The role of antiplatelet agents

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Key concepts

- Antiplatelet drugs reduce the incidence of cardiovascular events by about 20–25% in people with established cardiovascular disease or at high risk of cardiovascular disease.
- Aspirin is the most commonly used, extensively studied and cost effective antiplatelet drug. Aspirin monotherapy is appropriate for primary and secondary prevention of cardiovascular disease, but the combination of aspirin with other antiplatelet drugs, has become established for some indications.
- Clopidogrel is an effective alternative to aspirin for secondary prevention and is an effective adjunct, when added to aspirin for acute coronary syndromes, and following stenting or angioplasty.
- Aspirin is effective in the secondary prevention of stroke following non-cardioembolic stroke or TIA but the addition of extended release dipyridamole provides additional benefits.
- In people with atrial fibrillation (AF), anticoagulation (warfarin) is recommended over antiplatelet therapy for the primary prevention (in high risk patients) and the secondary prevention of cardioembolic stroke.

The oral antiplatelet drugs include aspirin, clopidogrel and dipyridamole. This article provides an overview of their current place in therapy.

Antiplatelet drugs have a major role in the secondary prevention of thrombotic cardiovascular events. Aspirin is also widely used for primary prevention in those with high vascular risk. Clopidogrel is an alternative to aspirin in allergic or intolerant patients, and in combination with aspirin it is more effective than aspirin alone in secondary prevention, following acute coronary syndromes (ACS). The combination of dipyridamole and aspirin is more effective than aspirin alone for secondary prevention following stroke or TIA.

Evidence shows that antiplatelet drugs can reduce the incidence of cardiovascular events in people with established cardiovascular disease or in people at high risk of cardiovascular disease.[1,2] It is estimated that antiplatelet drugs reduce the risk of any serious vascular event by about 25% (this figure is calculated from a reduction in non-fatal MI of 34%, non-fatal stroke of 25%, and vascular death of 17%).[3] The benefits in these high risk groups outweigh the risk such as major bleeding.[4] The evidence for benefit of antiplatelet treatment (primarily aspirin) in people at low risk of cardiovascular disease (i.e. for primary prevention) is less clear.[4]

Aspirin

Mechanism of action

Aspirin works by irreversibly inhibiting the enzyme cyclo-oxygenase (COX-1) which is required to make the precursors of thromboxane within platelets. This reduces thromboxane synthesis. Thromboxane is required to facilitate platelet aggregation and to stimulate further platelet activation. Because platelets do not have a nucleus and therefore contain no DNA, no new cyclo-oxygenase can be produced, so the effect of aspirin on platelets persists until enough new platelets have been formed to replace affected ones. This takes approximately seven to ten days, i.e. the lifespan of a platelet. Therefore the risk of increased bleeding, caused by aspirin, persists for some days after aspirin treatment has been stopped.

Aspirin also alters the COX-2 form of cyclo-oxygenase which is required in the prostaglandin pathway. This is the mechanism for the anti-inflammatory effects of aspirin at higher doses.

Therapeutic uses

In the primary prevention of cardiovascular events in people at high risk (15–20% risk of an event over five years) aspirin is the antiplatelet drug of choice, however some controversy exists (see box below).

In the primary prevention of stroke in people with AF, warfarin may be preferable to aspirin after assessment of the risk of bleeding versus the risk of embolism (see page 38).

In patients who have had a non-cardioembolic TIA or stroke (including post TIA) the combination of aspirin plus dipyridamole is more effective than aspirin alone. In situations of concomitant AF and ischaemic stroke warfarin should be used instead.

Controversy surrounds the use of aspirin for primary prevention of cardiovascular disease

The use of aspirin for primary prevention is increasingly controversial and several well controlled trials have shown that aspirin has no benefit for primary prevention of cardiovascular events, even in people at higher risk.[5] The evidence base for aspirin in primary prevention mainly involved studies almost a decade ago when statins were much less commonly used. Statins now appear to have an emerging role in primary prevention in some groups.[6] The role of aspirin and statins for primary prevention will continue to be debated.

