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Aspirin Use for Primary Prevention of Atherosclerotic Cardiovascular Disease: Summarizing Current Evidence

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By

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Introduction

Almost everyone has heard the saying, "One size does not fit all." This adage is especially true in medicine. Treatment options vary depending on an individual's risk. For this reason, risk calculators were created to help medical providers apply value to each risk and modify medical management accordingly. Preventative medical management also needs to be individualized. Aspirin is one of the most well-known preventative medications prescribed for the purpose of preventing cardiovascular events. It has become so well-known that patients have started taking it without recommendations from medical providers. An estimated 48.7 million US adults are currently taking aspirin as a preventative measure.[1] Using aspirin for secondary prevention of cardiovascular disease (CVD) has resulted in excellent benefits versus risks and was founded on good quality evidence. In contrast, recent trials for primary prevention have questioned the value of aspirin in individuals without CVD, specifically in patients with certain risk factors and comorbidities, such as diabetes mellitus type II.

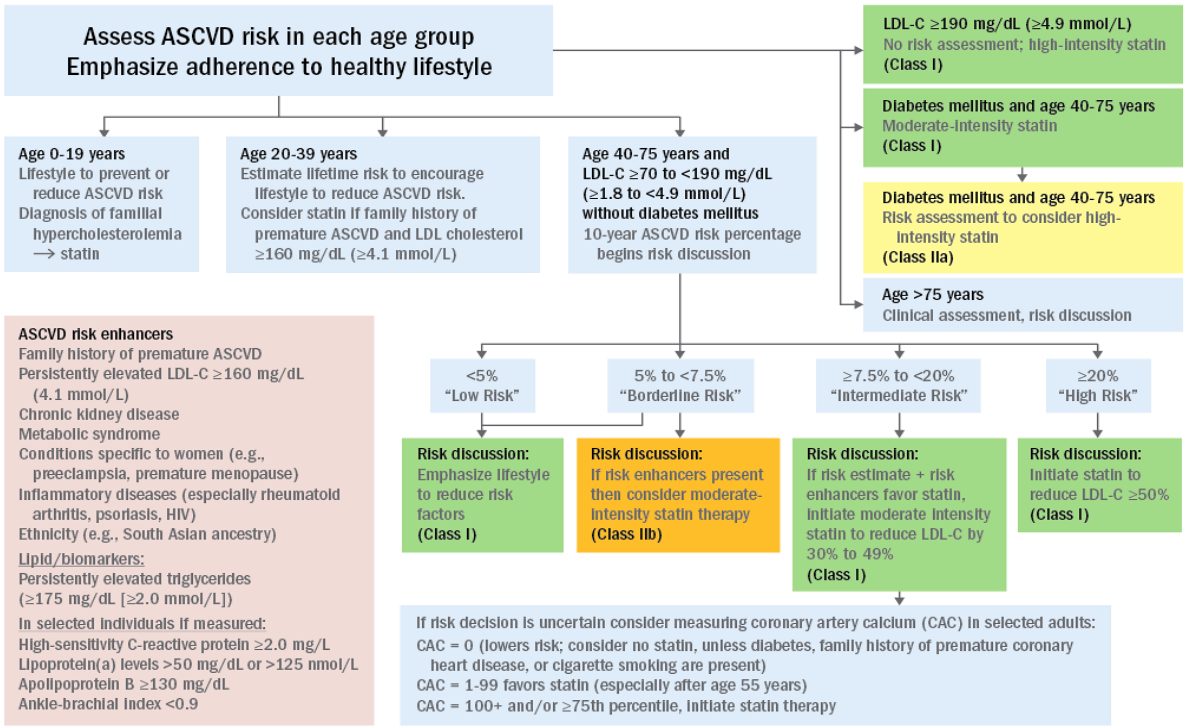
Background

Atherosclerotic cardiovascular disease (ASCVD) is defined as plaque accumulation within large or small vessel arteries causing deleterious changes within the vessels. According to UpToDate™, for CVD to be diagnosed, one of the following must occur:

- Coronary heart disease (CHD) manifested by fatal or nonfatal myocardial infarction, angina pectoris, and/or heart failure
- Cerebrovascular disease manifested by fatal or nonfatal stroke and/ or transient ischemic attack
- Peripheral artery disease manifested by intermittent claudication and/ or critical limb ischemia
- Aortic atherosclerosis and thoracic or abdominal aortic aneurysm [2]

