More Evidence to Help Guide Decision Making About Aspirin for Primary Prevention

Michael Pignone, MD, MPH, and Darren A. DeWalt, MD, MPH

Defining the role of aspirin in patients with no history of cardiovascular events (primary prevention) is challenging. Aspirin can have important benefits, including preventing cardiovascular events (1) and possibly reducing the incidence and mortality of some types of cancer (2). However, it can also have important harms, including increasing risk for gastrointestinal bleeding and possibly intracerebral hemorrhage (3). In 2016, the U.S. Preventive Services Task Force examined the body of evidence through a series of systematic reviews and issued a moderate-strength ("B") recommendation for use of aspirin in "adults aged 50 to 59 years who have a 10% or greater 10-year [cardiovascular disease] 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" (4).

Despite a relatively large number of trials, interpreting the evidence about aspirin for prevention is difficult because the benefits and downsides are closely balanced. Decision analytic and cost-effectiveness modeling find that aspirin's net health benefit may be good (with the potential for lower total costs) in middle-aged adults at increased cardiovascular risk, especially if aspirin also has a modest or greater effect on cancer mortality (5, 6).

Beyond the challenges in weighing benefits and harms, several important questions remain about the quality of evidence (bias and error) and the possibility that aspirin may work differently in various patient groups (effect modification). Of note, several trials that showed potential benefits were done decades ago in a very different health care environment (different risk factor profiles, fewer concurrent preventive therapies, and less access to early diagnostic and treatment services) (1, 2). The current environment, in which more attention is given to cardiovascular prevention and care, may reduce the benefits of aspirin—or simply decrease overall risk and hence affect the benefit–harm ratio. In addition, trials have typically enrolled healthy participants who have lower event rates than would be predicted by their risk factors.

These concerns have been bolstered by the recent publication of 2 large trials, 1 in healthy older adults and 1 in middle-aged and older adults with diabetes (7, 8). The ASPREE (Aspirin in Reducing Events in the Elderly) trial enrolled 19 114 patients aged 70 years or older (≥65 years among blacks and Hispanics). Participants were generally healthy: 4% were current smokers, 34% were receiving a statin, and only 11% were receiving aspirin before the trial. ASPREE found a nonstatistically significant effect that was smaller than expected on cardiovascular events among patients receiving aspirin compared with placebo (hazard ratio, 0.95 [95% CI, 0.83 to 1.08]) (7). However, the investigators found the expected increased risk for major bleeding (hazard ratio, 1.38 [CI, 1.18 to 1.62]) to be similar in magnitude to that in previous trials (7). All-cause mortality also increased, seemingly because of an unexpected increase in cancer mortality. (9). These results move the benefit–harm calculation toward harm for *initiating* aspirin therapy for primary prevention in older adults but do not inform treatment of patients who were receiving aspirin before age 70 years.

The second new trial, ASCEND (A Study of Cardiovascular Events in Diabetes), evaluated the benefit of aspirin in patients with diabetes (8). Understanding aspirin's role for primary prevention in this population is particularly challenging. Diabetes raises cardiovascular risk and may increase risk for relevant types of cancer (particularly colorectal cancer), which suggests that aspirin could have a greater preventive benefit (10). However, prior evidence (much of it from subgroups of larger trials, with attendant risks for confounding) suggests that aspirin is somewhat less effective in patients with diabetes, with smaller reductions (10%) in risk for cardiovascular events than those seen in some early trials in general populations. Potential explanations for this finding include the idea that patients with diabetes may have resistance to (low-dose) aspirin, or that the effect is the same in patients with diabetes and the observed difference is due to chance.

ASCEND is a large (n = 15 480), pragmatic, randomized trial that compared daily aspirin (100 mg) versus placebo in adults aged 40 years or older with diabetes and no previous cardiovascular disease. The mean age was 63 years, and 23.5% of participants were aged 70 years or older. Only 8% were current smokers, and 75% were receiving statins. After a mean follow-up of 7.4 years, those assigned to aspirin had a modest reduction in cardiovascular events (rate ratio, 0.88 [CI, 0.79 to 0.97]). The researchers found no clear evidence of effect modification. Younger participants (aged <60 years) seemed to derive somewhat more benefit than older participants, although the statistical test for interaction was not significant. Major bleeding increased moderately (rate ratio, 1.29 [CI, 1.09 to 1.52]) in those receiving aspirin compared with placebo. No effect was seen on cancer, but follow-up was shorter than in some trials that had previously shown benefit. Effects on all-cause mortality favored aspirin in direction but were not statistically significant (rate ratio, 0.94 [CI, 0.85 to 1.04]). The 12% relative reduction in the combined cardiovascular end point (without a clear effect on mortality and with a clear increased risk for bleeding) represents a modest net benefit for patients at increased cardiovascular risk.

This article was published at Annals.org on 27 November 2018.

