

# Review: Calcium antagonists do not reduce death or dependency in acute ischemic stroke

Horn J, Limburg M. Calcium antagonists for acute ischemic stroke. Cochrane Review, latest version 3 Oct 1999. In: The Cochrane Library. Oxford: Update Software.

## QUESTION

Do calcium channel antagonists reduce the risk for death or dependency in patients who have had an ischemic stroke?

## DATA SOURCES

Studies were identified by using the Specialised Register of Controlled Trials from the Cochrane Stroke Group. This register was produced by using MEDLINE, EMBASE/Excerpta Medica, BIOSIS, CINAHL, CRISP, Dissertation Abstracts online, Derwent Drug File, SCISEARCH, and hand searches of relevant journals up to March 1999.

## STUDY SELECTION

Controlled trials were selected if patients had acute ischemic stroke and were randomized within 14 days of the stroke, calcium antagonists were studied, and outcomes (death or dependency in activity of daily living measured using a functional outcome scale) and adverse effects were reported.

## DATA EXTRACTION

Data were extracted on study methods and quality; intervention, including dose, when

treatment began, and route of administration; patient characteristics and numbers; follow-up duration and numbers; outcomes (death or dependency) and how they were measured; and adverse effects.

## MAIN RESULTS

46 trials were reviewed, and 28 (7521 patients) met the inclusion criteria. 21 studies evaluated nimodipine, 3 evaluated isradipine, 2 evaluated flunarizine, and 1 each evaluated nicardipine and oral PY 108-608. 22 studies of 6877 patients provided data on poor outcome (death or dependency) at the end of follow-up. Calcium antagonists were not associated with a decreased risk (odds ratio [OR] 1.07, 95% CI 0.97 to 1.18). Calcium antagonists were also not associated with a decreased risk for death at the end of follow-up (28 studies, OR 1.10, CI 0.98 to 1.23), death at the end of treatment (OR 1.07, CI 0.92 to 1.24), recurrence of stroke at the end of follow-up (OR 0.92, CI 0.56 to 1.52), all adverse effects (OR 1.19, CI 0.97 to 1.47, with 1 trial taken out of the analysis because of large differences in the incidence of superficial thrombophlebitis with flunarizine), hypotension during treatment (2% for calcium

antagonists vs 1.4% for others, OR 1.37, CI 0.70 to 2.67), or change in mean systolic blood pressure during treatment. Sensitivity analyses of route of administration, dose, timing of start of treatment, and individual drugs and analyses according to trial methods (randomization, concealment, blinding, and publication status) did not alter the results: Calcium antagonists are not associated with a decreased risk for death or dependence. Publication bias was evident in that unpublished trials were associated with statistically significant worse outcomes for calcium antagonists than for placebo.

## CONCLUSION

Calcium channel antagonists do not reduce the risk for death or dependency in patients who have had an ischemic stroke.

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## COMMENTARY

The rationale for using calcium channel antagonists in acute ischemic stroke has a basis in stroke pathophysiology. Ischemia of cerebral tissue is associated with an influx of calcium ions into neuronal cells; reversing this process has a neuroprotective effect in animal models. The use of nimodipine to prevent death and disability after subarachnoid hemorrhage encouraged numerous trials of calcium antagonists in acute ischemic stroke (1).

The detailed systematic review by Horn and Limburg has used standard methods to make sense of the many small clinical trials. It indicates that no evidence supports the use of calcium antagonists in patients with acute ischemic stroke; indeed, the use of intravenous calcium antagonists in acute stroke is probably hazardous, which confirms the current standard practice in most western countries of avoiding calcium antagonist therapy.

Horn and Limburg have followed a careful and rigorous process, and the main limitation of their review is the quality of the original studies. Because of the diverse ways of reporting outcomes, the authors were compelled to use a complex process of outcome analysis to address their primary outcome of death or dependency. This

process seems unlikely to have led to bias in their conclusions. When they restricted their analysis to clinical trials that had clearly reported, high methodologic standards, calcium antagonists appeared to be hazardous. Furthermore, the studies that never reached full publication in a peer-reviewed journal showed that calcium antagonists had a significantly deleterious effect, which suggests that publication bias may well be taking place. These observations all suggest that any bias in this review would serve to underestimate hazards associated with the use of calcium antagonists. Therefore, it is hard to find fault with the authors' conclusion that no data support the use of calcium antagonists in acute ischemic stroke and that we have no grounds to support further clinical trials in this area.

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## Reference

1. Pickard JD, Murray GD, Illingworth R, et al. Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British Aneurysm Nimodipine Trial. *BMJ*. 1989;298:636-42.