Dipyridamole for preventing recurrent ischemic stroke and other vascular events: a meta-analysis of individual patient data from randomized controlled trials

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CRD summary
This review assessed the use of dipyridamole, with or without aspirin, for preventing stroke in patients with previous ischaemic cerebrovascular disease. The authors concluded that dipyridamole, with or without aspirin, reduced stroke recurrence in this population. The review appeared to support the authors’ conclusions, but the incomplete reporting of review methods makes it difficult to confirm the robustness of the conclusions.

Authors’ objectives
To determine the efficacy of dipyridamole, with or without aspirin, for the secondary prevention of stroke in patients with a history of ischaemic cerebrovascular disease.

Searching
MEDLINE (1966 to 2001), EMBASE (1980 to 2002), the Cochrane Library (2002, Issue 4), and the Web of Science (1981 to 2002) were searched; search terms were reported. The references from relevant articles and reviews were also searched. In addition, trialists and the manufacturer of dipyridamole were contacted. No language restrictions were applied, and both published and unpublished trials were eligible.

Study selection
Study designs of evaluations included in the review
The review included individual patient data (IPD) from randomised controlled trials (RCTs). The duration of follow-up in the included studies ranged from 15 to 72 months.

Specific interventions included in the review
Studies that compared dipyridamole, given with or without aspirin, with a control were eligible. The included studies used conventional release dipyridamole (daily dose 150 to 300 mg) or modified-release dipyridamole (daily dose 400 mg), with or without aspirin (where given, the daily dose ranged from 50 to 1,300 mg).

Participants included in the review
Individuals with a previous history of ischaemic cerebrovascular disease or transient ischaemic attack were eligible for inclusion. The average age was 65.4 years old (standard deviation, SD=11.0), and 60% of the participants were male. Where reported, the time from stroke onset to study entry averaged 33.8 days (SD=64.7), the average baseline blood pressure (systolic/diastolic blood pressure) was 152.3 (SD=22.4)/87.5 (SD=11.9) mmHg (based on 2 studies), and the percentage with hypertension ranged from 37 to 62%. The percentage of patients with stroke as a qualifying event ranged from 0 to 84%.

Outcomes assessed in the review
The primary outcome was total stroke (combined fatal and nonfatal). The secondary outcomes included nonfatal stroke, combined fatal and nonfatal myocardial infarction (MI), vascular death, and a composite outcome of nonfatal stroke, nonfatal MI and vascular death. The review also assessed changes in blood pressure, drop-outs, major bleeding and headache.

How were decisions on the relevance of primary studies made?
Two reviewers selected articles for inclusion. It was unclear whether this was completed independently, or how any disagreements were resolved.

Assessment of study quality
The methodological quality of the primary studies was assessed according to the following criteria: method of
randomisation, concealment of allocation, completeness of follow-up, and blinding of the outcome assessment. Trials satisfying at least three of the criteria listed were considered to be of a high quality. The authors sought to clarify differences between their analysis of the data according to methods used in trial publications and published results. The authors did not state how the quality of the primary studies was assessed, or how many reviewers carried out the quality assessment.

**Data extraction**

Trial investigators were contacted to provide IPD for their trial. The data requested included: demographics, clinical presentation, treatment assignment, treatment findings and outcome at the end of the trial. Data were re-coded by the authors and merged into a single dataset. Comparisons by treatment group included: dipyridamole versus control or placebo; combined aspirin and dipyridamole versus control or placebo; combined aspirin and dipyridamole versus aspirin; and combined aspirin and dipyridamole versus dipyridamole.

**Methods of synthesis**

How were the studies combined?

For each outcome, a pooled odds ratio (OR) with associated 95% confidence interval (CI) was calculated by intention-to-treat. A random-effects model was used to account for heterogeneity between trial results and a fixed-effect model for treatment assignment. Regression methods were used to adjust for age, gender, qualifying event and history of hypertension. Egger's test for asymmetry (based on the OR for stroke recurrence) was used to assess the potential for publication bias.

How were differences between studies investigated?