GI adverse effects and low dose aspirin

Risk factors associated with GI bleeding and NSAID use generally also apply to the use of aspirin. These include:

- A history of upper GI bleeding
- A history of peptic ulcer disease
- Concomitant use of drugs known to increase the risk of upper GI events

General measures to reduce the risk of GI bleeding may include:

- Ensuring that a low dose of aspirin (≤100 mg) is being taken
- Ensuring that there are no contraindications to the use of aspirin (e.g. active peptic ulceration)
- Reviewing medication – the risk of serious GI complications increases significantly in people who regularly take an antiplatelet drug and an NSAID (also consider OTC medication)

If dyspepsia develops in a person taking low dose aspirin or a person on aspirin is at increased risk of GI bleeding then:

- Consider if aspirin is necessary
- Consider the use of a PPI with ongoing low dose aspirin
- A check for *H. pylori* may be indicated
- Consider a switch to clopidogrel, although there is a lack of evidence that dyspeptic symptoms will resolve and clopidogrel is not subsidised for this indication. Taking aspirin with a PPI may be safer, and more effective at preventing recurrent ulcer bleeding in people with a previous aspirin induced bleeding ulceration, than switching to clopidogrel.[7]

For a number of indications including acute ST elevation myocardial infarction (STEMI), ACS, post intracoronary stenting and following coronary angioplasty the combination of aspirin with clopidogrel is more effective than aspirin alone and is currently subsidised for three to six months, depending on the indication. In the treatment of non-STEMI most benefit of clopidogrel occurs within the first three months. Once clopidogrel is stopped, aspirin alone should be continued.[8]

It is suggested that in ACS or in acute ischaemic stroke where an immediate anti-thrombotic effect is needed, a dose of 300 mg of aspirin should be given, to enable total inhibition of thromboxane dependent platelet aggregation.[1]

For emergency administration, patients should chew and suck uncoated aspirin tablet for quickest absorption. Peak plasma levels will be achieved after 30–40 minutes (it can take three to four hours to reach peak plasma levels when using enteric coated aspirin unless the tablets are chewed).[1]

Risks and benefits

Ten to twenty fatal and non-fatal vascular events can be prevented for every 1000 people, at high risk of vascular disease, treated for one year with low dose aspirin.[9] There is an approximately two-fold increase in the risk of major bleeding (predominately upper GI) with long term treatment with low dose aspirin. For the majority of high risk people the benefit of avoiding a serious vascular event is greater than the increased risk of bleeding.

The presence of uncontrolled hypertension in a person taking low dose aspirin may increase the risk of a haemorrhagic stroke or major GI bleeding.

Gastrointestinal effects

Aspirin use has long been associated with an increased risk of GI bleeding.[10] The risk of GI bleeding with aspirin use increases as the dose increases. A meta-analysis of

31 randomised controlled trials showed people taking aspirin at a dose of more than 100 mg daily, had a rate of bleeding complications that was approximately three times higher, than for people taking aspirin doses of less than 100 mg.[11]

The risk of GI bleeding in people taking low dose aspirin is lower than the risk for people taking standard doses of NSAIDs (a two-fold increase in risk compared to a five fold increase in bleeding in people taking NSAID for musculoskeletal pain).[12]

There is no convincing evidence that enteric coated aspirin reduces the risk of GI bleeding when low doses (75–100 mg) are used and some evidence that the enteric coating significantly reduces the bioavailability of aspirin particularly for people with a higher BMI.[13]

If dyspepsia becomes a concern in a person taking low dose aspirin it is recommended that general measures are taken to reduce risk (see box). Other medication that can cause dyspepsia should be reviewed e.g. NSAIDs, corticosteroids.

Clopidogrel

Mechanism of action

Clopidogrel is a thienopyridine that reduces platelet activation and aggregation by inhibiting the binding of ADP to its platelet receptor. Clopidogrel appears to have a similar permanent effect on platelet function to aspirin. After the drug is stopped, normal platelet function is only restored as new platelets are produced.[3]

Therapeutic uses

In the secondary prevention of atherothrombotic disease, the CAPRIE study[14] demonstrated that clopidogrel is at least as effective as aspirin but its higher cost has prevented it from superseding aspirin for this indication. In practice, monotherapy with clopidogrel is mainly used for secondary prevention as an alternative in people who are allergic to or intolerant of aspirin. There is little evidence to support the use of clopidogrel for primary prevention.

