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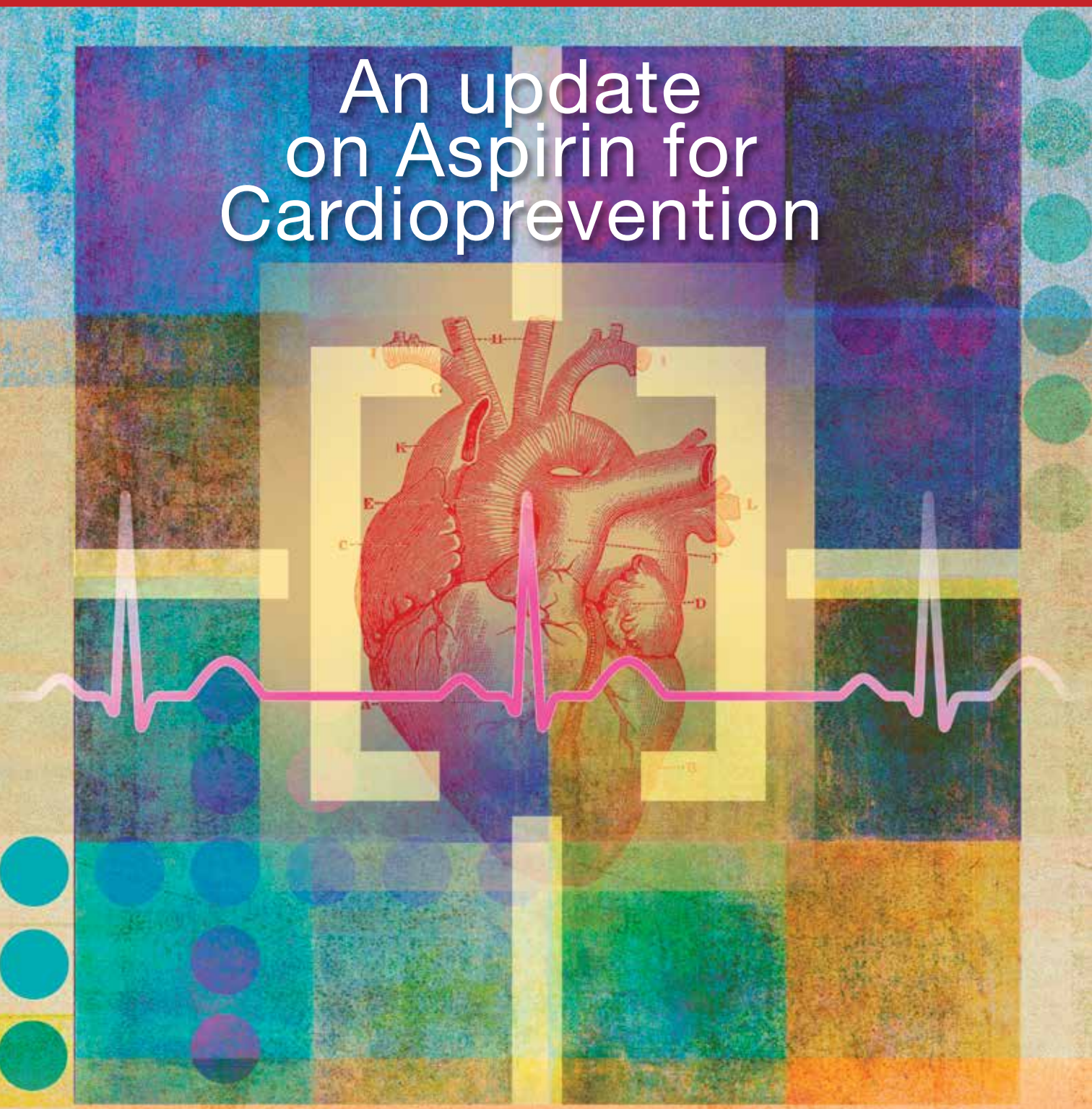
An update on Aspirin for Cardioprevention



An Update on Aspirin for Cardioprevention: Implications for Patient Care

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TARGET AUDIENCE

This activity is intended for cardiologists, primary care physicians, diabetologists, endocrinologists, nurses, and pharmacists.

