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Low-dose aspirin for preventing CVD

BY KEVIN MC NAMARA

An older man, Brian, comes into the pharmacy seeking the pharmacist’s advice on low-dose aspirin. He has heard it stops heart attacks and all his friends take it. What advice would you give?

How does low-dose aspirin work?

Aspirin is one of the key agents used for long-term secondary prevention of cardiovascular disease (CVD), and became the world’s most widely used drug of the 20th Century.1 Where lipid-modifying agents act on the underlying causes of CVD (i.e. atherosclerosis), aspirin and other antiplatelet act to prevent the acute manifestation of cardiovascular events i.e. the development of clots in the bloodstream. Aspirin prevents thrombus formation by inhibiting the activity of the platelet enzyme cyclooxygenase (COX). By irreversibly acetylating the active site of COX it prevents production of thromboxane A2, a powerful platelet aggregating agent. This essentially inhibits thrombus formation.2,3

Irreversible binding to the COX enzyme means that it continues to exert an effect for the lifespan of the platelet, typically about 10 days, despite aspirin’s short half-life of 15–20 minutes.3

Aspirin can bind to both COX-1 and COX-2 enzymes. The antiplatelet effect is mediated via COX-1 and can be inhibited by lower doses of aspirin than that required for inhibiting the COX-2 pathway. The COX-2 pathway, which mediates pain and inflammation, requires a higher dose. Thus long-term

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LEARNING OBJECTIVES

After reading this article, pharmacists should be able to:

- Recognise the role of low-dose aspirin as an antiplatelet in secondary CVD prevention
- Understand the adverse effects of low-dose aspirin and the impact on patient use
- Discuss the increased risk of bleeding (especially GI bleeding) in patients taking low-dose aspirin.


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CVD prevention requires a lower dose of aspirin than that required for analgesia. Low-dose aspirin is generally defined as 75–150 mg daily. The Antiplatelet Trialists’ Collaboration conducted one of the most thorough assessments of this issue, via a meta-analysis involving 195 randomised controlled trials. This study identified that aspirin in this low dose range is an effective long-term antithrombotic, with a proportional reduction in vascular events of 32%. The same study suggests that higher daily doses of aspirin for long-term prevention (160–325 mg) did not lead to any improvement in efficacy. This effect was actually hypothesised several decades previously when its initial mode of action was discovered. Using lower doses is thought to be preferred because it preserves the production of another prostaglandin called prostacyclin. Prostacyclin is largely generated by COX-2 within vascular endothelial cells, and its effects are essentially the opposite of thromboxane A2 – it causes vasodilation, and prevents platelet aggregation. Other mechanisms of action for aspirin have been explored but their clinical importance largely remains to be confirmed.

A few trials of lower dose aspirin (less than 75 mg) vs aspirin 75 mg or greater suggest no significant difference in outcomes. However, the absence of extensive trial data compared with those exploring doses of 75–150 mg means that some uncertainty remains about promoting doses less than 75 mg daily.

Who should use low-dose aspirin?

Indications for low-dose aspirin in CVD prevention have been widely explored, but some debate remains. There is quite compelling evidence of benefit for patients who have previously experienced a cardiovascular event, including ischaemic stroke or mini-stroke (transient ischaemic attack) and acute coronary syndrome (myocardial infection or unstable angina). In such patients, meta-analyses involving data from several hundred randomised controlled trials suggest that for every 1,000 treated patients with a stroke, there were 36 fewer vascular deaths over an average follow-up period of 27 months; for every 1,000 treated patients with previous stroke or transient ischaemic attack (TIA), there were 36 fewer vascular deaths over 29 months; and for every 1,000 treated patients with high-risk conditions, there were 22 fewer vascular deaths over 29 months.