CVD continues to be ranked in the top four causes of death in the United States. Of the risk factors for CVD, a person's age, sex, and race are non-modifiable, but diabetes mellitus, smoking, hypertension, and hypercholesterolemia, are modifiable. Better control of these diseases, therefore, will decrease the chances of CVD events. Primary prevention of CVD focuses on patients who have the highest risk, which is determined by assessing both modifiable and non-modifiable risk factors. The ASCVD risk calculator, created by David C. Goff, Jr., MD, PhD, uses those risk factors to predict the probability of atherosclerotic cardiovascular events within a 10-year time frame in adult patients without known ASCVD and with a low-density lipoprotein value ranging from 70 -189 mg/dL (normal <130 mg/dL). This calculator is used to provide recommendations for statin therapy, both its initiation and intensity. In addition, the calculator has been used according to American College of Cardiology/ American Heart Association **(**ACC/AHA) guidelines for recommending the use of aspirin in patients with a CVD risk of ≥10%.[3]

Primary prevention of atherosclerotic cardiovascular disease



Note: Color corresponds to class of recommendation: green = Class I (strong); yellow = Class IIa (moderate); orange = Class IIb (weak).
Source: J Am Coll Cardiol. 2018 Nov 10. doi: 10.1016/j.jacc.2018.11.003

New controversy about the use of aspirin for primary prevention of CVD arose after the United States Preventive Task Force (USPTF) released a statement recommending its use for that purpose. Even though the reduction in the occurrence of CVD events was nearly equivalent to the increased frequency of major bleeding episodes, a possible side effect due to the reduction in coagulation factors.[4] During this controversy, however, many new trials and meta-analyses were released that focused on patients with an intermediate ASCVD 10-year risk (≥7 to <20%). This research revealed that the use of aspirin among people without prior history of CVD resulted in comparable risks and benefits; specifically a 0.07% reduction in serious CVD events was observed, but was associated with an increased risk of 0.04% for major bleeding.[5] For this reason, aspirin use for primary prevention of CVD in patients who are not high risk should be examined further and individualized according to a patient's risk level and comorbidities.

Discussion

Several randomized clinical trials examined the primary prevention of CVD with aspirin in patients without known CAD and with an ASCVD 10-year risk calculated at a value of < 7.5%. The Atherosclerotic Cardiovascular Events in Diabetes (ASCEND) trial included 15,480 participants with diabetes mellitus without prior history of occlusive vascular disease in a prospective study in which they were randomized to either aspirin 100 mg once a day or omega-3 fatty acid supplementation.[6] The participants were followed for a median of seven years.[6] The diabetic adults who were taking aspirin 100 mg daily had a reduction in nonfatal vascular events but also had an increased number of major bleeding events without a reduction in cardiovascular mortality, which were of statistical significance. The Aspirin in Reducing Events in the Elderly (ASPREE) trial randomized 15,000 elderly patients to either aspirin 100 mg daily or placebo.[7] Findings at about 5 years after this double blind, randomized, placebo-controlled trial were similar in that the risk of major hemorrhage increased; however, reductions in cardiovascular events were not observed. The Aspirin to Reduce Risk of Initial Vascular

Events (ARRIVE) trial randomized 12,546 adults with a moderate risk of CVD (10-year ASCVD of 10-20%) to either aspirin 100 mg daily or placebo, and then followed them for approximately 6 years.[8] Even though bleeding events were low, ARRIVE did not show a reduction in adverse cardiovascular events. In all three trials, no reductions in cardiovascular events were found in diabetics, the elderly, and patients with moderate risk. Two out of these three trials revealed evidence of increased major bleeding episodes. Although this research evaluated the use of aspirin for primary CVD prevention specifically in diabetics, elderly, those at moderate risk, information is lacking about aspirin use in adults who are not diabetic, who are younger than 60 years old, who have a low risk of CVD, or who have risk factors that predispose them to bleeding events.