GOAL STATEMENT

The goal of this activity is to increase awareness among healthcare providers about the role of aspirin in the primary and secondary prevention of cardiovascular disease.

LEARNING OBJECTIVES

After participating in the activity, the cardiologist should be able to:
Have increased knowledge regarding the:
- Mechanism of action (MOA) of aspirin
- Clinical data supporting the use of aspirin in cardioprevention

Have greater competence related to
- Use of strategies to tailor antiplatelet therapy for cardioprevention in at-risk patients

DISCLOSURES

Faculty, Editors, CME/CE Reviewer/ Nurse Planner

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INTRODUCTION

Daily low-dose aspirin therapy has established benefit for secondary prevention in patients who have confirmed atherosclerotic cardiovascular disease (ASCVD).[1] However, published guidelines based on available primary prevention trial data vary. Consequently, there is confusion among clinicians about whether daily low-dose aspirin therapy should be initiated in their patients. The decision to recommend low-dose aspirin for primary prevention in the elderly or in patients with diabetes is controversial because these populations are at increased predicted risk of myocardial infarction and stroke, but they are also at the highest risk of bleeding.

Updated recommendations from the American College of Cardiology/American Heart Association (ACC/AHA)[1] and the American Diabetes Association (ADA)[2] reflect evidence from the ASPREE, ASCEND, and ARRIVE primary prevention trials that were completed in 2018. These new trials evaluated the efficacy and safety of low-dose aspirin therapy for primary prevention of ASCVD in the elderly (ASPREE),[3] in patients with diabetes (ASCEND),[4] and in non-diabetic patients with multiple risk factors for cardiovascular disease (ARRIVE).[5]