The role of aspirin in primary prevention has been heavily debated, after numerous conflicting randomised controlled trials (RCTs) and meta-analyses. One of the most comprehensive meta-analysis of six large primary prevention trials, with over 90,000 participants, suggests that the proportional reductions in major coronary events and ischaemic stroke are relatively similar to those for secondary prevention, but vascular mortality was not significantly reduced. More importantly, the absolute benefits in primary prevention trials were much lower than for secondary prevention studies, simply because the baseline levels of risk are lower for relatively healthy individuals. The opportunity for benefit in these trials did not appear to improve in the presence of key risk factors such as hypertension or diabetes, and nor did there appear to be any age- or gender-specific benefit. However, various trials are currently underway, including the ASPREE study in Australia, which might provide important evidence in underexplored subgroups such as the elderly and those with diabetes. Overall, trials to date have demonstrated little or no benefit from aspirin therapy in primary prevention of CVD, and any apparent benefits appear to be outweighed by bleeding complications, both in terms of gastrointestinal disease and haemorrhagic stroke. The continued recommendation of low-dose aspirin for this patient group has become hard to justify. Currently, the Heart Foundation does not support use of aspirin for individuals with no known coronary heart disease. Internationally, there are conflicting views in different guidelines and this may well reflect different physician attitudes in Australia. While it has been somewhat controversial in recent decades, recent data suggests aspirin may be of benefit to prevent the initial onset, and the recurrence of venous thromboembolism (VTE). Although the relative proportion of plateau is low in VTE compared with other clots, their role remains pivotal. Conversely, the routine use of low-dose aspirin (or any antiplatelet) for management of atrial fibrillation has become controversial and is increasingly discouraged in favour of anticoagulation for individuals requiring an antithrombotic effect.
**When aspirin is not appropriate?**

As an extensively researched drug the major contraindications for aspirin are well-documented, and include active peptic ulceration, an allergy to aspirin, bleeding disorders (e.g. thrombocytopenia, haemophilia), and aspirin-sensitive asthma.

As mentioned above, it is largely the bleeding risk associated with aspirin that makes it unsuitable for use in primary prevention. It is important to note that there is no evidence of a significant reduction in bleeding risk conferred through use of low-dose vs high-dose aspirin. Also, there is a concern that bleeding risk might not be reduced through use of enteric-coated formulations. The Antithrombotic Trialists' Collaboration found that the proportional increase in risk of major extracranial bleeds (generally requiring hospitalisation or blood transfusion) associated with antiplatelet use was about half. This proportional increase was roughly the same for all aspirin doses less than 325 mg daily. In summary, low dose may not mean low risk of bleeding.

Low-dose aspirin should also be used with caution in patients with severe kidney disease as it can lead to increased risk of both bleeding, and further deterioration of kidney function through its inhibition of renal prostaglandin synthesis.

Low-dose aspirin is considered safe in pregnancy (Australian Category C) and breastfeeding at doses up to 150 mg; higher doses should be avoided. It is usually advisable to stop aspirin seven days prior to surgery, with the possible exception of coronary artery bypass grafting. Myocardial infarction is the most common major vascular complication that occurs after non-cardiac surgery, but aspirin also significantly increases bleeding risk postoperatively – hence risks and benefits need to be weighed against each other.

**Can I take low-dose aspirin with other medicines?**

Some drug-drug interactions associated with higher dose aspirin (e.g. increased valproate concentration, increased salicylate clearance with corticosteroids) are less likely or do not occur with low-dose aspirin, hence as a pharmacist be mindful when advising patients in this regard.

Caution is required when aspirin is given with other drugs that can also increase bleeding risk such as warfarin. Because aspirin is extensively protein bound, protein binding displacement appears to be the basis for several interactions with drugs such as the NSAIDs ibuprofen and naproxen. Consequently, NSAIDs are also capable of reducing the antiplatelet effect of aspirin. Some studies have found that regular use of NSAIDs – defined as 60 days per year or more in one study – alongside low-dose aspirin, may double or treble the risk of myocardial infarction compared with aspirin alone. Intermittent use of an NSAID appears unlikely to exert such an effect. It is recommended, where NSAID use is unavoidable, to use to the lowest effective dose for the shortest duration possible. Proton pump inhibitors and histamine H₂-receptor antagonists appear to effectively reduce the incidence of ulcers in individuals treated long-term with low-dose aspirin. However, the long-term cost and risks of such treatment have been questioned, and the addition of such adjuvant therapy should be applied with due consideration.

Unlike most other COX inhibitors, low-dose aspirin does not affect blood pressure control, most likely related to an absence of any effect on renal prostaglandin synthesis. There have been suggestions that aspirin might reduce the efficacy of angiotensin-converting-enzyme (ACE) inhibitors for treatment post-acute myocardial infarction, or for treatment of hypertension, but there is no evidence that this occurs. There is some evidence that low-dose aspirin might reduce the gastrointestinal safety benefits of selective COX-2 inhibitors, compared with traditional NSAIDs, but this remains to be confirmed.

