunarizine trials showed a statistically significant unfavorable effect (RR, 1.3; 95% CI, 1.0 to 1.8). No difference was present in the analysis on mortality at the end of treatment. Adverse events were reported more often in patients treated with calcium antagonists than in the control groups. Again, with flunarizine the results were even worse (RR, 3.2; 95% CI, 1.9 to 5.2). However, in this analysis only data from 1 trial could be included, and the main adverse event was thrombophlebitis.[23]

Sensitivity Analyses

No difference was found between oral or intravenous administration of calcium antagonists in indirect comparisons (oral versus placebo and intravenous versus placebo), although intravenous administration tended to have worse results. Only 1 small trial (144 patients) directly compared these 2 routes of administration,[22] demonstrating a nonsignificant trend in favor of intravenous administration (RR, 7.1; 95% CI, 0.4 to 135.0).

In contrast to previously reported results,[8] we did not find a beneficial effect of early treatment (within 12 hours), nor was any effect present for treatment started after 12 hours. The separately analyzed data from trials using nimodipine (120 mg, oral administration) did not show a beneficial effect of early treatment. For these analyses data of 11 trials (660 patients in treatment arm, 619 in placebo group) were used (G. Lowe and C. Forbes, unpublished data, 1989).[5,25,27,32-34,36,38,40,41] For poor outcome the RR was 1.0 (95% CI, 0.9 to 1.2), and for mortality it was 0.9 (95% CI, 0.8 to 1.2).

With the criteria of Jadad et al,[17] 12 studies were graded as good quality trials, 12 as moderate quality trials, and 3 as poor