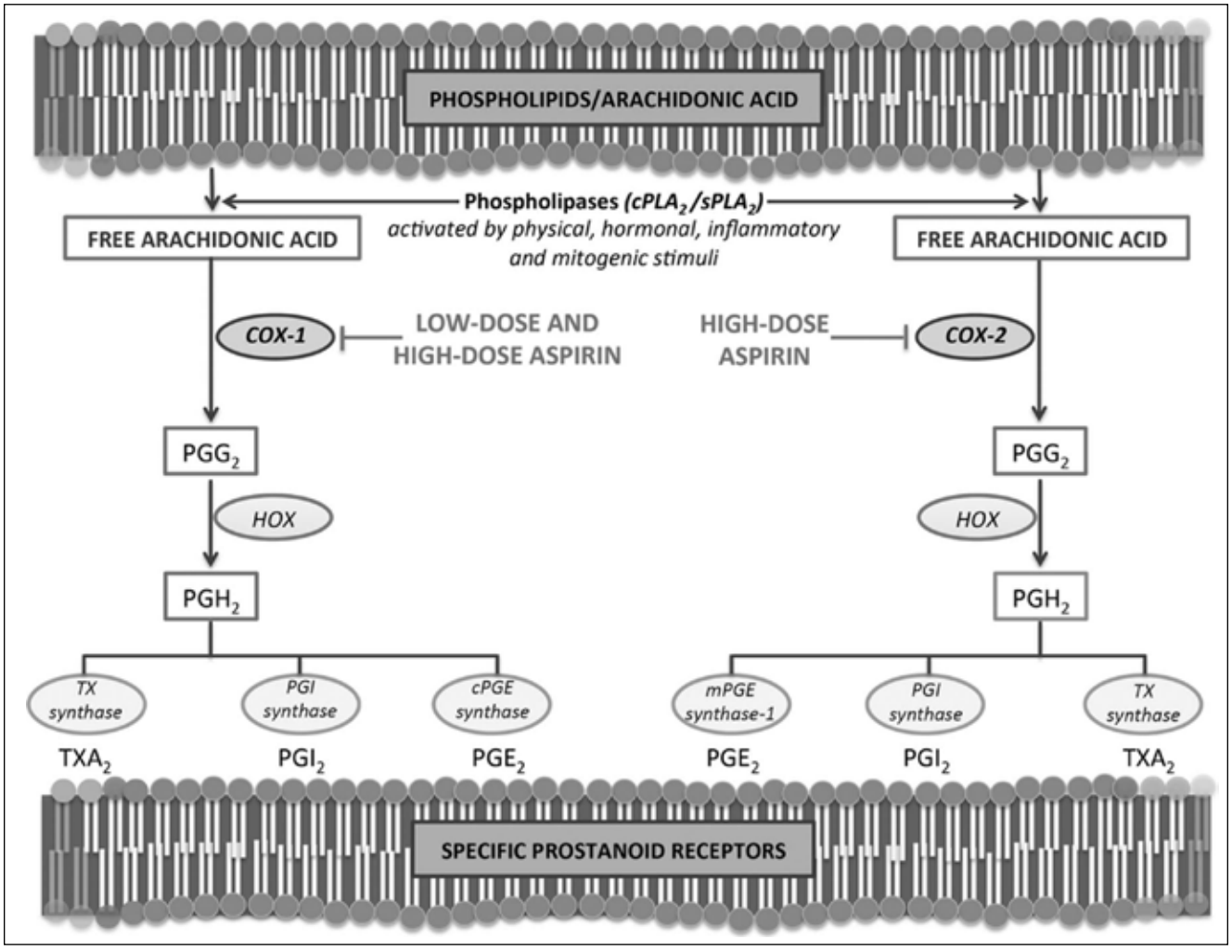
MECHANISM OF ACTION

Platelet activation and aggregation are parts of the multifactorial process of atherosclerotic plaque formation.[6] Acetylsalicylic acid, commonly referred to as aspirin, is a non-steroidal anti-inflammatory drug (NSAID) that inhibits platelet aggregation by irreversibly acetylating the serine residue of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) on platelets (**FIGURE 1**).[7,8] Inhibition of COX-1 blocks the production of thromboxane A2 (TXA2) which is necessary for thrombus formation.[7]

In healthy individuals, 30 mg to 40 mg of aspirin daily is sufficient to achieve complete suppression of TXA2 after 1 week.[8] Many clinical conditions (eg, in obese patients with diabetes) are associated with impaired antiplatelet inhibition by aspirin.[8] The typical aspirin dose between 75 mg and 100 mg is usually sufficient to accommodate individual differences in treatment response.[8]

Low doses of aspirin (75 mg to 81 mg) selectively and irreversible inhibit COX-1.[7] COX-1, which is also expressed in the gastrointestinal (GI) tract, plays a role in the maintenance of the mucosal integrity.[9] The GI effects associated with aspirin use (ie, erosive gastritis

FIGURE 1 **Aspirin Mechanism of Antiplatelet Action**[8]



Abbreviations: cPGE, cytosolic prostaglandin E; cPLA2, cytosolic phospholipase A2; HOX, hydroperoxidase; mPGE, microsomal prostaglandin E; PG, prostaglandin; sPLA2, secretory phospholipase A2; TX, thromboxane.

and bleeding) are due to COX-1 inhibition and subsequent inhibition of prostaglandins that normally protect the gastric mucosa.[9] At higher doses, aspirin also exerts its analgesic and antipyretic effect by inhibiting COX-2 and reducing the production of prostaglandins, which are key mediators of pain and inflammation.[7] In addition, COX-2 inhibition blocks prostaglandin-mediated vasodilation in the arterial vasculature, which has been associated with increased risk of cardiovascular events, including myocardial infarction.[9]

