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Annual Review of Changes in Healthcare

Benefits and Risk of Aspirin as Primary Prevention of Cardiovascular Disease

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Abstract

The use of aspirin for primary prevention has been a long-debated topic in healthcare. Up to 20% of the United States population takes aspirin daily or every other day with or without a recommendation from a physician. Aspirin has a well-established role in the secondary prevention of cardiovascular disease. However, in the setting of primary prevention, clinicians should balance the potential cardiovascular events prevented with the risk of major bleeding and should be a decision that providers make on an individual basis. The goal of this review article is to summarize and analyze the results of recent studies testing the use of daily low-dose aspirin in the setting of primary prevention.

Recently, new studies have tested the outcomes of aspirin as primary prevention and have added new information to the topic. The ASCEND trial, ARRIVE trial, and ASPREE trial each tested aspirin as primary prevention in a specific risk factor group. The groups studied were for cardiovascular disease including diabetes, high-risk, and elderly patients respectively. In the ARRIVE and ASPREE trials, patients taking daily low-dose aspirin did not differ significantly from placebo in the prevention of composite cardiovascular events but did have a significant increase in bleeding events. In the ASCEND trial a significant reduction in cardiovascular events among diabetes patients was offset by a significant increase in major bleeding.

The role of aspirin in primary prevention should be reevaluated based on the results of these new trials. The 2019 American Heart Association/American College of Cardiology Guideline on the Primary Prevention of Cardiovascular Disease recommends that low-dose aspirin may be considered for primary prevention of cardiovascular disease in adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding. It is also now recommended that low-dose aspirin not be given on a routine basis for the primary prevention of ASCVD among adults >70 years of age. Further studies should evaluate the use of daily low dose aspirin in different high-risk groups and groups without access to primary care.

Aspirin is one of the most widely available and inexpensive drugs used by patients in the United States and most developed countries.[1] In a 2005 survey conducted by the Agency for Healthcare Research and Quality, results showed that about one in five U.S. adults aged 18 and older reported taking aspirin every day or every other day, with or without recommendation from a physician, with over half the respondents being over the age of 65.[1] Among this sample of patients at least age 65 years old, 41% of these patients were using aspirin as primary prevention of cardiovascular disease (CVD) despite not being told they had indicators of heart disease by their health care provider. It is important for both patients and providers to have communication with one another especially when making the decision to take medication.[1]

With the availability of aspirin being so prevalent, inappropriate use of aspirin initiated by providers or patients may subject these patients to an increased risk of adverse effects without offering benefits towards prevention of cardiovascular events.

The use of daily low-dose aspirin does play a significant role in the prevention of cardiovascular events. Previous studies have shown that low-dose aspirin can be beneficial for certain patients in the setting of secondary prevention of stroke, coronary artery disease, and myocardial infarction (MI), and thus multiple guidelines have endorsed this recommendation.[2,3] Secondary prevention is defined as the actions taken to prevent the progression or recurrence of disease or injury after it has already happened, while primary prevention is defined as the actions taken to prevent disease or injury before initialonset.[4] The use of aspirin as primary prevention of CVD without a history of such disease, underlying condition, or other indication, has remained uncertain due to conflicting studies and differences in opinions of risks versus benefit.

The role of aspirin as primary prevention of CVD has been studied heavily over the past few decades. Current recommendations are largely influenced by the 2009 Antithrombotic Trialist Collaboration which found in a meta-analysis of 6 randomized control trials, that in the setting of primary prevention daily low dose aspirin was associated with a 12% reduction in serious vascular events compared to no daily aspirin.[5] Despite numerous studies, the benefits and risks of aspirin as primary prevention still remain uncertain in part due to difficulty balancing the benefits of CVD reduction and increase in bleeding risk and new trials presenting conflicting results.[6]

In 2018, three separate studies titled ASCEND, ARRIVE, and ASPREE trials were published, each testing the use of aspirin as primary prevention in select patient groups with a risk factor for cardiovascular events.[7,8-11] The goals of each of these trials was to ultimately gain a better understanding of the use of aspirin as primary prevention and to assess the safety and tolerability for each of their specific patient populations.