In light of this new evidence, how should physicians approach the use of aspirin for primary prevention? Among middle-aged adults with or without diabetes, we believe that an approach based on cardiovascular risk still holds. Aspirin can be offered as an additional risk-reducing therapy for those younger than 70 years if other such therapies have been used appropriately and the patient still has elevated cardiovascular risk (>1% per year) and no increased bleeding risk. Shared decision making should focus on the patient's values and preferences with respect to maximizing cardiovascular risk reduction versus the increased risk for bleeding (both minor and major).

In most adults older than 70 years with or without diabetes, aspirin therapy should not be initiated for primary prevention. The absolute risk for bleeding increases, and current evidence does not support net benefit. At this time, evidence does not clearly tell us whether to withdraw aspirin at age 70 years if a patient started receiving it for primary prevention at an earlier age. If an informed decision was made to start aspirin therapy before age 70 years, we tend to continue it unless non–age-related bleeding risk has increased.

Although much is written about aspirin and many patients take it without a second thought, the overall magnitude of net benefit is likely small. However, aspirin therapy should be considered after use of smoking cessation, statins, and blood pressure control. Additional follow-up from these trials and others will help us to better understand whether beneficial effects on cancer are confirmed, which would tilt the decision toward aspirin use.

From Dell Medical School, University of Texas, Austin, Texas (M.P.); and University of North Carolina School of Medicine, Chapel Hill, North Carolina (D.A.D.).

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M18-2637.

Corresponding Author: Michael Pignone, MD, MPH, Department of Internal Medicine, Dell Medical School, DMS Health Discovery Building, Room 7.70, 1701 Trinity Street, Stop Z0900, Austin, TX 78712; e-mail, pignone@austin.utexas.edu.

Current author addresses and author contributions are available at Annals.org.

Ann Intern Med. doi:10.7326/M18-2637

References

1. **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;164:804-13. [PMID: 27064410] doi:10.7326/M15-2113

2. **Chubak J, Whitlock EP, Williams SB, Kamineni A, Burda BU, Buist DS, et al.** Aspirin for the prevention of cancer incidence and mortality: systematic evidence reviews for the U.S. Preventive Services Task Force. Ann Intern Med. 2016;164:814-25. [PMID: 27064482] doi:10.7326/M15-2117

3. **Whitlock EP, Burda BU, Williams SB, Guirguis-Blake JM, Evans CV.** Bleeding risks with aspirin use for primary prevention in adults: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med. 2016;164:826-35. [PMID: 27064261] doi:10.7326/M15-2112

4. **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;164:836-45. [PMID: 27064677] doi:10.7326/M16-0577

5. **Pignone M, Earnshaw S, McDade C, Pletcher MJ.** Effect of including cancer mortality on the cost-effectiveness of aspirin for primary prevention in men. J Gen Intern Med. 2013;28:1483-91. [PMID: 23681842] doi:10.1007/s11606-013-2465-6

6. **Dehmer SP, Maciosek MV, Flottemesch TJ, LaFrance AB, Whitlock EP.** Aspirin for the primary prevention of cardiovascular disease and colorectal cancer: a decision analysis for the U.S. Preventive Services Task Force. Ann Intern Med. 2016;164:777-86. [PMID: 27064573] doi:10.7326/M15-2129

7. **McNeil JJ, Wolfe R, Woods RL, Tonkin AM, Donnan GA, Nelson MR, et al; ASPREE Investigator Group.** Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. N Engl J Med. 2018. [PMID: 30221597] doi:10.1056/NEJMoa1805819

8. **ASCEND Study Collaborative Group.** Effects of aspirin for primary prevention in persons with diabetes mellitus. N Engl J Med. 2018. [PMID: 30146931] doi:10.1056/NEJMoa1804988

9. **McNeil JJ, Nelson MR, Woods RL, Lockery JE, Wolfe R, Reid CM, et al; ASPREE Investigator Group.** Effect of aspirin on all-cause mortality in the healthy elderly. N Engl J Med. 2018. [PMID: 30221595] doi:10.1056/NEJMoa1803955

10. **Pignone M, Williams CD.** Aspirin for primary prevention of cardiovascular disease in diabetes mellitus. Nat Rev Endocrinol. 2010;6:619-28. [PMID: 20856266] doi:10.1038/nrendo.2010.169

Current Author Addresses: Dr. Pignone: Department of Internal Medicine, Dell Medical School, DMS Health Discovery Building, Room 7.70, 1701 Trinity Street, Stop Z0900, Austin, TX 78712.
Dr. DeWalt: UNC Chapel Hill, 5045 Old Clinic Building, CB 7110, Chapel Hill, NC 27516.

Author Contributions: Conception and design: M. Pignone, D.A. DeWalt.
Analysis and interpretation of the data: M. Pignone, D.A. DeWalt.
Drafting of the article: M. Pignone, D.A. DeWalt.
Critical revision of the article for important intellectual content: M. Pignone, D.A. DeWalt.
Final approval of the article: M. Pignone, D.A. DeWalt.
Administrative, technical, or logistic support: M. Pignone.