Is the antiplatelet effect of aspirin sufficient in atherosclerosis?

Implications for pharmacists

Vascular disease associated with atherosclerosis of peripheral, coronary or cerebral arteries can cause vascular events such as myocardial infarction (MI) and stroke — all of which are a major health burden. The antiplatelet action of aspirin is important in the reduction of vascular events in both primary and secondary thrombotic disease. Patients with a history of MI have an increased risk of developing strokes and peripheral artery disease. It is questionable whether aspirin alone is sufficient to reduce the risk of vascular events in atherosclerosis. There is some emerging evidence for combining dipyridamole and aspirin in the secondary prevention of stroke. Pharmacists therefore need to be aware of who might benefit the most from having antiplatelet therapy optimised.

FIRST PAPER

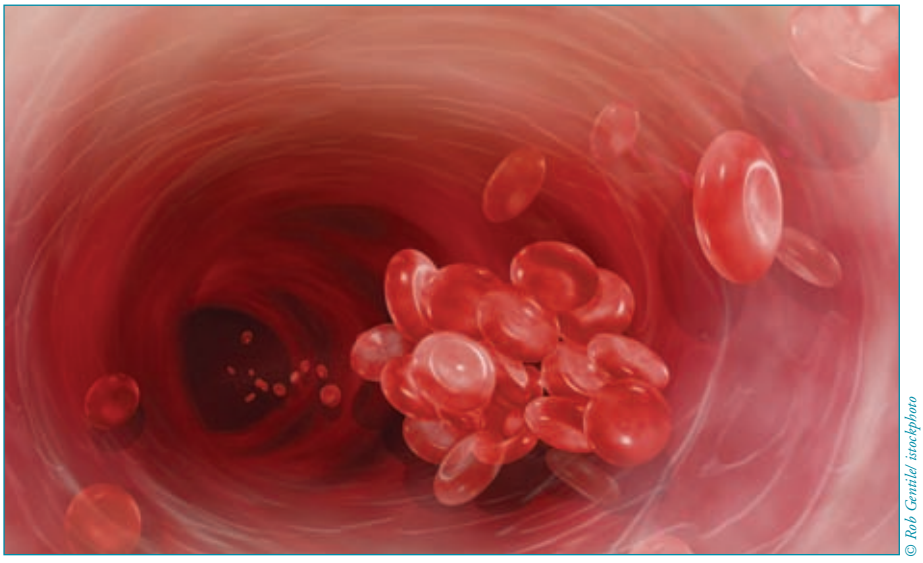
Anand *et al*. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. *NEJM* 2007; **357(3):** 217–27.

Context

Aspirin inhibits the synthesis of the potent platelet aggregator, thromboxane A_2 (TXA_2) by irreversibly inhibiting cyclo-oxygenase (COX). This lowers the risk of thrombus formation, because only newly generated platelets can aggregate, and this takes around 7–10 days.

Aspirin is often, therefore, given alone for the primary prevention of vascular events in high risk patients. Its antiplatelet effect also extends to secondary prevention of thrombotic cerebrovascular or cardiovascular disease. A myocardial infarction (MI) can result when atherosclerosis has advanced to the coronary arteries. Atherosclerosis that has advanced to the carotid and cerebral arteries can lead to a transient ischaemic attack (TIA) or stroke. Peripheral artery disease (PAD) results in atherosclerosis of large peripheral arteries. The National Service Framework (NSF) for coronary heart disease (CHD) recognises that PAD is a potential risk factor for CHD. Because atherosclerosis is often generalized throughout various arteries in the body, patients with a history of MI are more likely to develop strokes and PAD. It is important to optimise antiplatelet therapy in both primary and secondary prevention of vascular events.

The premise of this research was to investigate whether the antiplatelet effect of aspirin is enhanced by adding dipyridamole



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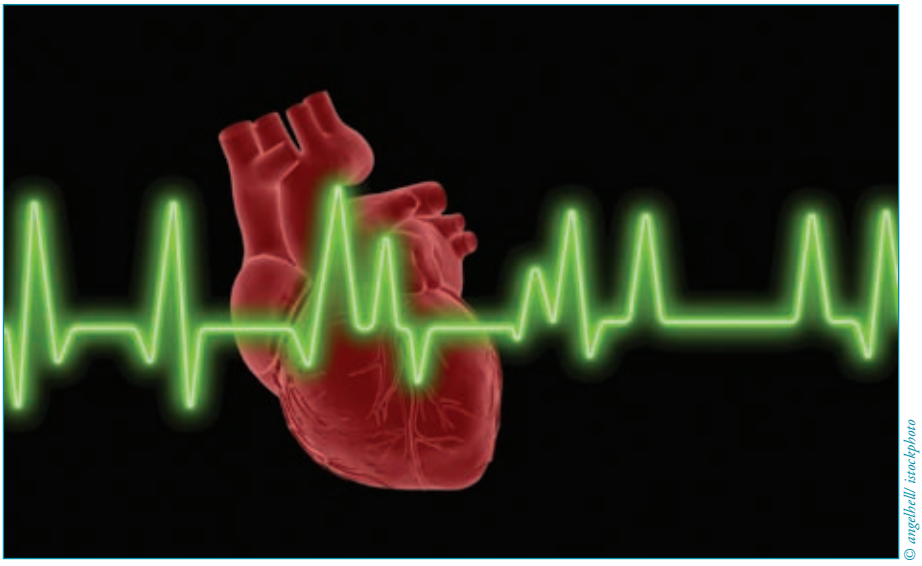

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for the secondary prevention of stroke on the basis that antiplatelet agents and oral anticoagulants both reduce the rate of vascular events.

