

ANALYSIS

What is the role of dipyridamole in long-term secondary prevention after an ischemic stroke or transient ischemic attack?

For over a decade there has been clear evidence for the benefits of antiplatelet treatment in the prevention of stroke, myocardial infarction and death in patients at high risk of serious vascular events, including people with a history of ischemic stroke or transient ischemic attack (TIA), with treatment-related reductions of about 20%–25% in the relative risk of serious vascular events.¹ Most of the randomized evidence relates to ASA, the most widely available and cheapest of all the antiplatelet drugs.¹

Randomized trials comparing the beneficial effects and hazards of different ASA doses have shown that daily doses of 75–150 mg are as effective as higher doses and are associated with fewer adverse effects. Data on ASA doses under 75 mg/d are still limited. Direct and indirect comparisons of the benefits of different doses have not shown clear differences, but the data are insufficient to conclude that those under 75 mg/d are definitely as effective as dosages of 75 mg/d or more.¹ An ASA dose of 75–150 mg/d is therefore generally seen as the standard against which other antiplatelet regimens should be compared.

The past decade has also seen the emergence of several large trials comparing alternative antiplatelet regimens with ASA. These trials have adopted 2 strategies: comparing another antiplatelet drug with ASA, or comparing ASA plus a different antiplatelet drug with ASA alone. Alternatives to ASA that have now been directly compared with ASA for long-term secondary prevention in randomized trials involving several thousand high-risk patients include dipyridamole alone or in combination with ASA, ticlopidine alone, clopidogrel alone or in combination with ASA, and triflusal. In this article I

focus on the evidence for use of dipyridamole, either alone or in combination with ASA, as alternatives to ASA alone for the secondary prevention after an ischemic stroke or TIA.

Mechanisms of action

ASA exerts its antiplatelet effect by irreversibly inhibiting the enzyme cyclooxygenase. This causes decreased production of the platelet agonist thromboxane A₂.

Dipyridamole is a pyrimidopyridine derivative with antiplatelet and vasodilator properties. Its mechanism of action on platelets remains a subject of controversy. Several possible antiplatelet actions have been observed *in vitro*, including inhibition of platelet phosphodiesterase, direct stimulation of prostacyclin release from endothelial cells and inhibition of adenosine uptake by platelets. All of these putative mechanisms result in an increase in intraplatelet adenosine 3',5'-cyclic monophosphate (cyclic AMP), which inhibits the mobilization of free calcium, central to platelet activation. Although dipyridamole is widely accepted to be an antiplatelet drug, none of these actions has been demonstrated *in vivo* at the doses of dipyridamole used in clinical practice.

Dipyridamole is also a vasodilator, and its coronary dilating effect is the reason for its use in diagnostic stress echocardiography and thallium imaging. During rapid intravenous administration in these procedures it tends to cause blood pressure to drop, but in a randomized comparison of ASA versus ASA plus 400 mg of dipyridamole orally (given daily to about 600 patients with recent cerebral ischemia of arterial origin, who were followed for an average of 15 months), the long-term oral administration of dipyridamole did not

appear to affect blood pressure.²

Evidence from randomized trials

The most recent systematic review by the Antithrombotic Trialists' (ATT) Collaboration¹ of randomized trials of antiplatelet treatments for the prevention of death, myocardial infarction and stroke in high-risk patients included all data that were available by September 1997. Although almost a decade has since passed and more antiplatelet trials have emerged, no further randomized trials have been completed comparing dipyridamole (either alone or in combination with ASA) against ASA alone. The ATT's meta-analysis of direct randomized comparisons between dipyridamole alone and ASA alone in high-risk patients found no significant difference in effect on serious vascular events, including stroke, myocardial infarction or vascular death (odds ratio [OR] 1.02, 95% confidence interval [CI] 0.85–1.21).¹ Since the largest body of evidence for the use of any single antiplatelet drug is that for ASA, and the wide confidence interval includes the possibility that dipyridamole is less effective than ASA, this implies that dipyridamole alone should not generally be considered as an alternative to ASA.

