Educational Objectives:

1. Understand and apply the current guidelines for aspirin for primary prevention
2. Critically appraise three landmark trials published since the USPSTF guidelines were updated in 2016: ASCEND, ASPREE, and ARRIVE
3. Evaluate bleeding risk associated with aspirin using an evidence-based approach

CASE ONE:

Mr. Whitney is a 63-year-old man with a history of hypertension, hyperlipidemia, and prior tobacco use. He has never had an MI or a stroke and he does not have known coronary artery disease or peripheral vascular disease. He has never had a history of GI bleeding, nor does he have renal or liver disease. He currently works as a store manager and leads an active lifestyle. As you are reviewing his medication list, you notice that although he is on two antihypertensive agents and a statin, he is not on aspirin. His ASCVD 10-year risk is 21%.

Questions:

1. What do current guidelines recommend about aspirin for primary prevention?
   Whether to use aspirin for primary prevention is a complex question, primarily because the benefits of aspirin for primary prevention are relatively modest and there are significant risks. Aspirin has been shown in a number of studies to reduce the risk of non-fatal myocardial infarction (MI) and may have a smaller effect on reducing risk of ischemic stroke. Aspirin may also prevent some cancers, including colorectal cancer. The potential benefits of aspirin, though, are tempered by important risks, including the risk of serious GI bleeding and intracranial bleeding. The current U.S. Preventive Services Task Force (USPSTF) Guidelines, which were published in 2016, recommend aspirin for the combined primary prevention of cardiovascular disease and colorectal cancer in the following populations (Bibbins-Domingo, 2016):

- Adults ages 50-59 with a 10-year ASCVD risk ≥ 10%, who do not have an increased risk of bleeding, who have a life expectancy ≥ 10 years, and who are willing to take aspirin for ≥10 years (B recommendation: High certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial).
• Adults ages 60-69 with a 10-year ASCVD risk ≥ 10% who do not have an increased risk of bleeding, who have a life expectancy ≥10 years, and who are willing to take aspirin for ≥10 years (C recommendation: There is at least moderate certainty that the net benefit is small).

Note that these guidelines were formulated with the dual purpose of reducing risk of cardiovascular disease and colorectal cancer, but only consider individualized risk of cardiovascular disease and assume average risk of colorectal cancer.

The USPSTF Guidelines were informed by two meta-analyses that evaluated randomized trials of aspirin for primary prevention of cardiovascular disease and cancer. These randomized trials concluded that aspirin reduces the risk of nonfatal MI, stroke, and colorectal cancer, though effects were modest, particularly for stroke (Chubak, 2016; Guirguis-Blake, 2016):

• Non-fatal MI (RR 0.78, 95% CI 0.71-0.87)
• Non-fatal stroke with low dose aspirin (RR 0.86, 95% CI 0.76-0.98)
• Incidence of colorectal cancer (HR 0.60, 95% CI 0.47-0.76). Note that time to benefit is long and was not observed within the first 10 years of starting aspirin. Thus, patients who take aspirin to prevent colorectal cancer must be willing to commit to long-term use
• Aspirin was also associated with a small though statistically significant reduction in all-cause mortality (0.94, 95% CI 0.89-0.99)

However, since publication of these guidelines, three important trials of aspirin were published, known as ASPREE, ASCEND and ARRIVE. These trials all evaluated aspirin for primary prevention and findings from these trials, which are discussed below, have tempered enthusiasm for aspirin. Incorporating findings from these trials, the American College of Cardiology/American Heart Association updated its guidelines in March 2019 as follows (Arnett, 2019):

• Low-dose aspirin (75-100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk (Class IIB recommendation: Usefulness/efficacy is less well established by evidence or opinion).
• Low-dose aspirin (75-100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 years of age (Class III recommendation: Conditions for which there is evidence, general agreement, or both that the procedure/treatment is not useful/effective and in some cases may be harmful).
Low-dose aspirin (75-100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding (Class III recommendation: Conditions for which there is evidence, general agreement, or both that the procedure/treatment is not useful/effective and in some cases may be harmful).

Note that the ACC/AHA guidelines do not take into account the potential reduction in colorectal cancer with long-term aspirin use. The guidelines also do not recommend a specific ASCVD risk threshold that defines “higher ASCVD risk”, nor do the guidelines specifically define what constitutes an increased bleeding risk.