TABLE 2. Characteristics of Included Studies (Sorted in Alphabetical Order)*

Study	Methods and Intervention	Participants	Outcome Assessment and Notes
ASCLEPIOS, 1990[18]	Methodological quality: good. Unpublished. IV isradipine, 28 d, 80 μg/h for 72 h, followed orally with 2.5 mg BID. Placebo: identical regimen.	120 Rx, 114 P. Poor outcome: 47 Rx, 44 P.	Dependency measurement used in review: Barthel Index. Last FU: 3 mo. Data available from principal investigator (J.M. Orgogozo).
Bogousslavsky, 1990[19]	Methodological quality: moderate, method of blinding not properly described. Published. Oral nimodipine, 30 mg QID. for 2 wk. Placebo: identical regimen.	30 Rx, 30 P. Poor outcome: 2 Rx, 3 P.	Dependency measurement used in review: functional item Mathew scale. Last FU: 4 mo. Data available from publication and database of Bayer AG.
Bridgers, 1991[20]	Methodological quality: poor, method of randomization and blinding not properly described, patients withdrawn or lost to FU not described. Published as abstract. IV nimodipine, 2 active groups: 1 or 2 mg/h for 5 d, followed by oral nimodipine 120 mg/d days 5–21. Placebo: identical regimen.	138 Rx, 66 P. Poor outcome: 103 Rx, 43 P.	Dependency measurement used in review: Glasgow Outcome. Last FU: 21 d (?). Data available from abstract and Bayer AG. Trial was stopped after inclusion of 204 of planned 720 patients because of deleterious effect in high-dosage group.
CANWIN, 1993[21]	Methodological quality: good. Published. IV nimodipine; days 1–10 2 mg/h, days 11-6 mo 180 mg/d orally. Placebo: identical regimen.	96 Rx, 93 P. Poor outcome: 39 Rx, 42 P.	Dependency measurement used in review: Toronto Stroke Scale. Last FU: 1 y. Data available from publication, principal investigator, Bayer Canada, and Bayer AG.
Capon, 1983†	Methodological quality: unknown, no information. Unpublished. Treatment: Nimodipine oral, 30 mg QID for 56 d. Placebo: identical regimen.	30 Rx, 30 P. Mortality: 1 Rx, 2 P.	No dependency measurement available. Last FU: at end of treatment. Very limited data available from Bayer AG.
Chandra, 1995[22]	Methodological quality: moderate, randomization procedure not mentioned. Published. Oral vs IV treatment. Arm 1: oral nimodipine 30 mg QID and IV placebo. Arm 2: nimodipine 2.5 mg/h IV and oral placebo. Treatment period 10 d, followed by oral nimodipine for all.	93 IV RX, 93 oral Rx. Poor outcome: 3 IV Rx, 0 oral Rx.	Dependency: data reported in unsuitable method. Last FU: day 14. Data from publication, average scores on functional items available, hence not used in meta-analysis. Trial is only used for direct comparison of route of administration.
FIST, 1990[23]	Methodological quality: good. Published. IV flunarizine; days 1–7 mg BID, days 8–14 oral 21 mg/d, days 15–28 oral 7 mg/d. Placebo: identical regimen.	166 Rx, 165 P. Poor outcome: 93 Rx, 83 P.	Dependency measurement used in review: Modified Rankin Scale. Last FU: 24 wk. Data available from publication and Janssen Pharmaceuticals.
Gelmers, 1984[24]	Methodological quality: poor, open trial with inadequate treatment concealment. Method of randomization and patients withdrawn or lost to FU not properly described. Published. Oral nimodipine, 30 mg QID, 28 d. Placebo: none.	29 Rx, 31 P. Poor outcome: 2 Rx, 12 P.	Dependency measurement used in review: functional item in Mathew scale. Last FU: 28 d. Data available from publication and Bayer AG.
Gelmers, 1988[5]	Methodological quality: moderate, method of randomization and patients withdrawn or lost to FU not described. Published. Oral nimodipine, 30 mg QID, 28 d. Placebo: identical regimen.	93 Rx, 93 P. Poor outcome: 24 Rx, 34 P.	Dependency measurement used in review: functional item in Mathew scale. Last FU: 6 mo. Data available from publication and Bayer AG.
German-Austrian, 1994[25]	Methodological quality: moderate, method of randomization not described. Published. Oral nimodipine, 30 mg QID, 21 d. Placebo: identical regimen.	239 Rx, 243 P. Poor outcome: 60 Rx, 63 P.	Dependency measurement used in review: functional item in Mathew scale. Last FU: 6 mo. Data available from publication and Bayer AG.
Heiss, 1990[26]	Methodological quality: good. Published. IV nimodipine, 1 mg/h in first 2 h, 2 mg/h next 5 d, followed by 30 mg oral QID days 6–21. Placebo: identical regimen.	14 Rx, 13P. Poor outcome: 5 Rx, 4 P.	Dependency measurement used in review: Barthel Index. Last FU: 6 mo. Data available from publication and Bayer AG.
INWEST, 1994[16]	Methodological quality: good. Published. IV nimodipine 1 or 2 mg/h for 5 days, followed by oral nimodipine 120 mg/d days 5–21. Placebo: identical regimen.	195 Rx, 100 P. Poor outcome: 133 Rx, 54 P.	Dependency measurement used in review: Barthel Index. Last FU: 24 wk. Trial was terminated early after including 295 patients (planned 600) because of safety concerns. Data available from publication and Bayer AG.
Kaste, 1994[27]	Methodological quality: good. Published. Oral nimodipine, 30 mg QID, 21 d. Placebo: identical regimen.	176 Rx, 174 P. Poor outcome: 44 Rx, 31 P.	Dependency measurement used in review: Rankin Scale. Last FU: 12 mo. Data available from authors and publication.
Kornhuber, 1993[28]	Methodological quality: moderate, 1 trial center was excluded because of data inhomogeneity. Published. IV flunarizine, 25 mg BID, 7 d, followed by oral 10 and 20 mg/d, days 8–28. Placebo: identical regimen.	215 Rx, 218 P. Mortality: 25 Rx, 20 P.	Data on dependency: not available from all patients randomized because data from 1 center were excluded from analysis. Mortality data were available from all centers. Last FU: 28 d. Data available from publication.
Limburg, 1990[29]	Methodological quality: good. Published.IV flunarizine; bolus of 0.1 mg/kg, followed after 3 h by continuous IV 0.3 mg/kg/24 h during 72 h. Subsequently, oral administration of 10 mg/24 h for 11 d. Placebo: identical regimen.	12 Rx, 14 P. Poor outcome: 3 Rx, 8 P.	Dependency measurement used in review: Rankin Scale. Last FU: 6 mo. Data available from authors and publication.

