How important is it to keep taking the aspirin?

Stan Heptinstall

Cardiovascular Medicine, School of Medicine, University of Nottingham, Nottingham, UK

Those with cardiovascular disease or cerebrovascular disease who are prescribed low-dose aspirin to reduce the risk of a further thrombotic event are advised to take the aspirin for the rest of their lives (1). But do they do so? And if not, why not? And if they do discontinue, what are the disadvantages concerning further cardiovascular events? And what are the advantages regarding reduced side effects such the incidence of upper gastrointestinal bleeding? And finally, what is the overall cost to the health service of aspirin discontinuation?

In this edition of *Thrombosis and Haemostasis* Cea Soriano et al. (2) describe their attempts to answer these questions. They used The Health Improvement Network (THIN) primary care database to identify 39,513 patients aged 50–84 years during 2000–2007 who received a first prescription for low-dose aspirin (75–300 mg/day) for secondary cardiovascular prevention, and followed these up to see what happened. In summary, here is what Cea Soriano et al. found:

**How many patients stopped taking aspirin?**

The authors say that approximately 30% of the patients stopped taking aspirin, and this number concurs with data from earlier investigations (3, 4). It is stated that there were no significant differences between patients who discontinued and those who continued with their medication in terms of age, sex, cardiovascular risk factors and comorbidities.

**Why did they stop taking aspirin?**

A manual review of patient profiles identified non-adherence as the main reason for aspirin discontinuation. This accounted for 70% of the patients and included forgetfulness and lack of perceived therapeutic benefit. About 12% of patients stopped taking aspirin because of a change in treatment, and less that 10% stopped through safety concerns. It was estimated that only 10% of patients switched to over-the-counter aspirin as a replacement for prescribed aspirin, and that this should not have affected the study results.

**What are the disadvantages of discontinuation?**

Detailed analysis of those patients who discontinued aspirin compared with controls who remained on aspirin determined that discontinuing aspirin led to eight extra cardiovascular events per 1,000 patients per year. There were five additional coronary events (non-fatal myocardial infarction [MI]) and three additional cerebrovascular events (not fatal or fatal ischaemic stroke). The data confirms previous data pointing out the association with a significant increased risk of MI and stroke (5–9). Extrapolation of the data extracted by Cea Soriano et al. to the whole population of the UK suggests that an additional 12,786 cases of MI and 7,672 cases of stroke will arise consequent to aspirin discontinuation.

**What are the advantages of discontinuation?**

The most common major bleeding disorder associated with aspirin use is upper gastrointestinal bleeding (10), so to what extent was this reduced in aspirin discontinuers? Actually, the number is very low. It works out at a reduction of 0.4 events per 1,000 patients per year, which equates to a UK total of 1,023 cases. It is stated that there was no significant association between the use of aspirin and the risk of haemorrhagic stroke. Thus the disadvantages of discontinuation as evidenced by increased thrombosis would seem to far outweigh the advantages of reduced bleeding, as attested to previously by others (11–15).

**How much does it all cost?**

Taking into account both the increased incidence of cardiovascular events after aspirin discontinuation which is estimated to cost the UK Health Service an additional £102 million, and the savings associated with not treating upper gastrointestinal bleeding estimated at £2 million, it can be seen that continuation of aspirin treatment could save the Health Service about £100 million/year.

**Is there anything else should be considered?**

This study looks at the issues concerning aspirin use, but the authors suggest that further studies should be performed regarding the use of other antiplatelet agents including the P2Y<sub>12</sub> antagonists clopidogrel and ticagrelor.

Finally, what about the effectiveness of aspirin in the treated patients? The aspirin doses used in the study population was 75–300 mg/day. The rationale for low-dose aspirin, of course is to inhibit platelet cyclooxygenase leading to reduced platelet function through inhibition of synthesis of thromboxane A<sub>2</sub>, with no or little effect on vascular cyclooxygenase thus maintaining synthesis of prostaglandin I<sub>2</sub> (prostacyclin) and other vascular prostaglandins that act as natural inhibitors of platelet function.
What is not known is how effectively aspirin inhibits platelet function in individual patients.

Since there are clear advantages to maintaining aspirin treatment in patients at risk of thrombosis perhaps it would also be worthwhile checking that the dose of aspirin administered to an individual patient has the required effect? Certain doses of aspirin are more effective in some patients compared with others and there may be a case for more frequent dosing in some patients (16, 17). Nonetheless, determinants of aspirin “efficacy” (at least when assessed by surrogate markers) may be multifactorial and associated with various clinical comorbidities [18–20].

Although it is not that easy to check that vascular prostaglandin synthesis is unaffected by the aspirin, it is relatively easy to check its effectiveness as an inhibitor of platelet function. This is best done using measures that are specific to cyclooxygenase activity such as arachidonic acid-induced platelet aggregation or P-selectin expression (21, 22).

Conflicts of interest
S. Heptinstall is director of Platelet Solutions Ltd. which is engaged in producing easy-to-use approaches to platelet function testing.

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References