Low-dose acetylsalicylic acid for primary prevention of cardiovascular disease

Do not misinterpret the recommendations

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Low-dose acetylsalicylic acid (ASA) for prevention of cardiovascular disease (CVD), including myocardial infarction (MI) and stroke, is likely something that comes up frequently at family physician appointments. Acetylsalicylic acid has substantial benefits for secondary prevention in most cases. Based on current recommendations, most would also agree that the benefits of ASA (risk reduction of first MI by 20%) usually do not outweigh the risks (small but significant increase in hemorrhaging, mainly gastrointestinal [GI] bleeding; $P = .039$) for primary prevention.[1] A substantial body of evidence supporting this comes from the Japanese Primary Prevention Project,[2] which looked at patients with asymptomatic atherosclerosis and found that ASA did not significantly reduce cardiovascular events. In addition, the US Food and Drug Administration issued an advisory that the evidence does not support the general use of ASA for primary prevention of MI or stroke.[3] However, careful consideration should be taken when interpreting the recommendations.

There are 3 important questions to ask regarding ASA for primary prevention, as there are patients who might actually benefit from ASA and there are risks associated with discontinuation of ASA in patients who are already taking it.

Questions and answers

Should we routinely offer ASA for primary prevention? There is not enough robust evidence that the benefits of ASA outweigh the risks. The expected benefit of ASA for primary prevention of CVD is a reduction in fatal and nonfatal MI and stroke.[1] Studies have demonstrated mixed outcomes, including statistically significant reduction of MI and stroke, the occurrence of one without the other, or no benefit in prevention of either.[4-6] Meta-analyses have suggested ASA has little or no benefit for primary prevention.[4-6]

The primary risk with ASA therapy is bleeding. Studies have consistently found significant increases in hemorrhaging with daily ASA use, mainly GI bleeding (relative risk = 1.40; 95% CI 1.07 to 1.83).[4-6] The absolute rate of GI bleeding with ASA is 3 per 10 000 in the overall population and the absolute rate of intracranial bleeding is 1 per 10 000.[1]

When should we offer ASA for primary prevention? Acetylsalicylic acid should be offered when the benefits outweigh the risks (ie, it should be offered to patients who are at high risk of cardiovascular events and not at increased risk of bleeding). Patients at high risk of cardiovascular events include men older than 50 years or women older than 60 years with 1 or more of the following important risk factors: smoking, hypertension, dyslipidemia, family history of premature CVD, albuminuria, or atrial fibrillation with a $CHADS_2$ (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and stroke or transient ischemic attack) score of 0 to 1.[1,7,8] Patients at increased risk of bleeding include those with previous GI bleeding, those with peptic ulcer disease, or those taking concurrent medications that can increase bleeding (eg, anticoagulants, nonsteroidal anti-inflammatory drugs).[1,7,8]

Because ASA can reduce the risk of first MI by up to 20%,[1] we can offer ASA for primary prevention for those at high risk of CVD events and low risk of bleeding.

Should we stop ASA in patients who have been using it for primary prevention for many years? We cannot discontinue ASA without careful consideration. This is not an easy question to answer, as there is not a lot of robust evidence to support one option over another. The guidelines do not advise starting ASA for primary prevention but this might not translate into stopping ASA for primary prevention.

When you discontinue daily ASA, there is a risk of hypercoaguability owing to a rebound increase in platelet aggregability.[9-11] Studies have shown a 3-fold increase in thrombotic events upon discontinuation (highest within 11 days after discontinuation but it can last up to 1 year).[9-11] Patients who have been advised to stop ASA based on the recommendation that ASA should not be started for primary prevention have experienced substantial ASA withdrawal effects, as demonstrated in meta-analyses of data from these patients. Case-control studies have demonstrated that people who had recently

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Cet article se trouve aussi en français à la **page 973.**

stopped ASA had a significantly increased risk of nonfatal MI or death (rate ratio=1.43; 95% CI 1.12 to 1.84); over 1 year, for every 1000 patients there were 4 more cases of nonfatal MI in patients who discontinued low-dose ASA compared with patients who continued taking ASA.[10]

Therefore, we might be introducing harm when we stop ASA. A thorough assessment of risk versus benefit should be conducted.

Future considerations

Clinicians can look forward to the results of 4 large, ongoing randomized controlled clinical trials relating to ASA for primary prevention: ARRIVE (Aspirin to Reduce Risk of Initial Vascular Events),[12] ASCEND (A Study of Cardiovascular Events in Diabetes),[13] ASPREE (Aspirin in Reducing Events in the Elderly),[14] and ACCEPT-D (Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes).[15] These studies recruited patients from across Europe and North America, which should allow for generalizability of the results to the Canadian population. The inclusion criteria focused on specific populations, such as patients with several risk factors, older adults, patients with diabetes, and patients with no CVD history, which will help further answer the first 2 questions mentioned above. The results of these studies will hopefully shed additional light on the efficacy of ASA for primary prevention, as well as provide guidance on appropriate use.

Finally, there are current investigations that suggest there might also be benefits of ASA in cancer protection, but these data were not reviewed for this article.

Conclusion

Even with a plethora of data, there remains uncertainty about the use of ASA for primary prevention of CVD. Therefore, it should not be routinely recommended for all patients. In a select population, the risk of cardiovascular events is high and might outweigh the risks of ASA therapy. These patients should be offered ASA for primary prevention. Consider the risks when you discontinue ASA in patients who have been using it daily for primary prevention. Keep patients involved in the decision making and use clinical judgment. Clearly explain that ASA therapy shows mixed benefit with a small risk of GI bleeding. Also discuss that the acute period upon discontinuation might put patients at higher risk of MI or stroke. If they choose to continue taking ASA (and some will), make sure it is a low dose (81 mg), the tablets are enteric coated, and the patients are not taking other nonsteroidal anti-inflammatory drugs.

To help you do no harm when considering ASA for primary prevention of CVD, whether offering or discontinuing the medication, think about the 3 questions discussed above. The results of ongoing studies should provide additional guidance on this topic in the near future.

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Competing interests
None declared

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