

THERAPEUTICS

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

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

Clinical impact ratings: Cardiology ★★★★★☆ Neurology ★★★★★★

QUESTION

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

METHODS

Design: Randomized 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 Europe, Singapore, Australia, and the United States.

Patients: 2763 patients (mean age 63 y, 65% men) who had had a minor ischemic stroke (≤ 3 on the modified Rankin scale) (66% of patients), transient ischemic 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 to 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 endpoint 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 ischemic events, all vascular events, first cardiac event, and major bleeding event.

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

MAIN RESULTS

Risks for the composite endpoint, death from all vascular causes or nonfatal 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 ischemic events, first cardiac event, or major bleeding event (Table). 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 ischemia of arterial origin, aspirin plus dipyridamole was more effective than aspirin alone for preventing vascular events.

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*See Glossary.

Aspirin plus dipyridamole vs aspirin alone to prevent vascular events after minor cerebral ischemia 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 ischemic 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.

COMMENTARY

ESPRIT is the second randomized trial to show the superiority of ASA+DP over ASA in patients with TIA or minor ischemic stroke. This finding 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 (1).

Patients with a possible cardiac source of embolism or significant carotid disease were excluded from this study, and the results cannot be generalized to them. Patients with disabling stroke were also excluded; ASA+DP may not be cost-effective compared with ASA in such patients (2). Since most ESPRIT patients were randomized 1 to 6 months after TIA or stroke, the study does not address the matter of the best antiplatelet agent for acute stroke treatment. The nonblinding 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 ischemic heart disease has been debated. In neither trial comparing ASA+DP with ASA was the risk for 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 (3, 4).

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

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References

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