Aspirin: Friend or Foe?

Elmien Bronkhorst
Hanneke De Klerk
School of Pharmacy, Sefako Makgatho Health Sciences University (SMU)

Correspondence to: Elmien Bronkhorst, e-mail: elmien.bronkhorst@smu.ac.za

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Abstract
Aspirin can be regarded as one of the oldest drugs still in use in modern-day medicine. Since 1979, different actions of aspirin have been flourishing, including the acetylation of platelet cyclooxygenase, which inhibits thromboxane formation and explains its antithrombotic effects. Since those first reports, aspirin remains the cornerstone of antiplatelet therapy for different indications. Low-dose aspirin is the single most cost-effective medicine for the prevention of the secondary events of thrombosis.

Low-dose aspirin has been found to selectively inhibit the synthesis of thromboxane A2, by preferentially inhibiting the COX-1 isozyme, without having much effect on prostacyclin. It has been indicated in the prevention of colon cancer, cardiovascular diseases, such as myocardial infarction, strokes and atherothrombotic events, as well as the reduction in risk of developing pre-eclampsia during pregnancy.

Low-dose aspirin does not increase blood pressure, cause renal impairment, or interfere with the antihypertensive effects of angiotensin-converting enzyme (ACE) inhibitors or diuretics. Many of the risk factors, like risk for bleeding, gastrointestinal bleeding and intracranial haemorrhage, increase with age. Every patient’s treatment needs to be individualised to decide whether the potential benefits outweigh any potential harm.

The benefits in secondary prevention are favourable, and efforts should be made to ensure that all patients with symptomatic cardiovascular or cerebrovascular disease are treated with low-dose aspirin on a regular basis.

Introduction
Aspirin can be regarded as one of the oldest drugs still in use in modern-day medicine. Aspirin was derived from the bark of the willow tree, which was prescribed by Hippocrates around 500 years ago to relieve pain and fever. In 1928, salicin was purified and proposed as the main component with antipyretic activity from the willow extract. Acetylsalicylic acid was originally marketed by Bayer Laboratories as aspirin, which has become the generic name of this substance in many countries. Aspirin was used widely as a household medicine for the treatment of pain, fever and inflammation, although the mechanism of action was unknown. It was only in the early 1970s that it was shown that aspirin suppressed the production of some eicosanoid-like prostaglandins. Since 1979, different actions of aspirin have been flourishing, including the acetylation of platelet cyclooxygenase, which inhibits thromboxane formation and explains its antithrombotic effects. Since those first reports, aspirin has remained the cornerstone of antiplatelet therapy for different indications. Numerous reports have followed on the prevention of colon cancer, cardiovascular diseases, such as myocardial infarction, strokes and atherothrombotic events, as well as the reduction in risk of developing pre-eclampsia with regular intake of low-dose aspirin during pregnancy.

Low-dose aspirin is the single most cost-effective medicine for the prevention of the secondary events of thrombosis.

Mechanism of action of aspirin
Platelets participate in the development of atheromatous plaques and are key cellular components of arterial occlusive thrombi. This can be viewed, for example, as a physiological repair response to an acute vascular lesion, mediated through thromboxane A2. Prostanoids, like prostacyclines, prostaglandins and thromboxane, are produced by the action of cyclooxygenase (COX) 1 and 2. These enzymes are inhibited by the actions of aspirin. When arachidonic acid interacts with 5-lipoxygenase, leukotrienes are produced, which also act as important mediators of inflammation.

