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 All randomized trials (published and unpublished) investigating a calcium antagonist (acting on voltage-sensitive calcium channels) were included.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 In subgroups of unpublished and methodologically sound trials, a statistically significant negative effect for calcium antagonists was found.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. 

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

A 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.

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...
**TABLE 1. Dichotomized Functional Outcome Scales**

<table>
<thead>
<tr>
<th>Name of Scale</th>
<th>Good Outcome</th>
<th>Poor Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Rankin Scale</td>
<td>1–3</td>
<td>4–6</td>
</tr>
<tr>
<td>Barthel ADL Index</td>
<td>60–100</td>
<td>&lt;60</td>
</tr>
<tr>
<td>Glasgow Outcome Scale</td>
<td>4, 5</td>
<td>&lt;4</td>
</tr>
<tr>
<td>Toronto Stroke Scale</td>
<td>1–3</td>
<td>4, 5</td>
</tr>
<tr>
<td>Mathew Impairment Scale</td>
<td>14, 21, 28</td>
<td>7, 0</td>
</tr>
</tbody>
</table>

ADL indicates activities of daily living.

Certainly cannot live independently,13 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 past analyses by which other randomized 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 studies17: 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, 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 χ² 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).35–38 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)*

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods and Intervention</th>
<th>Participants</th>
<th>Outcome Assessment and Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCLEPIOS, 1990</td>
<td>Methodological quality: good. Unpublished. IV isradipine, 28 d, 80 μg/h for 72 h, followed orally with 2.5 mg BID. Placebo: identical regimen.</td>
<td>120 Rx, 114 P.</td>
<td>Dependency measurement used in review: Barthel Index. Last FU: 6 mo. Data available from principal investigator (J.M. Orgogozo).</td>
</tr>
<tr>
<td>Kornhuber, 1993</td>
<td>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.</td>
<td>215 Rx, 218 P.</td>
<td>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.</td>
</tr>
<tr>
<td>Bridgers, 1991</td>
<td>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/days 5–21. Placebo: identical regimen.</td>
<td>103 Rx, 43 P.</td>
<td>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.</td>
</tr>
<tr>
<td>Heiss, 1990</td>
<td>Methodological quality: good. Published. IV nimodipine; days 1–10 2 mg/h, days 11–20 1 mg/d orally. Placebo: identical regimen.</td>
<td>96 Rx, 93 P.</td>
<td>Dependency measurement used in review: Toronto Stroke Scale. Last FU: 1 y. Data available from publication, principal investigator, Bayer Canada, and Bayer AG.</td>
</tr>
<tr>
<td>Gelmers, 1984</td>
<td>Methodological quality: poor, open trial with inadequate treatment concealment. Method of randomization and patients withdrawn or lost to FU not described. Published. Oral nimodipine, 30 mg QID, 28 d. Placebo: none.</td>
<td>29 Rx, 31 P.</td>
<td>Dependency measurement used in review: functional item in Mathew scale. Last FU: 28 d. Data available from publication and Bayer AG.</td>
</tr>
<tr>
<td>Chandra, 1995</td>
<td>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.</td>
<td>93 IV Rx, 93 oral Rx.</td>
<td>Dependency measurement used in review: functional item in Mathew scale. Last FU: 6 mo. Data available from publication and Bayer AG.</td>
</tr>
<tr>
<td>German-Austrian, 1994</td>
<td>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.</td>
<td>239 Rx, 243 P.</td>
<td>Dependency measurement used in review: functional item in Mathew scale. Last FU: 6 mo. Data available from publication and Bayer AG.</td>
</tr>
<tr>
<td>Gern, 1990</td>
<td>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.</td>
<td>166 Rx, 165 P.</td>
<td>Dependency measurement used in review: Modified Rankin Scale. Last FU: 24 wk. Data available from publication and Janssen Pharmaceuticals.</td>
</tr>
<tr>
<td>INWEST, 1994</td>
<td>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.</td>
<td>14 Rx, 13 P.</td>
<td>Dependency measurement used in review: Barthel Index. Last FU: 6 mo. Data available from publication and Bayer AG.</td>
</tr>
<tr>
<td>Limburg, 1990</td>
<td>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.</td>
<td>12 Rx, 14 P.</td>
<td>Dependency measurement used in review: Rankin Scale. Last FU: 6 mo. Data available from authors and publication.</td>
</tr>
<tr>
<td>Study</td>
<td>Methods and Intervention</td>
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<tr>
<td>Lisk, 1993§</td>
<td>Methodological quality: moderate, method of randomization not properly described. Published. Oral nimodipine, 20 mg TID for 3 d. Placebo: identical regimen.</td>
<td>5 Rx, 6 P.</td>
<td>Mortality: 0 Rx, 0 P. Data on dependency: not available. Last FU: 3 d. Data available from publication. Trial compared treatment with nimodipine or captopril vs placebo. Trial designed to find differences in CBF measured with SPECT in hypertensive stroke patients.</td>
</tr>
<tr>
<td>NEST, 1993³³</td>
<td>Methodological quality: moderate, method of randomization and blinding not properly described. Published. Oral nimodipine, 30 mg QID for 21 d. Placebo: identical regimen.</td>
<td>437 Rx, 443 P.</td>
<td>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 679 patients.</td>
</tr>
<tr>
<td>Oczkowski, 1989³⁵</td>
<td>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.</td>
<td>9 Rx, 10 P.</td>
<td>Mortality: 1 Rx, 1 P. Data on dependency, not presented in a useful manner. Last FU: 12 wk. Data available from publication.</td>
</tr>
<tr>
<td>Paci, 1989³⁶</td>
<td>Methodological quality: moderate, method of randomization not properly described. Published. Oral nimodipine, 40 mg TID, for 28 d. Placebo: identical regimen.</td>
<td>19 Rx, 22 P.</td>
<td>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.</td>
</tr>
<tr>
<td>TRUST, 1990³⁸</td>
<td>Methodological quality: good. Published. Treatment: oral nimodipine 40 mg TID for 21 days. Placebo: identical regimen.</td>
<td>607 Rx, 608 P.</td>
<td>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.</td>
</tr>
<tr>
<td>Uzunor, 1995¹⁹</td>
<td>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. Placebo: no nimodipine.</td>
<td>50 Rx, 50 P.</td>
<td>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.</td>
</tr>
<tr>
<td>VENUS, 1999⁴⁰</td>
<td>Methodological quality: good. Published. Oral nimodipine, 30 mg QID, 10 d. Placebo: identical regimen.</td>
<td>225 Rx, 229 P.</td>
<td>Poor outcome: 71 Rx, 62 P. Dependency measurement used in review: Rankin Scale. Last FU: 3 mo. All data available.</td>
</tr>
<tr>
<td>Wimalaratna, 1994⁴¹</td>
<td>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.</td>
<td>146 Rx, 69 P.</td>
<td>Poor outcome: 57 Rx, 28 P. Dependency measurement used in review: Barthel Index. Last FU: 24 wk. Data available from publication and Bayer AG.</td>
</tr>
<tr>
<td>Yordanov, 1984§</td>
<td>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 (?).</td>
<td>121 Rx, 117 P.</td>
<td>Poor outcome: 70 Rx, 62 P. Dependency measurement used in review: Toronto Stroke Scale. Last FU: 6 mo. Limited data available from Bayer AG.</td>
</tr>
</tbody>
</table>

