Aspirin for CV Primary Prevention

The FAQ below provides information to assist clinicians in estimating aspirin's risk/benefit ratio in patients **without CVD**. Use for colorectal cancer prevention is also addressed. See our FAQ, *The Truth About Aspirin*, for information on aspirin formulations (e.g., *Vazalore*, *Yosprala*, *Durlaza*), when and how to take it, risk of side effects, myths, and misconceptions.

Question	Answer/Pertinent Information
Who **might** be a candidate for aspirin for primary prevention of CV events, **per current guidelines**?	Note that no guideline recommends routine aspirin use for primary prevention of CV events. Use shared decision-making to **individualize** decisions based on CV risk vs bleeding risk in the following groups.[1,2] • **USPSTF (2022 recommendations)**: **age 40 to 59 years** with ≥10% 10-year risk of CVD not at increased risk of bleeding.[1] • **ACC/AHA (2019)**: **age 40 to 70 years** with higher CV risk (e.g., especially those with poorly controlled risk factors) but not at increased risk of bleeding.[2] • **ESC (2021)**: **age <70 years** with diabetes or high/very high CV risk, if there are no contraindications.[10] • **Heart and Stroke Foundation (Canada)/CSC (2020)**: not recommended but use shared decision-making.[19] • **ADA (2022)**: patients with diabetes and increased CV risk (e.g., patients **50 to 70 years** with at least one additional major risk factor: family history of premature atherosclerotic CVD, hypertension, dyslipidemia, smoking, or albuminuria) who are not at increased risk of bleeding.[4] • **Diabetes Canada (2018)**: may be used for patients with multiple risk factors and increased inflammatory markers (e.g., C-reactive protein [CRP]).[3]
Why might recommendations differ among guidelines?	• The **USPSTF** 2022 recommendations are based on a new systematic review (including ASPREE, ARRIVE, and ASCEND, reviewed below), and a microsimulation modeling study of aspirin risk/benefit based on age, sex, and CV risk.[9,14,15] • **ACC/AHA** 2019 guidelines were based on ASPREE, ARRIVE, and ASCEND, plus older meta-analyses (2016) and studies that found no aspirin benefit (e.g., POPADAD, ASCB, JPAD, JPPP).[2] • The **Heart and Stroke Foundation (Canada)/CSC** 2020 guideline relied on ASPREE, ARRIVE, and ASCEND, a meta-analysis of these and other studies, and two older randomized, controlled trials (AAA, ASCB) that found no aspirin benefit in patients with asymptomatic atherosclerosis.[19]

Question	Answer/Pertinent Information
What new trials have influenced recent recommendations?	• **ARRIVE** (n = 12,546) compared enteric-coated aspirin 100 mg once daily to placebo for primary prevention of CV events (CV death, MI, unstable angina, stroke, or TIA) in men ≥55 with two to four risk factors and women ≥60 years of age with three or more risk factors (10-year CV risk ~10% to 20% per the 2013 ACC/AHA pooled cohort equations calculator).[5] Patients with a history of GI bleed, frequent NSAID use, antiplatelet or anticoagulant use, or **diabetes were excluded**. Aspirin was not beneficial during 5 years of follow-up (event rate 4.29% vs 4.48%, HR 0.96, 95% CI 0.81 to 1.13, p=0.6038), but doubled the risk of GI bleeding (0.97% vs 0.46%, HR 2.11, 95% CI 1.36 to 3.28, p=0.0007).[5] The actual 10-year CV event rate in this study was lower than estimated (about 8% to 9%), perhaps due to optimization of modern medical therapies (e.g., statins, antihypertensives), making the study population essentially a low-risk population.[5] The GI bleed event rate was similar to the expected event rate.[5] • **ASCEND** (n = 15,480) compared enteric-coated aspirin 100 mg once daily to placebo in patients ≥40 years of age **with diabetes** (but without CVD) for prevention of CV events (e.g., vascular death, MI, stroke, or TIA).[6] Aspirin provided some benefit for prevention of serious vascular events (8.5% vs 9.6%, rate ratio 0.88, 95% CI 0.79 to 0.97, p= 0.01, NNT = 91 over 7.4 years to prevent one event). No benefit was seen for any specific event (e.g., MI). Benefit was mainly seen in the first five years of use. This benefit was largely offset by bleeding events (NNH = 112 over 7.4 years to cause one major bleeding event). • **ASPREE** (n = 19,114) compared enteric-coated aspirin 100 mg once daily to placebo in patients ≥70 years of age (African Americans or US Hispanics ≥65 years of age). Patients taking antiplatelets or anticoagulants, and patients with BP ≥180/105 mmHg were excluded. Short-term NSAID use at the lowest dose was allowed. Eleven percent of enrollees had diabetes.[8] Aspirin did not reduce CV events or death from any cause, or improve quality of life, but increased the risk of major bleeding (8.6 vs 6.2 events per 1,000 person-years, p<0.001).[20] There was no evidence that any subgroup responded differently, including patients with diabetes.[8] All-cause mortality was higher in the aspirin group (12.7 vs 11.1 per 1,000 person years [HR 1.14, 95% CI 1.01 to 1.29]), mostly due to excess cancer deaths.[8] **Bottom line**: aspirin does not likely provide net benefit for primary prevention patients ≥70 years of age, or patients without diabetes with an estimated 10-year event rate <20%, especially those with bleeding risks [Evidence Level A-1].[5,6,8]
Do patients with **diabetes** benefit from aspirin for primary prevention of CV disease?	• See ASCEND and ASPREE, above. • Diabetes Canada 2018 recommendations (above) are based on subgroup analysis of JPAD (i.e., potential benefit in patients with elevated C-reactive protein), and meta-analyses suggesting no benefit but potential harm.[3] • A meta-analysis suggests an NNT of 95 for five years to prevent one CV event in patients with diabetes.[13] • The relative increase in aspirin-associated bleeding risk is the same regardless of diabetes status; however, people with diabetes have a higher baseline risk of bleeding (e.g., GI bleeding, hemorrhagic stroke) that should be considered.[1]

