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Aspirin for primary prevention: USPSTF recommendations for CVD and colorectal cancer

Patient age, baseline cardiovascular disease risk, bleeding risk, and personal preference regarding aspirin use are key to decision making. A clinical decision tool can help.

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PRACTICE RECOMMENDATIONS

› *Consider aspirin for patients 50 to 59 years of age who have a 10-year cardiovascular disease (CVD) risk of ≥ 10% and low bleeding risk.* (C)

› *Discuss prophylactic aspirin (using a shared decision-making model) with patients 60 to 69 years of age who have a 10-year CVD risk of ≥ 10% and low bleeding risk.* (C)

› *Avoid using aspirin for primary prevention in patients ≥ 70 years of age.* (B)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

Which patients are likely to benefit from using aspirin for primary prevention? In this article, we review the evidence to date, summarized for primary care settings in guidelines issued by the US Preventive Services Task Force (USPSTF). We supplement this summary with a rundown of the risks associated with aspirin use. And then we wrap up by identifying a clinical decision tool that is available to help make personalized decisions in a busy clinic setting, where determining an individual's potential cardiovascular benefits and bleeding risk can be challenging.

The "roadmap" from the guidelines. In 2014, after performing a review of the literature, the US Food and Drug Administration recommended against the routine use of aspirin for primary prevention of cardiovascular disease (CVD).[1] In 2016, the USPSTF published 4 separate systematic reviews along with a decision analysis using a microsimulation model, which informed their position statement on aspirin for primary prevention.[2-6] These USPSTF reviews and recommendations incorporated both CVD and colorectal cancer (CRC) benefits with the bleeding risks from aspirin. Generally, for individuals 50 to 59 years old, the benefits are deemed to outweigh the harms; shared decision making is advised with those 60 to 69 years of age. For patients younger than 50 or 70 and older, evidence is inconclusive.

The benefits of primary prevention with aspirin

Cardiovascular disease

The Antithrombotic Trialists' (ATT) Collaboration was one of the first meta-analyses that addressed the benefit-to-harm balance and called into question the routine use of aspirin for primary prevention.[7] The USPSTF systematic review included the studies from the ATT Collaboration as well as trials per-

formed after its publication, bringing the total number of eligible randomized controlled trials reviewed to 11.[2]

The benefit of aspirin for primary prevention of nonfatal myocardial infarction (MI) has been shown in multiple randomized controlled trials. The USPSTF systematic review showed a statistically significant relative risk reduction of 17% in patients taking low-dose aspirin (≤ 100 mg; relative risk [RR] = 0.83; confidence interval [95% CI], 0.74-0.94), although the heterogeneity of the studies was high. The same low dose of aspirin showed a statistically significant reduction in nonfatal stroke (RR = 0.86; 95% CI, 0.76-0.98), although the same benefit was not observed when all doses of aspirin were included. Cardiovascular disease mortality and all-cause mortality were not statistically different for patients taking low-dose aspirin when compared with placebo (RR = 0.97; 95% CI, 0.85-1.10 for CVD mortality; RR = 0.95; 95% CI, 0.89-1.01 for all-cause mortality).[2]

One study of more than 14,000 older (≥ 60 years) Japanese patients showed a statistically significant reduction in nonfatal MI (hazard ratio [HR] = 0.53; 95% CI, 0.31-0.91, *P* = .02) and nonfatal strokes (HR = 0.57; 95% CI, 0.32-0.99; *P* = .04). The study was stopped early because at 5 years of follow-up there was no statistically significant difference in a composite primary outcome, which included death from cardiovascular causes, nonfatal MI, and nonfatal stroke (HR = 0.94; 95% CI, 0.77-1.15; *P* = .54).[8]

Several recent landmark studies have called into question the benefit of aspirin for cardiovascular primary prevention, especially in obese individuals, patients with diabetes, and the elderly. A meta-analysis of 10 trials showed that the effectiveness of aspirin doses between 75 mg and 100 mg for primary prevention decreased as weight increased; patients weighing 70 kg or more received no benefit.[9] The ASCEND (A Study of Cardiovascular Events in Diabetes) trial included more than 15,000 patients with diabetes but no cardiovascular disease. Patients randomized to receive the low-dose aspirin did have fewer serious vascular events (incidence rate ratio [IRR] = 0.88; 95% CI, 0.79-0.97; *P* = .01), but they also had high risk of major bleeding events (IRR = 1.29; 95% CI, 1.09-1.52; *P* = .003).[10] The ASPREE (Aspirin in Reducing Events in the Elderly) trial included more than 19,000 patients ages 70 years and older with no cardiovascular disease and compared low-dose aspirin to placebo. There was no statistically significant cardiovascular benefit, although there was an increase of major hemorrhage (HR = 1.38; 95% CI, 1.18-1.62; *P* < .001).[11] The ARRIVE (A Randomized Trial of Induction Versus Expectant Management) trial included 12,546 moderate atherosclerotic CVD (ASCVD) risk patients. Although a per-protocol analysis showed a decrease in rates of fatal and nonfatal MI (HR = 0.53; 95% CI, 0.36-0.79; *P* = .0014), the more reliable intention-to-treat analysis showed no improvement for any outcomes.[12]