EARLY EVIDENCE FOR ASPIRIN IN CARDIOVASCULAR PREVENTION

Antithrombotic Trialists' (ATT) Collaboration. This meta-analysis compared the benefits and risks of aspirin use in the primary and secondary prevention of ASCVD.[10] Published in 2009, the ATT Collaboration meta-analysis summarized data from most of the aspirin cardioprevention trials available at that time. Six primary prevention trials (95,000 individuals at low-average risk; 660,000 person-years; 3554 serious vascular events) and 16 secondary prevention trials (17,000 individuals at high-average risk; 43,000 person-years; 3306 serious vascular events) were included in the analyses.[10] Serious vascular events were defined as myocardial infarction, stroke, or vascular death. Major bleeding was defined as a bleeding event requiring transfusion or resulting in death.[10]

In secondary prevention trials, patients on low-dose aspirin regimens had a greater absolute reduction in serious vascular events compared to control groups (6.7% vs

8.2% per year, $P < .0001$) with a nonsignificant increase in hemorrhagic stroke and in coronary events.[10] This translated to a number needed to treat (NNT) of 66.7. In both primary and secondary trials, the reductions in serious vascular events was similar for men and women.[10]

In the primary prevention trials, low-dose aspirin therapy resulted in a 12% reduction in serious vascular events compared with control (0.51% vs 0.57% per year, $P = .0001$, NNT 1666), with the greatest reduction in nonfatal myocardial infarction (0.18% vs 0.23% per year, $P < .0001$, NNT 2000).[10] There was no significant effect on stroke or vascular mortality.[10] Aspirin use was associated with increased GI and extracranial bleeds (0.10% vs 0.07% per year, $P < .0001$), with a number needed to harm (NNH) of 3333.[10]

LATEST EVIDENCE FROM THE ASCEND, ASPREE, AND ARRIVE PRIMARY PREVENTION TRIALS

ASCEND. Investigators of the ASCEND study assessed the efficacy and safety of aspirin (100 mg daily, oral) vs placebo in patients with diabetes without established ASCVD at the outset of the study.[4] A total of 15,480 patients were enrolled in the randomized trial. Eligible patients were adults ≥ 40 years of age with diabetes mellitus of any type.[4] The primary efficacy endpoint was the first serious vascular event defined as myocardial infarction, stroke or transient ischemic attack or death from any vascular cause, except intracranial hemorrhage. The primary safety outcome was the first major bleeding event, defined as intracranial hemorrhage, sight-threatening bleeding event in the eye, GI bleeding, or other serious bleeding. During the mean follow-up of 7.4 years, daily low-dose aspirin therapy resulted in a 12% reduction in the primary efficacy endpoint compared to placebo (8.5% vs. 9.6%; risk ratio [RR] 0.88; 95% CI: 0.79, 0.97; $P = .01$; NNT 90.9).[4] In addition, the incidence of major bleeding in the aspirin group was higher compared to the placebo group (4.1% vs 3.2%; RR 1.29; 95% CI: 1.09, 1.52; $P = .003$; NNH 111.1).[4] Gastrointestinal bleeding was the most common major bleeding event in the aspirin group.[4] The incidence of fatal bleeding was similar between both groups.[4] Investigators concluded that aspirin reduced the risk of serious vascular events in patients with diabetes without established ASCVD, but the benefits of daily low-dose aspirin were counterbalanced by the increased risk of major bleeding.

ASPREE. The goal of the ASPREE trial was to assess the efficacy and safety of aspirin (100 mg daily, oral) vs placebo for primary prevention of ASCVD in older patients.[3] A total of 19,114 patients were enrolled in the randomized, controlled trial. Eligible patients were adults ≥ 70 years or ≥ 65 years of age (blacks and Hispanics in the United States).[3] The primary endpoint was a composite of death, dementia, or persistent physical disability. The secondary endpoints were major hemorrhage and cardiovascular disease (ie, fatal coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal stroke, or hospitalization for heart failure). During the median of 4.7 years of follow-up, the rate of cardiovascular disease was lower per 1000 person-years in the aspirin group compared to the placebo group (10.7 events vs 11.3 events; HR 0.95; 95% CI: 0.83, 1.08; NNT 186).[3] Rates of major bleeding events were higher in the aspirin group compared to the placebo group (8.6 events vs 6.2 events per 100 person-years; HR 1.38; 95% CI: 1.18, 1.62; $P < .001$; NNH 44.9), with GI bleeding accounting for the most of the major bleeding events in the aspirin group.[3] Investigators concluded that daily, low-dose aspirin did not significantly reduce the risk of ASCVD in older patients and that aspirin therapy resulted in a significantly higher risk of major bleeding in these patients.

