

Review: dipyridamole given with or without aspirin reduces recurrent stroke

Leonardi-Bee J, Bath PM, Bousser MG, *et al*. Dipyridamole for preventing recurrent ischaemic stroke and other vascular events: a meta-analysis of individual patient data from randomized controlled trials. *Stroke* 2005;**36**:162–8.

Clinical impact ratings GP/FP/Primary care ★★★★★☆ IM/Ambulatory care ★★★★★☆ Internal medicine ★★★★★☆ Neurology ★★★★★☆ Haematology ★★★★★☆

Q In patients with a history of ischaemic cerebrovascular disease, does dipyridamole given with or without aspirin reduce the risk of recurrent stroke?

METHODS

 **Data sources:** *Cochrane Library* (Issue 4, 2002), *Medline* (1966–2001), *EMBASE/Excerpta Medica* (1980–2002), *Web of Science* (1981–2002), bibliographies of relevant articles, researchers, and a manufacturer of dipyridamole (Boehringer Ingelheim, Ingelheim, Germany).

 **Study selection and assessment:** randomised controlled trials (RCTs) in any language that evaluated dipyridamole for secondary prevention of stroke in patients with previous cerebrovascular disease. Study quality was assessed using criteria that included method of randomisation, concealment of allocation, completeness of follow up, and blinding of outcome assessment.

 **Outcomes:** recurrent stroke (combined fatal and non-fatal), non-fatal stroke, combined fatal and non-fatal myocardial infarction (MI), vascular death, and a composite outcome of non-fatal stroke, non-fatal MI, and vascular death.

MAIN RESULTS

5 RCTs (n = 11 240) (mean age 65 y, 60% men) were included in the intention to treat meta-analysis of individual patient data using a logistic regression model with random effects for trial and fixed effects for treatment assignment. Odds ratios (ORs) were adjusted for trial, age, sex, qualifying event, and history of hypertension. *Dipyridamole plus aspirin (combination group) v control (including placebo) (4 RCTs)*. Risk of recurrent fatal and non-fatal stroke (all stroke) was lower in the combination group than in the control group (table). Risk of non-fatal stroke (OR 0.59, 95% CI 0.49 to 0.72), MI (all) (OR 0.67, CI 0.48 to 0.95), and the composite endpoint (OR 0.66 CI, 0.57 to 0.75) were also lower in the combination group than in the control group. Groups did not differ for vascular death. *Dipyridamole v control (1 RCT)*. Risk of recurrent all stroke (table) and the risk of non-fatal stroke (OR 0.75, CI 0.59 to 0.94) were lower in the dipyridamole group than in the control group. Groups did not differ for other outcomes. *Dipyridamole plus aspirin v aspirin (4 RCTs)*. Risk of recurrent stroke (all) (OR 0.78, CI 0.65 to 0.93), non-fatal stroke (OR 0.73, CI 0.59 to 0.90), and the composite endpoint (OR 0.84, 0.72 to 0.97) were lower in the combination group than in the aspirin group. Groups did not differ for all MI or vascular death. *Dipyridamole plus aspirin v dipyridamole (1 RCT)*. Risk of recurrent stroke (all) (OR 0.74,

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CI 0.60 to 0.90) and the composite endpoint (OR 0.76, CI 0.64 to 0.90) were lower in the combination group than in the dipyridamole group. Groups did not differ for other outcomes.

CONCLUSION

In patients with a history of ischaemic cerebrovascular disease, dipyridamole given with or without aspirin reduces the risk of recurrent stroke.

Abstract and commentary also appear in ACP Journal Club.

Commentary

The meta-analysis by Leonardi-Bee *et al* and that by De Schryver *et al*¹ suggest that a combination of dipyridamole and aspirin is significantly, but marginally, more effective than aspirin in preventing major vascular events (OR 0.84, CI 0.72 to 0.97). However, the combination remains to be established as first line treatment for transient ischaemic attack (TIA) and stroke because it costs more than aspirin and may cause more headache, gastrointestinal upset, and angina in patients with occlusive coronary artery disease. It is important to note that the positive result is mainly driven by a single RCT, the European Stroke Prevention Study 2 (ESPS II),² and the size of the effect may be as low as a 3% odds reduction. Completion of the European/Australian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) (equivalent to ESPS II in power)³ will add data and substantially improve the precision of the estimate of the treatment effect for combination therapy.

For the time being, aspirin remains the most affordable and widely available antiplatelet therapy for patients with TIA and ischaemic stroke (relative risk reduction of recurrence 13% CI 6 to 19).⁴ Clopidogrel is indicated for patients who are allergic to or intolerant of aspirin. Clopidogrel or the combination of aspirin and dipyridamole is reserved for patients who are at sufficiently high risk of vascular events for it to be cost effective. Little or no role exists for dipyridamole alone. At best, it may only exert a modest beneficial effect in preventing major vascular events (OR 0.86, CI 0.73 to 1.03). After all, antiplatelet drugs must prevent both recurrent stroke and coronary events because long term risk of coronary events is at least as great as that for recurrent stroke after TIA and ischaemic stroke.

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- 1 De Schryver EL, Algra A, van Gijn J. *Stroke* 2003;**34**:2072–80.
- 2 Diener HC, Cunha L, Forbes C, *et al*. *J Neurol Sci* 1996;**143**:1–13.
- 3 De Schryver EL. *Cerebrovasc Dis* 2000;**10**:147–50.
- 4 Algra A, van Gijn J. *J Neurol Neurosurg Psychiatry* 1999;**66**:225.

Dipyridamole plus aspirin (combination) or dipyridamole alone v control (including placebo) at 24–72 months*

Outcome	Number of trials (n)	Comparisons	RRR (95% CI)	NNT (CI)
Fatal and non-fatal stroke	4 (10 146)	Combination v control	36% (27 to 46)	24 (19 to 32)
		Dipyridamole v control	16% (0 to 29)	53 (29 to ∞)

*Abbreviations defined in glossary; RRR, NNT, and CI calculated from odds ratio (adjusted for trial, age, sex, qualifying event [ischaemic stroke or transient ischaemic attack], and history of hypertension) in article.