8th Annual Women's Heart & Vascular Symposium

What Do the Guidelines Really Say About Aspirin?

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★ ***CME Credit***

Presented at the 8th Annual Women's Heart & Vascular Symposium, Texas Heart Institute; Houston, 20 January 2018.

Section Editor: *Stephanie A. Coulter, MD*

Key words: *Anticarcinogenic agents/therapeutic use; aspirin/administration & dosage/adverse effects/therapeutic use; cardiovascular diseases/prevention & control; colorectal neoplasms/prevention & control; hemorrhage/chemically induced; practice guidelines as topic; primary prevention/methods/standards*

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According to the latest available national mortality data, cardiovascular disease (CVD) and malignant neoplasm remain the 2 leading causes of death in the United States, accounting for 45.4% of all deaths in 2015. Among the malignant neoplasms, colorectal cancer (CRC) was the second leading cause of death, behind only lung cancer.[1] Aspirin has reduced the incidence of both cardiovascular (CV) events and CRC, and thus taking aspirin may have a substantial epidemiologic effect on morbidity and mortality rates.[2,3] However, to determine aspirin's role in primary and secondary prevention of CVD, the beneficial effects on CVD and CRC prevention must be weighed against the bleeding risks associated with its use.

Aspirin irreversibly inactivates cyclooxygenase-1 (COX-1), leading to decreases in the biosynthesis of prostaglandin H_2 and thromboxane A_2.[4] Suppression of thromboxane A_2 production inhibits platelet aggregation, a key event in coronary thrombosis and acute myocardial infarction. As a result of COX-1 inactivation, complete suppression of thromboxane A_2 can be achieved through the cumulative effects of a daily regimen of low-dose (<100 mg) aspirin. As one of several postulated mechanisms for reducing CRC risk, aspirin suppresses numerous lipid mediators released by activated platelets via COX-dependent mechanisms that alter the progression of normal colonic mucosa to adenoma and, subsequently, to carcinoma.[5] However, aspirin-mediated COX-1 inhibition also leads to mucosal damage in the gastrointestinal tract, and, in conjunction with aspirin's antiplatelet effect, increases gastrointestinal and nongastrointestinal bleeding, including intracranial hemorrhage and hemorrhagic stroke.

In patients with known CVD, the benefits of taking aspirin to reduce CV events outweigh the risks of bleeding. A collaborative meta-analysis conducted by the Antithrombotic Trialists' Collaboration showed a statistically significant reduction in severe vascular events (nonfatal myocardial infarction, nonfatal stroke, or vascular death) in patients with acute or prior vascular disease who were taking low-dose aspirin.[6] The reduction in vascular events substantially outweighed the absolute risks of major extracranial bleeding. These findings led to the 2012 American College of Cardiology/American Heart Association (ACC/AHA) recommendation that "treatment with aspirin 75 to 162 mg daily should be continued indefinitely in the absence of contraindications in patients with stable ischemic heart disease."[7]

In patients who have no known CVD, the net clinical benefit obtained from aspirin use is less clear when weighing the associated reduction in the incidence of CV events and CRC against increased bleeding in this population. In 2016, the U.S. Preventive Services Task Force (USPSTF) issued updated recommendations for the use of low-dose aspirin for primary prevention of CVD and CRC.[8] In separate meta-analyses of primary prevention trials, the USPSTF found that aspirin use reduced the incidence of nonfatal myocardial infarction by 22%, had no effect on the incidence of stroke or cardiovascular death, and reduced 20-year CRC mortality rates by 33%. Aspirin therapy had little or no effect on all-cause death; it increased the risk of major gastrointestinal bleeding by 58% and that of hemorrhagic stroke by 27%.[2,3,9] The data also suggested that the CV benefits of aspirin began within the first 5 years of therapy, whereas the decrease in CRC mortality rates was not seen until after 10 years of therapy. After performing a decision analysis with use of a microsimulation model, the USPSTF made a class B recommendation to initiate "low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years."[8] An individualized approach was recommended for patients 60 to

69 years of age. Evidence was insufficient to formulate recommendations for adults younger than 50 years or older than 70 years.

The clinical equipoise of aspirin use for primary prevention of CVD has led to the issuance of contradictory guidelines by major organizations. The 2015 AHA/American Diabetes Association (AHA/ADA) guidelines recommend low-dose aspirin for patients who have a 10-year CVD risk of at least 10% but are not at increased risk of bleeding (class IIa), and they note that taking low-dose aspirin is reasonable for adults who have diabetes mellitus and a 10-year CVD risk between 5% and 10% (class IIb).[10] Contrary to the USPSTF and AHA/ADA recommendations, the 2016 CVD prevention guidelines from the European Society of Cardiology include a class III recommendation, stating that "antiplatelet therapy is not recommended in individuals without CVD due to increased risk of major bleeding."[11]

Results of 3 large randomized controlled trials that evaluated the role of aspirin in primary prevention populations were published in 2017 and 2018.[12-14] The Ascend trial[12] randomized 15,480 participants with diabetes mellitus and no known CVD upon trial entry to low-dose daily aspirin and placebo. After a mean follow-up time of 7.4 years, severe vascular events (nonfatal myocardial infarction, stroke, transient ischemic attack, and death from vascular causes) occurred in a significantly lower percentage of the aspirin group (rate ratio, 0.88). However, this reduction in vascular events occurred at the expense of a statistically significant increase in major bleeding in the aspirin group (rate ratio, 1.29). The Arrive trial[13] randomized 12,546 nondiabetic participants (age, ≥55 yr; 2–4 CV risk factors) to low-dose daily aspirin and placebo. At a median follow-up time of 5 years, there was no statistically significant difference in the primary endpoint of time to first occurrence of CV death, myocardial infarction, unstable angina, stroke, or transient ischemic attack, although the event rates were lower than expected and more representative of a low-risk population. In the Aspree study,[14] 19,114 participants without known CVD (age, >70 yr) were randomized to daily low-dose aspirin versus placebo. The investigators found a significantly higher rate of major hemorrhage and no reduction in CV events. An additional ongoing trial involves using aspirin for primary prevention in patients who have diabetes mellitus.[15]

It remains to be seen how these trials will be incorporated into the guidelines. The use of other risk-modifying therapies, such as statins, antihypertensive medications, and newer drugs for hyperglycemia, may attenuate the benefits of aspirin and explain the mixed results of the above recent trials. Using biomarkers or coronary calcium scores may help to identify patients who benefit from daily aspirin use; however, further research is warranted.

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