Aspirin is considered the prototype for nonsteroidal anti-inflammatory drugs (NSAIDs) that have salicylic acid as the active agent. Salicylic acid is composed of a benzene ring with two radicals, one a hydroxyl group, and the other, a carboxyl group.
Pro-resolving pathway

Aspirin acetylates

Prostanoids

Leukotrienes

Prostanoids

Leukotrienes

Aspirin in the management of myocardial infarction and percutaneous coronary intervention (PCI)

Aspirin alone, or in combination with adenosine diphosphate receptor inhibitors, has been the standard of care for patients with acute myocardial infarction, as well as patients undergoing percutaneous coronary intervention (PCI). High versus low-dose aspirin found similar outcomes in this population, although high-dose aspirin showed increased harm. This has led to the American College of Cardiology revising their guidelines to change the maintenance dosage of aspirin to the low-dose range.

Aspirin for the prevention of platelet aggregation

Key components of arterial occlusive thrombi include platelets that participate in the development and progression of atheromatous plaques. Adhesion and aggregation of platelets in response to fissuring or rupture of an atheromatous plaque can be viewed as a physiological repair response to an acute vascular lesion. Uncontrolled multiplication and persistence of platelet activation through self-sustaining amplification loops (e.g. platelet thromboxane A\(_2\) (TXA\(_2\)) and adenosine diphosphate (ADP) interactions) can lead to intraluminal thrombus growth, vascular occlusion, and the ischaemia of myocardial infarction (MI).

Other prostacyclin inhibitors, such as other classes of NSAIDs, increase the risk of major atherothrombotic complications, particularly MI, whereas low-dose aspirin reduces these risk factors. Aspirin exerts an antithrombotic effect on platelets by irreversibly blocking the COX-1 isozyme in platelets. This leads to depletion in the production of an important platelet agonist, TXA\(_2\), which is an important mediator of atherothrombosis. This result is effective in preventing atherothrombosis.

Aspirin for the prevention of cardiovascular diseases (CVD)

Thrombosis plays an important role in CVD, which includes events such as MI or ischaemic stroke. According to an estimation made

Low-dose aspirin (75–100 mg/day) is sufficient to irreversibly acetylate the serine-530 of COX-1, thereby inactivating cyclooxygenase, and thus selectively inhibiting the COX-1 isozyme. Subsequently, this also inhibits platelet generation of thromboxane A\(_2\). This acetylation is responsible for the antithrombotic effects of aspirin by inhibiting platelet aggregation as well. Low-dose aspirin has been found to selectively inhibit the synthesis of thromboxane A\(_2\), without having much effect on prostacyclin. Higher dosages of aspirin (650 mg to 4 g/day) will inhibit both COX-1 and COX-2, leading to anti-inflammatory effects, by blocking the formation of prostanoids.

Low-dose aspirin does not increase blood pressure, cause renal impairment, or interfere with the antihypertensive effects of ACE inhibitors or diuretics, because it has no measurable effects on COX-2 and prostacyclin (PGI\(_2\))-mediated vascular functions.

Indications for using low-dose aspirin

The suggested dosage for treatment with low-dose aspirin is usually between 75 and 150 mg. Some preparations contain 81 mg of aspirin in an enteric-coated tablet form, although no benefits were proven with the use of enteric-coated tablets.

Aspirin for the prevention of pre-eclampsia

Pre-eclampsia is defined as persistent hypertension during pregnancy, or the postpartum period, associated with symptoms such as proteinuria, thrombocytopaenia, impaired liver function, progressive renal insufficiency, pulmonary oedema, or cerebral disturbances. Pre-eclampsia originates from the placenta, where poor trophoblast invasion and remodelling of spiral arteries occur, leading to reduced utero-placental arterial flow and episodes of hypoxia. It is suggested that women at high risk for pre-eclampsia include those with a medical history of pre-eclampsia, diabetes, chronic hypertension, renal disease, or autoimmune disease. Most studies have found no association between the use of low-dose aspirin and complications in the mother or foetus, whether used in the first or third trimester.
by the World Health Organization (WHO), the annual global mortality rate will approach 25 million by 2030, due to CVD.  