ARRIVE. The goal of the ARRIVE trial was to assess the efficacy and safety of aspirin (100 mg daily, oral) vs placebo for primary prevention of ASCVD in patients with a moderate estimated risk of a first cardiovascular event.[5] There were 12,546 patients enrolled in this randomized, double-blind, placebo-controlled multicenter study.[5] Eligible patients were ≥ 55 years (men) or ≥ 60 years of age (women) with 3 or more of the following risk factors: elevated total cholesterol or low-density lipoprotein (LDL) cholesterol or low high-density lipoprotein (HDL) cholesterol irrespective of current treatment, any cigarette smoking in the past year prior to enrolling in the study, hypertension, receiving medication to treat hypertension, and a positive family history of cardiovascular disease. Notably, patients with diabetes were excluded from the study. The primary efficacy endpoint was the composite outcome of time to first occurrence of cardiovascular death, myocardial infarction, unstable angina, stroke, or other transient ischemic attack. The safety endpoints of the study were hemorrhagic events and incidence of other adverse events. During the follow-up (which was an average of 5 years), the primary endpoint occurred in 4.29% vs 4.48% of patients in the aspirin vs placebo group (HR 0.96; 95% CI: 0.81, 1.13; $P = .60$; NNT 526.3).[5] Gastrointestinal bleeding events were mild and occurred in 0.97% of patients in the aspirin group vs 0.46% in the placebo group HR 2.11; 95% CI: 1.36, 3.28; $P = .0007$).[5] There were several limitations to

TABLE 1 **Current Guidelines for the Use of Aspirin for Secondary Cardioprevention**

Acute Coronary Syndromes (ACSs). The ACC/AHA guidelines recommend that aspirin (162 mg to 325 mg) before percutaneous coronary intervention (PCI) and that aspirin therapy (81 mg) be continued indefinitely after PCI.[14]
ST-Elevation Myocardial Infarction (STEMI). The ACC/AHA guidelines recommend that aspirin (162 mg to 325 mg) before PCI and that aspirin therapy (81 mg) be continued indefinitely after PCI.[14]
Non-ST-Elevation Acute Coronary Syndromes (NSTE-ACS). ACC guidelines recommend that aspirin be given to all patients with NSTE-ACS without contraindications as soon as possible after initial presentation and that a maintenance dose (81 mg to 325 mg/day) be continued indefinitely.[15]
Diabetes and Established ASCVD. Current ADA guidelines recommend aspirin therapy (75 mg to 162 mg/day) in patients with diabetes and an established history of ASCVD.[2]

this study. First, the event rate was lower than expected, which resulted in several protocol amendments. Based on these changes, the trial became time-driven, rather than event-driven. And, with fewer events, the study was not powered to detect treatment differences. The compliance rate was also lower (ie, there were many patients from the placebo group taking aspirin and many patients from the active treatment group who discontinued aspirin therapy), which affected the intention-to-treat analysis.[5] Investigators concluded that the results of the study were more consistent with findings from previously published low-risk primary prevention studies.

Meta-Analyses of Aspirin Use in Primary Prevention of ASCVD. Results from recent meta-analyses of aspirin use for primary prevention of cardiovascular events confirm that daily low-dose aspirin therapy is not associated with a reduction in the incidence of all-cause mortality,[11] although it was associated with significant reductions in the composite risk of cardiovascular events.[12] These meta-analyses also confirmed that daily aspirin use is associated with increased risk of major hemorrhage, particularly GI and cerebrovascular bleeding.[11-13] These meta-analyses confirm that low-dose aspirin therapy is of cardiovascular benefit, but these benefits are counterbalanced by increased bleeding.