Subsequently, a retrospective observational study examined the incidence of upper gastrointestinal bleeds (UGIB) and lower gastrointestinal bleeds (LGIB) in new low-dose aspirin users compared with nonusers over time. The odds ratio for increased risk of UGIB and LGIB in low-dose aspirin users were 1.53 and 1.63, respectively. The increased risk was stable for LGIB, but was slightly higher for UGIB during the first three months of therapy.[9] The results were statistically significant. The study focused on reported bleeds between January 2000 and December 2012, also the timeframe in which aspirin was used prior to the event. Current low-dose aspirim users were defined as those who had aspirin between 0-30 days prior to event. Nonusers of low-dose aspirin were those who did not have aspirin within 365 days prior to event. The two groups were evenly matched, which was a strength in this trial. The large sample size included people ranging from 40-84 years old. Further breakdown demonstrated that the primary CVD prevention population taking low-dose aspirin had a 60% increased risk of both UGIB and LGIB. Although similar findings were concluded from the USPTF meta-analysis, the trial did not have access to all the clinical information regarding the GI events. Overall, the risk of bleeding did not outweigh the benefit of preventing CVD events.[5] No association was found between GI bleeds and aspirin dose. Hence, each adult that could potentially benefit from aspirin for primary

prevention of CVD should also be evaluated for their individual bleeding risk in order to determine the clear risks and benefits of aspirin.

The PREDICT study, which was a prospective study with 385,191 participants assessed over a 9 year timeframe, acknowledged the wide range of risk factors that contribute to CVD and sought to provide insight on prognostic bleeding risk models among people in whom aspirin might be considered for the primary prevention of CVD.[10] The study focused on a younger population than that in the ASPREE trial. Participants were between 30-79 year old. Several statiscal tools were used, including the Cox proportional hazards models for prediction models. This prediction model found that the benefits of aspirin outweighed the risks of bleeding among this population, specifically in individuals without adequate control of hyperlipidemia and hypertension. These results further substantiated the need to individualize preventive therapy, especially when patients may not be compliant with treatment of comorbid conditions such as hypertension and hyperlipidemia. Of note, hemoglobin and platelet counts, which can be predictors for potential bleeds or complications, were not reported in this investigation; hence, this omission limited the evidence. Nonetheless, those patients without control of their lipids and blood pressure would benefit the most from aspirin as primary prevention of CVD.[10]

Modification of the aspirin dose depending upon the patient's weight is yet another approach when considering aspirin for primary prevention of CVD. The standard dose of aspirin is 81 mg daily, standard medication therapies in US are based on a 70 kilogram male. Therefore, those individuals who weigh more than 70 kg may not achieve therapeutic levels.[11] Many adults in the United States are overweight, which makes the standard dose questionable since original recommendations from ACC/AHA are currently set for 81 mg daily. Murphy et al. commented on 3 trials addressing aspirin for primary CVD prevention and found that the reductions in cardiovascular events with low-dose aspirin in people weighing over 70 kg were significantly lower compared to adults weighing 50-69 kg.[11] Although,

this report was not original research, but was a commentary referencing other studies, it did provide links to the cited meta-analyses. Thus, the dose of aspirin may affect its efficacy and should be considered in both primary and secondary CVD prevention.

The research findings summarized herein came from well designed studies with large sample sizes, the smallest sample size was over 15,000. Investigations included prospective, retrospective, and randomized controlled studies. The major studies, ARRIVE, ASPREE, and ASCEND trials had large sample sizes and were randomized controlled studies.

Conclusion

In patients without known CAD and a 10-year ASCVD risk <7.5% the use of low dose aspirin compared to no aspirin showed no superior efficacy for prevention of primary CVD. Where as those at an intermediate risk (≥7 to <20%), need to be individually stratisfied to identify if the risks outweigh the benefit. As noted, aspirin can increase the risk of bleeding in different settings, prior to reducing the risk of cardiovascular disease. More recent research suggests that aspirin should not be used as a blanket coverage for primary prevention of cardiovascular disease. Clinicians should individualize primary prevention of CVD with aspirin based on the patient's ASCVD risk, lipid and blood pressure control, body weight, and bleeding risk. Further research is required for patients who are younger than 40 years and therefore their ASCVD risk cannot be calculated. This is important as adults under 40 years of age who are overweight, diabetic, and have hypertension should be also be risk stratisfied for primary prevention.

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