CASE ONE CONTINUED:

You explain to Mr. Whitney that aspirin may afford a small benefit and, according to the ACC/AHA guidelines, is something he might consider. He furrows his brow and says, “But Doc, I just saw on the news that aspirin doesn’t help.” He pulls up a news article on his phone highlighting the ARRIVE trial. A quick PubMed search leads you to the right study.

2. What was the ARRIVE trial and do its findings apply to Mr. Whitney?
The ARRIVE trial (Use of Aspirin to Reduce Risk of Initial Vascular Events in Patients at Moderate Risk of Cardiovascular Disease) was a randomized trial of aspirin for the primary prevention of cardiovascular disease. The trial randomized men aged 55 and older and women 60 and older to aspirin or placebo and included adults at moderate risk of cardiovascular disease (10-year ASCVD risk of 20-30%) without overt cardiovascular disease. The primary endpoint was a composite of time to cardiovascular death, MI, unstable angina, stroke, or TIA. In the intention to treat analysis, the hazard ratio for the primary endpoint was 0.96 (95% CI 0.81-1.13) after a median follow-up of 60 months. Gastrointestinal bleeding was more common in the aspirin arm (HR 2.11, 95% CI 1.36-2.38). Absolute gastrointestinal bleeding rates were 0.97% vs. 0.46% over a median follow up of 60 months (Gaziano, 2018).

The trial included patients much like Mr. Whitney, so it’s reasonable to think that the findings may indeed apply to him.

3. Why was ARRIVE a negative trial?
   - The hazard ratio for the primary endpoint was 0.96 and was not statistically significant.
   - One possible explanation is that adherence was low with about 40% of participants in each arm reporting poor adherence. In a per-protocol analysis, HR for the primary endpoint was 0.81 (95% CI 0.64-1.02), and 0.53 (95% CI 0.36-0.79) for total MI, suggesting there may be a benefit among patients who actually...
take aspirin. However, per-protocol analyses should be interpreted with caution as they can introduce bias.

- Another possibility is that patients in ARRIVE benefited from modern therapies that also prevent cardiovascular disease, like statins and blood pressure control. In the context of these modern therapies, the need for aspirin may be attenuated. Indeed, the primary outcome occurred infrequently (4.19% in the aspirin arm vs 4.48% in the placebo arm) which is much lower than what investigators initially anticipated.

4. **Based on ARRIVE, should you recommend against aspirin for Mr. Whitney?**

   It is difficult to say if ARRIVE constitutes the final word on aspirin for primary prevention. On one hand, this is a contemporary trial that included patients similar to Mr. Whitney. On the other hand, there is a broader literature on aspirin for primary prevention, which could be considered. A meta-analysis by Zheng et al., incorporated data from 13 trials of primary prevention, including ARRIVE (Zheng, 2019). Aspirin was associated with significant reductions in the risk of composite CV outcome (CV mortality, non-fatal MI, non-fatal stroke) with a hazard ratio of 0.89, 95% CI 0.84-0.95. This was largely driven by a reduction in risk of MI (HR 0.85, 95% CI 0.73-0.99) and ischemic stroke (HR 0.81, 95% CI 0.76-0.87). Risk of major GI bleeding was higher with aspirin (HR 1.56, 95% CI 1.38-1.78), as was risk of intracranial bleeding (HR 1.34, 95% 1.14-1.57).

   For patients like Mr. Whitney, it might be reasonable to say that aspirin may provide a small benefit, particularly in reducing risk of cardiovascular disease. Absolute risk reduction is related to underlying risk of CVD, so patients at higher risk may benefit more. In general, benefits are approximately balanced by harms. Patient preference, individual risk of CVD, and risk of bleeding complications can all be considered when making a decision. There is some evidence that aspirin can reduce the risk of colorectal cancer, which could be a consideration for some patients.

**CASE ONE CONTINUED:**

After further discussion of risks and benefits, Mr. Whitney wants to know more about whether he is at risk for bleeding from aspirin.

5. **What do you tell him?**

   The USPSTF guidelines note the following risk factors for GI bleeding with aspirin use:

   - Higher dose and longer duration
   - History of GI ulcers or upper GI pain
   - Bleeding disorder
   - Renal failure
• Severe liver disease
• Thrombocytopenia

Other factors that increase the risk of GI and intracranial bleeding:

• Use of non-steroidal anti-inflammatory drugs (NSAIDs) or concurrent anticoagulation
• Uncontrolled hypertension
• Male sex
• Older age

Interestingly, many of the factors that contribute to cardiovascular risk (such as age and hypertension) are also associated with bleeding risk, such that as CVD risk increases, bleeding risk increases.