Question	Answer/Pertinent Information
Does aspirin risk differ in males vs females?	• The relative increase in aspirin-associated bleeding risk is the same regardless of sex. However, males have a higher baseline risk of bleeding (e.g., GI bleeding, hemorrhagic stroke) that should be considered.[1]
How do I decide whether to start/continue aspirin for primary prevention?	• **Do not** start aspirin for primary prevention in patients **>70 years of age**.[2] • For ages **40 to 70 years**: o **Assess CV risk**. The **ACC/AHA pooled cohort equations calculator** is available at https://www.cvriskcalculator.com. This calculator might overestimate CV risk in many populations, including patients without diabetes, African Americans, and otherwise healthy older patients.[5,9] This may result in aspirin use in patients for whom benefit does not outweigh risk. ▪ ACC/AHA guidelines suggest considering the totality of evidence of individual risk (e.g., estimated risk using the calculator; family history of early MI; coronary calcium score; ability to meet lipid, BP, and glucose goals).[2] ▪ The ADA suggests considering noninvasive tests such as coronary artery calcium score to help clarify the decision to start aspirin therapy in patients with diabetes, particularly in patients with low estimated risk.[4] o **Assess bleeding risk.** ▪ Bleeding risk increases with age.[9] Do not start aspirin for primary prevention in patients with a history of intracranial bleed, GI ulcer, or bleed; thrombocytopenia; coagulopathy; severe kidney or liver disease; recent bleeding; use of medications that increase bleeding risk (e.g., anticoagulants, antiplatelets, NSAIDs).[2,11] o **Balance CV and Bleeding Risks**: ▪ **Generally** do not **start** aspirin for primary prevention in patients ≥60 years of age.[9] USPSTF models suggest a reduction in net life-years for most patients ≥60 years of age, and all-cause mortality was higher in ASPREE (described above).[1,8] Initiation in patients 60 to 69 years of age may slightly increase or decrease quality-adjusted life-years, depending on CVD risk.[1] Consideration could be given to starting aspirin for primary prevention in patients 60 to 69 years of age with a 10-year risk of ≥20%, or with diabetes.[4,7,10,14] ▪ The **Aspirin-Guide app** is available at http://www.aspiringuide.com/. It is based on the ACC/AHA (2019), ESC (2021), USPSRF (2022), ADA (2022). It calculates a 10-year risk score and a bleeding risk score so that potential benefit can be weighed against potential harm.
How/when do I stop aspirin?	• Data to inform stopping aspirin is limited. • For patients already taking aspirin who wish to continue, consider **stopping** it at ~75 years of age.[9] o Most bleeding events occur in the first year after starting aspirin.[15] o People who meet criteria at a younger age (i.e., in their 40s or 50s) have even higher CV risk in their 60s or 70s, so incremental net benefit increases until the mid to late 70s.[9] • Tapering is NOT necessary because aspirin "self-tapers;" effects diminish over days as new platelets are made.[18] There was no clear evidence of harm (e.g., rebound) in stopping aspirin in a primary prevention population (ASPREE).[17]