Dipyridamole plus ASA was compared with ASA alone in 25 trials in the ATT overview; overall (Fig. 1), the combination produced a nonsignificant reduction in serious vascular events (OR 0.94, 95% CI 0.83–1.06). When the separate components of the composite outcome were assessed, the combination appeared to be particularly effective in reducing nonfatal stroke (OR 0.76, 95% CI 0.62–0.92), but not nonfatal myocardial infarction (OR 1.13, 95% CI 0.89–1.44) or vascular death (OR 1.03, 95% CI 0.76–1.46; Fig. 1).

The nonfatal stroke result was derived mainly from one large study, the second European Stroke Prevention Study (ESPS-2),³ in which about 3000

patients with a previous ischemic stroke or TIA were randomly allocated to groups given ASA (50 mg) daily either with modified-release dipyridamole (400 mg) or alone.³ The other studies found no difference in nonfatal stroke outcomes between the combined drugs and ASA alone.^{1,3} The favourable results for stroke from the ESPS-2 trial could be explained by chance (since the number of patients and relevant outcome events was relatively small), the dose of ASA used (since 50 mg might be less effective than 75 mg or more daily) or the particular dose and preparation of dipyridamole used. Analyses that included only trials with ischemic stroke and TIA patients, or that considered only the ESPS-2 trial (the only study to use the modified-release preparation of dipyridamole), suggest that the combination reduces vascular events compared with ASA alone,^{3,4} but since these results are also dominated by the stroke outcomes in the ESPS-2 study, they are also subject to the possible effects of chance and the very low dose of ASA. So, although the addition of modified-release dipyridamole to ASA may re-

duce the risk of recurrent stroke and vascular events in patients with a prior ischemic stroke or TIA, in my view this remains uncertain.

The nonsignificant trend toward an increased risk of nonfatal myocardial infarction with the combination of dipyridamole and ASA (compared with ASA alone; see Fig. 1) has made some clinicians anxious about using the drug combination in patients with ischemic stroke and TIA who also have a history of ischemic heart disease and may be at high risk of subsequent infarction. Some reassurance is available from analyses restricted to trials among patients with ischemic stroke or TIA, and from a post hoc subgroup analysis of patients with prior ischemic heart disease in the ESPS-2 trial: in neither case did the combination increase the risk of myocardial infarction over that of ASA alone.^{4,5}

Adverse effects

The ATT overview found no evidence that the combination of ASA and dipyridamole caused major hemorrhage any more than did ASA alone.¹ Dipyrida-

mole is, however, associated with other adverse effects, diarrhea and headache in particular. In the largest randomized trial assessing the combination of dipyridamole plus ASA versus ASA alone,³ more premature cessations of study treatment occurred owing to adverse effects with the combination (262/1650 = 15.9%) than with ASA alone (141/1649 = 8.6%).

What should clinicians do?

Additional evidence on the effectiveness of the combination of dipyridamole and ASA will be available in a few years, from the ongoing European–Australian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT), in which some 3000 patients with a prior ischemic stroke or TIA are being randomly assigned to receive ASA alone or in combination with dipyridamole (400 mg) daily (see www.strokecenter.org/trials/TrialDetail.aspx?tid=16). Until then, recommendations for the routine use, after an ischemic stroke or TIA, of modified-release dipyridamole plus ASA rather than ASA alone (75–150 mg/d) (e.g., as per the guidelines at www.nice.org.uk/pdf/TA090guidance.pdf from the United Kingdom's National Institute for Health and Clinical Excellence) seem to me to go beyond what is justified by the current evidence.

Some stroke physicians may favour adding modified-release dipyridamole to ASA if the patient experiences an ischemic cerebrovascular event while already taking ASA, on the basis that these patients are likely to be at particularly high risk and it seems more reasonable to do something than nothing. In my view, this reaction is rarely justified. No randomized trial addressing this specific issue has been completed, and the effect of adding another medication of uncertain additional benefit may simply be to reduce compliance with those already prescribed.

