Long-Term Care Updates

February 2023

Risk vs. Benefit: The Use of Low-Dose Aspirin in Elderly Adults for Primary Prevention

PharMerica

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Introduction

Aspirin is a nonsteroidal anti-inflammatory drug (NSAID) that irreversibly inhibits cyclooxygenase 1 and 2 at both low and high doses resulting in decreased prostaglandin formation.[1] In the past, low-dose aspirin has been commonly utilized for cardiovascular benefit and the prevention of atherosclerotic cardiovascular disease (ASCVD). For years, health care providers have been recommending low-dose aspirin to their adult patients because of its proven cardiovascular benefit, along with its affordable cost and convenience as a nonprescription drug. However, recent research and findings from clinical trials have shown that although low-dose aspirin has a cardiovascular benefit, the risk of bleed in elderly patients, specifically gastrointestinal (GI) bleed, may outweigh the benefit.[2]

The United States Preventative Services Task Force (USPSTF) is an independent panel of experts specializing in preventative services and evidence-based medicine. The primary goal of the USPSTF is to review current evidence and literature to provide guidance on screening, counseling, and preventative medications to improve the health of the public.[3] In April 2022, the USPSTF released their final updated recommendation on low-dose aspirin stating that it should be initiated as primary prevention in patients 40-59 years old with a 10-year ASCVD risk of 10% or greater; however, if a patient is 60 or older, low-dose aspirin for primary prevention of cardiovascular events should be avoided due to the increased risk of bleeding. This is a change from USPTF's previous recommendation; however, it is important to note that this update does not apply to the use of low-dose aspirin as secondary prevention.[4] The updated guidance is similar to the joint 2019 American College of Cardiology (ACC)/ American Heart Association (AHA) recommendation which stated that low-dose aspirin can be considered in patients 40-70 years old with higher ASCVD risk and low bleed risk; however, low-dose aspirin should be avoided for primary prevention in patients who are at a high bleed risk or are over the age of 70.[5]

The purpose of this newsletter is to review clinical trials that support the USPSTF updated recommendation to consider the risk of bleeding with low-dose aspirin in patients over 60 years old when used for primary prevention.

Clinical Evidence

The Aspirin in Reducing Events in the Elderly (ASPREE) trial was conducted in Australia and the United States from 2010-2014. ASPREE enrolled 19,114 community-dwelling patients ≥65 years if they were Black or Hispanic, or ≥70 years if the patient was any other race. Participants were without a history of dementia, disability, or cardiovascular disease. Patients were randomly assigned to receive either enteric-coated aspirin 100 mg or a matching placebo throughout the trial. The primary endpoint was disability-free survival, defined as survival without any chronic physical disability or dementia. The secondary end point was death from any cause. For the analysis of the secondary endpoint, participants were contacted via telephone quarterly and were expected to attend annual visits in person; therefore, trial conductors were notified relatively quickly upon the death of a participant. The trial was stopped early by the investigators because aspirin was not displaying a significant benefit in terms of the primary outcome and was associated with an increase in all-cause mortality. When investigators examined the most prevalent causes of death, they were cancer, cardiovascular disease (including myocardial infarction) and major hemorrhage (such as major gastrointestinal bleed). Although the number of participants who died from cardiovascular causes was lower in the aspirin arm (1%) compared to the placebo (1.2%), this was not a statistically significant reduction (hazard ratio [HR] 0.82; 95% CI: 0.62-1.08). Participants in the aspirin arm had a slightly increased risk of cancer and major hemorrhage as the underlying cause of death (295 and 28 participants respectively) compared to the placebo arm (227 and 23 participants respectively; HR 1.31; CI: 1.10-1.56). ASPREE concluded by stating that aspirin utilized as primary prevention in patients ≥70 years old resulted in an increased all-cause mortality, with cancer being the most prominent cause.[6]

Results from the Use of Aspirin to Reduce Risk of Initial Vascular Events in Patients at Moderate Risk of Cardiovascular Disease (ARRIVE) trial were published in 2021. A total of 12,546 patients were enrolled and included males ≥55 years old or females ≥60 years old who had a moderate risk of cardiovascular disease based on their number of risk factors. Patients were excluded if they were deemed to be at high risk of GI bleed or other bleeding, had diabetes, or a history of vascular event. Trial participants were randomly assigned to receive enteric-coated aspirin 100 mg or a placebo daily for primary prevention from July 2007 to November 2016. The primary efficacy endpoint was a composite of time to first occurrence of cardiovascular death, myocardial infarction, stroke, unstable angina, or transient ischemic attack. In terms of safety, trial investigators looked at hemorrhagic events along with other adverse effects using an intention-to-treat population. ARRIVE found that 269 patients in the aspirin treatment group experienced the primary outcome compared to 281 patients in the placebo treatment group (HR 0.96; 95% CI: 0.81-1.13; p=0.6038). Although there was not a statistically significant reduction in the primary outcome, there was a statistically significant increase in GI bleeds with 61 in the aspirin arm as opposed to 29 in the placebo arm. (HR 2.11; 95% CI: 1.36-3.28; p=0.0007). Additionally, the results of a subgroup analysis of patients ≥65 years were similar to the overall findings, confirming that there was no benefit of aspirin use for primary prevention in this population.[7]

Results from The Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus (ASCEND) trial were published in 2018. ASCEND specifically studied patients with diabetes, due to the increased cardiovascular risk seen in this patient population. A total of 15,480 patients with diabetes were randomly assigned to either aspirin 100 mg or a matching placebo for primary prevention of cardiovascular disease. The primary efficacy endpoint was first serious vascular event such as myocardial infarction, stroke, or trans ischemic attack. The primary safety endpoint was the first major bleeding event, including intracranial hemorrhage, ocular bleeding that threatened vision, GI bleed, or any other serious bleed. The trial found a statistically significant reduction in cardiovascular events in the aspirin arm (658 participants vs 743; Rate ratio [RR] 0.88; 95% CI: 0.79-0.97; p=0.01). However, in a subgroup analysis after trial completion, this cardiovascular benefit was not seen in patients 70 years and older who accounted for approximately 25% of the patients enrolled in ASCEND. When examining the participants' major bleeds, there was a clinically significant increase in GI and extracranial bleeds with 314 participants in the aspirin group and 245 participants in the placebo group experiencing a major bleed at some point throughout the seven-year trial duration (RR 1.29; 95% CI: 1.09-1.52; p=0.003). ASCEND concluded that although aspirin was shown to decrease cardiovascular disease when used as primary prevention in patients with diabetes, there was also an increase in bleeding.[8]

Conclusion

The cardiovascular benefit of low-dose aspirin has been supported for years resulting in its widespread use, particularly in elderly patients. However, recent clinical trials have concluded that the benefit of cardiovascular protection needs to be weighed against the risk of GI bleeding. Although low-dose aspirin is recommended as secondary prevention in patients who have a history of a cardiovascular event, its use in geriatric patients for primary prevention is no longer recommended due to the lack of benefit and increased risk.

References

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