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Aspirin for primary prevention of cardiovascular disease: What do the current USPSTF guidelines say?

ABSTRACT

The 2022 US Preventive Services Task Force (USPSTF) recommendation notes that the decision to initiate daily aspirin therapy for primary prevention of cardiovascular disease (CVD) should be made on a case-by-case basis for adults ages 40 to 59 with a 10% or greater 10-year CVD risk. The recommendation applies to those without signs or symptoms of clinically evident CVD who are not at an increased risk of bleeding. Clinicians are encouraged to use their judgment in weighing the risks and benefits of aspirin therapy, while taking patient preference into account for patients ages 40 to 60.

KEY POINTS

To calculate the 10-year CVD risk, clinicians are referred to the American College of Cardiology/American Heart Association pooled cohort equation, which uses the variables age, sex, blood pressure, lipids, diabetes mellitus, and tobacco use, but not family history.

For patients age 60 or older, the USPSTF now advises against initiating aspirin therapy as there is a lack of net benefit and as risk of harm may outweigh benefit.

The USPSTF guidelines are based on evidence from 13 studies that suggest that aspirin provides a small benefit for select patients ages 40 to 59, and no net benefit (with potential for harm) for patients age 60 or older.

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The 2022 US Preventive Services Task Force (USPSTF) recommendation statement on the role of aspirin (acetylsalicylic acid, ASA) in primary prevention of cardiovascular disease (CVD)[1] replaces the previous 2016 statement.[2] The update notes that the decision to initiate daily ASA therapy for primary prevention of CVD should be made on a case-by-case basis for adults ages 40 to 59 with a 10% or greater 10-year CVD risk (grade C recommendation, ie, small net benefit for select patients based on individual circumstances).[1] These recommendations apply to those without signs or symptoms of clinically evident CVD who are not at an increased risk of bleeding.

Clinicians are encouraged to use judgment in weighing the risks and benefits of ASA, while taking patient preference into account for patients between ages 40 and 60. When calculating the 10-year CVD risk, clinicians are referred to the American College of Cardiology (ACC)/American Heart Association (AHA) pooled cohort equations (PCE) used in the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk[3] that include age, sex, blood pressure, lipids, diabetes mellitus, and tobacco use, but importantly do not include family history. For patients age 60 or older, the USPSTF now advises against initiating ASA (grade D recommendation, ie, either there is no net benefit, or harm outweighs benefit).[1]

In summary, the 2022 USPSTF recommendation statement, based on evidence from 13 studies, suggests that ASA provides a small

TABLE 1
Summary of 3 large trials on daily aspirin therapy for primary prevention

Trial	Population	Findings
ASCEND[4]	15,480 patients with diabetes and no prior CVD history	Therapy resulted in a 12% reduction in myocardial infarction and ischemic stroke Therapy resulted in a 30% increased risk for a major bleeding event, especially prominent in patients age 60 or older
ARRIVE[5]	12,546 patients with mean 17% 10-year CVD risk	No significant benefit in CVD prevention with therapy compared with placebo Twofold increase in gastrointestinal bleeding seen in aspirin therapy group
ASPREE[6,7]	19,114 patients, average age 74	Therapy provided no benefit in preventing first nonfatal cardiovascular event or death Therapy showed a 30% increased risk of major nonfatal hemorrhage, particularly in upper-gastrointestinal bleeds and intracranial hemorrhage

ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = Aspirin in Reducing Events in the Elderly; CVD = cardiovascular disease

benefit for select patients ages 40 to 59 and no net benefit (with potential for harm) for patients age 60 or older.

WHAT IS DIFFERENT FROM PRIOR GUIDELINES?

In reviewing the USPSTF guidelines from 2016,[2] the authors carefully reviewed 11 randomized controlled trials, but only 2 were of good quality. While there was a statistically significant benefit in the meta-analysis regarding nonfatal myocardial infarction, the heterogeneity of the studies was high. There was no statistically significant impact on CVD mortality, nonfatal ischemic stroke, or all-cause mortality. Based on the best evidence at the time, in 2016 the USPSTF gave a stronger recommendation for ASA use in younger patients, suggesting initiating low-dose ASA for primary prevention of CVD in adults ages 50 to 59 with a 10% or greater 10-year CVD risk, if risk for bleeding was not increased (grade B recommendation, ie, moderate certainty of overall benefit).[2] Patients ages 40 to 49 were not included in the 2016 guidelines.