Guideline Review

Aspirin is a mainstay treatment of secondary prevention of MI or stroke according the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines for the management of acute coronary syndrome and the American Heart Association/ American Stroke Association guidelines for management of stroke. Each of these guidelines support the efficacy of aspirin therapy and conclude that the benefits outweigh the risks in the setting of secondary prevention (Grade A evidence).[2,3]

The United States Preventive Services Task Force currently recommends that aspirin may have a role in the setting of primary prevention for adults aged 50 to 59 years with a ≥10% 10-year CVD risk may have a benefit with the initiation of daily low-dose aspirin as long as the patient is not at increased risk for bleeding, has a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years (Grade B). This group has been shown to have the greatest benefit. The decision to initiate daily low-dose aspirin in adults aged 60-69 who have a 10% or greater 10-year CVD risk is not routinely recommended and should be based on clinical judgement (Grade C).[12]

The 2012 American College of Chest Physicians CHEST guidelines recommend that for primary prevention of CVD, low-dose aspirin in patients aged > 50 years should be used over no aspirin therapy (Grade 2B).[13]

The 2016 European guidelines on cardiovascular disease prevention in clinical practice sponsored by the European Society of Cardiology suggest that individuals without cardiovascular or cerebrovascular disease are not recommended to take daily low dose aspirin for primary prevention (Grade IIIB).[14]

In regards to patients with diabetes, the 2019 American Diabetes Association Standards of Care for Diabetes suggest that daily low dose aspirin may be considered as a primary prevention strategy in patients with diabetes who are at increased cardiovascular risk as long as the risks of increased bleeding are discussed (Grade C).[15]

Guidelines are overall conflicting specific to different factors. Individual clinic judgement of risk versus benefit should be considered in all patients.

Mechanism Overview

Aspirin is well defined as an irreversible COX-1 and COX-2 inhibitor.[16] This mechanism leads to decreased platelet aggregation and anti-inflammatory effects secondary to decreased synthesis of thromboxane A2 and prostaglandin, respectively.[16] Serious side effects of this medication include, but are not limited to, gastrointestinal bleeding, ulceration, and cerebral hemorrhage.[16]

ASCEND Trial

Data representing the use of aspirin in primary prevention for diabetic patients is still uncertain and controversial. Diabetes is associated with a 2-4 times greater risk of CVD compared to those without diabetes.[6] Previous primary prevention trials have

shown that aspirin can significantly reduce the incidence of CV events in patients with diabetes but newer studies, such as the Prevention and Progression of Arterial Disease and Diabetes (POPADAD) trial showed that aspirin failed to significantly reduce CV events in patients with diabetes.[6,17] The ASCEND trial has added further information regarding this dilemma.
The goal of the ASCEND trial was to address this need by evaluating the safety and efficacy of aspirin use in diabetic patients without a history of CVD.[7] This trial randomly assigned 15,480 adults in the United Kingdom with diabetes and no evident CVD, to receive daily enteric-coated aspirin 100 mg or placebo.[7] Relevant inclusion criteria included: age of at least 40 y/o, any type of diagnosed diabetes, and no history of CVD.[7] Primary efficacy outcomes measured were nonfatal myocardial infarction, nonfatal ischemic stroke, transient ischemic attack, or death from any vascular damage.[7] Primary safety outcomes measured were first occurrence of major bleeding, including gastrointestinal bleeding, intracranial hemorrhage, sight-threatening bleeding event in the eye, or other bleeding event that required hospitalization or transfusion.[7]

Significant results of this study showed that patients with diabetes who did take daily aspirin had a 12% reduction in serious vascular events compared to placebo ($p=0.01$).[7] The risk of serious bleeding however was 29% higher in the daily aspirin group versus placebo ($p=0.003$).[7] A majority of the serious bleeding episodes included gastrointestinal bleeding. Between the two groups there was no significant difference seen in all-cause mortality.[7] Despite the reduction in cardiovascular events the results of this trial are difficult to interpret due to significantly increased instances of bleeding events.