**Pharmacist counselling**

As with any preventive medicine, monitoring patient adherence with therapy is important. As a pharmacist, this is an area where ongoing advice and patient monitoring on aspirin use can be incredibly valuable. The key difficulty with its use is to minimise the risk of bleeding – long-term use of low-dose aspirin roughly doubles the risk of major extracranial bleeding (mostly upper GI bleeding), or in other words about 1–2 excess major bleeds each year for every 1,000 treated patients. Monitor patients for signs of bleeding, review strategies for reducing the risk of bleeding and review the appropriateness of concomitant therapy. Do not advise individuals to take aspirin on alternate days rather than once daily, as individual variation in the rate of platelet regeneration may lead to varying durations of platelet inhibition. Encourage the patient to take aspirin with food, and not to crush enteric-coated capsules. Your advice becomes particularly important if patients seek to buy this product over the counter. No prescription is required for aspirin in packs of less than 100 tablets/capsules, whereas aspirin is the only active ingredient and the product is clearly labelled for use in the prevention of cardiovascular disease. However, it is highly recommended to refer patients to GPs to discuss initiation of therapy. This decision requires a thorough evaluation of the patient's entire medical history, and patients may not be able to accurately report to pharmacists on key previous diagnoses that affect the decision. Given the changing nature of clinical guidance on aspirin use at this time, it is very important that health messages delivered to the patient are consistent.
COUNSELLING IN PRACTICE
CONTINUING PROFESSIONAL DEVELOPMENT

It is equally important to make sure that patients tell their GPs if they are taking OTC aspirin. As mentioned above, there is a range of drugs that can interfere with the efficacy and bleeding risk associated with aspirin. The current uncertainty around the need for aspirin therapy in primary prevention might also result in conflicting messages to patients if prescribers are not involved with the discussion. If a patient has been advised by their GP to take aspirin, it is likely due to a high risk of CVD. Some patients who may currently be taking aspirin, but have no history of CVD, should be advised to review the need for this therapy with their doctor in light of recent debates.

Advising Brian

In the scenario above, it turned out that the patient in question did not have a history of heart disease. He was interested because his wife had just had a heart attack and had been prescribed low-dose aspirin. You explain that aspirin is probably not appropriate in his case, but advise him that he can improve his cardiovascular health in other ways. You offer to conduct a ‘heart health’ screening program and communicate results to his GP, provide some educational materials and work with him to develop practical strategies to help him and his wife improve their health behaviours.

TAKING HOME MESSAGES

- The optimal dose of aspirin for long-term CVD prevention is between 75 mg and 150 mg daily.
- The evidence for aspirin use in secondary prevention of CVD is extensive. Justification for use in primary prevention is very uncertain.
- Enteric coated aspirin tablets and capsules may not offer additional protection from bleeding. Hence it is important to continue monitoring for signs of bleeding.
- Regular NSAID use may reduce the antiplatelet effect of low-dose aspirin and increase CVD risk.

References


1. For which of the following conditions does low-dose aspirin use have the MOST evidence?
   a) Peripheral oedema.
   b) Primary prevention of heart disease.
   c) Atrial fibrillation.
   d) Transient ischaemic attack (TIA).

2. Which of the following is NOT an absolute contraindication for use of low-dose aspirin?
   a) Haemophilia.
   b) Hypertension.
   c) Peptic ulceration.
   d) Aspirin-sensitive asthma.

3. Based on available evidence, what is the MOST appropriate dose of aspirin for the secondary prevention of CVD?
   a) 30–75 mg once daily.
   b) 75–150 mg once daily.
   c) 160–325 mg once daily.
   d) 150–300 mg on alternate days.

4. Which of the following have clinically important drug-drug interactions with low-dose aspirin?
   a) Sodium valproate.
   b) Warfarin.
   c) Naproxen.
   d) B and C only.

5. Which of the following statements is TRUE?
   a) Low-dose aspirin reduces the proportion of heart disease by about 15%.
   b) The rate of excess bleeding incurred through aspirin use is about 1–2 bleeds per year for every 1,000 patients.
   c) Part of the efficacy of low-dose aspirin is through the inhibition of prostacyclin.
   d) None of the above.