TABLE 2. Continued

Study	Methods and Intervention	Participants	Outcome Assessment and Notes
Lisk, 1993[30]	Methodological quality: moderate, method of randomization not properly described. Published. Oral nicardipine, 20 mg TID for 3 d. Placebo: identical regimen.	5 Rx, 6 P. Mortality: 0 Rx, 0 P.	Data on dependency: not available. Last FU: 3 d. Data available from publication. Trial compared treatment with nicardipine or captopril vs placebo. Trial designed to find differences in CBF measured with SPECT in hypertensive stroke patients.
Lowe, 1989‡	Methodological quality: good. Unpublished. Oral nimodipine, 40 mg TID for 16 wk. Placebo: identical regimen.	56 Rx, 56 P. Poor outcome: 34 Rx, 23 P.	Dependency measurement used in review: Barthel Index. Last FU: 24 wk. Data available from investigators and Bayer AG.
Martinez-Vila, 1990[31]	Methodological quality: moderate, method of randomization and patients withdrawn or lost to FU not properly described. Published. Oral nimodipine, 30 mg QID for 28 d. Placebo: identical regimen.	81 Rx, 83 P. Poor outcome: 18 Rx, 22 P.	Dependency measurement used in review: Toronto Stroke Scale. Last FU: 28 d. Data available from publication and Bayer AG.
American Nimodipine Study, 1992[32]	Methodological quality: good. Published. Oral nimodipine, 20, 40, or 80 mg oral TID for 2 wk. Placebo: identical regimen.	800 Rx, 264 P. Poor outcome: 475 Rx, 155 P.	Dependency measurement used in review: Barthel Index at 21 d. Last FU: 6 mo (only deaths). Data available from publication and Bayer AG.
NEST, 1993[33]	Methodological quality: moderate, method of randomization and blinding not properly described. Published.Oral nimodipine, 30 mg QID for 21 d. Placebo: identical regimen.	437 Rx, 443 P. Poor outcome: 197 Rx, 211 P.	Dependency measurement used in review: Barthel Index. Last FU: 3 mo. Data available from publication and Bayer AG. In publication 195 patients were excluded from analysis, but data set from Bayer included 879 patients.
NIMPAS, 1999[34]	Methodological quality: good. Published. Oral nimodipine, 30 mg QID for 14 d. Placebo: identical regimen.	25 Rx, 25 P. Poor outcome: 11 Rx, 10 P.	Dependency measurement used in review: Barthel Index. Last FU: 3 mo. Data available from publication and investigators.
Oczkowski, 1989[35]	Methodological quality: moderate, method of randomization and blinding not properly described. Published. Oral PY108-608; 100 mg day 1, 112.5 mg day 2, 125 mg day 3, 150 mg days 4–21, divided in 4 daily doses. Placebo: identical regimen.	9 Rx, 10 P. Mortality: 1 Rx, 1 P.	Data on dependency, not presented in a useful manner. Last FU: 12 wk. Data available from publication.
Paci, 1989[36]	Methodological quality: moderate, method of randomization not properly described. Published. Oral nimodipine, 40 mg TID, for 28 d. Placebo: identical regimen.	19 Rx, 22 P. Poor outcome: 2 Rx, 5 P.	Dependency measurement used in review: functional item from Mathew score. Last FU: 28 d. Data available from publication and Bayer AG.
Sherman, 1986[37]	Methodological quality: moderate, method of randomization not properly described. Published. Treatment: oral nimodipine 30 mg QID for 21 d. Placebo: identical regimen.	11 Rx, 11 P. Mortality: 0 Rx, 0 P.	No data available on functional outcome. Last FU: 60 d. Data available from publication.
TRUST, 1990[38]	Methodological quality: good. Published. Treatment: oral nimodipine 40 mg TID for 21 days. Placebo: identical regimen.	607 Rx, 608 P. Poor outcome: 275 Rx, 257 P.	Dependency measurement used in review: Barthel Index. Last FU: 24 wk. Data available from publication and Bayer AG. We used original data set for analysis on time interval after stroke onset.
Uzuner, 1995[39]	Methodological quality: poor, blinding, randomization or placebo use unclear. Published. Oral nimodipine, 180 mg/d. If CT scan demonstrated intracranial hemorrhage, IV nimodipine 2 mg/h. Control: no nimodipine.	50 Rx, 50 P. Mortality: 6 Rx, 7 P.	Data on dependency: not available. Last FU: discharge from hospital, maximum 40 d. Data available from publication, received from principal investigator.
VENUS, 1999[40]	Methodological quality: good. Published. Oral nimodipine, 30 mg QID, 10 d. Placebo: identical regimen.	225 Rx, 229 P. Poor outcome: 71 Rx, 62 P.	Dependency measurement used in review: Rankin Scale. Last FU: 3 mo. All data available.
Wimalaratna, 1994[41]	Methodological quality: moderate, patients withdrawn or lost to FU not properly described. Published. Oral nimodipine, 120 or 240 mg/d for 16 wk. Placebo: identical regimen.	146 Rx, 69 P. Poor outcome: 57 Rx, 28 P.	Dependency measurement used in review: Barthel Index. Last FU: 24 wk. Data available from publication and Bayer AG.
Yordanov, 1984§	Methodological quality: unknown, no data available. Unpublished. IV nimodipine 0.5 mg/h for 7 d, followed by 30 mg QID for 21 d. Placebo: identical regimen (?).	121 Rx, 117 P. Poor outcome: 70 Rx, 62 P.	Dependency measurement used in review: Toronto Stroke Scale. Last FU: 6 mo. Limited data available from Bayer AG.

