COMMENTARY

Counting the true cost of antiplatelet therapy for stroke prevention

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Antiplatelet therapy is highly cost effective in reducing the risk of occlusive vascular events (OVEs) in high-risk patients. There is now powerful evidence from 195 randomised trials that antiplatelet therapy reduces the risk of serious vascular events (non-fatal stroke, myocardial infarction or vascular death) by about one quarter in high-risk vascular patients [1]. Although there is accumulating evidence for the effectiveness of new antiplatelet therapies in cerebrovascular disease (both clopidogrel and modified release (MR) dipyridamole are licensed for the secondary prevention of OVEs), their use remains limited, and the cornerstone of preventive therapy remains aspirin when used alone or in combination with other agents [2]. The actual drug costs of these therapies are not insignificant, although aspirin when used alone is extremely cheap (£4.81 for 2 years) and thereby cost effective when widely used for secondary prevention. In comparison, the combination of aspirin/MR dipyridamole (Asasantin Retard) increases this by £237.25. Clopidogrel when used alone as an alternative would cost £920.58 over a similar period [3].

The National Institute for Clinical Excellence was recently invited to conduct an appraisal of clopidogrel and MR dipyridamole in the secondary prevention of occlusive vascular events and provide guidance on its use to the NHS in England and Wales. The final appraisal, which is available on their website [2], advises:

As part of the prevention of occlusive vascular events in patients who have had an ischaemic stroke or TIA

- The combination of MR dipyridamole and aspirin is recommended for a period of 2 years from the most recent event. Thereafter, or if MR dipyridamole is not tolerated, preventative therapy should revert to standard care (including long-term treatment with low-dose aspirin).
- Clopidogrel alone (within its licensed indications) is recommended for people who are intolerant of low-dose aspirin and either have experienced an occlusive vascular event or have symptomatic peripheral arterial disease.

Following acute ischaemic stroke, it has been estimated that in patients treated for a mean duration of 3 weeks, early aspirin therapy is associated with an 11% proportional reduction in vascular events. This equates to four fewer patients with a non-fatal stroke and five fewer patients dying from a vascular cause for every 1,000 treated [4, 5]. Beyond the acute phase of stroke, longer-term aspirin therapy is associated with substantial further reductions in vascular risk; 36 fewer serious vascular events including 25 fewer non-fatal strokes per 1,000 patients treated over an average of 29 months [1].

Beyond the evidence for aspirin, other secondary prevention trials have shown that clopidogrel is at least as effective as aspirin [6] and one trial suggests that the addition of MR dipyridamole to aspirin also confers additional benefit to that of aspirin alone [7].

Antiplatelet medication is not without risk, however. Following acute treatment with aspirin the clinical trial evidence suggests there may be two more extracranial bleeds per 1,000 patients treated and in the longer term 1–2 additional major extracranial bleeds per 1,000 patients per year [1].

Bleeding side-effects with clopidogrel alone or the combination of aspirin and MR dipyridamole were similar to the aspirin alone groups in the major comparative trials [6, 7]. It would appear, however, that adding aspirin to clopidogrel in high-risk ischaemic stroke or TIA patients confers little additional benefit and is associated with an increased risk of life-threatening and major gastrointestinal (GI) bleeding [8]. Despite these concerns the benefits of antiplatelet therapy still clearly exceed the risk of major bleeding in the majority of study populations.

Beyond the manifest bleeding risks of antiplatelet therapies it is important to consider tolerability. Low levels of tolerability can lead to poor concordance and therefore reduced treatment effect. The implications of this in terms of need for GI investigations, co-prescription of antacids, proton pump inhibitors, or failure to prevent major vascular events is not known. Approximately 1 in 10 patients withdrew from antiplatelet therapy in the CAPRIE trial [6]; 11.94% withdrew from clopidogrel and 11.92% from aspirin due to all adverse events. Concurrent with this additional risk of antiplatelet side-effects, there may be a high level of underlying GI symptoms; for example in the ESPS2 trial [7].
comparing dipyridamole with or without the addition of aspirin, 28% of the placebo group reported GI side-effects, 30% on dipyridamole, 32.8% on aspirin plus dipyridamole and 30.4% on aspirin alone. Thus, patient risk is likely to be influenced not only by the choice and dose of antiplatelet therapy used but also their underlying GI risk.