At the time the guidelines were developed, no validated prognostic models to estimate an individual’s risk of bleeding existed. Subsequently, investigators from New Zealand developed and validated a model that could be used to calculate an individual’s risk of bleeding from aspirin for primary prevention (Selak, 2019). Two important limitations of this model are that the population in New Zealand may be different from that in the U.S., and the model incorporates a measure of socioeconomic status specific to New Zealand. Still, it is likely that many of the risk factors identified apply broadly. A tool to apply the risk model in practice is under development.

The strongest risk factors identified by the study included:

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Women (Hazard ratio)</th>
<th>Men (Hazard Ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year)</td>
<td>1.04</td>
<td>1.04</td>
</tr>
<tr>
<td>Prior bleeding event</td>
<td>3.18</td>
<td>3.13</td>
</tr>
<tr>
<td>Alcohol-related condition</td>
<td>2.59</td>
<td>1.96</td>
</tr>
<tr>
<td>Chronic liver disease or pancreatitis</td>
<td>2.66</td>
<td>2.17</td>
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<tr>
<td>Current smoker</td>
<td>1.64</td>
<td>1.46</td>
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<tr>
<td>Peptic ulcer disease</td>
<td>1.53</td>
<td>1.25</td>
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<tr>
<td>Medication for peptic ulcer disease</td>
<td>1.45</td>
<td>1.44</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>1.39</td>
<td>1.34</td>
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</tbody>
</table>

In general, aspirin should be avoided among patients who are at elevated risk of bleeding, though precisely determining an individual’s risk remains challenging.
CASE ONE CONTINUED:

Just as you are finishing up your discussion of bleeding risks, Mr. Whitney’s wife, who is also your patient, has joined him after parking the car. She interjects, “Doc, I know it’s not my visit today, but what about me? Should I be taking aspirin?” Mrs. Whitney, who is 56 years old, has a history of type II diabetes that has been moderately well-controlled. She has no overt cardiovascular disease and no complications from her diabetes. Her 10-year ASCVD risk score is 11%.

6. What would you suggest for Mrs. Whitney?

Older studies that evaluated aspirin for primary prevention in people with diabetes suggested that aspirin had a similar effect for CVD risk reduction among patients with diabetes as among patients without diabetes. However, because people with diabetes may be at higher risk of CVD, the absolute risk reduction may be greater.

In 2018, the ASCEND Trial examined aspirin for primary prevention of cardiovascular disease among adults ages 40 and older with diabetes and no clinical CVD. Participants were randomized to 100 mg ASA or placebo. The primary endpoint was a composite of MI, stroke, TIA, or death from any vascular cause other than hemorrhagic stroke. During 7.4 years of follow-up, the primary endpoint occurred at a lower rate in the aspirin arm (RR 0.88, 95% CI 0.79-0.97). Major bleeding was more common in the treatment group (RR 1.29, 95% CI 1.09-1.52). Gastrointestinal cancers were evaluated as a secondary endpoint, with no reduction in risk (RR 0.99, 95% CI 0.80-1.24). Absolute risk reduction for vascular events was very similar to increase in rate of bleeding, and the authors conclude that the risks of aspirin may approximately balance any benefits in this population (ASCEND, 2018).

Should the ASCEND Trial dissuade us from using aspirin in patients with diabetes since significant adverse events approximately balanced the reduction in vascular events? Much as with patients who do not have diabetes, the answer may depend on the patient. For patients who are at significantly elevated risk of CVD, aspirin still may be a reasonable choice. Some patients may also be more concerned specifically about CVD than bleeding. On the other hand, some patients may have risk factors for bleeding that suggest the balance of benefit and harm is not favorable or they may particularly prefer to avoid therapies that increase the risk of bleeding.

CASE ONE CONTINUED:

Armed with the latest data, you engage Mr. and Mrs. Whitney in shared decision making, explaining the risks and benefits of aspirin and eliciting their preferences.
A first step to all shared decision-making is to ask patients what they know about the topic or decision at hand. A second step is to understand Mr. Whitney’s goals and preferences - is he more concerned about reducing his risk of cardiovascular disease or is he worried about bleeding risk? Open ended questions can help patients voice concerns. For example, you can ask, “From your point of view, what matters most to you?” Once you have a sense of what patients know and what their goals and worries are, you can provide information about aspirin. Information should include risks and benefits. The sophistication of this information can be tailored to your patient’s needs, interest, and health literacy. Put very simply, aspirin probably does reduce the risk of myocardial infarction and stroke by a modest amount, however it clearly also increases the risk of bleeding, such that the reduction in CVD outcomes is roughly balanced by bleeding events. Aspirin likely does reduce the risk of gastrointestinal cancer, but only when taken for a very long time - more than 10 years - so patients who are considering it for this reason should understand this. Once you have conveyed and discussed this information, you can ask patients if they are ready to decide, or defer a decision, if that is their preference.

