

Does an Aspirin a day keep the doctor away? Acetylsalicylic acid for the primary prevention of cardiovascular disease

More evidence is needed before ASA can be recommended for routine use to reduce the risk of CV disease, especially in women and diabetic patients.

ABSTRACT: Acetylsalicylic acid was introduced to the pharmaceutical market just over 100 years ago. Although it was originally intended for use as an analgesic, physicians quickly realized it provided many other therapeutic benefits. Dr Lawrence Craven first suggested ASA could prevent cardiovascular events with his publication of a large case series in 1950. Since then, several large randomized controlled trials involving more than 100 000 patients have investigated the role of ASA for primary prevention of cardiovascular events. These trials suggest that ASA provides modest protection at the expense of a small but real increase in bleeding. Based on these findings, several governing bodies have recommended using ASA for primary prevention. However, in light of recent studies, particularly in several selected subgroups, there continues to be debate regarding the use of ASA for preventing cardiovascular events.

The Greek physician Hippocrates was first to describe the analgesic effects of bark from the willow tree, a salicylate-containing plant. Although the mechanism through which willow bark relieved pain was not understood, it was used as an effective herbal remedy for over 2000 years. In 1826, two Italian researchers, Brugnatelli and Fontana, successfully isolated the active compound, salicin.¹ Unfortunately, because of its significant gastrointestinal side effects, the compound's clinical utility was limited.

In 1894, German chemist Felix Hoffman joined the Bayer Pharmaceutical Company. In search of a compound to relieve his father's arthritis pain, he looked again at Brugnatelli and Fontana's salicin, which had been further refined by chemists to produce pure salicylic acid. By adding a buffer to the salicylic acid to create acetylsalicylic acid (ASA), Hoffman developed a compound that was better tolerated and had fewer gastrointestinal side effects.² In 1899, acetylsalicylic acid was released on the market and sold as "Aspirin." Although Bayer initially maintained that their compound had no effect on the heart, ASA would eventually become one of the most widely used medications for the treat-

ment and prevention of cardiovascular (CV) disease.

Dr Lawrence Craven, a general practitioner from Glendale, California, first proposed that ASA could prevent myocardial infarctions after he noted increased bleeding rates in children who chewed ASA gum after tonsillectomy and tooth extractions.^{3,4} In 1950, he published a case series of 400 patients prescribed ASA.⁵ After 2 years of follow-up, none of these patients had experienced a CV event.

Evidence for ASA continued to build in the 1960s and 1970s, although research was largely confined to the secondary prevention population. Studies suggested that ASA prevented 10 to 20 reinfarctions for every 1000 patients treated and had a small but significant effect on mortality.⁶ However, ASA use was also associated with a small increase in nonfatal bleeding. Given the lower CV risk in the primary prevention population, researchers questioned whether the benefits of ASA in this group would

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be significant enough to outweigh its adverse effects.

Early primary prevention trials

In the early 1980s, investigators from Harvard's Brigham and Women's Hospital in Boston designed the Physicians' Health Study, the first randomized controlled trial to investigate ASA for the primary prevention of CV events.⁷ Over 260 000 American male physicians aged 40 to 84 were screened, with 22 071 subjects eventually assigned to ASA (325 mg daily) or placebo arms. This study was stopped early at 60 months because of a significant 44% relative risk reduction (RRR) in MI. Although there was a 32% increase in risk of bleeding, this increase was mostly attributed to easy bruising.

At approximately the same time that the Physicians' Health Study was underway, a group from Oxford University in England was conducting a large randomized trial, the British Doctors' Trial.⁸ Over 20 000 invitations were mailed to healthy male doctors who had previously responded to a smoking questionnaire. Ultimately, 5139 subjects were randomly assigned to this open-label trial and asked to take ASA (500 mg daily) or to avoid ASA. The results of this study failed to show any significant difference in the incidence of nonfatal MI, stroke, or mortality.