Low-dose regimens of aspirin significantly reduce the risk of serious vascular events, including stroke and coronary events, in both men and women. Low-dose aspirin was associated with a 12% proportional reduction in serious vascular events, compared with no aspirin, and a decreased risk of total cardiovascular events. A lifelong low-dose aspirin regimen is widely recommended for the secondary prevention of CVD, but evidence to support primary prevention of CVD is somewhat contentious.

**Aspirin in diabetic patients**

The American Diabetic Association suggests that a low dosage of aspirin should be prescribed, primarily for diabetic men over 50 years of age and women over 60 years of age, or any diabetic patient with a moderate risk of CVD, or who has had a previous stroke or MI. Individuals with diabetes have a two to four-fold increased risk for developing cardiovascular events. However, having diabetes also increases the risk for extra-cranial haemorrhage.

**Aspirin as an anti-cancer drug**

A large number of clinical trials and experimental evidence indicate that low-dose aspirin can be used as a protective mechanism in different cancer types, particularly in colorectal cancer. The US Preventive Services Task Force recommended the initiation of low-dose aspirin for all patients between the ages of 50 and 59 years, who have a 10% or greater 10-year CVD risk, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years. The use of long-term, low-dose aspirin, exceeding three years, reduces the incidence of gastric cancer significantly. The benefits of low-dose aspirin increase with the duration of treatment, especially after 10 years of treatment.

**Prevention of venous thromboembolism**

A low-dose aspirin given as a short-term treatment reduces the incidence of fatal pulmonary embolism and symptomatic non-fatal deep vein thrombosis of pulmonary embolism in patients with hip fractures. After discontinuation of oral anticoagulants, long-term treatment with low-dose aspirin reduces the risk of recurrence with a first unprovoked venous thromboembolism (VTE).

The mechanism for aspirin’s protective effect against VTE includes acetylation of fibrinogen and other proteins in blood coagulation. This results in more efficient fibrinolysis and the reduction of thrombin generation at the sites of vascular injury, possibly due to acetylation of prothrombin.

**Prevention of vascular dementia**

Post-stroke dementia occurs in the chronic phase after a stroke and is related to increased TXA2, biosynthesis. Low-dose aspirin reduces the risk for ischaemic stroke, but also may have the potential to reduce the rate of cognitive lessening in older patients.

In the immune response, platelets can behave as innate inflammatory cells with roles in leukocyte recruitment, tissue remodelling following injury, releasing of cytotoxic mediators, and migration into tissues. This pro-inflammatory platelet function involves both complex formation with circulating leukocytes and the secretion of soluble factors. Therefore, low-dose aspirin exerting an anti-inflammatory effect, could also contribute towards decreasing neurodegeneration that does not necessarily require blockage of COX-1 in inflammatory cells, but may simply reflect its antiplatelet action. Moreover, aspirin-triggered lipoxins have been suggested to play a role in attenuating brain inflammation by stimulating alternative activation pathways of microglia. This hypothesis has not been tested in clinical trials yet.

Table I lists the various indications, with specific dosing regimens and length of therapy, of aspirin.

<table>
<thead>
<tr>
<th>Indication: Prevention of:</th>
<th>Dose</th>
<th>Duration</th>
</tr>
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<tbody>
<tr>
<td>Angina pectoris</td>
<td>75–150 mg daily</td>
<td>Lifelong</td>
</tr>
<tr>
<td>Cardio-vascular disease</td>
<td>75–100 mg daily</td>
<td>Lifelong</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>75–100 mg daily</td>
<td>10 years</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>75–325 mg daily</td>
<td>6 months post-intervention to lifelong</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>75–100 mg daily</td>
<td>During pregnancy</td>
</tr>
<tr>
<td>Platelet aggregation</td>
<td>75–100 mg daily</td>
<td>Lifelong</td>
</tr>
<tr>
<td>Vascular dementia (post-stroke)</td>
<td>100 mg daily</td>
<td>Lifelong (follow up 5-yearly)</td>
</tr>
<tr>
<td>Venous thrombo-embolism</td>
<td>75–100 mg daily</td>
<td>Short term: to prevent PE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lifelong: to prevent recurrence</td>
</tr>
</tbody>
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**Table I. Dosing regimens and various uses of low-dose aspirin**

