

Review: Dipyridamole given with or without aspirin reduces recurrent stroke

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

Clinical impact ratings: GIM/FP/GP ★★★★★☆ Hospitalists ★★★★★☆ Hematol/Thrombo ★★★★★☆☆ Neurology ★★★★★☆☆

QUESTION

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

METHODS

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

Study selection and assessment: Randomized 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 randomization, concealment of allocation, completeness of follow-up, and blinding of outcome assessment.

Outcomes: Recurrent stroke (combined fatal and nonfatal), nonfatal stroke, combined fatal and nonfatal myocardial infarction (MI), vascular death, and a composite outcome of nonfatal stroke, nonfatal MI, and vascular death.

MAIN RESULTS

5 RCTs ($n = 11\ 036$) (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) vs control (including placebo) (4 RCTs):* Risk for recurrent fatal and nonfatal stroke (all stroke) was lower in the combination group than in the control group (Table). Risk for nonfatal 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 vs control (1 RCT):* Risk for recurrent all stroke (Table) and the risk for nonfatal 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 vs aspirin (4 RCTs):* Risk for recurrent

stroke (all) (OR 0.78, CI 0.65 to 0.93), nonfatal 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 vs dipyridamole (1 RCT):* Risk for recurrent stroke (all) (OR 0.74, 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 ischemic cerebrovascular disease, dipyridamole given with or without aspirin reduces the risk for recurrent stroke.

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

Outcome	Number of trials (n)	Comparisons	RRR (95% CI)	NNT (CI)
Fatal and nonfatal stroke	4 (10 146)	Combination vs control	36% (27 to 46)	24 (19 to 32)
	1 (6602)	Dipyridamole vs 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 [ischemic stroke or transient ischemic attack], and history of hypertension) in article.

COMMENTARY

The meta-analysis by Leonardi-Bee and colleagues and that by De Schryver and colleagues (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 ischemic attack (TIA) and stroke because it costs more 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 ischemic stroke (relative risk reduction for 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 for 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 for coronary events is at least as great as that for recurrent stroke after TIA and ischemic stroke.

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