ARRIVE Trial
The objective of the ARRIVE trial was to assess the efficacy and safety of aspirin compared to placebo in patients with moderate risk of their first cardiovascular event.[8] Moderate risk was defined as having two to four risk factors for males and three to five risk factors for women.[8] These risk factors included: dyslipidemia, current smoker, high systolic blood pressure, receiving medication for high blood pressure, and a positive family history of CVD.[8] Based on these risk factors, subjects were estimated to have a 10-year ASCVD risk score between 10-20%.[8] There were 12,546 participants enrolled in the study, with a median follow-up of 60 months.[8] Over 90% of the participants were from Germany, Poland, and the United Kingdom and each study group had approximately equal baseline characteristics.[8] Patients were randomized to receive either 100 mg aspirin daily or placebo daily.[8] Primary outcomes measured were a composite of time to first occurrence of confirmed myocardial infarction, stroke, cardiovascular death, unstable angina, or transient ischemic attack.[8] Hemorrhagic and major bleeding events were monitored for safety.[8]

Results of this study showed that that aspirin did not significantly decrease the risk of composite major cardiovascular events

(p=0.619) or any individual type of cardiovascular event.[8] The ARRIVE trial did show that the aspirin group had a significant increase in gastrointestinal bleeding (p=0.0007).[8] Most of the gastrointestinal bleeding was diagnosed as mild and non-fatal and there was no difference seen in fatal bleeding between the aspirin and placebo group.[8]

The results of the ARRIVE trial suggest that aspirin use does not have a significant effect on the occurrence of cardiovascular events but did increase the risk of gastrointestinal bleeding. It is important to note that the event rate of cardiovascular events was much lower than expected and may have been a contributing factor.[18] The mean estimated 10 year-ASCVD risk score among participants was 17.3% but the actual 10-year rate in this trial was estimated to be 8.43% in the aspirin group and 8.80% in the placebo group, both of which are much lower than expected and suggest that this sample of subjects represents patients in a low to moderate risk of ASCVD. This may have played a role in why little benefit was seen in the aspirin group.[18]

ASPREE Trial

The ASPREE trial was published in the *New England Journal of Medicine* in October 2018. This study was conducted between 2010-2014, with 19,114 participants, aged 70 years of age or older from Australia and the United States.[9] The objective of this study was to determine whether daily use of aspirin provides benefit with the primary end point of disability-free survival.[9]

The ASPREE trial originally aimed at determining whether low-dose aspirin increases healthy life-span (survival free of dementia and disability).[9] It was a randomized, double-blind, placebo-controlled, primary prevention trial of daily 100 mg aspirin in an older, healthy population with an average treatment duration of 4.5 years.[9] The original primary efficacy measured endpoint of the study was death from any cause, incident dementia, or persistent physical disability, which was assessed every 6 months.[9] Secondary outcome measures were major health issues related to aging (all-cause mortality, fatal and non-fatal cardiovascular events, dementia, mild cognitive impairment, physical disability, major hemorrhagic events, and depression), which were also assessed every 6 months.[9] Inclusion criteria for participants in the trial included: age 65 years or older for African American and Hispanic persons, and any person from another ethnic minority group as well as Caucasian persons 70 years or older.[9] Some notable exclusion criteria included: a history of a diagnosed cardiovascular event, a serious illness likely to cause death within the next 5 years, diagnosed atrial fibrillation, a current or recurrent condition with a high risk for major bleeding, current continuous use of aspirin or other antiplatelet drug or anticoagulant for secondary prevention, a systolic blood pressure ≥180 mmHg and / or a diastolic blood pressure ≥105 mmHg, a history of dementia.[9]

The results of this trial suggested that daily low dose aspirin did not prolong disability-free survival among healthy adults and increased the rate of all-cause mortality compared to placebo.