CASE ONE CONTINUED:

After a long afternoon, you finish your work in clinic and head home. Not a minute after putting up your feet on the couch, your phone buzzes. It’s your grandmother texting you (she’s very hip). Unbelievably, she wants to know if she should start taking aspirin after seeing an ad on TV. She’s 78 years old and in remarkably good health. She has osteoporosis and osteoarthritis, but no other significant medical conditions.

8. Should your very hip grandmother be on aspirin?
The ASPREE trial randomized community-dwelling adults age 70 and older (or 65 and older for Black and Hispanic participants in the US) to aspirin for primary prevention vs. placebo. The trial enrolled nearly 20,000 adults, 89% of whom were not on aspirin at the time of enrollment. The primary endpoint was disability-free survival. Over 4.7 years of follow-up, aspirin was associated with a slightly higher risk of death (HR 1.14, 95% CI 1.01-1.29). Participants in the treatment arm had a higher rate of cancer-related death in particular (3.1% vs 2.3%, HR 1.31, 95% CI 1.10-2.56) (McNeil, 2018).

The ASPREE trial conclusively answers the question of initiating aspirin for older adults for primary prevention: don’t do it. But it doesn’t answer a more common clinical question: should an older adult who is already on aspirin for primary prevention continue to take it?
In summary, three recent trials, ASPREE, ASCEND, and ARRIVE can help inform our approach to aspirin for primary prevention. For adults over 70, results of the ASPREE trial clearly indicate that initiating aspirin is harmful. For other age groups, aspirin may still play a role, but benefits are closely balanced by harms, necessitating an approach that considers individual risk and preferences.

**Editor’s Note:**
The discussion leader may opt to divide the group into thirds prior to meeting and ask each group to review one of the three aspirin trials and serve as the group experts during the case discussion.
Primary References:


Additional References:


Ilana Richman is a general internist whose research interests include evaluating the effectiveness and cost-effectiveness of clinical preventive services. She is also interested in understanding the impact of health policies on use of preventive services and health outcomes. Dr. Richman attended medical school at the University of California, San Francisco and completed her residency in internal medicine at Stanford University where she also served as chief resident. She received additional training in health services research as a post-doctoral fellow at the Palo Alto VA and Stanford University. Following her fellowship, she joined the faculty at the Yale School of Medicine.
Knowledge Questions:

1. Aspirin is associated with a range of potential benefits and harms. For which outcome does aspirin offer the greatest relative risk reduction when used for primary prevention?
   
   a. Nonfatal myocardial infarction  
   b. Cardiovascular mortality  
   c. GI bleeding  
   d. Hemorrhagic stroke

2. The ASPREE trial suggested that initiating aspirin in adults 70 and older is not beneficial. Which of the following is a limitation of ASPREE?
   
   a. It included older adults living in long-term care settings  
   b. It did not address aspirin discontinuation among older adults already taking aspirin  
   c. It was unblinded  
   d. It evaluated an intermediate endpoint

3. A recent large cohort study from New Zealand developed a prognostic model for bleeding among adults using aspirin for primary prevention. Which risk factors were the strongest predictors of bleeding risk?
   
   a. Platelet count, prior bleeding, and chronic liver disease  
   b. Prior bleeding, chronic liver disease, and an alcohol-related condition  
   c. Chronic liver disease, history of peptic ulcer disease, and diabetes  
   d. History of peptic ulcer disease, corticosteroid use, and SSRI use

Answers:

1. a Several meta analyses have consistently found that aspirin is associated with a reduced risk of nonfatal MI. Aspirin has not been found to consistently lower risk of cardiovascular mortality and it raises risk of GI bleeding and hemorrhagic stroke.

2. b Most participants in ASPREE started aspirin for the first time at age 70; thus the trial does not necessarily address whether or when to stop aspirin among older patients.

3. b Platelet count, while intuitive, was not included in the risk model because of data limitations. History of peptic ulcer disease is not as strong a risk factor as liver disease and alcohol-related conditions.