USPSTF Report on Aspirin for Primary Prevention

Donald M. Lloyd-Jones, MD, ScM

As with many therapies in modern medicine, aspirin for the primary prevention of atherosclerotic cardiovascular disease (ASCVD) is neither all good nor all bad. Specifically, aspirin may benefit selected patients, but that comes at the price of a narrower therapeutic window than desirable because of the risks of major bleeding, particularly intracranial and gastrointestinal hemorrhage.

Bolstered by favorable results in tertiary and secondary ASCVD prevention trials in the 1980s, the early trials of aspirin in primary prevention also appeared favorable. For example, in the Physicians’ Health Study of men, treatment with 325 mg of aspirin every other day reduced myocardial infarction (MI) incidence by 44%. More importantly, this represented differential rates of MI of 0.25% per year in the aspirin group vs 0.44% in the placebo group, for a 5-year difference of 0.93% and a number needed to treat for 5 years of approximately 100 to prevent 1 MI.1 A subsequent trial in women health care professionals2 demonstrated no significant benefit for major cardiovascular disease (CVD) events but demonstrated a significant reduction in ischemic stroke. In both trials and others, there were signals of small absolute increases in risk for major bleeding. Countless meta-analyses of the many early trials saw the pendulum swing back and forth on aspirin benefits and harms, with most guidelines favoring use of aspirin in higher-risk primary prevention patients who had no elevated risk of bleeding.

Indeed, the 2016 recommendations from the US Preventive Services Task Force (USPSTF)3 reflected these syntheses in the context of absolute benefits and absolute risks. At that time, the USPSTF gave a grade B recommendation (Table) for primary prevention of CVD in adults aged 50 to 59 years at elevated CVD risk and without risk for bleeding and a grade C recommendation to individualize decisions for adults aged 60 to 69 years at elevated risk. The USPSTF judged that the evidence was insufficient to make recommendations for adults younger than 50 years or older than 69 years. Whereas these recommendations were evidence-based and sound, clinicians may have felt uncertain how to weigh potential risks and benefits for individual patients.

However, there were larger preventive forces in play across the 1980s to the 2010s as well. The introduction of statin medications and their increasing use for primary prevention revolutionized thinking about risk-based prevention for ASCVD4 and provided greater tools for application of evidence to individual patients and to shared decision-making.5,6 At the same time, antihypertensive agents were becoming widely available in generic and combination formulations, and great strides were made in understanding successful strategies for maximizing blood pressure–lowering benefit while reducing adverse reactions. Accordingly, more and more high-risk individuals in need of primary prevention received effective and safe drug therapy and also pursued evidence-based lifestyle interventions to control causal risk factors. Persisting questions lingered regarding the net benefit of low-dose aspirin in primary prevention for older patients, those with diabetes, and in the current context of risk factor prevalence and control. As they often do, clinical trialists answered the call.

The year 2018 proved to be a landmark in the reevaluation of the net benefits of aspirin. The ASPREE (Aspirin in Reducing Events in the Elderly) trial7 found that compared with placebo among healthy older patients (age ≥65 years), 100 mg of aspirin daily was unexpectedly associated with significantly increased risk for total mortality (5.9% for aspirin vs 5.2% for placebo throughout a median of 4.7 years) and cancer mortality (3.1% vs 2.3%), with nonsignificant associations with fatal or nonfatal CVD (1.0% vs 1.2%) and major hemorrhage (0.3% vs 0.3%). At the same time, the ASCEND (A Study of Cardiovascular Events in Diabetes) trial8 reported that compared with placebo among patients with diabetes, 100 mg of aspirin daily significantly reduced risks for CVD events (8.5% vs 9.6% throughout a mean of 7.4 years). However, the CVD risk reduction was offset by higher risk of major bleeding events (4.1% vs 3.2%), with no difference in incident cancers. The ARRIVE (Use of Aspirin to Reduce Risk of Initial Vascular Events in Patients at Moderate Risk of Cardiovascular Disease) trial9 randomized middle-aged and older adults at intermediate risk for ASCVD, but without diabetes or high risk for bleeding, to 100-mg daily aspirin or placebo. Throughout a median of 5 years of follow-up, aspirin was associated with nonsignificant reduction in ASCVD events (4.29% vs 4.48%) and a significant doubling in gastrointestinal bleeding events (0.97% vs 0.46%). The ARRIVE investigators noted that CVD event rates in the placebo group were substantially lower than anticipated.

Whereas bleeding risks associated with aspirin have remained, has something changed with regard to aspirin’s efficacy for primary prevention? A close examination of the patient samples in these contemporary trials suggests an answer. There were fairly high rates of use of antihypertensive and statin medications, and it is likely that these were targeted to those with higher risk and greater cumulative exposures to risk factors (ie, those formerly likely to receive the greatest absolute benefit from aspirin). For example, in the ARRIVE trial, 65% of participants were taking antihypertensive medication and 43% were taking statins, in the ASCEND trial, 76% of pa-
Table. Recommendations on the Use of Aspirin for the Primary Prevention of CVD

