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ASPIRIN IN PRIMARY PREVENTION

Aspirin is one of the most widely used medicines, with analgesic, antipyretic, anti-inflammatory and antiplatelet actions. Aspirin inhibits platelet aggregation by irreversibly inhibiting cyclo-oxygenase, reducing the synthesis of thromboxane A2 (an inducer of platelet aggregation) for the life of a platelet. The Australian Medicines Handbook (AMH) recommends low-dose aspirin in patients with diabetes and established cardiovascular disease.

High quality evidence supports the use of low-dose aspirin in people with acute coronary syndrome (ACS) or previous myocardial infarction, stroke or transient ischaemic attacks (TIAs). This is referred to as secondary prevention. For secondary prevention, the benefits of aspirin outweigh the risks of bleeding in most patients.

Primary prevention

Primary prevention refers to preventing a disease before it occurs. The benefits and risks of aspirin in the primary prevention (preventing first heart attack or stroke) of cardiovascular disease has been controversial. The risk of bleeding with aspirin generally outweighs the slight reduction in stroke and myocardial infarction in people without cardiovascular (CV) or cerebrovascular disease or peripheral artery disease.

Several early primary prevention trials in middle-aged people demonstrated a benefit of daily low-dose aspirin. However early primary prevention trials were conducted at a time when smoking was more common and blood pressure and lipid lowering regimens were less aggressive. Three recently published trials have explored the role of aspirin in primary prevention in different patient populations:

- ASCEND – participants with diabetes
- ARRIVE – high-risk participants without diabetes
- ASPREE – older participants

ASCEND trial

The ASCEND (A Study of Cardiovascular Events in Diabetes) trial involved almost 15,500 UK patients aged 40 or older with type 1 or type 2 diabetes but no evidence of cardiovascular disease. Participants were randomly assigned either aspirin 100mg/day or placebo and followed for an average of 7.4 years.

Those in the aspirin group had a 12% lower risk of vascular events, including myocardial infarction and stroke compared with controls, but their likelihood of experiencing a major bleeding event was 29% higher than those on placebo. Major bleeding events included intracranial haemorrhage, sight-threatening bleeding event in the eye, gastrointestinal bleeding or other serious bleeding. These results show 91 people need to take aspirin for 5 years to prevent one serious vascular event, at a cost of a major bleeding event in one in 112 people.

No effect on gastrointestinal or any other cancer was seen in the trial. There was no significant reduction in mortality or disability. Current guidelines suggest aspirin should be considered on an individual basis for primary prevention in people with diabetes, as people with diabetes are at 2 to 3-fold increased risk of cardiovascular events. Good control of blood glucose levels, blood pressure and cholesterol and smoking cessation have a beneficial effect. Use of statins in primary prevention trials is associated with a 25% decrease in the risk of major vascular events for every 1mmol/L decrease in LDL cholesterol.

ARRIVE trial

The ARRIVE (Aspirin to Reduce Risk of Initial Vascular Events) trial looked at more than 12,500 younger patients without diabetes at moderate risk of cardiovascular disease. Men aged 55 or older with 2 or

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more risk factors and women aged 60 or older with 3 or more risk factors were included in the trial. Cardiovascular risk factors included current smoking, high blood pressure, high cholesterol, or a family history of CV disease. Participants were randomised to receive 100mg of enteric-coated aspirin or placebo over 5 years. People at high risk of bleeding, history of a vascular event or with diabetes were excluded from the trial. In the trial aspirin did not lower the risk of major CV events and stroke, or death by any cause; however, aspirin caused a significant 2-fold increase in the risk of bleeding complications. 1% of the aspirin group experiencing gastrointestinal bleeding compared to 0.5% of the placebo group. There was no difference in the incidence of fatal bleeding events between the two groups.

ASPREE trial

ASPREE (Aspirin in Reducing Events in the Elderly) trial included over 19,000 people, older than 70 years from Australia and the US. They were followed in the trial for an average of 4.7 years. Participants in the trial did not have cardiovascular disease, dementia or physical disability. They received 100mg per day of enteric-coated aspirin or placebo. ASPREE trial showed that aspirin was likely to do more harm than good with no evidence of a cardiovascular benefit.

The use of low-dose aspirin did not prolong disability-free survival. The rate of the composite of death, dementia, or persistent physical disability was similar with 21.5 events per 1000 person-years in the aspirin group and 21.2 per 1000 person-years in the placebo group. At 4.7 years, the rate of cardiovascular disease was also similar, with 10.7 events per 1000 person-years with aspirin, and 11.3 events per 1000 person-years with placebo. The risk for death from any cause was slightly higher with aspirin, at 12.7 events per 1000 person-years with aspirin compared to 11.1 events per 1000 person-years with placebo. This means for every 100 patients treated with aspirin, one extra death is experienced over a 5-year period. However, it has been suggested that this is a chance effect.

Use of daily low-dose aspirin significantly increased the risk of major bleeding by nearly 40%. The rate of major bleeding was 8.6 events per 1000 person-years with aspirin and 6.2 events per 1000 person-years with placebo.

Conclusion

Use of aspirin for primary prevention of cardiovascular events has minimal benefit, with a significant risk of bleeding events. Daily low-dose aspirin slightly lowers the risk of serious cardiovascular events in adults with diabetes, but at a cost of increased major bleeds. Smoking cessation and lifestyle changes, control of high blood pressure, and use of statins have significant benefit in preventing heart attacks and stroke.
The findings from these three studies suggest that aspirin has no role in the primary prevention of heart disease.

References
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