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*The authors reported no
potential conflict of interest
relevant to this article.*

Aspirin for CV prevention—for which patients?

Put your patient on aspirin? Take him off? Here's what you need to know to get it right.

PRACTICE RECOMMENDATIONS

› Calculate a patient's 10-year global risk of cardiovascular events using a risk-assessment tool before recommending aspirin for primary prevention. **A**

› Keep in mind that diabetes is not an indication for aspirin as primary cardiovascular protection, unless the patient's calculated 10-year risk is >10%. **A**

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

Among individuals at high risk ($\geq 10\%$) for coronary heart disease (CHD) within 10 years, only 44% are taking aspirin.¹ In addition, for patients at high risk for CHD events, estimated aspirin use varies among ethnic groups: 53% for whites, 43% for African Americans, 38% for Hispanics, and 28% for Chinese Americans.¹

In contrast to this underuse of aspirin by those who need it, patients who do not need aspirin have been told otherwise,² following widespread publicity of US Preventive Services Task Force (USPSTF) recommendations from 2002 (that have since been updated). Overuse of aspirin is also likely among individuals whose CHD risk has never been formally assessed but who take it on their own, based on direct-to-consumer advertising about the cardiovascular (CV) benefits of aspirin. Also, the American Diabetes Association (ADA) once recommended aspirin for all patients with diabetes. But it now advises avoiding the use of aspirin for primary prevention of CV events unless a patient's calculated CV risk over 10 years is >10%.³

Our review summarizes the latest evidence on the use of aspirin for primary prevention of CV events, including the determination of benefit vs harm, the variability in aspirin responsiveness among individuals, and the efficacy of aspirin treatment in men vs women and in those with diabetes.

When does benefit outweigh risk?

In 2002, the USPSTF concluded that patients with a 5-year risk of coronary events $\geq 3\%$ had the most favorable benefit-to-risk ratio with aspirin use.⁴ It based its recommendation on 5 randomized, controlled primary prevention studies with aspirin that demonstrated a reduction in the risk of a first myocardial infarction (MI) in men.⁵⁻⁹ In 2009, the USPSTF updated its recommendations regarding the risks and benefits of aspirin for primary prevention of CHD,¹⁰ in part to include data from the Women's Health Study¹¹ that demonstrated a 24% relative risk (RR) reduction of ischemic stroke without

TABLE

Should you recommend aspirin? See how these patients “scored”*

Patient	Risk score	Prophylaxis
53-year-old woman, HTN on medication, SBP 152, nonsmoker, Chol 260, HDL 50	4%	No
48-year-old man, HTN on medication, SBP 138, nonsmoker, Chol 220, HDL 41	7%	No [†]
68-year-old woman, HTN on medication, SBP 152, nonsmoker, Chol 260, HDL 50	11%	Yes
58-year-old man, HTN on medication, SBP 138, nonsmoker, Chol 220, HDL 41	14%	Yes
51-year-old man, HTN on medication, SBP 140, nonsmoker, Chol 180, HDL 41, Diabetes	6%	No [†]

*Score for 10-year risk of CHD calculated with Framingham Heart Study data.¹⁴

[†]Under 2009 USPSTF recommendations, may consider aspirin therapy.¹⁰

Chol, total cholesterol; HDL, high-density lipoprotein; HTN, hypertension; SBP, systolic blood pressure.

reducing the risk of MI.

The USPSTF now recommends aspirin for men ages 45 to 79 to prevent a first MI, and for women ages 55 to 79 to prevent an ischemic stroke when the potential benefit outweighs the increased risk of gastrointestinal (GI) hemorrhage.¹⁰ Evidence does not support the use of aspirin for primary CHD prevention in men younger than 45 years or women younger than 55. Evidence is insufficient to recommend aspirin for primary prevention of CHD for individuals ≥ 80 years of age in the absence of other compelling indications such as atrial fibrillation.