It is far more important to ensure that the diagnosis is really correct and, if so, that such patients really are taking daily ASA (or an oral anticoagulant, if atrial fibrillation is present and there are no contraindications), along with an appropriate dose of a statin and adequate blood-pressure-lowering treat-

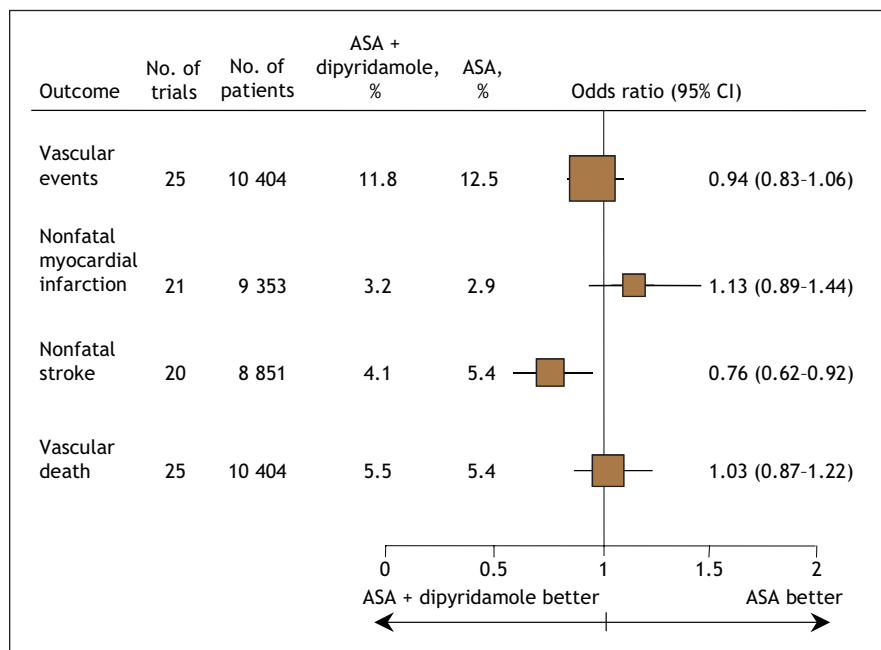


Fig. 1: Meta-analysis of randomized trials of dipyridamole in combination with ASA versus ASA alone in high-risk patients, using data from the Antithrombotic Trialists' Collaboration¹ for the effects on vascular events, combined and separately. Odds ratios are shown as squares of a size proportional to the inverse variance of the odds ratio for that outcome; the 95% confidence interval (CI) for each vascular outcome is indicated by a horizontal bar.

ment; that they have made appropriate modifications to their lifestyle (especially cessation of smoking); and, if appropriate, that they undergo an adequate and timely assessment of their suitability for carotid endarterectomy.

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Competing interests: A few years ago, I was a member of the planning committee for a proposed large, international, multicentre, randomized trial involving patients with a previous ischemic stroke or transient ischemic attack. The aim was to compare ASA alone with ASA in combination

with modified-release dipyridamole or clopidogrel. Despite the joint support of the United Kingdom Medical Research Council, the US Department of Veterans Affairs and the Canadian Institute of Health Research, further funding was required. Boehringer Ingelheim initially showed substantial interest; however, it became clear that the company was only willing to help fund the trial if we made important modifications to the protocol, including abandoning the ASA-only arm. The planning committee held to the opinion that any industrial sponsor should have no influence over the trial's design or conduct, and the trial did not go ahead.

I was involved in producing the technology assessment report commissioned by the Health Technology Assessment Programme on behalf of the National Institute for Health and Clinical Excellence (an independent organization providing guidance to the National Health Service in England and Wales) on the clinical and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events.

In 1998 I received fees from Sanofi for speaking on the Antithrombotic Trialists' Collaboration results at an educational meeting for general practitioners.

I am a member of the Antithrombotic Trialists'

Collaboration steering committee and was previously assistant coordinator of the collaboration.

I am a recently signed-up member of the No Free Lunch movement (www.nofreelunch-uk.org).

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