IV indicates intravenous; Rx, treatment group; P, placebo group; FU, follow-up; CBF, cerebral blood flow; and SPECT, single-photon emission CT.

*More details are available in the "Characteristics of Included Studies" table in the Cochrane Library.

†A. Capon, unpublished data, 1983.

‡G. Lowe and C. Forbes, unpublished data, 1989.

§ Yordanov, unpublished data, 1984.

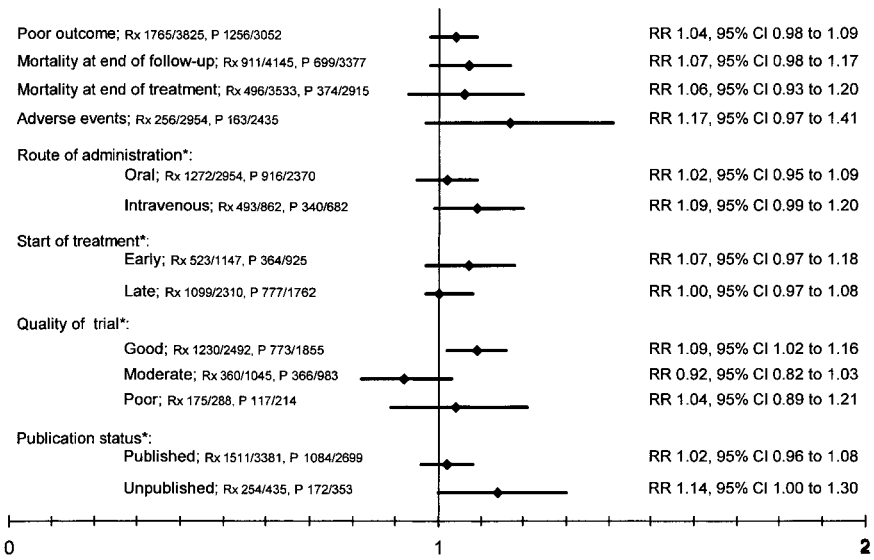
TABLE 3. Excluded Studies and Trials Awaiting Assessment

Study	Reason for Exclusion
Ameriso, 1992[43]	Nimodipine trial. Seems to be part of another larger trial, unknown which. Hemorheological data of few patients are reported.
Dalal, 1995[44]	Possibly suitable for review. Critical information for inclusion not available. Investigator promised to search for data in patient records.
Davalos, 1989[45]	Possibly suitable for review. Critical information for inclusion not available. Limited data from abstract, no response from principal investigator.
Davalos, 1992[46]	Possibly suitable for review. Critical information for inclusion not available. Limited data from abstract, investigator did not respond. Probably this trial is identical to the Davalos 1989 trial.
Fagan, 1988[47]	Possibly suitable for review. Critical information for inclusion not available.
Garcia Tigeria*	Possibly suitable for review. Critical information for inclusion not available.
Hakim, 1989[48]	Possibly suitable for review. Critical information for inclusion not available. Stroke patients were studied with PET scans, unknown whether outcome was assessed.
Laszlo Csiba	Nimodipine trial performed in Hungary. Investigators and company unable to retrieve data.
Lamsudin, 1995[49]	Possibly suitable for review. Critical information for inclusion not available. Abstract with limited data available. Investigator has announced final publication, which we have not been able to retrieve. Investigator has not answered out request for further data.
Marin Gamez, 1988[50]	Nicardipine trial. Spanish article. 75 patients included in study. Unknown how many patients in which treatment group. More than 30% of patients (24/75) excluded after randomization; no follow-up data provided.
Matias-Guiu, 1992[50a]	Nicardipine trial. Aim of study was to assess effect on cognitive impairment after minor stroke. Inclusion >14 d after stroke.
Molto, 1994[51]	Nicardipine trial. Included patients with transient ischemic attacks. Spanish article.
Orgogozo	Nicardipine trial. Investigator could not supply data from this unpublished trial.
Petrogiannopoulos, 1996[52]	Nimodipine trial. Patients were included 1–2 mo after acute ischemic stroke.
Rosselli, 1992[53]	Possibly suitable for review. Critical information for inclusion not available. Patients were studied with SPECT, no outcome data provided.
Rosenbaum, 1991[54]	Nicardipine trial. Safety study without a control group.
Szczechowski, 1994[55]	Possibly suitable for review. Critical information for inclusion not available. Polish article. Author has not responded to requests for further data. Severe imbalance in treatment allocation needs explanation.
Yao, 1991[56]	Nimodipine trial. Chinese report of "preliminary study," no outcome data available.

