

Editorials

Rethinking Aspirin for the Primary Prevention of Cardiovascular Disease

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Administering aspirin during a heart attack or stroke can be lifesaving. The benefits of daily low-dose (81 mg) aspirin therapy to prevent recurrent cardiovascular disease (CVD) events are also well established.¹ Aspirin's routine use for primary prevention, however, has been the subject of controversy because of questionable benefits and increased bleeding risk.^{2,3} Aspirin therapy may reduce the relative risk of a first heart attack or stroke, but this benefit could be outweighed by the risk of gastrointestinal bleeding.⁴ According to a 2011-2012 national survey, one-third of Americans 40 years or older take a daily aspirin, including 28% of adults without known CVD⁵; therefore, delineating these risks and benefits has significant implications.

The U.S. Preventive Services Task Force (USPSTF) currently recommends that adults 50 to 59 years of age start taking a daily low-dose aspirin if they have a 10% or greater 10-year CVD risk, do not have bleeding risk factors, and are willing to take a daily aspirin for at least 10 years. Adults 60 to 69 years of age with similar CVD risk may consider starting low-dose aspirin therapy but are at higher risk of bleeding and less likely to benefit overall, according to the USPSTF. The USPSTF found insufficient evidence to assess the balance of benefits and harms of starting low-dose aspirin therapy for primary prevention in adults younger than 50 or older than 69 years.⁶

Supporting evidence for the 2016 USPSTF recommendations included a systematic review of 11 randomized, controlled trials of aspirin therapy with myocardial infarction and stroke outcomes published between 1988 and 2014⁷ with a review of major gastrointestinal bleeding and hemorrhagic strokes in trial participants.⁸ According to one member of the USPSTF at the time of the 2016 recommendation, the goal was to select adults at high enough cardiovascular risk that their expected benefit from aspirin therapy (including a possible reduction in the risk of developing colorectal cancer)⁶ would outweigh the harms of bleeding.⁹ However, in the decade or more since most of the trials analyzed by the USPSTF took place, fewer U.S. adults are smoking, and more have become eligible for statins and antihypertensives, which could have reduced aspirin's incremental benefit. Also, the USPSTF review suggested that the presence of diabetes mellitus did not alter the effectiveness of aspirin therapy in reducing CVD events, but only three trials specifically recruited these patients.⁷

In 2014, the U.S. Food and Drug Administration, citing concerns about insufficient evidence, advised the general public against using low-dose aspirin therapy for primary prevention of heart attack or stroke.¹⁰ Indeed, three recent studies' findings are more supportive of the U.S. Food and Drug Administration recommendation than the USPSTF recommendation. In the Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE) trial, more than 12,000 European and U.S. adults 55 years or older without diabetes were randomized to take 100 mg of enteric-coated aspirin or placebo daily for a median follow-up of five years. The researchers for the ARRIVE trial enrolled participants determined to be at a moderate risk of CVD (participants' mean atherosclerotic CVD risk score was 17.3% to 17.4%). With the caveat that less than 5% of participants had a cardiovascular event during the study, no difference occurred between the groups in a composite outcome of cardiovascular death, myocardial infarction, unstable angina, stroke, or transient ischemic attack. However, 1% of the aspirin group experienced gastrointestinal bleeding compared with only 0.5% of the placebo group (hazard ratio = 2.11; 95% confidence interval, 1.36 to 3.28).¹¹

The aspirin-placebo comparison in the ARRIVE trial was mirrored by another trial, A Study of Cardiovascular Events in Diabetes, but this trial enrolled 15,000 adults 40 years or older with diabetes in U.K. primary care practices. After a mean follow-up of 7.4 years, a lower percentage of the aspirin group had experienced serious vascular events than the placebo group, but this benefit was offset by an increased percentage of major bleeding events. The researchers calculated a number needed to treat of 91 to prevent a vascular event and number needed to harm of 112 to cause a major bleeding event, from which they concluded that aspirin provided no net benefit.¹²

Finally, the Aspirin in Reducing Events in the Elderly trial examined the effect of five years of daily low-dose aspirin therapy on community-dwelling adults 70 years or older in the United States and Australia. There were no differences in the primary endpoint of disability-free survival (a composite of death, dementia, and persistent physical disability) or the prespecified secondary endpoint of CVD deaths, events, and hospitalizations.^{13,14} However, the aspirin group had a significantly higher rate of major hemorrhage and higher all-cause mortality.¹⁵

A meta-analysis that pooled data from older primary prevention trials with these three new studies calculated a number needed to treat of 265 to prevent a composite cardiovascular outcome (cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke) and number needed to harm of 210 to prevent a major bleeding event, suggesting that aspirin provided no net benefit.¹⁶ Studies

with an estimated population 10-year CVD risk of greater than 10% experienced a similar balance of benefits and harms (number needed to treat = 196; number needed to harm = 152).