Although the results from the British Doctors' Trial conflicted with those of the Physicians' Health Study, it is important to note that the British trial was open-labeled and had an event rate 3 times lower, consequently making it significantly underpowered. An overview of these two trials did suggest an overall 33% reduction in the incidence of a first MI.⁹ Based on this evidence, the Cardio-Renal Drugs Advisory Committee recom-

American Heart Association	European Society of Cardiology	US Preventive Services Task Force																		
Recommends use of ASA when 10-year risk of cardiovascular event exceeds 10%	Recommends use of ASA when there is markedly increased 10-year risk of cardiovascular disease mortality and controlled blood pressure	Recommends use of ASA when the potential benefit of MIs prevented (men) and strokes prevented (women) outweighs the potential harm of increased GI hemorrhage																		
		<table border="1"> <thead> <tr> <th colspan="2">Risk level at which benefit exceeds harm</th> </tr> </thead> <tbody> <tr> <td colspan="2">Men: 10-year coronary heart disease risk</td> </tr> <tr> <td>age 45–59 years</td> <td>> 4%</td> </tr> <tr> <td>age 60–69 years</td> <td>> 9%</td> </tr> <tr> <td>age 70–79 years</td> <td>> 12%</td> </tr> <tr> <td colspan="2">Women: 10-year stroke risk</td> </tr> <tr> <td>age 55–59 years</td> <td>> 3%</td> </tr> <tr> <td>age 60–69 years</td> <td>> 8%</td> </tr> <tr> <td>age 70–79 years</td> <td>> 11%</td> </tr> </tbody> </table>	Risk level at which benefit exceeds harm		Men: 10-year coronary heart disease risk		age 45–59 years	> 4%	age 60–69 years	> 9%	age 70–79 years	> 12%	Women: 10-year stroke risk		age 55–59 years	> 3%	age 60–69 years	> 8%	age 70–79 years	> 11%
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Table. Recommendations for ASA use to prevent cardiovascular disease.

mended that the US Food and Drug Administration approve professional labeling of ASA to reduce the risk of a first MI. However, the FDA did not follow this recommendation because the two trials were interpreted to have divergent results.¹⁰

The Thrombosis Prevention Trial was a two-by-two factorial trial that randomly assigned subjects to warfarin (goal INR 1.3–1.8), ASA (75 mg daily), or a combination of the two.¹¹ Acetylsalicylic acid and warfarin individually showed a 20% RRR in ischemic heart disease, mostly driven by a reduction in nonfatal MI. Although the combination of ASA and warfarin had a 34% RRR in MI, it was also associated with a threefold increase in bleeding complications.

The Hypertension Optimal Treatment (HOT) study was designed to assess the safety and efficacy of ASA in patients with hypertension, particularly in terms of ASA's effect on bleeding and hemorrhagic stroke.¹² Acetylsalicylic acid demonstrated a 15% RRR in major CV events. While a small increase in nonfatal major and minor bleeding was observed, there was no difference in fatal major bleeding.

Finally, the Primary Prevention Project recruited 4495 patients with one or more cardiac risk factors from a general practitioner's clinic and assigned them to ASA (100 mg daily) or placebo.¹³ This trial was stopped early because of a 23% RRR in CV events and a 44% reduction in cardiac death. As in other studies, there was a small increase in bleeding complications over the 3.6 years of follow-up (absolute risk increase 0.7%), mainly driven by an increase in GI bleeds.

These five landmark trials found that using ASA was associated with a 15% to 44% RRR of a first major CV event. Although bleeding rates were mildly increased, the events were mostly small and nonfatal. Based on these results and subsequent meta-analyses, the American College of Cardiology (ACC) recommended the use of ASA for the prevention of CV events in patients who had a 10-year risk exceeding 10%.¹⁴ The US Preventive Services Task Force and the European Society of Cardiology (ESC) have made similar recommendations, endorsing ASA for primary prevention in an intermediate- to high-risk population (**Table**).^{15,16} However, the

FDA has yet to approve professional labeling of ASA for this indication because of ongoing uncertainties and the need for more evidence, especially regarding women and diabetic patients.

ASA in women

Cardiovascular disease is the largest single cause of death among women.¹⁷ Despite this fact, only two of the five trials reviewed above enrolled women (HOT and the Primary Prevention Project). Subgroup analysis from these trials suggests that ASA did not provide women with protection from CV events. Some have postulated that ASA may be ineffective in women because of male-female differences in salicylate metabolism or interactions with hormones.¹⁸ However, only 180 of the 2402 CV events from all five of the primary prevention trials occurred in women, making it difficult to draw any firm conclusions.