CLINICAL IMPLICATIONS

Assessing ASCVD Risk

Assessment of ASCVD risk is the cornerstone of primary prevention. An individual's 10-year absolute ASCVD risk enables the clinician to match the intensity of preventive interventions to the patient's absolute risk, in order to maximize anticipated benefit and minimize potential harm for overtreatment.[1] Electronic and paper risk calculators are available. The 2019 ACC/AHA guidelines recommend using the ASCVD Risk Estimator Plus (www.acc.org/tools-and-practice-support/mobile-resources/features/2013-prevention-guidelines-ascvd-risk-estimator) to estimate 10-year ASCVD risk for asymptomatic adults aged 40 years to 79 years. Adults should be categorized into low (< 5%), borderline (5% to < 7.5%), intermediate (≥ 7.5% to < 20%), or high (≥ 20%) 10-year risk.[1]

Secondary Prevention of ASCVD

In patients with known ASCVD, daily, low-dose aspirin is recommended for secondary prevention of recurrent CV events. The ACC AHA secondary prevention guidelines highlight this in several different risk groups of patients with ASCVD (**TABLE 1**).[2,14,15]

Primary Prevention of ASCVD

When considering low-dose aspirin therapy in patients without established ASCVD, it is important to assess and balance the cardioprotective benefits of therapy with the potential bleeding risks. Ultimately, the decision to initiate therapy should be made on an individual basis, using shared-decision making.

Assessing Bleeding Risk. The issue of balancing the benefit and risk highlights the need for assessment of bleeding risk. As described above, aspirin is an antiplatelet agent that increases bleeding, but also blocks GI protective prostaglandins. Aspirin use is associated with increased risk of GI and intracranial bleeding and should be generally avoided for primary ASCVD prevention in patients at increased risk for bleeding. Established risk factors for bleeding include[16,17]:

- Diabetes
- Prior bleeding event
- Family history of cardiovascular disease

TABLE 2 **Current Guidelines for the Use of Aspirin for Primary Cardioprevention**

American College of Cardiology and the American Heart Association (ACC/AHA). According to the 2019 ACC/AHA recommendations, daily low-dose aspirin (75 mg to 100 mg/day) may be considered in adults 40 to 70 years old who are at higher risk of ASCVD (10-year risk ≥ 20%) and have low bleeding risk.[1] The ACC/AHA do not recommend daily low-dose aspirin therapy for the primary ASCVD prevention in adults older than 70 years or among adults who are at increased risk of bleeding.[1]
American Diabetes Association (ADA). In 2020 the released the ADA revised Standards of Medical Care in Diabetes.[2] According to these guidelines, low-dose aspirin therapy (75 mg to 162 mg/day) may be considered for primary prevention in patients with diabetes and increased ASCVD risk, following a comprehensive clinician-patient discussion regarding the benefits of aspirin therapy vs the increased risk of bleeding.[2]
United States Preventive Services Task Force (USPSTF). This group's recommendations came out prior to the 3 new trials. The 2016 USPSTF Statement on Aspirin Use recommends daily low-dose aspirin therapy (81 mg/day) for primary prevention of ASCVD in adults 50 to 59 years of age who are willing to take low-dose aspirin daily for at least 10 years and have 1) a 10% or greater 10-year CVD risk, 2) no increased risk for bleeding, and 3) a life expectancy of 10 years.[18] The bleeding risk is slightly higher compared with the benefit of aspirin therapy in adults 60 years to 69 years of age with a 10% or greater 10-year CVD risk; therefore, the USPSTF recommends shared-decision making before initiating a daily low-dose aspirin regimen in these patients.[18] The USPSTF determined that there was insufficient evidence to recommend daily low-dose aspirin regimens in adults younger than 50 years or adults 70 years and older.[18] As of October 2020, the USPSTF was in the process of updating its statement on aspirin use.
European Society of Cardiology (ESC). The ESC guidelines recommend low-dose aspirin therapy (75 mg to 100 mg/day) in patients with diabetes at high/very high risk of ASCVD.[19]

Abbreviations: ASCVD, atherosclerotic cardiovascular disease.