■ Calculating benefit. The American Heart Association (AHA) recommends low-dose aspirin for primary prevention of CV events in all individuals with a calculated 10-year CHD risk of $\geq 10\%$, while cautioning about its use in patients at increased risk for GI bleeding and hemorrhagic stroke.¹² The Framingham risk score¹³ is available online at <http://hp2010.nhlbihin.net/atp/iii/calculator.asp?usertype=prof> to estimate an individual's 10-year CHD risk (TABLE).¹⁴

■ Judging risk. There are no validated tools for assessing the long-term risk of intracranial or GI hemorrhage with low-dose aspirin. The risk factors for GI bleeding with nonsteroidal anti-inflammatory drugs

(NSAIDs) are well known,¹⁵ but less data exist for low-dose aspirin. Likely risk factors include a history of peptic ulcer disease, concomitant NSAID therapy, high-dose corticosteroids or anticoagulants, dual antiplatelet therapy, age >60 years, and male sex.¹⁶ Although proton-pump inhibitors prevent recurrent peptic ulcers secondary to low-dose aspirin use, little data exist on their value or cost effectiveness for this purpose.¹⁷

■ Why the AHA recommendation makes sense. The 2009 USPSTF recommendations still identify different tiers of risk according to 3 age brackets within the range of 45 (or 55) to 79 years. Since then, however, further studies seem to favor a less aggressive approach to aspirin use, more in keeping with the AHA recommendation.

The Antithrombotic Trialists' (ATT) Collaboration¹⁸ published a meta-analysis using individual participant data from the same studies that served as the basis of the USPSTF recommendations.^{5-9,11} It found that aspirin did not reduce the risk of death due to CHD, stroke, or other vascular causes. The risk of nonfatal stroke also did not decline. Aspirin use decreased the risk of nonfatal MI (RR=0.77; 99% confidence interval [CI], 0.67-0.89), any major coronary event (RR=0.82; 95% CI, 0.75-0.90), and serious



The AHA recommends low-dose aspirin for primary prevention of CV events in patients with a calculated 10-year risk $\geq 10\%$, taking into account risks for bleeding.

➤ A subgroup analysis of the Physicians' Health Study suggests that nonadherence with aspirin therapy or concomitant NSAID use negated the benefit of aspirin.

vascular events (RR=0.88; 95% CI, 0.82-0.94). The risk of extracranial hemorrhage, including GI bleeding, increased (RR=1.54; 95% CI, 1.30-1.82). Based on this analysis, the absolute reduction in serious ischemic events was partially offset by a small increase in serious bleeding. However, long-term disability from a nonfatal extracranial hemorrhage is likely less than that from a nonfatal stroke or MI.¹⁸

In the ATT Collaboration¹⁸ analysis, the 5-year risk of bleeding with low-dose aspirin increased with the predicted 5-year CHD risk. Patients with the lowest CHD risk (<5%) demonstrated a 0.4% risk of bleeding vs 2.7% among patients having the highest CHD risk (>10%). However, the high-risk patients also had the largest benefit with low-dose aspirin therapy. According to the ATT Collaboration data, using aspirin alone vs placebo, the estimated number needed to treat (NNT) to prevent 1 serious vascular event (defined as vascular death, nonfatal MI, or stroke) was 50 patients for 5 years. When aspirin was added to other therapies such as statins, the NNT was 100 patients for 5 years. To cause 1 nonfatal extracranial bleeding event with aspirin in the same high-risk patients, the estimated number needed to harm (NNH) was also 100 patients for 5 years. A meta-analysis of 22 trials estimated a NNH to cause 1 additional major bleeding event with aspirin per year was 769 patients (95% CI, 500-1250).¹⁹

The Aspirin for Asymptomatic Atherosclerosis Trial (AAAT)²⁰ involved 3350 men and women ages 50 to 75 years with low ankle-brachial index and no history of CV disease (CVD). Participants were randomized to receive 100 mg enteric-coated aspirin or placebo daily and were followed for a mean of 8.2 years. The primary and secondary end points, which included fatal and nonfatal MI or stroke, were similar in the 2 groups, as were all-cause mortality and total adverse events. A difference in the incidence of major hemorrhage did not reach statistical significance—34 patients in the aspirin arm vs 20 in the placebo arm (hazard ratio [HR]=1.71; 95% CI, 0.99-2.97). One caution: the relative lack of benefit from aspirin reported in the AAAT may be due to the fact that it was powered to detect a 25% reduction in the event rate between groups, whereas the ATT Col-

laboration study¹⁸ found a 12% risk reduction in MI among those taking aspirin.