The Women's Health Study set out to definitively answer questions of effectiveness of ASA in women.¹⁹ In 1992, 1.7 million invitations were sent to female health professionals. Eligible subjects had to be older than 45 and have no history of CV disease. After the completion of a 3-week run-in phase, a total of 39 876 women were assigned to ASA (100 mg on alternate days) or placebo. After a follow-up of 10 years, there was no significant difference in the incidence of MI or mortality. However, a significant 24% RRR in ischemic stroke was observed.

Although these results raise questions regarding the efficacy of ASA in women, there are important details that should be highlighted. Women in this study were generally younger than the male subjects enrolled in previous trials. Only 10% of the participants were older than 65. In this small subgroup there was a significant 26% RRR in major CV events, suggesting

a potential benefit in older women. Furthermore, only 24% of subjects had more than one CV risk factor. The yearly major CV event rate was 0.26%, indicating that this was a low-risk group of patients. Finally, the dose of ASA used in this study was lower than in previous studies, suggesting a higher dose might have been more effective. Despite the lack of any substantial evidence suggesting a benefit in women, the ACC guidelines still recommend ASA for all intermediate- to high-risk individuals regardless of sex.

Emerging evidence

The Antithrombotic Trialists' Collaboration performed a meta-analysis using all of the individual participant data from the primary prevention trials reviewed above. The results of this study were published recently in *The Lancet* and included over 95 000 individuals with a total of 330 000 person-years of follow-up.²⁰ The absolute risk of a serious vascular event per year was 0.51% in the ASA group compared with 0.57% in the placebo group. This equates to a statistically significant but clinically modest absolute risk reduction (ARR) of 0.06% and a relative risk reduction of 12%. Thus, 1666 patients would need to be treated with ASA for a year to prevent one serious CV event. Although the relative risk reduction of CV events is similar for both primary and secondary prevention studies, the absolute risk reduction is much smaller in the primary prevention population (ARR 0.06% vs. 1.49%). A small increase in hemorrhagic stroke was seen in the ASA arm (0.04% vs. 0.03%), which was counterbalanced by a small reduction in ischemic stroke. There was also a small absolute increase in major bleeding of 0.03%. In response to these disappointing results, the Antithrombotic Trialists' Collaboration

deemed ASA of uncertain value for primary prevention and stated that the potential benefits with ASA needed to be carefully weighed against the risk of major bleeding.

The recently published Aspirin for Asymptomatic Atherosclerosis Trial found no evidence supporting the efficacy of ASA for primary prevention.²¹ This study involved 3350 subjects aged 50 to 80 with an ankle brachial index of less than 0.95, an accepted surrogate for vascular disease. After 8.2 years of follow-up there was no difference in the composite outcome of fatal and nonfatal coronary event, stroke, or revascularization. However, as observed with the Antithrombotic Trialists' Collaboration, the yearly rate of major bleeding was approximately 0.1%. Researchers hope the results of two ongoing studies, ASPREE (ASpirin in Reducing Events in the Elderly) and ARRIVE (Aspirin to Reduce the Risk of Vascular Events) will provide some further insight.

ASA in diabetes

Patients with diabetes are known to be at increased risk for CV events, having a twofold to fivefold increase in risk of MI and stroke over the general population.^{6,22} Both the American National Cholesterol Education program and the ESC guidelines consider diabetes to be a "coronary equivalent," consequently placing all diabetic patients into the high-risk category.^{23,24} Diabetic patients are also known to have abnormal platelet function, including alterations in platelet turnover, enhanced aggregation, and augmented thromboxane A₂ synthesis (Figure).²⁵ Antiplatelet agents are therefore a seemingly logical choice for reducing CV events. Disappointingly, subgroup analysis from the primary prevention trials and the Antithrombotic Trialists' Collaboration

have failed to show a benefit in this population.^{20,26}

There have been two large randomized trials investigating the effectiveness of ASA in the diabetic population. The JPAD trial was a multicentre randomized trial at 163 institutions throughout Japan.²⁷ Because Japanese law prohibits the administration of a placebo in clinical trials, this was an open-label trial. In addition to diabetes, 60% of subjects had a history of smoking, 60% had hypertension, and 55% had a history of dyslipidemia. Despite this seemingly high-risk population, there was no significant difference in CV events after just over 4 years of follow-up. However, the event rate was 3 times lower than expected, which indicates that this group was not as high-risk as expected, despite the presence of significant CV risk factors.