Question	Answer/Pertinent Information
How do I explain the more narrow indications for aspirin to patients?	• Newer studies are not finding as much CV benefit because of all the other things we are now doing to reduce CV event risk (e.g., statins, BP control, smoking cessation).[2,7] So that means that the much smaller CV benefit does not generally outweigh bleeding risks (GI, brain bleeding) for most people. • Previous guidelines considered the potential benefit of aspirin for colon cancer prevention. Newer data casts doubt on colon cancer benefits, so the overall benefit of taking aspirin is probably less than previously thought.[14] o Aspirin taken for four to ten years may prevent a CV event in about one in 250 patients but may cause a major bleed in about one in 200 patients.[15,16]
Should aspirin be used for primary prevention in a patient with GI bleed risk?	• Low-dose aspirin is linked to about two GI bleeds per 1,000 patients each year. But the risk is up to 10 times higher after a GI bleed.[7] So, in patients who have had a bleed, net benefit of aspirin for primary prevention is unlikely. Also, avoid aspirin for primary prevention in patients with a history of GI ulcer.[11] • Use a PPI for GI prophylaxis in patients taking aspirin who have a history of ulcer disease or upper GI bleeding, are taking an additional antiplatelet (including an NSAID or COX-2 inhibitor), or who take an anticoagulant.[12] • Also use a PPI in patients who have **more than one** of the following GI bleed risk factors: age 60 years and older, corticosteroid use, or dyspepsia or gastroesophageal reflux symptoms.[12] • Ensure patients with a history of peptic ulcer are treated for *Helicobacter pylori*, if appropriate.[12] • Note that the use of enteric-coated or buffered aspirin formulations does not mitigate bleeding risk, as it is due to aspirin's systemic effect.[12]
What is the aspirin dose for primary prevention of CV disease?	• **USPSTF**: 81 mg daily.[1] • **AHA/ASA**: 75 to 100 mg daily.[2] • **ADA**: 75 to 162 mg daily[4]
Is aspirin effective for primary prevention of colon cancer?	• It is unclear whether aspirin prevents colon cancer or decreases colon cancer mortality.[1]

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ACC = American College of Cardiology; ADA = American Diabetes Association; AHA = American Heart Association; ARRIVE = A Study to Assess the Efficacy and Safety of Enteric-Coated Acetylsalicylic Acid in Patients at Moderate Risk of Cardiovascular Disease; ASA = American Stroke Association; ASCB = ASymptomatic Carotid Bruit; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; BP = blood pressure; CSC = Canadian Stroke Consortium; COX-2 = cyclo-oxygenase-2; CV = cardiovascular; CVD = cardiovascular disease; ESC = European Society of Cardiology; GI = gastrointestinal; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP = Japanese Primary Prevention Project; MI = myocardial infarction; NSAID = nonsteroidal anti-inflammatory drug; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPI = proton pump inhibitor; TIA = transient ischemic attack; USPSTF = United States Preventive Services Task Force.

Users of this resource are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.

Levels of Evidence

In accordance with our goal of providing Evidence-Based information, we are citing the **LEVEL OF EVIDENCE** for the clinical recommendations we publish.

Level	Definition	Study Quality
A	Good-quality patient-oriented evidence.*****	1. High-quality randomized controlled trial (RCT) 2. Systematic review (SR)/Meta-analysis of RCTs with consistent findings 3. All-or-none study
B	Inconsistent or limited-quality patient-oriented evidence.*****	1. Lower-quality RCT 2. SR/Meta-analysis with low-quality clinical trials or of studies with inconsistent findings 3. Cohort study 4. Case control study
C	Consensus; usual practice; expert opinion; disease-oriented evidence (e.g., physiologic or surrogate endpoints); case series for studies of diagnosis, treatment, prevention, or screening.	

***Outcomes that matter to patients** (e.g., morbidity, mortality, symptom improvement, quality of life).

[Adapted from Ebell MH, Siwek J, Weiss BD, et al. Strength of Recommendation Taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *Am Fam Physician* 2004;69:548-56. https://www.aafp.org/afp/2004/0201/p548.pdf.]

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