Test for aspirin resistance? It's still too soon

Patients receiving aspirin therapy may demonstrate residual platelet reactivity (laboratory resistance) or recurrent ischemic CV events (clinical resistance).²¹ Estimates of the prevalence of aspirin resistance vary widely.²² And available assays of residual platelet activity yield different results. Higher estimates of aspirin resistance may occur with assays that use an agonist other than arachidonic acid, such as collagen or adenosine diphosphate platelet aggregation, the whole blood platelet function analyzer (PFA-100), or urinary 11-dehydro-thromboxane B₂.²³

Several secondary prevention studies have demonstrated a positive association with laboratory resistance and adverse CV events, regardless of methods and assays used.²⁴ However, prospective primary prevention studies of this association are lacking. A meta-analysis of 20 clinical studies reported an increased risk of recurrent CV events including graft failure, acute coronary syndrome (ACS), and death among patients who exhibited aspirin resistance (odds ratio [OR]=3.85; 95% CI, 3.08-4.80). The authors identified a high level of heterogeneity among the studies, with 9 of the 20 failing to demonstrate an increased risk of events.²⁵

Using the PFA-100 assay, a prospective cohort study verified the presence or absence of aspirin resistance in 140 patients who presented to the emergency department with a non-ST-elevation ACS and who reported using aspirin daily for at least 7 days before the event.²⁶ Fifty-three patients (37.8%) were found to have aspirin resistance. Baseline characteristics of patients with and without aspirin resistance were similar except for an older age (mean 63.8 vs 58.3 years, respectively) and higher cardiac troponin values (mean 1.11 vs 0.41 ng/mL). Both groups were monitored for an average of 20 months; 45 patients with aspirin resistance and 79 without resistance completed follow-up. The presence of aspirin resistance increased the risk of MI (HR=3.02; 95% CI, 1.15-7.95) and decreased the risk of event-free survival

(HR=2.46; 95% CI, 1.18-5.13). Adjusted for age, platelet count, cardiac troponin values, and coronary artery disease severity scores, the presence of aspirin resistance was associated with a 3-fold increased risk of CV events (HR=3.03; 95% CI, 1.06-8.62).

Mechanisms for aspirin resistance may involve an inability of aspirin to partially or completely inhibit the cyclo-oxygenase-1 (COX-1) enzyme leading to thromboxane A₂ production, or factors independent of the COX-1 pathway such as elevated levels of C-reactive protein.²⁷ COX-1-related factors include aspirin nonadherence, reduced aspirin bioavailability, competitive inhibition by NSAIDs, inadequate aspirin dosage, genetic COX-1 polymorphisms, and increased platelet turnover.^{27,28} A subgroup analysis of the Physicians' Health Study²⁹ suggests that nonadherence with aspirin therapy or concomitant NSAID use negated the benefit of aspirin. In a small cohort study (n=18), patients who took ibuprofen or naproxen and aspirin did not demonstrate inhibition of platelet aggregation and had a 72% rate of recurrent ischemic events despite aspirin therapy.³⁰

Until clinical trials can demonstrate benefit and cost effectiveness of empiric laboratory testing for aspirin resistance in patients without a history of CVD, emphasize adherence to the prescribed antiplatelet therapy and warn against concomitant NSAID use for patients at risk for CHD events.