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.
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.

TABLE 3. Excluded Studies and Trials Awaiting Assessment

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ameriso, 1992</td>
<td>Nimodipine trial. Seems to be part of another larger trial, unknown which. Hemorheological data of few patients are reported.</td>
</tr>
<tr>
<td>Divalos, 1992</td>
<td>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 Divalos 1989 trial.</td>
</tr>
<tr>
<td>Garcia Tigera*</td>
<td>Possibly suitable for review. Critical information for inclusion not available.</td>
</tr>
<tr>
<td>Hakim, 1989</td>
<td>Possibly suitable for review. Critical information for inclusion not available. Stroke patients were studied with PET scans, unknown whether outcome was assessed.</td>
</tr>
<tr>
<td>Laslo Csiba</td>
<td>Nimodipine trial performed in Hungary. Investigators and company unable to retrieve data.</td>
</tr>
<tr>
<td>Lamsudin, 1995</td>
<td>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.</td>
</tr>
<tr>
<td>Marin Gamez, 1988</td>
<td>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.</td>
</tr>
<tr>
<td>Matías-Guix, 1992</td>
<td>Nicardipine trial. Aim of study was to assess effect on cognitive impairment after minor stroke. Inclusion &gt;14 d after stroke.</td>
</tr>
<tr>
<td>Orgogozo</td>
<td>Nicardipine trial. Investigator could not supply data from this unpublished trial.</td>
</tr>
<tr>
<td>Petrogiannopoulos, 1996</td>
<td>Nimodipine trial. Patients were included 1–2 mo after acute ischemic stroke.</td>
</tr>
<tr>
<td>Rosselli, 1992</td>
<td>Possibly suitable for review. Critical information for inclusion not available. Patients were studied with SPECT, no outcome data provided.</td>
</tr>
<tr>
<td>Rosenbaum, 1991</td>
<td>Nicardipine trial. Safety study without a control group.</td>
</tr>
<tr>
<td>Szczechowski, 1994</td>
<td>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.</td>
</tr>
</tbody>
</table>

PET indicates positron emission tomography; SPECT; single-photon emission CT.

*J. Garcia Tigera et al, unpublished data.
Complete the previous task...


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