PET indicates positron emission tomography; SPECT; single-photon emission CT.
*J. Garcia Tigera et al, unpublished data.

quality trials. The methodological quality of 2 (unpublished) trials could not be assessed because information was lacking. The comparison between active and placebo treatment in the good quality trials yielded a statistically significant negative effect for active treatment. In the moderate and poor quality trials, no effect of active treatment was found.

Data of 18 published or presented trials were included, and we identified 4 unpublished trials from which we obtained data. Comparison between treatment and placebo in published trials yielded no difference, whereas in unpublished trials a statistically significant unfavorable effect of treatment was found.



Results of analyses. Rx indicates treatment group; P, placebo group. *Poor outcome was assessed in these analyses.

Heterogeneity

No statistical heterogeneity was found in the main analyses (poor outcome, mortality) ($P=0.14$ and $P=0.68$, respectively). We found statistically significant heterogeneity ($P=0.003$) in the analysis of adverse events. This was mainly caused by the Flunarizine in Stroke Treatment (FIST) trial, in which more statistically significant adverse events were present.[23] After this trial was deleted from the adverse events analysis, no heterogeneity was present. Clinical heterogeneity was addressed in the sensitivity analyses.

Discussion

This systematic review of all available data, published and unpublished, failed to demonstrate a reduction of death and dependency in acute stroke after treatment with calcium antagonists. The CIs are fairly narrow, and the overall result is therefore subject to limited statistical uncertainty.

In the sensitivity analyses we found no differences between oral or intravenous administration and early or late start of treatment. This last result is intriguing, since Mohr et al[8] reported a statistically significant beneficial effect of early administration of nimodipine. In their meta-analysis no effect of nimodipine was found in the overall analysis, but in the subgroup analysis of patients treated within 12 hours of stroke onset, the odds ratio was 0.62 (95% CI, 0.44 to 0.87) for neurological impairment in favor of nimodipine. Similar results were reported for functional outcome assessments. By separate analysis of nimodipine trials, we tried to confirm the results found by Mohr et al but were unable to do so. We included more trials because at the time of the former meta-analysis data of 2 trials were not available,[34,40] and data of 2 trials were excluded by Mohr et al because data of these trials were not available from the Bayer database (G. Lowe and C. Forbes, unpublished data, 1989).[27] Differences between structured reviews may occur as a result of differences in the design of the meta-analysis.[57,58] The methods section of the meta-analysis by Mohr et al did not describe all decisions taken. Moreover, the exact numbers of patients with poor outcome of each included trial were not reported and could not be retrieved from the authors or from the pharmaceutical company involved. As a result, we could not compare the analyses in detail.

Trial methodology can cause considerable bias in a systematic review.[59,60] Although scoring the quality of trials can be hazardous,[61] we decided to address this issue in a sensitivity analysis. Sensitivity analyses are subgroup analyses, and the conclusions should therefore be regarded with caution. Nevertheless, we found strong indications for the presence of publication bias in our sensitivity analyses. While the published trials showed no overall effect on death and dependency, unpublished trials were associated with a statistically significant worse outcome in the active treatment group. It is likely that more "negative" trials have been performed that have not been published. In fact, we have some indications for the existence of these trials, of which we could not acquire further information.

From this review we conclude the following: (1) the use of calcium antagonists is not justified in patients with ischemic stroke; (2) positive results of subgroup analyses within a meta-analysis should be judged with caution; and (3) there is a clear difference in results from published versus unpublished trials, and this effect is also found for good quality trials compared with moderate or poor quality trials.

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