- Cancer
- Concomitant use of anticoagulant or other antiplatelet medications
- Current or past smoking history
- Chronic liver disease, chronic pancreatitis or alcohol-related conditions
- *Helicobacter pylori* infection or history of peptic ulcer disease
- Asian ethnicity

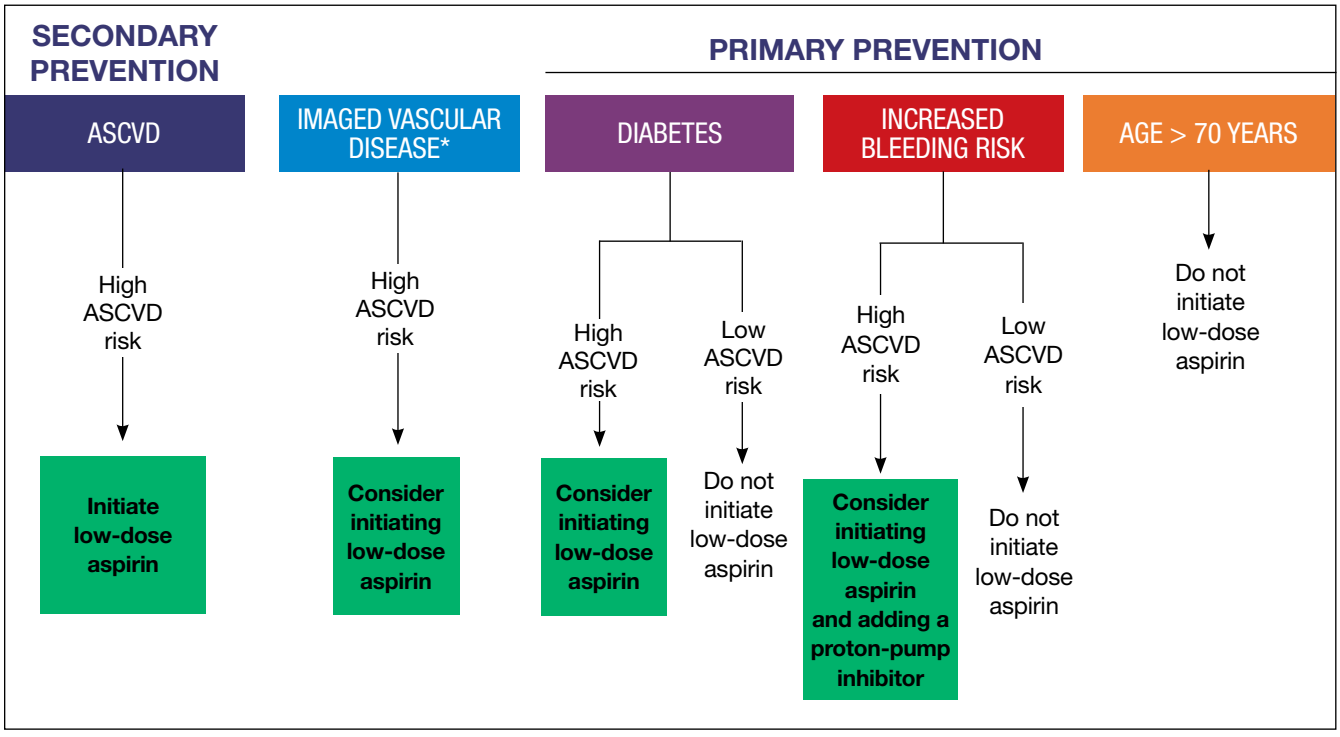
Patient Groups for Consideration of Aspirin for Primary Prevention. The figure lays out a potential framework for use of aspirin, based on ASCVD risk as well as bleeding risk. For primary prevention, one group where daily low-dose aspirin for primary prevention of ASCVD is recommended is in adults ≥ 50 years who have diabetes and at least one additional major risk factor (eg, family history of premature ASCVD, hypertension, dyslipidemia, smoking, or chronic kidney disease/albuminuria) (**TABLE 2**).[1,2,18,19]