Though not designed to determine whether long-term use of daily aspirin reduces colorectal cancer incidence or mortality, as other evidence has suggested,¹⁷ the new evidence should prompt the USPSTF to reevaluate their 2016 aspirin guideline. The new data do not exclude the possibility that aspirin may still benefit adults at very high CVD risk (e.g., 20% or more over 10 years) or those at lower risk who are unable to tolerate statins, but the data otherwise suggest that the risks of low-dose aspirin therapy for primary prevention outweigh any potential benefits. For most patients, we should be deprescribing aspirin for primary prevention of CVD. To prevent heart attacks and strokes, family physicians should focus instead on smoking cessation and lifestyle changes, controlling high blood pressure, and prescribing statins when indicated.

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References

1. Baigent C, Blackwell L, Collins R, et al.; Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet*. 2009;373(9678):1849-1860.
2. Bailey AL, Smyth SS, Campbell CL. The case against routine aspirin use for primary prevention in low-risk adults. *Am Fam Physician*. 2011; 83(12):1387-1390.
3. Miser WF. Appropriate aspirin use for primary prevention of cardiovascular disease. *Am Fam Physician*. 2011;83(12):1380-1386.
4. Sutcliffe P, Connock M, Gurung T, et al. Aspirin in primary prevention of cardiovascular disease and cancer: a systematic review of the balance of evidence from reviews of randomized trials. *PLoS One*. 2013;8(12): e81970.
5. Gu Q, Dillon CF, Eberhardt MS, Wright JD, Burt VL. Preventive aspirin and other antiplatelet medication use among U.S. adults aged \geq 40 years: data from the National Health and Nutrition Examination Survey, 2011-2012. *Public Health Rep*. 2015;130(6):643-654.
6. Bibbins-Domingo K; U.S. Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2016;164(12):836-845.
7. Guirguis-Blake JM, Evans CV, Senger CA, O'Connor EA, Whitlock EP. Aspirin for the primary prevention of cardiovascular events: a systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2016;164(12):804-813.
8. Whitlock EP, Burda BU, Williams SB, Guirguis-Blake JM, Evans CV. Bleeding risks with aspirin use for primary prevention in adults: a systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2016;164(12):826-835.
9. Owens DK. Aspirin for the prevention of cardiovascular disease and colorectal cancer: new recommendations from the USPSTF. *Am Fam Physician*. 2017;95(4):222-223.
10. U.S. Food and Drug Administration. Use of aspirin for primary prevention of heart attack and stroke. May 2, 2014. Updated December 30, 2016. <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm390574.htm>. Accessed September 26, 2018.
11. Gaziano JM, Brotons C, Coppolecchia R, et al.; ARRIVE Executive Committee. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2018; 392(10152):1036-1046.
12. Bowman L, Maffham M, Wallendszus K, et al.; ASCEND Study Collaborative Group. Effects of aspirin for primary prevention in persons with diabetes mellitus. *N Engl J Med*. 2018;379(16):1529-1539.
13. McNeil JJ, Woods RL, Nelson MR, et al.; ASPREE Investigator Group. Effect of aspirin on disability-free survival in the healthy elderly. *N Engl J Med*. 2018;379(16):1499-1508.
14. McNeil JJ, Wolfe R, Woods RL, et al.; ASPREE Investigator Group. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. *N Engl J Med*. 2018;379(16):1509-1518.
15. McNeil JJ, Nelson MR, Woods RL, et al.; ASPREE Investigator Group. Effect of aspirin on all-cause mortality in the healthy elderly. *N Engl J Med*. 2018;379(16):1519-1528.
16. Zheng SL, Roddick AJ. Association of aspirin use for primary prevention with cardiovascular events and bleeding events: a systematic review and meta-analysis. *JAMA*. 2019;321(3):277-287.
17. Chubak J, Kamineni A, Buist DS, Anderson ML, Whitlock EP. Aspirin use for the prevention of colorectal cancer: an updated systematic evidence review for the U.S. Preventive Services Task Force. AHRQ publication no. 15-05228-ER-1. Rockville, Md.: Agency for Healthcare Research and Quality; September 2015. ■