The research

The aim of the study was to investigate whether the combination of anticoagulant and antiplatelet therapy was superior to antiplatelet monotherapy in preventing cardiovascular complications in patients with PAD. PAD was defined as atherosclerosis of the arteries of the lower extremities, the carotid arteries, or the subclavian arteries. Of the 2161 patients recruited, 1766 (81.8%) had PAD of the lower extremities with 1985 (91.9%) receiving aspirin at baseline.

In this three-year randomised, open-label trial, patients were assigned to combined oral antiplatelet and anticoagulant therapy (target international normalised ratio; INR 2–3) or antiplatelet monotherapy. Aspirin (daily dose, 81–325mg) and warfarin were the main therapies used. Patients were initially put through an active run-in phase of 2–4 weeks with combined therapy. If a stable INR, within range was achieved, patients were then further randomised to either combined or antiplatelet monotherapy. Patients were excluded if they had an indication for oral anticoagulation treatment, were actively bleeding or at high risk of bleeding, or had a stroke within six months before enrollment.

Two co-primary composite outcomes were defined. The first co-primary outcome was MI, stroke, or death from cardiovascular causes. The second co-primary outcome was MI, stroke, severe ischaemia of the peripheral or coronary arteries leading to urgent intervention, or death from cardiovascular causes.

Key findings

There was no statistical difference between each outcome based on the prevention of cardiovascular events. The first primary outcome occurred in 132 of the 1080 patients receiving combination therapy (12.2%) and in 144 of 1081 patients receiving antiplatelet monotherapy (13.3%) (relative risk [RR], 0.92, 95% confidence interval [CI], 0.73 to 1.16, P= 0.48). The second primary outcome occurred in 172 patients receiving combination therapy (15.9%) as compared with 188 patients receiving antiplatelet monotherapy (17.4%) (RR 0.91, 95% CI, 0.74 to 1.12, P=0.37). Life-threatening bleeding occurred in 43 patients receiving combination therapy (4.0%) compared with 13 patients receiving just antiplatelet therapy (1.2%) (RR, 3.41, 95% CI, 1.84 to 6.35, P<0.001).

The author's concluded that combination therapy was no more effective than antiplatelet monotherapy in prevent ing major cardiovascular complications. Treating 1000 patients with combination therapy as compared with antiplatelet monotherapy for three years would lead to 24 fewer cardiovascular events, but 28 more episodes of life-threatening bleeding.

SECOND PAPER

ESPRIT study group. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomized controlled trial. *Lancet* 2006; **367:** 1665–73.

Context

Dipyridamole is licensed for the secondary prevention of ischaemic stroke and TIA either alone or with aspirin. In comparison with the enzymatic action of aspirin on COX, dipyridamole prevents platelet adhesion and aggregation at receptor level, through the inhibition of phosphodiesterase. This action inhibits receptors located on the platelets required for their activation and expression.

Without secondary preventive treatment, patients with a TIA or ischaemic stroke of presumed arterial origin have an increased risk of a major vascular event. Aspirin has been found to prevent a minority of vascular complications and the authors question whether more can be done to reduce the risk. The addition of dipyridamole to aspirin in the secondary prevention of major vascular complications has produced conflicting results in previous trials.

The research

The aim of this study was to clarify whether

dipyridamole and aspirin combined was superior to aspirin alone in preventing vascular events after ischaemic stroke of presumed arterial origin. This was an open-label clinical trial where 2769 patients were assigned to aspirin and dipyridamole (n = 1363) or aspirin alone (n = 1376) within 6 months of a TIA or minor stroke. Dipyridamole was prescribed mostly as the extended-release formulation at a dose of 200mg twice daily. Aspirin was given at a dose range of 30–325mg daily (median dose, 75mg) depending on the physician's discretion.

The primary outcome was the composite of death from all vascular causes, non-fatal stroke, non-fatal MI or major bleeding complication, whichever occurred first. Secondary outcome events included death from all vascular causes and non-fatal stroke, all major ischaemic events and major bleeding complications.

Key findings

Over a mean follow-up of 3.5 years, primary outcome events arose in 173 (13%) on combined aspirin and dipyridamole therapy and in 216 (16%) on aspirin alone (RR 0.80, 95% CI 0.66 to 0.98; ARR 1.0% per year, 95% CI 0.1 to 1.8). Treating 104 patients with combined therapy instead of monotherapy would prevent one death from any vascular event per year. Patients taking combined therapy also discontinued treatment more often than those taking aspirin alone, mainly because of headache (470 vs 184). There were no significant differences in major bleeding complications between the groups.

Addition of this data to the meta-analysis of previous trials produced an overall risk ratio for the composite of vascular death, stroke, MI of 0.82 (95% CI 0.74 to 0.91). The authors conclude that they provide sufficient evidence for the preference of combined therapy with dipyridamole over aspirin alone as antithrombotic therapy after cerebral ischaemia of arterial origin. This study does add weight to the evidence supporting combined therapy but does not form the basis to change standard treatment because the NNT of 104 will prevent just one death. More evidence is needed with fixed aspirin doses, a double blinded approach and an emphasis on lifestyle changes and cost.

Both papers highlight that certain patient subgroups with atherosclerosis can benefit from having their antiplatelet therapy optimised. There is more supportive evidence for secondary prevention of ischaemic stroke and this appears to be the subgroup most likely to benefit in comparison with patients with PAD.

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Declaration of competing interests

The author declares that she has no competing interests.

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