The 2016 guidelines also recommended shared decision-making for individuals ages 60 to 70 with high cardiovascular risk and low risk of bleeding, and "indeterminate" recommendations for those younger than 50 or older than 70.[2]

The 2022 USPSTF guidelines incorporate 3 more recent large, randomized trials[4–7] (all published in 2018) that convincingly showed either minimal or no benefit in terms of ASA use and reduced ischemic events, with a large relative risk of bleeding in all 3 trials (**Table 1**).[1] Thirteen randomized control trials that investigated ASA in primary CVD prevention were included in a recent meta-analysis[8] comprising more than 160,000 participants.

While ASA use showed an absolute risk reduction of 0.38% (number needed to treat of 265) in nonfatal myocardial infarction and ischemic stroke in patients with no history of CVD, there was no significant reduction in cardiovascular or all-cause mortality.[9] The meta-analysis had a large number of participants under age 50 and over age 70, unique compared with prior trials. The benefit of ASA was similar across age groups. However, the risk associated with bleeding was significantly higher in patients age 60 and older.[1] Thus, the risks were felt to outweigh the potential benefits.

Overall, the 2022 USPSTF guidelines are substantially different from the previous guidelines in terms of clinical actions recommended, age ranges for the impacted population, and grades of recommendation.

DO OTHER SOCIETIES AGREE OR DISAGREE?

The 2019 ACC/AHA guidelines[10] for ASA use in primary prevention differ slightly from the 2016 and 2022 USPSTF guidelines, recommending individualized approaches in those ages 40 to 70 with a "higher risk" for cardiovascular disease, and against ASA use for primary prevention in those over age 70. There was no explicit 10-year CVD risk threshold above

TABLE 2
A comparison of the 2022 USPSTF and 2019 ACC/AHA guidelines for daily aspirin use for primary prevention, by age

	Age 40 to 60	Age 60 to 70	Age > 70
USPSTF 2022[1]	Individualize for risk > 10% for CVD events using pooled cohort equation (grade C)	No aspirin (grade D)	No aspirin (grade D)
ACC/AHA 2019[10]	Individualize for higher risk patients (COR IIb/LOE A)	Individualize for higher risk patients (COR IIb/LOE A)	No aspirin (COR III/LOE B-R)

ACC = American College of Cardiology; AHA = American Heart Association; COR = class of recommendation; COR IIb/LOE A = high-quality evidence showing treatment may be reasonable, but effectiveness is not well established; COR III/LOE B-R = moderate-quality evidence showed no benefit and potential harm; CVD = cardiovascular disease; grade C = small benefit in select patients; grade D = no net benefit or harm outweighs benefit; LOE = level of evidence

which one should consider initiating ASA therapy for those ages 40 to 70. **Table 2** highlights differences between the 2019 ACC/AHA guidelines and the 2022 USPSTF recommendations.[1,10]

HOW WILL THIS CHANGE DAILY PRACTICE?

Heart disease and stroke remain the leading causes of mortality in the United States, accounting for over 1 in 4 deaths. Individuals ages 40 to 59 with no history of CVD should be assessed for CVD risk factors using the ACC/AHA pooled cohort equation[3] (also referred to as the atherosclerotic CVD [ASCVD] risk estimator) and initiated on ASA only on an individual basis if benefit is judged to exceed risk.

Recent trials (**Table 1**)[1,4–7] brought to light the significantly increased risk of bleeding associated with ASA that was not previously recognized. Therefore, assessment of bleeding risk should be a strong consideration in deciding whether to initiate ASA. The ACC notes numerous clinical circumstances related to potential bleeding risks where they suggest avoiding ASA, including gastrointestinal bleeding history, peptic ulcer disease, use of nonsteroidal anti-inflammatory drugs, steroids, anticoagulants, age over 70, thrombocytopenia, and coagulopathies.[10] Unfortunately, there is no available validated calculator in the United States to assess bleeding risk in aspirin use for patients.

A prospective cohort study in New Zealand developed the Predicting Risk of Death in Cardiac Disease Tool (PREDICT), a web-based prognostic bleeding risk model to estimate absolute bleeding harm of ASA in the context of primary prevention of CVD.[11] This study has certain measures that are not available in the United States (eg, deprivation, a measure of social determinants that would need to be recalibrated) and has considerable complexity to assess 5-year risk of CVD events and major bleeding, including numerous variables: eg, age, sex, ethnicity, socioeconomic deprivation, smoking, diabetes, family history of coronary artery disease, cancer history, liver or renal disease, peptic ulcer disease, prior bleeding, alcohol use, chronic pancreatitis, systolic blood pressure, hyperlipidemia, and use of nonsteroidal anti-inflammatory drugs, steroids, or serotonin reuptake inhibitors.[11] While PREDICT is not validated for clinical use in the United States, the variables can likely be used by clinicians in shared decision-making to qualitatively assess bleeding risk for patients ages 40 to 59.