A subgroup analysis was used to examine the effect on stroke recurrence of prognostic factors (age, stroke as a qualifying event and history of hypertension). A sensitivity analysis was used to assess the influence on total stroke of the formulation of dipyridamole (conventional or modified release), risk of recurrence, each trial in turn, inclusion of a non-randomised clinical trial, and the inclusion of tabular data from the two studies with unobtainable IPD.

**Results of the review**

Seven trials (n=11,509) were eligible; IPD from 5 RCTs were included in the meta-analysis (n=11,290). Six RCTs were considered to be of a high quality.

**Vascular events:** After adjusting for age, gender, and qualifying event, recurrent stroke was reduced by dipyridamole compared with control or placebo (OR 0.82, 95% CI: 0.68, 1.00). Similarly, recurrent stroke was statistically significantly reduced by dipyridamole combined with aspirin compared with aspirin alone (OR 0.78, 95% CI: 0.65, 0.93), dipyridamole alone (OR 0.74, 95% CI: 0.60, 0.90), or control (OR 0.61, 95% CI: 0.51, 0.71). When data from the largest trial were excluded (accounting for 57% of the data), the comparison of combined aspirin and dipyridamole with control remained statistically significant (OR 0.63, 95% CI: 0.48, 0.82), but demonstrated a non-statistically significant trend (OR 0.88, 95% CI: 0.64, 1.19) compared with aspirin alone. Similar findings were demonstrated for nonfatal stroke. The composite outcome of nonfatal stroke, nonfatal MI and vascular death was statistically significantly reduced by dipyridamole combined with aspirin when compared with aspirin alone (OR 0.84, 95% CI: 0.72, 0.97), dipyridamole alone (OR 0.76, 95% CI: 0.64, 0.90), or control or placebo (OR 0.66, 95% CI: 0.57, 0.75). Type of treatment did not statistically reduce the odds of vascular death in any group.

**Blood pressure:** Dipyridamole, with or without aspirin, lowered blood pressure by 1.1/0.9 mmHg (0.7/0.6%; P=0.037, P=0.001; based on 2 RCTs). However, the reduction in stroke seen with dipyridamole was not statistically significantly associated with the fall in blood pressure (P=0.37).

**Drop-out rate and adverse events:** The drop-out rate was higher with dipyridamole alone (29.3%) and dipyridamole plus aspirin (30.8%) compared with aspirin alone (24%) or control (23.4%). Headaches were more common with dipyridamole alone (37.2%) and aspirin alone (33.1%) compared with aspirin plus dipyridamole (26.7%) or control (22.8%). Bleeding was greatest in patients receiving aspirin alone (8.2%) or aspirin plus dipyridamole (8.1%) compared with dipyridamole alone (4.7%) or control (4.2%).
There was no evidence of publication bias when assessed using Egger's test for asymmetry for stroke recurrence (P=0.43).

**Authors' conclusions**
Dipyridamole, given alone or in combination with aspirin, reduced stroke recurrence in patients with previous ischaemic cerebrovascular disease.

**CRD commentary**
The review question was supported by clear inclusion criteria. Several electronic databases were searched and attempts were made to minimise language and publication bias; publication bias was assessed using appropriate methods. While the study selection process was carried out in duplicate, the procedures used for the data extraction and quality assessment were not reported, so there was the possibility of reviewer error or bias.

The validity of the eligible trials was assessed by checking the raw data from each trial and resolving any problems with the trial investigators. The data appeared to have been analysed using appropriate techniques for the meta-analysis of IPD; heterogeneity was investigated and discussed in the text. IPD for two of the identified trials were not available, although inclusion of tabular data from these studies did not appear to quantitatively change the results.

The evidence presented appeared to support these conclusions, but poor reporting of review methods makes it difficult to confirm the robustness of the conclusions.

Several of the authors have received grants and/or honoraria from Boehringer Ingelheim (manufacturers of dipyridamole) and Sansofi/BMS, or have been involved in previous trials or are involved in ongoing trials of antiplatelet agents.

**Implications of the review for practice and research**

**Practice:** The authors stated that dipyridamole has a place in secondary prevention after ischaemic stroke or transient ischaemic attack, although which antiplatelet regimen is used will depend on patient characteristics such as underlying risk, experience on existing antiplatelet drugs, tolerance or allergies, as well as cost.

**Research:** The authors did not state any implications for further research.

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**Other publications of related interest**

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