

# Aspirin plus dipyridamole was more effective than aspirin alone for preventing vascular events after minor cerebral ischaemia

Halkes PH, van Gijn J, Kappelle LJ, *et al.* Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. *Lancet* 2006;**367**:1665–73.

Clinical impact ratings GP/FP/Primary care ★★★★★★ IM/Ambulatory medicine ★★★★★★  
Neurology ★★★★★★ Cardiology ★★★★★★



This article contains extra text on the EBM website

**Q** In patients with recent minor cerebral ischaemia of arterial origin, is aspirin plus dipyridamole (ASA+DP) more effective than aspirin (ASA) alone for preventing vascular events?

## METHODS

**Design:** randomised controlled trial (European/Australasian Stroke Prevention in Reversible Ischaemia Trial [ESPRIT]).

**Allocation:** concealed.\*

**Blinding:** blinded (outcome auditing committee).\*

**Follow up period:** mean 3.5 years.

**Setting:** 79 hospitals in 11 European countries, Singapore, Australia, and the US.

**Patients:** 2763 patients (mean age 63 y, 65% men) who had had a minor ischaemic stroke ( $\leq 3$  on the modified Rankin scale) (66% of patients), transient ischaemic attack (TIA) (28%), or transient monocular blindness (5%) of presumed arterial origin in the previous 6 months. Exclusion criteria included a possible cardiac source of embolism, high grade carotid stenosis, blood coagulation disorder, and limited life expectancy.

**Intervention:** ASA, 30–325 mg (median 75 mg) daily, plus DP, 200 mg twice daily (83% received the extended release formulation) ( $n = 1375$ ), or ASA alone ( $n = 1388$ ).

**Outcomes:** composite end point of death from all vascular causes, stroke, myocardial infarction, or major bleeding event. Secondary outcomes included death from all causes, death from all vascular causes, death from all vascular causes or stroke, all major ischaemic events, all vascular events, first cardiac event, and major bleeding event.

**Patient follow up:** 99% (intention to treat analysis).

\*See glossary.

Abstract and commentary also appear in ACP Journal Club.

## Commentary

ESPRIT is the second randomised trial to show the superiority of ASA+DP over ASA in patients with TIA or minor ischaemic stroke. This should lead to greater confidence in the effectiveness of ASA+DP over ASA and more patients being treated with this combination. However, the number needed to treat of 104 per year to prevent 1 primary outcome suggests a small absolute benefit; cost effectiveness will be a factor in many settings. If cost remains a concern, ASA alone or combined with generic DP is a reasonable alternative.<sup>1</sup>

Patients with a possible cardiac source of embolism or significant carotid disease were excluded from this study and the results cannot be generalised to them. Patients with disabling stroke were also excluded; ASA+DP may not be cost effective compared with ASA in such patients.<sup>2</sup> Since most ESPRIT patients were randomised 1–6 months after TIA or stroke, the study does not address the matter of the best antiplatelet agent for acute stroke treatment. The non-blinding of patients and clinicians and the finding of less benefit in the “on treatment” analysis potentially undermine the validity of the main study findings.

The use of ASA+DP in patients with comorbid ischaemic heart disease has been debated. In neither trial comparing ASA+DP with ASA was the risk of cardiac events increased with ASA+DP. However, guidelines recommend against using DP for patients with chronic stable angina and advocate the combination of ASA and clopidogrel for patients with unstable angina or myocardial infarction.<sup>3–4</sup>

Aggressive management of blood pressure, cholesterol, diabetes, tobacco use, and exercise further reduces risk of recurrence after ischaemic stroke. Combined with appropriate use of ASA+DP or other antithrombotic agents, this multimodal approach should effectively reduce vascular risk.

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1 Jonas S, Grieco G. *Cerebrovasc Dis* 2006;**22**:1–3.

2 Jones L, Griffin S, Palmer S, *et al.* *Health Technol Assess* 2004;**8**(38):1–196.

3 Gibbons RJ, Abrams J, Chatterjee K, *et al.* *Circulation* 2003;**107**:149–58.

4 Antman EM, Anbe DT, Armstrong PW, *et al.* *Circulation* 2004;**110**:588–636.

## MAIN RESULTS

Risks of the composite end point, death from all vascular causes or non-fatal stroke, and all vascular events were lower in the ASA+DP group (table). Groups did not differ for death from all causes, death from all vascular causes, all major ischaemic events, first cardiac event, or major bleeding event (see table at [www.evidence-basedmedicine.com](http://www.evidence-basedmedicine.com)). 34% of patients in the ASA+DP group discontinued the study medication compared with 13% in the ASA group.

## CONCLUSION

In patients with recent minor cerebral ischaemia of arterial origin, the combination of aspirin and dipyridamole was more effective than aspirin alone for preventing vascular events.

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Sources of funding: Council of Singapore; European Commission; Janivo Foundation; French Ministry of Health; Netherlands Heart Foundation; Netherlands Thrombosis Foundation; UK Stroke Association.

## Aspirin plus dipyridamole v aspirin alone to prevent vascular events after minor cerebral ischaemia\*

Outcomes at mean 3.5 years	Aspirin + dipyridamole	Aspirin alone	RRR (95% CI)	NNT (CI)
Composite end point†	13%	16%	19% (2 to 32)	35 (20 to 347)
Death from all vascular causes or stroke	10%	12%	21% (3 to 36)	39 (23 to 287)
All vascular events	11%	14%	21% (3 to 35)	35 (21 to 257)

\*Abbreviations defined in glossary; RRR, NNT, and CI calculated from hazard ratios in article. †Death from all vascular causes, stroke, myocardial infarction, or major bleeding event.

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### Aspirin plus dipyridamole v aspirin alone to prevent vascular events after minor cerebral ischaemia at mean 3.5 years\*

Outcomes	Aspirin + dipyridamole	Aspirin alone	RRR (95% CI)	NNT (CI)
Composite endpoint†	13%	16%	19% (2 to 32)	35 (20 to 347)
Death from all causes	6.8%	7.8%	12% (–16 to 32)	Not significant
Death from all vascular causes	3.2%	4.4%	25% (–10 to 48)	Not significant
Death from all vascular causes or stroke	10%	12%	21% (3 to 36)	39 (23 to 287)
All major ischaemic events	10%	13%	18% (–1 to 33)	Not significant
All vascular events	11%	14%	21% (3 to 35)	35 (21 to 257)
First cardiac event	3.2%	4.4%	27% (–8 to 50)	Not significant
Major bleeding event	2.6%	3.9%	33% (–3 to 56)	Not significant

\*Abbreviations defined in glossary; RRR, NNT, and CI calculated from hazard ratios in article. †Death from all vascular causes, stroke, myocardial infarction, or major bleeding event.