In summary, both sets of guidelines (USPSTF[1] and ACC/AHA[10]) confirm avoiding ASA use in patients age 70 or older, while the 2022 USPSTF guidelines now recommend against using ASA in all patients over age 60. USPSTF recommends customizing the decision for those ages 40 to 60 with a 10% or greater 10-year CVD risk, while AHA/ACC recommends customizing in higher-risk patients ages 40 to 70. Both guidelines will likely lead to an increased recognition of bleeding risk with ASA, and we anticipate a marked reduction in ASA use for primary prevention of CVD, particularly in older age groups. The meta-analysis from 2022[8] suggests that for patients older than 60, the risk of bleeding outweighs the small benefit ASA may have on CVD prevention.

For this reason, our recommendation aligns with the 2022 USPSTF guidelines to not initiate ASA therapy for patients age 60 or older. It is possible that the future iteration of the AHA/ACC guidelines may also assume this stance, as the trials used for the meta-analysis were not available in 2019. Clinicians

will still wish to customize their decision regarding when to initiate ASA therapy for individuals ages 40 to 59 with a 10% or greater 10-year CVD risk.

Quantitative risk estimators should be used in conjunction with many other factors to guide management.[3] In addition to the PCE, we recommend taking additional risk factors into account to guide decisions. The 2019 ACC/AHA guideline[10] on primary prevention of cardiovascular disease provides an in-depth analysis of risk-increasing factors that can guide the clinician-patient risk discussion, and risks of bleeding have been described in detail above.

WHEN WOULD THE GUIDELINES NOT APPLY?

The ACC/AHA ASCVD risk estimator has been validated in non-Hispanic White and non-Hispanic African American individuals, leading to uncertainty regarding evaluation in other racial and ethnic groups.[3] Recently, Gomez et al[12] highlighted increased and unique cardiovascular risk in Hispanic and Latinx cohorts, suggesting that they should be included in shared decision-making discussions regarding primary prevention of CVD. The ACC/AHA PCE also tend to underpredict CVD risk in individuals of lower socioeconomic status and individuals with chronic inflammatory diseases. Further studies are needed to determine increased risk and tools to help quantify risk in these groups.

Additionally, patients with the genetic condition familial hypercholesterolemia (FH) have increased risk for early and premature ASCVD events.[13,14] Although homozygous FH is relatively uncommon and can present in childhood, heterozygous FH is a common condition affecting nearly 1 in every 220 individuals globally.[13] FH is typically diagnosed based on family history of hypercholesterolemia, clinical examination findings, early-onset ASCVD, and elevated levels of low-density lipoprotein cholesterol.[13,14] Based on the ACC/AHA guidelines, risk calculators are not applicable to the FH population, who are generally treated aggressively with medications to lower low-density lipoprotein levels. In this high-risk population, lipid experts generally recommend ASA for primary prevention.[14] But considering recent evidence, future studies should reevaluate its role in primary prevention in those over age 60.

Other risk factors to consider in individualizing risk assessment include a family history of coronary artery disease,[15] chronic kidney disease, and chronic inflammatory conditions,[16] which can accelerate atherosclerosis. Certain genotypes associated with elevated lipoprotein(a) are also associated with higher CVD risk,[17] but the ability to use genomics to quantify that risk is still under investigation.

Some groups have studied the role of coronary artery calcium (CAC) in identifying individuals who are more likely to benefit from ASA for primary prevention. Cainzos-Achirica et al[18] concluded that CAC may be superior to the PCE to inform personalized allocation of ASA in primary prevention. Similarly, Miedema et al[19] have shown that those with a CAC score of 100 or higher had a favorable risk-benefit ratio with ASA use, whereas those with a CAC score of 0 had net harm from ASA use.[19] The risk of radiation should be especially discussed with women of childbearing age, and CAC scoring should be avoided in pregnant women. In patients for whom the risk-benefit assessment and shared decision-making are equivocal, CAC could serve as a mechanism to guide clinical practice.

DISCLOSURES

Dr. Linzer reports research as principal investigator for American Board of Internal Medicine and United Healthcare, and consulting for Harvard. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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