Although clinical trials have previously focused upon the overt bleeding risks, there is a wide spectrum of adverse GI effects relating to aspirin therapy in particular. These range from an inability to tolerate the drug because of dyspepsia with endoscopically normal mucosa, to erosions and ulcers whether symptomatic or not. The gastrotoxicity of aspirin therapy appears to be dose related [9] and there is no evidence that higher doses (>160 mg) are more effective than lower doses (75–150 mg) [1]. Furthermore, it has been estimated that approximately one-third of subjects taking aspirin will have endoscopically visible lesions within one hour of ingestion and up to 10% of patients taking low-dose aspirin (10–300 mg/day) for 12 weeks may have endoscopic gastric ulcers [10]. The complications of ulcers (i.e. bleeding and perforation) may be further aggravated by the anaemia-mostatic effects of aspirin.

Factors associated with increased risk of ulcer type complications include advancing age, past history of peptic ulcer disease, use of concomitant NSAIDs or drugs such as steroids or anticoagulants [11].

The issue is further complicated by infection with Helicobacter pylori. This is associated not only with changes in GI physiology but also with increased risk of peptic ulceration [12]. Both H. pylori and aspirin therapy are independent and synergistic risk factors for peptic ulceration [13]. The combination also increases risk of complications [14, 15]. Furthermore, eradication of H. pylori in combination with long-term acid suppression therapy in low-dose aspirin users has been shown to reduce the risk of ulcer recurrence and long-term complications of peptic ulceration [16]. The prevalence of H. pylori infection in an ischaemic stroke population may be as much as 69% [17] and it has been estimated that up to 80% of 80 year olds may be infected. Older people are at greatest absolute risk of vascular disease and thus potentially have the most to gain from antiplatelet therapy. The risks/benefits of antiplatelet drugs in older people may, however, differ from those demonstrated in the clinical trials and in some older people preventive antiplatelet therapy may be withheld or be discontinued because of reduced GI tolerability or perceived risk of GI ulceration.

With increasing trial evidence, the population of at-risk patients who could potentially benefit from antiplatelet medication is widening. However, with increasing age and co-morbidity there may be a divergence of risk of complications compared to the trial populations. There are also little data on concordance with therapy in our target groups. In order to realise the maximum benefits of antiplatelet therapies in an ageing population we need to be able to deliver this simple intervention to the maximum number of appropriate patients as possible. To enable such an approach we need to increase our understanding of the age-related changes in the GI tract [18] and the role played by co-morbidity, co-prescription and H. pylori infection. From this we may develop simple interventional strategies, improve tolerability and reduce the GI side-effects of antiplatelet therapy.

In our pursuit to reduce the risk of overt vascular events we need to consider not just the cost benefits of antiplatelet therapies based upon clinical trial evidence but also that which influences patient concordance, namely GI tolerability, and its subsequent management. Guidelines for the widespread prescribing of antiplatelet therapies need to be complemented by evidence-based guidance on how and what to prescribe in patients with a history of GI symptoms, previous GI bleeding and in patients who develop symptoms whilst taking antiplatelet therapies.

Key points
- Antiplatelet therapy is highly cost effective in reducing the risk of occlusive vascular events.
- In the large randomised trials one-third of patients had underlying GI symptoms.
- Gastrointestinal infection with H. pylori is common in older people and may increase the risk of complications in patients receiving antiplatelet agents.
- The clinical effectiveness of antiplatelet therapy is likely to be influenced by tolerability.
- Reducing the risk of overt vascular events in older patients with antiplatelet therapy requires consideration of tolerability and strategies to improve concordance.

References

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