Aspirin for patients with diabetes: Only when CVD risk is high

In 2010, the ADA revised its clinical practice recommendations to reflect the results of 2 studies that questioned the value of aspirin for primary prevention of CVD events in patients with diabetes.³ Instead of a global statement to use low-dose aspirin, the ADA guideline now recommends its use only in patients with diabetes who have a 10-year risk >10%. This includes men over the age of 50 and women over the age of 60, with at least one major risk factor in addition to diabetes. The studies driving this change were the Prevention of Progression of Arterial Disease and Diabetes (POPADAD)³¹ and the Japanese Pri-

mary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD).³²

■ **The POPADAD study** enrolled 1276 patients over the age of 40 with type 1 or type 2 diabetes who also had asymptomatic peripheral arterial disease but without symptomatic CHD. Participants were randomized to take aspirin 100 mg daily or placebo (POPADAD also included a study of antioxidants vs placebo). The participants had diabetes for a mean of 6.3 years. The study had 2 primary composite end points: death from CHD or stroke, nonfatal MI or stroke, or amputation above the ankle for critical ischemia; and death from CHD or stroke. The aspirin and placebo groups were similar at baseline in terms of demographic characteristics and use of statins, beta-blockers, and angiotensin-converting enzyme (ACE) inhibitors among other treatments. The composite end point of death from CHD or stroke was similar in the 2 groups. Nonfatal MI and nonfatal stroke were also similar in the 2 groups.³¹

■ **The JPAD study** enrolled individuals with type 2 diabetes who were over the age of 30 and had no evidence of CVD. Participants were randomized to receive either 81 mg aspirin or placebo daily. The composite end point was sudden death; death from CHD, stroke, or aortic causes; nonfatal MI; nonfatal stroke; unstable angina; transient ischemic attack; or nonfatal peripheral vascular disease. The 2 groups were similar in terms of the composite end point, nonfatal MI, and nonfatal stroke. The risk of death from MI and stroke was lower in the aspirin group.³²

■ **The authors of a 2010 consensus report** from the ADA, the AHA, and the American College of Cardiology (ACC) evaluated the findings of individual placebo-controlled aspirin studies as well as those included in prior meta-analyses.³³ They also conducted a separate meta-analysis, which indicated that aspirin decreased the risk of CHD in patients with diabetes by 9% (RR=0.91; 95% CI, 0.79-1.05), but the reduction was not statistically significant. If the findings of the Early Treatment of Diabetic Retinopathy Study, which included some individuals with prior CVD events, had been excluded from this meta-analysis, the risk reduction due to aspirin would have been smaller.

CONTINUED



The ADA now recommends aspirin use in patients with diabetes only if they have a 10-year CVD event risk >10%.

Results of this meta-analysis are mitigated by certain factors. The 9 studies analyzed were published between 1989 and 2008, and the use of drugs such as statins, beta-blockers, and ACE inhibitors increased over this 20-year period. Also, the age of study participants at enrollment varied, as did the presence of subclinical CVD. The rates of CHD in the placebo groups of the studies also varied significantly.

Accounting for differences between the sexes

A person's sex in part determines the importance of certain CV risk factors, the prevalence of CV and related comorbid diseases, and the frequency of adverse drug effects. Women with diabetes have a 50% increased relative risk of CVD than men with diabetes, in part because they are often older and have more risk factors.³⁴

■ **A 2011 AHA update on the prevention of CVD in women** indicates that women ≥ 65 years may use aspirin, 81 mg daily or 100 mg every other day, if the benefit in re-

ducing CHD or ischemic stroke is not outweighed by the potential risk of GI bleeding or hemorrhagic stroke. It also deems aspirin an option that women younger than 65 could consider with their physicians for prevention of ischemic stroke, and recommends aspirin 75 to 325 mg daily for women with diabetes.³⁵

■ **The study populations in the ADA/AHA/ACC meta-analysis** of aspirin for primary prevention in patients with diabetes varied in the percentage of women enrolled. Three trials did not include women, while one study enrolled women exclusively. The remaining studies had similar numbers of men and women. Aspirin decreased the risk of CHD events in men (RR=0.77; 95% CI, 0.67-0.89) and stroke in women (RR=0.77; 95% CI, 0.59-0.99). The consensus report acknowledged that the findings of the Women's Health Study strongly influenced this difference in outcomes for men and women.³³ **JFP**

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