The POPADAD trial was conducted by the Scotland Diabetic Registry Group.²⁸ This study randomly assigned diabetic patients with an ankle brachial index of less than 0.99 to ASA (100 mg daily) or placebo. Patients enrolled in this trial also had a significant burden of traditional CV risk factors. Unfortunately, low enrollment and funding issues led to premature termination of the study before a target sample size of 1600 was reached. After nearly 7 years of follow-up POPADAD failed to demonstrate a benefit in composite CV outcomes. As in the JPAD trial, CV event rates were threefold lower than originally predicted, again a surprising finding given the seemingly high-risk population.

There are potentially many reasons ASA was not beneficial in these trials. Both studies had a lower than predicted event rate and POPADAD fell significantly short of its enrollment target. Consequently, they were both underpowered for their primary

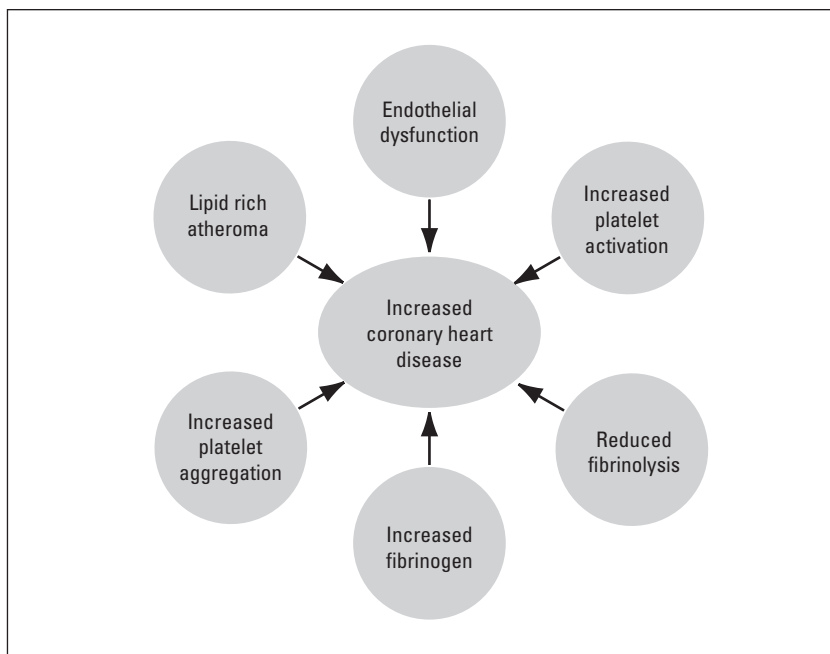


Figure. Factors contributing to accelerated coronary heart disease in diabetic patients.

outcome. Patients may have also been “better treated,” limiting ASA’s ability to reduce CV risk any further. Finally, diabetic patients may require higher doses of ASA because of an increased turnover rate of thromboxane A₂. Despite the lack of evidence, many governing bodies continue to recommend ASA for diabetic patients.²⁹ The ASCEND and ACCEPT D trials are currently enrolling patients and aim to further investigate the effectiveness of ASA in the diabetic population.

Conclusions

Acetylsalicylic acid is one of the most widely used preventive medications in the era of modern medicine. Since Dr Craven proposed that the anticoagulant effect of ASA would protect against CV disease, thousands of patients have been enrolled in several large clinical trials. Overall, ASA appears to have only a modest reduction (ARR 0.06% per year) in the prevention of a first CV event, which is of

questionable clinical benefit. Furthermore, there has been no evidence to date suggesting that ASA is of benefit in either female or diabetic subgroups. The current guidelines continue to endorse ASA for primary prevention in those at moderate to high risk of cardiovascular disease. Researchers hope that the results of several ongoing trials will provide us with more insight into several unanswered questions and help further define the patient population in which ASA should be used.

Competing interests

None declared.

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