Colorectal cancer

The literature base on prevention of cancer has been growing rapidly. However, the deluge of findings over the past 2 decades of trials and analyses has also introduced ambiguity and, often, conflicting results. The first journal article suggesting aspirin for primary prevention of cancer, published in 1988, was a case-control study wherein a population with CRC was matched to controls to look for potential protective factors.[13] The most notable finding was the CRC risk reduction for those taking aspirin or aspirin-containing medications. Since then numerous studies and analyses have explored aspirin's potential in primary prevention of many types of cancer, with overall unclear findings as denoted in the 2016 USPSTF systemic reviews and recommendations.

One major limiting factor is that most data come from CVD prevention trials, and only a limited number of trials have focused specifically on cancer prevention. For the USPSTF, these data showed no statistically significant risk reduction in overall cancer mortality (RR = 0.96; 95% CI, 0.87-1.06) or in total cancer incidence (RR = 0.98; 95% CI, 0.93-1.04).[4] Other ongoing trials may yield more definitive data.[14]

The particular interest in CRC was due to it being the first cancer found to be preventable with aspirin therapy. The USPSTF, while

Preventive benefits of aspirin outweigh risks for those 50-59 years of age who have a 10-year cardiovascular disease risk of ≥ 10%.

acknowledging the homogeneous nature of supporting studies, noted that their significant number and resulting evidence made CRC the only cancer warranting evaluation. Population studies have now shown more benefit than the few randomized control trials. The Women's Health Study and the Physicians' Health Study were both limited by their duration. But such studies conducted over a longer period revealed notable benefits in the second decade of use, with a statistically significant lower CRC incidence (RR = 0.60; 95% CI, 0.47-0.76). Additionally, CRC mortality at 20 years was decreased in patients taking aspirin regularly (RR = 0.67; 95% CI, 0.52-0.86).[4] Multiple studies are in progress to better establish aspirin's CRC benefit.

While not directly applicable to the general population, use of aspirin for patients with Lynch syndrome to prevent CRC has strong supporting evidence.[15] Beyond CRC, there is nascent evidence from limited observational studies that aspirin may have a preventive effect on melanoma and ovarian and pancreatic cancers.[16-18] Further studies or compilations of data would be needed to draw more significant conclusions on other types of cancers. Larger studies would prove more difficult to do, given the smaller incidences of these cancers.

Interestingly, a recent study showed that for individuals 70 years and older, aspirin might increase the risk for all-cause mortality, primarily due to increased cancer mortality across all types.[19] Although this result was unexpected, caution should be used when prescribing aspirin particularly for patients 70 or older with active cancer.

A look at the harms associated with aspirin use

Aspirin has long been known to cause clinically significant bleeding. Aspirin inhibits platelet-derived cyclooxygenase-1 (COX-1), a potent vasoconstrictor, and thereby decreases platelet aggregation, reducing thromboembolic potential and prolonging bleeding time. These effects can confer health benefits but also carry the potential for risks. A decision to initiate aspirin therapy for primary prevention relies on an understanding of the benefit-to-harm balance.

Initial aspirin studies did not show a statistically significant increase in bleeding, likely due to too few events and inadequate powering. Subsequent meta-analyses from multiple evaluations have consistently shown bleeding to be a risk.[3,7] The risk for bleeding with aspirin has also been examined in multiple cohort studies, which has helped elucidate the risk in greater detail.

Gastrointestinal bleeding

Epidemiologic data show that among patients who do not use nonsteroidal anti-inflammatory drugs (NSAIDs), the rate of upper gastrointestinal (GI) complications is 1 case per 1000 patient-years.[20] Multiple studies have consistently shown that aspirin use increases the rate of significant upper GI bleeding over baseline risk (odds ratio [OR] = 1.54-1.58).[3,21,22] Interestingly, these increases seem not to be influenced by other factors, such as comorbidities that increase the risk for ASCVD. Analysis of cancer prevention studies showed similar epidemiologic trends, with aspirin use exceeding a baseline bleeding risk of 0.7 cases of upper GI complications per 1000 patient-years (OR = 1.31-1.73).[23]

Other risk factors. Evaluation of risk factors for bleeding primarily comes from 2 studies.[3,7] Most data concern the impact of individual factors on significant GI bleeding, with fewer data available for evaluating risk for intracerebral hemorrhage (ICH). Initial analysis of individual prospective studies showed little or no correlation between risk for bleeding and such factors as gender, age, or history of hypertension or ASCVD.[21] Subsequent analysis of meta-data and large cohorts did show statistically significant impact on rates of bleeding across several factors (**TABLE 1**[3,7]).

