Dipyridamole for Preventing Stroke and Other Vascular Events in Patients With Vascular Disease
An Update

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Patients with limited cerebral ischemia of arterial origin are at risk of serious vascular events (4% to 11% annually). Aspirin reduces that risk by 13%. In one trial, adding dipyridamole to aspirin was associated with a 22% risk reduction compared with aspirin alone. However, a systematic review of all trials of antiplatelet agents by the Anti-Thrombotic Trialists’ Collaboration showed that, in high-risk patients, there was virtually no difference between the aspirin-dipyridamole combination and aspirin alone.

Objectives
To assess the efficacy and safety of dipyridamole versus control in the secondary prevention of vascular events in patients with vascular disease.

Search Strategy
We searched the Cochrane Stroke Group trials register (searched June 2006), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 2, 2006), MEDLINE (1966 to May 2006) and EMBASE (1980 to May 2006). We contacted authors and pharmaceutical companies in the search for further data on published and unpublished studies.

Selection Criteria
We selected randomized long-term secondary prevention trials with concealed treatment allocation, treatment for >1 month, starting within 6 months after presentation of an arterial vascular disease. Treatment consisted of dipyridamole with or without other antiplatelet drugs compared with no drug or another antiplatelet drug other than dipyridamole.

Data Collection and Analysis
Two review authors independently selected trials for inclusion, assessed trial quality and extracted data. Data were analyzed according to the intention-to-treat principle.

Main Results
Twenty-nine trials were included (3 new since the previous review), with 23,019 participants (previously 19,842), among whom 1,503 vascular deaths and 3,438 fatal and nonfatal vascular events occurred during follow-up. Compared with control, dipyridamole had no clear effect on vascular death (relative risk (RR) 0.99, 95% CI, 0.87 to 1.12). This result was not influenced by the dose of dipyridamole or type of presenting vascular disease. Compared with control, dipyridamole appeared to reduce the risk of vascular events (Figure, RR 0.88, 95% CI, 0.81 to 0.95). On analysis per qualifying event, this effect was statistically significant only in patients presenting with cerebral ischemia.

Authors’ Conclusions
For patients who present with arterial vascular disease, there is no evidence that dipyridamole, in the presence or absence of another antiplatelet drug (chiefly aspirin) reduces the risk of vascular death, though it reduces the risk of further vascular events. This benefit is found only in patients presenting after cerebral ischemia. There is no evidence that dipyridamole alone is more efficacious than aspirin.

Implications for Practice
Routine use of dipyridamole alone as first line antiplatelet treatment in patients at high risk of vascular events is not supported. Among patients presenting with arterial vascular disease, especially ischemic stroke or transient ischemic attack, the combination of dipyridamole plus aspirin is associated with a lower risk of further vascular events than aspirin alone.

Implications for Research
More trials are needed in high-risk groups of patients other than after ischemic stroke or transient ischemic attack, such as those with arterial peripheral vascular disease, diabetic
retinopathy and patients undergoing hemodialysis to determine the role of dipyridamole in secondary prevention. Also, trials with aspirin plus extended release dipyridamole versus standard treatment (cloniprodol, or clodiprodol plus aspirin—whichver is the present standard) might be warranted in patients with previous symptomatic atherothrombosis of the coronary arteries.

Disclosures

The authors are the principal investigators of ESPRIT, the European/Australian Stroke Prevention in Reversible Ischaemia Trial. The trial was run independently of any pharmaceutical company. The authors have received fees and expenses from producers of dipyridamole (Boehringer Ingelheim). After completion and full analysis of ESPRIT, we accepted financial support from Boehringer Ingelheim for post hoc exploratory analyses of the ESPRIT trial data, for which a contract was signed. These post hoc analyses pertain to the comparison of dipyridamole and aspirin versus aspirin alone; we negotiated complete scientific freedom in the contract. No money was received for any version of this review.

Key Words: dipyridamole | prevention | review | stroke | vascular disease

Figure. Outcome vascular event (Figure 04.02.00. De Schryver ELLM, Algra A, van Gijn J. Dipyridamole for preventing stroke and other vascular events in patients with vascular disease [Cochrane review]. In: The Cochrane Library, Issue 3, 2007. Oxford: Update Software. MetaView © Update Software, Oxford.)
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