6th Risk, Diagnosis and Treatment of Cardiovascular Disease in Women

Aspirin for Primary and Secondary Prevention of Cardiovascular Disease

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The first reported use of salicylate-rich plants as an analgesic and anti-inflammatory agent comes from the Ebers Papyrus, an Egyptian medical text from ca. 1,543 BC.[1] It wasn't until the mid-1800s that silicon was isolated as the active component from willow tree bark extract, and then purified to acetylsalicylic acid. Bayer patented the compound in 1900, after the German chemist Felix Hoffmann's successful use of it to treat his father's severe arthritis. Finally, in 1950, the physician Lawrence Craven recognized that aspirin reduced the risk of heart attacks in men.[2]

The cardioprotective benefits of aspirin are probably a result of its ability to inhibit the formation of prostaglandins and thromboxane A_2 (potent promoters of platelet aggregation and vasoconstriction, through the irreversible inhibition of the COX-1 enzyme). Although the prevention of thrombosis is desirable in certain patient populations, such an effect also increases the risk of serious bleeding complications, including intracranial hemorrhage. In patients without verified vascular disease, the determination of benefits and risks has proved difficult.

The benefit of aspirin use for secondary prevention is well established. Extensive evidence from hundreds of clinical trials has shown that daily, low-dose aspirin reduces the risk of vascular events (myocardial infarction [MI], stroke, and vascular death) in patients who have experienced an MI or a stroke, or who are at high risk of vascular disease by Framingham risk score. The absolute risk reduction for treatment over 2 years is 36 ± 5 per 1,000 in patients who have had an MI, 36 ± 6 per 1,000 in patients who have had a stroke or transient ischemic attack, and 22 ± 3 per 1,000 in other high-risk patients.[3] Many investigators have looked at the optimal aspirin dose needed to derive these benefits. Near-complete inhibition of the COX-1 enzyme is achieved with doses well below 162 mg, and, in general, studies have shown that high doses of aspirin increase the risk of bleeding complications without providing further reduction in vascular events. Given this information, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines include a level A, class I recommendation for the use of daily aspirin (75–162 mg) in both men and women with known coronary heart disease or atherosclerotic vascular disease.

The benefits of aspirin use in primary prevention are less well established and more idiosyncratic. In addition to a number of smaller studies, there have been 2 large, sex-specific, randomized, double-blinded, placebo-controlled studies of primary prevention in men (Physicians' Health Study) and women (Women's Health Study). The Physicians' Health Study included 22,071 male participants with 60 months of follow-up. This study showed a 44% relative reduction in the risk of first MI, with no reduction in total cardiovascular mortality rate among participants who took low-dose daily aspirin in comparison with placebo.[4] In addition, they found a nonsignificant increase in the risk of hemorrhagic stroke and gastrointestinal (GI) bleeding. The Women's Health Study investigators randomized 39,876 women without clinical vascular disease to placebo or low-dose daily aspirin and monitored them for 10 years. Although the results showed no effect on the risk of fatal or nonfatal MI, there was a 24% relative risk reduction for ischemic stroke without an increase in hemorrhagic stroke.[5] A subgroup analysis showed that women over age 65 years not only had a reduction in ischemic stroke, but also had a 26% relative risk reduction for major cardiovascular events; however, this came with an increased risk of major GI bleeding.

In addition to these large randomized trials, the Antithrombotic Trialists' Collaboration[3] was a meta-analysis examining severe vascular events versus major bleeding in

patients taking aspirin for both primary and secondary prevention trials. The conclusion was that, despite the similarity of relative-risk reduction in primary and secondary prevention, the absolute number of events (and therefore the absolute risk reduction) was dramatically lower in primary prevention. This relationship held true in all subgroup analyses. Furthermore, the benefit is almost entirely in reduction of MI, without a major effect on vascular mortality rates.

Given the idiosyncrasies of these data sets, organizational guidelines tend to differ in their recommendations for aspirin use in primary prevention. The ACC/AHA primary-prevention guidelines for aspirin include a level A, class I recommendation for the use of low-dose aspirin in men and a level B, class IIa recommendation for women—all of whom have an estimated cardiovascular risk score of >10% over the next 10 years.[6] The United States Preventive Services Task Force provides a practical approach. In order to assist the physician and the patient in deciding whether to start aspirin for primary prevention, it tabulates the risk–benefit analysis for MI reduction in men of age 45 to 79 years by using risk of MI versus risk of GI bleeding and intracranial hemorrhage, and it tabulates the risk–benefit analysis for stroke reduction in women of age 55 to 79 years by using risk of GI bleeding alone.[7] Currently, there are several ongoing studies (for example, the ARRIVE,[8] ASPREE,[9] ASCEND,[10] and ACCEPT-D[11] trials) of aspirin use for primary prevention in various subgroups, and of aspirin use in patients who are currently undergoing optimal medical therapy for the prevention of vascular disease.

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