Combination therapy with clopidogrel and aspirin is now established in acute STEMI, ACS, post intracoronary stenting and following coronary angioplasty. For these indications, several major trials (CURE, CLARITY, COMMIT)[15–17] have shown reduced secondary events and decreased mortality with the addition of clopidogrel to aspirin compared with aspirin monotherapy.[5] Taking both clopidogrel and aspirin is not routinely recommended for people who have had a TIA or ischaemic stroke because of an increased risk of haemorrhage.[14]

The recent ProFESS trial,[18] on over 20,000 patients within 120 days of a non-cardioembolic ischaemic stroke, has provided good quality evidence that clopidogrel alone (75 mg daily) is as effective as aspirin (25 mg) plus dipyridamole (slow release 200 mg twice per day) in the secondary prevention of ischaemic stroke, but clopidogrel is not currently subsidised for this indication.

Clopidogrel is available on special authority as an additional antiplatelet agent for patients who have had one of the following:[19]

- An acute MI
- Chest pain at rest for more than 20 minutes duration, requiring hospital admission for more than 24 hours
- A troponin T or troponin I test result above the upper limit of the reference range
- A revascularisation procedure
- Patients awaiting revascularisation, post stenting and documented stent thrombosis
- Aspirin allergy (defined as a history of anaphylaxis, urticaria or asthma within four hours of ingestion), and any of the indications listed above and also for TIA or stroke, or severe symptomatic peripheral vascular disease.[19]

Dipyridamole

Mechanism of action

Dipyridamole has both antiplatelet and vasodilating properties. It is thought to act primarily to reduce platelet aggregation but it also has other inhibitory effects on various enzymes that are required for normal platelet function.

Therapeutic uses

For the secondary prevention of stroke following non-cardioembolic TIA or stroke, combination treatment with dipyridamole (as the extended release formulation) and low dose aspirin has been shown to produce more benefit than aspirin alone.

Most of the evidence comes from two trials; ESPS-2 and ESPRIT.

In ESPS-2, the stroke rate at 24 months follow up was significantly reduced in the aspirin plus dipyridamole group compared with aspirin alone (absolute risk reduction 3%).

In the ESPRIT trial, death from all vascular causes, non-fatal stroke, non-fatal MI, or major bleeding complication after a mean follow-up of 3.5 years, was significantly lower in the combination group compared with aspirin alone (absolute risk reduction 1% per year).

Therefore there is considerable debate about the cost effectiveness of adding dipyridamole to aspirin for these indications and some experts still consider that aspirin alone should remain the first line treatment. However most current international guidelines recommend aspirin plus dipyridamole (or clopidogrel monotherapy in aspirin allergic patients) as the preferred treatment.[20]

Aspirin plus dipyridamole is recommended for up to two years after the most recent ischaemic event. After this time aspirin alone can be used (unless there are ongoing ischaemic events).[21]

Currently dipyridamole is only subsidised if a person continues to have TIAs whilst taking aspirin or is aspirin intolerant (aspirin induced asthma, urticaria, anaphylaxis, or significant aspirin induced bleeding excluding bruising). This restriction is currently under review.

Dipyridamole is also available on special authority for use in patients who have prosthetic heart valves and after CABG surgery.[19]

Adverse effects

Dipyridamole can cause a range of unpleasant adverse effects. Effects such headache, dizziness, nausea and diarrhoea may occur but are usually short lived and most patients can persevere with treatment. Rarely symptoms of ischaemic heart disease, particularly angina, can become worse with dipyridamole use. Dipyridamole should therefore be used cautiously in people with severe coronary artery disease including unstable angina, recent MI and heart failure. It may also exacerbate migraine, postural hypotension and myasthenia gravis.

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