# Update on acetylsalicylic acid for primary prevention of cardiovascular disease

## Not initiating is not the same thing as discontinuing

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It has been almost 4 years since I addressed questions in this journal about the use of acetylsalicylic acid (ASA) for primary prevention of cardiovascular disease.[1] We have long awaited the results of 4 studies to help shed light on and assist with reliably deciding whether to use ASA in patients without established cardiovascular disease. To date, the results of 3 large trials designed to specifically look at this indication have been published: Aspirin in Reducing Events in the Elderly (ASPREE),[2,3] Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE),[4] and A Study of Cardiovascular Events in Diabetes (ASCEND).[5] The results of the fourth study, ACCEPT-D (Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes),[6] have not been published yet. These new studies were also reviewed in an article published in *JAMA* earlier this year.[7]

## Trial result summaries

***The ASPREE trial.***[2,3] This trial looked at 19 114 patients older than 70 years of age, or older than 65 if black or Hispanic (5%). Patients were followed for 4.7 years. They had similar cardiovascular event rates: 448 (10.7 events per 1000 person-years) in the ASA group versus 474 (11.3 events per 1000 person-years) in the placebo group (hazard ratio [HR] of 0.95; 95% CI 0.83 to 1.08). In terms of bleeding, there were higher rates of major hemorrhage with ASA use: 361 in the ASA group versus 265 in the placebo group (HR = 1.38; 95% CI 1.18 to 1.62; $P < .001$).

***The ARRIVE trial.***[4] This trial looked at 12 546 patients and included men older than 55 and women older than 60 who were deemed "moderate risk." They were followed for 6 years. The trial found no significant difference in primary end point (composite outcome of time to first occurrence of cardiovascular death, myocardial infarction, unstable angina, stroke, or transient ischemic attack): 269 (4.29%) in the ASA group versus 281 (4.48%) in the placebo group (HR = 0.96; 95% CI 0.81 to 1.13; $P = .6038$). Similarly, they also found no difference in the rate of serious adverse events: 1266 (20.19%) in the ASA group versus 1311 (20.89%) in the placebo group.

***The ASCEND trial.***[5] This trial looked at 15 480 patients with diabetes who were older than 40 years of age. They were followed for 7.5 years. The trial found a 12% reduction in vascular events in the ASA group compared with placebo: 658 (8.5%) in the ASA group versus 743 (9.6%) in the placebo group (rate ratio of 0.88; 95% CI 0.79 to 0.97; $P = .01$). However, they also found a 29% increase in major bleeding: 314 events (4.1%) in the ASA group versus 245 events (3.2%) in the placebo group (rate ratio of 1.29; 95% CI 1.09 to 1.52; $P = .003$).

***Limitations.*** There are a few general limitations to these studies. The incident rates of ASPREE and ARRIVE were much lower than in previous studies. This might suggest confounding factors such as better management of blood pressure and dyslipidemia when angiotensin-converting enzyme inhibitors or statins are used for the prevention of cardiovascular disease. Another word of caution is that the populations were predominantly white (95% of ASPREE; 98% of ARRIVE; 96% of ASCEND) and thus, there is questionable generalizability to the population as a whole. Next, adherence rates present an ongoing concern that might lead to underestimation of benefit. The ASPREE and ASCEND trials report adherence rates of two-thirds and 70%, respectively, whereas ARRIVE only comments that adherence was a considerable challenge in these studies.

## Discussion

Have these trials changed my answers to the questions posed in my first article?[1] Yes and no.

***Should we routinely offer ASA for primary prevention?*** My answer remains no. These studies continue to caution that the absolute benefit of cardiovascular risk reduction does not outweigh the risk of bleeding.

***When should we offer ASA for primary prevention?*** My answer used to be "It depends." Then, I would go into more detail about how to calculate cardiovascular risk. However, given the results, especially of ASPREE in the older population and ARRIVE in patients at moderate cardiovascular risk, I am now inclined to give a more definitive response of "Almost never." Especially in the absence of diabetes, where ASCEND showed us a 12% reduction in vascular events with ASA at the expense of a 29% increased risk of bleeding,[5] the benefits likely do not outweigh the risks.

Before we get to the third question, I will summarize that, given the previous controversy with ASA for primary prevention, we can now confidently conclude we should not be initiating ASA for primary prevention

in patients with no established cardiovascular disease. However, and this is a big *however,* the results of these wonderfully designed studies do not tell us to jump up and down and start discontinuing ASA in the studied populations. I have the same argument for statins. At this point in time, we do not know what happens to patients who have been taking ASA and statins for many years. Perhaps these patients continue to take these medications because they have a low risk of side effects and, thus, the perceived benefits might actually outweigh the risks. It was recently discussed in the *New England Journal of Medicine* whether we should stop or continue ASA for patients taking it for primary prevention.[8] It should be stressed there might be concerns with discontinuing low-dose ASA, as pointed out in a recent population-based cohort study.[9]

***Should we stop ASA in patients who have been using it for primary prevention for many years?*** This is my favourite of the 3 questions and my answer is still a definitive no. Unfortunately, none of these new trials directly addresses the question of whether these persons who have been taking ASA for primary prevention should continue its use or stop it. The authors of ASPREE clearly point this out in the discussion.

If anyone has the time and interest, I would suggest conducting a study designed to look at what happens if you discontinue ASA for primary prevention in patients who have been taking it for decades. The ideal population would be patients older than 65 years of age without established cardiovascular disease. They should have been taking ASA for a minimum of 10 years for primary prevention. The study design would be a randomized controlled trial with 2 treatment arms: patients continuing ASA and patients discontinuing ASA. Then, we should follow them for at least 5 years. Similar to the other trials, primary end points would be cardiovascular mortality for efficacy and major hemorrhage for safety. This will be the only way to address this question using evidence-based medicine.

To date, the US Preventive Services Task Force[10] is the only advocate of initiating ASA based on age and 10-year cardiovascular disease risk. The European,[11] Australian,[12] and Canadian[13] guidelines do not recommend using ASA for primary prevention in the absence of established cardiovascular disease. Perhaps the United States might revisit their position with the results of these recently published studies.

## Conclusion

These study findings reinforce that we should not be routinely offering ASA for primary prevention. The results also emphasize there is likely more harm than benefit to offering ASA for primary prevention in patients at moderate cardiovascular risk and in the older population, especially in the absence of diabetes. Finally, we still do not know what might happen to patients who continue to take ASA versus if they discontinue it.

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**Competing interests**
None declared

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