Aspirin for the Primary Prevention of Atherosclerotic Cardiovascular Disease in Women

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The efficacy of aspirin for the secondary prevention of atherosclerotic cardiovascular disease (ASCVD) has been well established in both men and women; however, evidence on aspirin use for primary prevention has been controversial. In 2022, the US Preventive Services Task Force (USPSTF) released new recommendations that advise against the use of aspirin for primary prevention of ASCVD in adults 60 years or older (grade D; recommend against initiating), with no differences in treatment effect or guidance by sex. For primary prevention in individuals aged 40 to 59 years who have an estimated 10-year ASCVD risk of at least 10% per the American College of Cardiology/American Heart Association pooled cohort equations, a grade C recommendation was given, indicating that there is at least moderate certainty that the net benefit in this group is small and shared decision-making should be considered on a case-by-case basis.

The updated recommendations are based on pooled analyses of 13 randomized clinical trials for primary prevention, including a total of 161,680 participants without a history of ASCVD, of whom 53% were women. Low-dose aspirin (≤100 mg/d) was evaluated in 11 trials (N = 134,470 [63% women]) and was not associated with significant reduction in ASCVD mortality (odds ratio [OR], 0.95 [95% CI, 0.86-1.05]) or all-cause mortality (OR, 0.98 [95% CI, 0.93-1.03]). However, low-dose aspirin was associated with a significant reduction in major ASCVD events (total myocardial infarction [MI], total stroke, ASCVD mortality) (OR, 0.90 [95% CI, 0.85-0.95]), nonfatal MI (OR, 0.88 [95% CI, 0.80-0.96]), and nonfatal stroke (OR, 0.88 [95% CI, 0.80-0.97]).

When further analyzed by sex, there were no significant differences in treatment effects for ASCVD composite outcomes, all-cause mortality, myocardial infarction, or stroke, with no evidence to support different guidelines by sex. However, approximately half of the data used for women (46%) were from 1 trial, the Women’s Health Study (39,876 women), powered for age-stratified analyses in women. The Women’s Health Study was the first large-scale primary prevention trial that focused on the effects of aspirin on ASCVD events in women and found that low-dose aspirin significantly lowered the risk of total stroke (absolute risk reduction [ARR], 0.23%; RR, 0.83 [95% CI, 0.69-0.99]) and ischemic stroke (absolute risk reduction, 0.26%; RR, 0.76 [95% CI, 0.73-0.83]), with similar reductions across age groups. Women aged 65 years or older also experienced reductions in major ASCVD events (total MI, total stroke, ASCVD mortality) (absolute risk reduction, 2.1%; RR, 0.74 [95% CI, 0.59-0.92]), MI (absolute risk reduction, 1.0%; RR, 0.66 [95% CI, 0.44-0.97]), and stroke (absolute risk reduction, 0.88%; RR, 0.70 [95% CI, 0.49-1.0]), whereas younger women (≤64 y) did not have reductions in these outcomes. Most other trials have not been powered for age-stratified analyses in women, and of the 13 trials analyzed in the 2022 USPSTF pooled analyses, 6 had prespecified subanalyses by sex and 3 trials were conducted only in men.

As with previous USPSTF recommendations, the new recommendations used a simulation model to estimate lifetime net benefit, measured by quality-adjusted life-years (QALYs) and net life-years gained from taking aspirin. One difference is that the current model, compared with previous models, did not assume benefit for reduction in colorectal cancers. Despite this difference, the equation in the simulations model still estimated a lifetime net benefit measured by QALYs for both women and men aged 40 to 59 years with predicted 10-year ASCVD risk of at least 5% and benefit for individuals aged 60 to 69 years with predicted 10-year ASCVD risk of at least 10%. Net life-years gained was also positive for those aged 40 to 59 years with predicted 10-year ASCVD risk of at least 10% and was neutral or positive for those aged 60 to 69 years with predicted 10-year ASCVD risk of at least 20%.

The updated systematic review showed consistent increases in bleeding risk soon after aspirin initiation with the absolute risk of bleeding higher in men. In a pooled analysis of 10 trials (N = 1,19,130), low-dose aspirin use was associated with a significantly increased risk of major gastrointestinal bleeding (OR, 1.58 [95% CI, 1.38-1.80]), intracranial bleeding (OR, 1.31 [95% CI, 1.11-1.54]), and total major bleeding, defined as bleeding requiring transfusion or resulting in hospitalization or death (OR, 1.44 [95% CI, 1.32-1.57]). Although the relative risk of bleeding did not differ by age, the absolute risk of bleeding increased with age and male sex, especially after age 60, because older age is a major risk factor for bleeding.

Guidelines Begin to Align
There is consensus across clinical guidelines that aspirin for primary prevention recommendations should not differ by sex and should be individualized based on assessment of the benefit to bleeding risk ratio, as well as patient preferences. The American College of Cardiology and American Heart Association issued a guideline on the primary prevention of ASCVD in 2019 that advised against the routine use of aspirin in adults older than 70 years or in adults of any age with an increased risk for bleeding (defined as those taking concurrent medications that increase bleeding risk, history of previous gastrointestinal bleed, or peptic ulcer disease) (Box). The guideline stated that low-dose aspirin may be considered for patients aged 40 to 70 years and those at higher ASCVD risk. The 2021 European Society of Cardiology guidelines for primary ASCVD prevention advised against aspirin for those older than 70 years or at low/moderate risk of ASCVD. The 2022 American Diabetes Association Standards of Medical Care in Diabetes also recommended considering low-dose aspirin for patients aged 50 years or older with diabetes who are at increased ASCVD risk (1 major ASCVD risk factor); however, the risk appeared greater than the benefit for those 70 years or older. None of the guidelines made sex-specific recommendations.
Box. Summary of Current Guidelines for Aspirin in the Primary Prevention of Atherosclerotic Cardiovascular Disease (ASCVD)

All guidelines emphasize shared decision-making with consideration of cardiovascular benefit vs increased risk of bleeding

**US Preventive Services Task Force 2022**
Low-dose aspirin (75-162 mg/d) may be considered for those aged 40 to 79 y who have an estimated 10-year ASCVD risk ≥10%.(recommendation grade C)
Advises against the use of aspirin for primary prevention of ASCVD in adults ≥80 y (grade D)

**American College of Cardiology/American Heart Association 2019**
Aspirin should be used infrequently in the routine primary prevention of ASCVD.
Low-dose aspirin (75-100 mg/d) might be considered for primary prevention of ASCVD among select adults aged 40 to 70 y who are at higher ASCVD risk (>10% 10-y risk) who are not at increased risk of bleeding.a,b
Not recommended in adults >70 years or any individual at an increased risk of bleeding.b

**American Diabetes Association 2022**
Low-dose (75-162 mg/d) aspirin should be considered for prevention of ASCVD in adults older than 50 years with diabetes and at least 1 major ASCVD risk factor and not at increased risk of bleeding.a,b
For patients older than 70 years with or without diabetes, the risk appears greater than benefit.

**European Society of Cardiology 2021**
Aspirin is not recommended in individuals with low/moderate ASCVD risk due to the increased risk of major bleeding.
For persons <70 years of age with (very) high ASCVD risk, decision should be case-by-case taking into account both ischemic and bleeding risk.

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**References**