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**REVIEW**
Drug-interactions with low-dose aspirin
Concomitant use of reversible COX-1 inhibitors, like other NSAIDs such as ibuprofen and naproxen, may exert a competitive effect on the irreversible acetylation of platelets by aspirin. This interaction does not occur with the COX-2 selective inhibitors.4

Side-effects associated with low-dose aspirin
A holistic patient approach is necessary when it comes to the decision whether to start or continue aspirin therapy, as many of the risk factors increase with age. Every patient’s treatment needs to be individualised to decide whether the potential benefits outweigh any potential harms.13

Risk of bleeding
Aspirin therapy will increase the risk of bleeding, with a higher risk in patients treated for primary prevention than in the secondary prevention population. The risk for bleeding is also higher in those individuals with an increased cardiovascular risk over 10 years, when compared to the low-risk population.9

Recurrent acute gout attacks
Using a low-dose aspirin regimen for more than two consecutive days is associated with an increased risk of recurrent gout attacks. To avoid gout attacks associated with low-dose aspirin, it is recommended to monitor serum urate with concomitant use, and to make use of suitable dosage adjustments of a urate-lowering therapy in patients with gout.14

Haemorrhagic stroke
Although a haemorrhagic stroke is less common than an ischaemic stroke, the mortality and morbidity rates are much higher with haemorrhagic stroke. A vascular event, without trauma, which results in an injury within the CNS may be classified as a stroke. A haemorrhagic stroke can be defined as rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system, which is not caused by trauma.16

A significant increase of 22% in the incidence of haemorrhagic stroke was found in patients on antiplatelet treatment.9 Furthermore, aspirin therapy did not seem to have an effect on stroke occurrence, with only a small protective effect with regard to mortality.9

Although aspirin increases the risk for haemorrhagic stroke, the overall benefits of preventing MI and ischaemic stroke may outweigh this adverse effect.16

Gastrointestinal bleeding
According to Lin et al. (2014)17 patients who take low-dose aspirin for primary prevention have a 90% higher risk of upper gastrointestinal bleeding, compared to non-users, and a 40% higher risk for secondary prevention patients. A higher incidence of upper gastrointestinal bleeding is found in patients with a history of upper gastrointestinal bleeding and peptic ulcers.18

Other risk factors that increase the risk for gastrointestinal bleeding include concurrent use of aspirin and anticoagulants, or NSAIDs, uncontrolled hypertension, male sex and older age. Male patients’ risk for gastrointestinal bleeding is two times greater than in women, and points to the reason why a holistic decision should be made, whether to start or continue aspirin therapy.13

The risk for upper gastrointestinal bleeding with the use of permanent low-dose aspirin can occur through two mechanisms: the dosage-dependent impairment of PGI2-mediated cytoprotection in the gastric mucosa, and inhibition of TXA2-mediated platelet aggregation. The impairment of PGI increases the risk for perforation and bleeding through worsening existing lesions in the mucosa and creating new lesions.4 Aspirin may also cause direct damage to the gastric mucosa, because of the acidic pH of the stomach contents, in which aspirin is found in its un-ionised form.

Conclusion
Low-dose aspirin has therapeutic potential in the prevention of several diseases such as myocardial infarction, atherothrombotic events, and more. Besides the benefits in preventing cardiovascular disease, it also proved beneficial in reducing the risk of pre-eclampsia in pregnant women that are at risk, as well as the risk for colorectal cancer in high-risk persons with a life expectancy of more than 10 years. The benefits in secondary prevention are favourable, and efforts should be made to ensure that all patients with symptomatic cardiovascular or cerebrovascular disease are treated with low-dose aspirin on a regular basis.

References