The ADA recommends however, that aspirin therapy for primary prevention may be considered in the context of shared decision-making, which carefully weighs the cardiovascular benefits with the fairly comparable increase in risk of bleeding.[2] Specifically they recommend: aspirin therapy (75 mg to 162 mg/day) may be considered as a primary prevention strategy in those with diabetes who are at increased cardiovascular risk, after a comprehensive discussion with the patient on the benefits vs the comparable increased risk of bleeding.[2]

Patients at Increased Bleeding Risk. One major challenge of assessing the net benefit of aspirin is that patients with high ASCVD risk are also often at increased risk for major bleeding.[20] One strategy for overcoming this barrier is through the use of proton-pump inhibitors (PPIs). In clinical trials, PPIs have been shown to provide gastroprotection and reduce GI bleeding in patients using low-dose aspirin.[21] Therefore, using low-dose aspirin and a PPI may be a viable strategy in patients with high-ASCVD risk and high bleeding risk.[1] But in patients not at high ASCVD risk, if they have high bleeding risk, aspirin would not be recommended since risk would outweigh benefit.[1]

Adults > 70 years of age are at increased risk of ASCVD events; however, they are also at increased risk for bleeding.[20] The most recent clinical trial, ASPREE, studied this population specifically and found no benefit and increased risk.[3] Thus, daily low-dose aspirin therapy should not be routinely used in the population.[1] If aspirin use is being considered because of individual patient factors, clinicians need to discuss the benefits of therapy, as well as the bleeding risks.[1]

FIGURE 2 **Making Decisions About Initiating Low-Dose Aspirin (LDA) Therapy for Cardiovascular Protection**



Abbreviations: ASCVD, atherosclerotic cardiovascular disease.

*Evidence of atherosclerosis on CT scan or vascular ultrasound tests, or an elevated coronary calcium score.

EXPERT GUIDANCE FOR PATIENTS THAT ARE "IN BETWEEN" PRIMARY AND SECONDARY PREVENTION

Cardioprevention guidance in primary prevention patients who have evidence of ASCVD on vascular imaging but have never had an event (ie, the patients who are "in between" primary and secondary prevention) can be based on evidence of atherosclerosis on computed tomography (CT) scans done for other reasons, or evidence of plaque on carotid ultrasound (**FIGURE 2**). Calcium scoring (based on a chest CT) has been robustly studied and found in many studies to be the strongest marker of increased risk compared with other factors.[22] These patients have increased risk and, thus, fall in between those with primary and secondary prevention.[1] Use of aspirin in this population has not had a dedicated large clinical outcomes trial, but the benefit-to-risk ratio for use of aspirin could be considered as favoring aspirin therapy. As for patients with diabetes, the decision for use of aspirin should be based on shared decision-making between the patient and physician.[1]

CONCLUSIONS

Aspirin reduces cardiovascular morbidity and mortality in patients with ASCVD. In patients without ASCVD, the bleeding risks counterbalance the cardioprotective benefits of low-dose aspirin therapy. Furthermore, aspirin use is associated with increased bleeding. Based on current evidence, low-dose aspirin therapy can still be considered as an option for primary prevention in some patients with high ASCVD risk. Daily, long-term use of low-dose aspirin should generally not be initiated in patients with low ASCVD risk, patients at increased risk for bleeding, and adults > 70 years of age. The decision to initiate low-dose aspirin therapy should be based on individual patient factors. Before initiating aspirin therapy, clinicians should discuss the benefits and risks of treatment with their patients. ●

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