Of note is a large heterogeneous cohort study conducted in Spain. Data showed significant increases in baseline risk for GI bleeding in older men with a history of GI bleeding and NSAID use. The absolute risk for GI bleed in this group was potentially as high as 150 cases per 1000 patient-years, well above the risk level assumed for the average patient.[24] A seemingly small OR of 1.5 could dramatically increase the absolute risk for bleeding in such patients, and it suggests

TABLE 1
Baseline risk factors and rate ratios for major GI or extracranial bleeding[3,7]

	ATT Collaboration
Risk factors	Rate ratio (95% CI)
Age	2.15 (1.93-2.39)
Male sex	1.99 (1.45-2.73)
Diabetes mellitus	1.55 (1.13-2.14)
Smoking	1.56 (1.25-1.94)
Mean BP, per 20 mm Hg	1.32 (1.09-1.58)
BMI, per 5 kg/m^2	1.24 (1.13-1.35)

ATT, Antithrombotic Trialists; BMI, body mass index; BP, blood pressure; CI, confidence interval; GI, gastrointestinal.

that a generalized risk for bleeding probably shouldn't be applied to all patients. Individuals may be better served by a baseline risk calculation reflecting multiple factors.

Intracerebral hemorrhage

Due to the comparatively uncommon nature of ICH, fewer data are available to support definitive conclusions about its increased risk with aspirin use. Aspirin use appeared to increase the risk for ICH with ratios between 1.27 and 1.32 in meta-analyses (measured as an OR or as an RR),[3,7,21] with an IRR of 1.54 in a cohort study.[22] The only statistically significant factors suspected to increase the risk of ICH at baseline were smoking (RR = 2.18) and mean BP > 20 mm Hg over normal (OR = 2.18). Age, gender, and diabetes all showed a nonsignificant trend toward risk increase.[7]

Risk based on dose and formulation

The effect of aspirin dose and formulation on bleeding risk is uncertain. Some studies have shown an increased risk for bleeding with daily doses of aspirin ≥ 300 mg, while others have shown no significant increase in rates for bleeding with differing doses.[21,25] Enteric coating does appear to lower the rates of gastric mucosal injury, although there are few data on the effect toward reducing clinically significant bleeding.[26] Currently, several prospective studies are underway to help clarify the evidence.[27]

Enteric coating on aspirin does appear to lower the rates of gastric mucosal injury.

Putting it all together

For the general population, the evidence shows that the benefits and harms of aspirin for primary prevention are relatively even. The USPSTF guidelines are the first to recommend aspirin for both CVD and cancer prevention while taking into account the bleeding risk. According to the findings of the USPSTF, the balance of benefits and harms of aspirin use is contingent on 4 factors: age, baseline CVD risk, risk for bleeding, and preferences about taking aspirin.[6] The complete recommendations from the USPSTF, along with other leading organizations, are outlined in **TABLE 2**.[6,28-31]

Applying the evidence and varying guidelines in practice can feel daunting. Some practical tools have been developed to help clinicians understand patients' bleeding risk and potential benefits with aspirin use. One such tool is highlighted below. Others are also available, and each has its own strengths and weaknesses.

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TABLE 2

Summary of guideline recommendations on use of low-dose aspirin for primary prevention

Organization	Year	Recommendation
USPSTF[6]	2016	In adults ages 50-59 y, initiate low-dose aspirin to prevent CVD (if 10-y risk is ≥ 10%) or to prevent CRC. In adults ages 60-69 y, use shared decision making to initiate low-dose aspirin to prevent CVD (if 10-y risk is ≥ 10%) or to prevent CRC. Evidence is insufficient to recommend aspirin in patients < 50 or ≥ 70 y of age.
European Society of Cardiology[28]	2016	Antiplatelet therapy is not recommended for individuals without CVD due to increased risk for major bleeding.
American Diabetes Association[29]	2017	Consider aspirin for patients with type 1 or 2 diabetes who are at increased CVD risk (most men and women ≥ 50 y of age who have at least 1 additional major risk factor) and not at increased risk for bleeding.
American College of Chest Physicians[30]	2012	Recommend low-dose aspirin for patients > 50 y of age without symptomatic CVD.
ACC/AHA[31]	2019	Consider low-dose aspirin in patients 40-70 y of age who have a high ASCVD risk and are not at increased risk for bleeding. Aspirin is not recommended for patients > 70 y of age. Avoid aspirin in patients with increased risk for bleeding.

ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CRC, colorectal cancer; CVD, cardiovascular disease; USPSTF, US Preventive Services Task Force.

Aspirin-Guide (www.aspiringuide.com) is a Web-based clinical decision support tool with an associated mobile application. It uses internal calculators (including the pooled cohort calculator prepared jointly by the American College of Cardiology and the American Heart Association) to assess CVD risk as well as bleeding risk. This tool gives clinicians patient-specific numbers-needed-to-treat and numbers-needed-to-harm when considering starting aspirin for primary prevention. It gives specific recommendations for aspirin use based on the data entered, and it also gives providers information to help guide shared decision-making with patients.[32] Unfortunately, this decision support tool and others do not take into account the data from the most recent trials, so they should be used with caution. **JFP**

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