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>Grade/class of recommendation (suggestions for practice)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior 2016 USPSTF recommendations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults aged 50-59 y with 10% or greater 10-y ASCVD risk</td>
<td>Initiate low-dose aspirin for primary prevention of CVD and CRC in those who are not at increased risk for bleeding, have a life expectancy of at least 10 y, and are willing to take low-dose aspirin daily for at least 10 y.</td>
<td>B (offer or provide this service)</td>
</tr>
<tr>
<td>Adults aged ≥70 y</td>
<td>The decision to initiate low-dose aspirin for primary prevention of CVD and CRC should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 y, and are willing to take low-dose aspirin daily for at least 10 y are more likely to benefit. Persons who place a higher value on potential benefits than potential harms may choose to initiate low-dose aspirin.</td>
<td>C*</td>
</tr>
<tr>
<td>Adults aged &lt;50 y</td>
<td>Current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin for the primary prevention of CVD and CRC.</td>
<td>Ib</td>
</tr>
<tr>
<td>Adults aged ≥70 y</td>
<td>Current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin for the primary prevention of CVD and CRC.</td>
<td>Ib</td>
</tr>
<tr>
<td>Current 2019 ACC/AHA/multispecialty guidelines</td>
<td></td>
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</tr>
<tr>
<td>Adults aged 40-70 y at higher ASCVD risk</td>
<td>Low-dose aspirin (75-100 mg daily) might be considered for the primary prevention of ASCVD among select adults at higher ASCVD risk but not at increased bleeding risk.</td>
<td>Ib (might be considered)</td>
</tr>
<tr>
<td>Adults aged &gt;70 y</td>
<td>Low-dose aspirin (75-100 mg daily) should not be administered on a routine basis for the primary prevention of ASCVD.</td>
<td>III: harm (should not be performed)</td>
</tr>
<tr>
<td>All adults</td>
<td>Low-dose aspirin (75-100 mg daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding.</td>
<td>III: harm (should not be performed)</td>
</tr>
<tr>
<td>Current 2021-2022 USPSTF recommendations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults aged 40-59 y with 10% or greater 10-y ASCVD risk</td>
<td>The decision to initiate low-dose aspirin for primary prevention of CVD should be an individual one. Evidence indicates that the net benefit of aspirin use in this group is small. Persons who are not at increased risk for bleeding and are willing to take low-dose aspirin daily are more likely to benefit.</td>
<td>C*</td>
</tr>
<tr>
<td>Adults aged ≥60 y</td>
<td>USPSTF recommends against initiating low-dose aspirin use for primary prevention of CVD.</td>
<td>D (discourage use of this service)</td>
</tr>
</tbody>
</table>

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CRC, colorectal cancer; CVD, cardiovascular disease; USPSTF, US Preventive Services Task Force.

* Offer or provide this service for selected patients depending on individual circumstances.

† Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

of current cigarette smoking were less than 10% (although they were higher in the ARRIVE trial). It is difficult to escape the conclusion that the lower efficacy of aspirin for ASCVD prevention seen in these contemporary trials is a direct result of the fact that there is now less room for aspirin to make a difference when dyslipidemia, hypertension, and health behaviors are being controlled.

The more recent TIPS-3 (International Polycap Study 3) trial appears to be the exception that supports the point. In this trial, participants at elevated risk for ASCVD were randomized to a polypill containing simvastatin, atenolol, hydrochlorothiazide, and ramipril, with or without aspirin. At baseline, 84% of participants had hypertension and 37% had diabetes, but antihypertensive use was low (approximately 11%), and only 1 participant (of 5713) was taking a statin. In this setting of higher risk and low prior treatment, aspirin appeared to add value in combination with the polypill compared with double placebo (4.1% vs 5.8% CVD event rates over a mean of 4.6 years).10

In 2019, the American College of Cardiology (ACC)/American Heart Association (AHA)/multispecialty guidelines for primary prevention, responding to the ASPREE/ASCEND/ARRIVE (and other) data, recommended a change in the approach to use of aspirin. The recommendation of class III: harm (Table) was provided to avoid aspirin use among adults older than 70 years and among adults at any age at increased risk of bleeding. Likewise, recommendations for aspirin use in primary prevention among adults aged 40 to 70 years were softened considerably to class Ib with a focus on individualized decision-making and consideration focused on individuals at particularly high ASCVD risk and with uncontrolled risk factors. Subsequent analyses have also identified potential net benefit among individuals with coronary artery calcium scores of 100 Agatston units or more (who would be at particularly high predicted risk for ASCVD).12

As part of its scheduled quintennial review of the topic, the USPSTF has now changed its recommendations for aspirin use for primary prevention of ASCVD.13 The evidence report and systematic review has also been updated. The USPSTF now recommends against initiating low-dose aspirin in any adults 60 years or older (grade D; Table). Furthermore, the USPSTF has downgraded aspirin for primary prevention in adults aged 40 to 59 years to grade C. (Persons who are not at increased risk for bleeding and are willing to take low-dose aspirin daily are more likely to benefit.) These recommendations align well with the ACC/AHA 2019 guidelines and for similar underlying evidence-based reasons.

The draft version of the new USPSTF recommendations, following the standard approach, was released for public comment in October 2021. However, some media coverage failed to understand or clearly report the distinction between primary prevention (which the new recommendations address) and secondary prevention (which they do not) with ensuing confusion among some patients who were appropriately taking aspirin for secondary prophylaxis of MI or stroke or for prior history of vascular stenting.

The draft and final versions of the new USPSTF recommendations for primary preventions were and are correct and
appropriately reflect the progress of the evidence base, although they differ somewhat in substance and scope from the ACC/AHA guidelines. The lesson for all guideline-producing organizations is the importance of ensuring clear and broad-based communication strategies in the introduction of updated recommendations, and whom they affect and do not affect, based on new and improved evidence. Patients depend on us to do that.

REFERENCES