The ASPREE trial had several sub-analyses conducted. Significant sub-studies to cardiovascular risk were observed and one of the published sub-studies focused on the comparison of the aspirin versus placebo on cardiovascular events and major bleeding in healthy elderly. The sub-analysis measured the endpoints of composite fatal coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal stroke, and hospitalization for heart failure.[10] In the aspirin group the rate of CVD was 10.7 events per 1000 person-years versus 11.3 events per 1000 person-years in the placebo group (hazard ratio, 0.95; 95% confidence interval [CI], 0.83 to 1.08).[10] This sub-study also analyzed major hemorrhagic events such as upper gastrointestinal bleeding and intracranial bleeding for safety.[10] The rate of major hemorrhage in the aspirin group was measured to be 8.6 events per 1000 person-years and 6.2 events per 1000 person-years, in the placebo group (hazard ratio, 1.38; 95% CI, 1.18 to 1.62; P<0.001).[10]
These results suggested that the group receiving daily aspirin had an increased risk of major bleeding or hemorrhage without significantly lowering the risk of CVD when compared to the placebo group.[10] It should be noted that the rate of cardiovascular events was much lower than anticipated and could account for the lack of difference seen.[10]

The trial investigators went on to conclude that based on their analysis, daily low dose aspirin was associated with a greater all-cause mortality, among healthy older adults compared to those who received placebo.[11] This conclusion was different from what was seen in the ASCEND and ARRIVE trial where no difference in overall mortality was observed. An important note on this conclusion is that the higher rate of death seen in the aspirin group was seen in the population from Australia and cancer-related death was the primary cause of most deaths.[11] No specific cancer type was more prevelant.[11]

Discussion

The ASCEND, ARRIVE, and ASPREE trial each addressed an important individual predictor of CVD which includes diabetes, high risk, and old age, respectively. Each of these groups are potentially a higher risk for cardiovascular events and the need for preventative therapy, such as aspirin may be beneficial. Previous studies have not had definitive results as to what patient populations benefit the most from primary prevention with aspirin therapy, and to what extent the benefits outweigh the risk of severe bleeding.[6,9-11] Each of the trials discussed in this article investigated whether aspirin use as primary prevention would provide a significant benefit in cardiovascular outcomes. In the ASCEND trial, patients with diabetes did show a significant benefit in reduction of cardiovascular events but was offset by a significant increase in incidences of bleeding.[7] The ARRIVE trial did not show a benefit in cardiovascular events but did increase the risk of gastrointestinal bleeding.[8] Lastly, the ASPREE trial showed there was no benefit of aspirin therapy in patients >70 years old or >65 if black or Hispanic, but again, increased the risk of bleeding.[9-11] All three studies showed patients had a significant increase in bleeding across all

aspirin groups. How a clinician balances the potential benefits and risks of aspirin therapy is still a gray area and the results of these studies suggest that aspirin therapy may not be appropriate for some groups and should be a more selective treatment option for patients based on individual past medical history.

Studies examining aspirin in the setting of primary prevention have been an ongoing dilemma for decades.[6] With significant changes in healthcare technology and the healthcare system, this further confounds the results of studies. Successful treatment of many different comorbidities such as hypertension and dyslipidemia has generally improved the overall health of patients and in some instances reduced the event rate of CVD outcomes.[6,8] This was a suggested cause for the lower event rate seen in the ARRIVE and ASPREE trial. In the ASCEND, ARRIVE, and ASPREE trials a significant number of patient were on statin therapy with those percentages being 75%, 43%, and 34% respectively.[7,8-11] In previous primary prevention trials patients on statin therapy were associated with up to a 25% decrease in risk of major CV events for every 1 mmol/L decrease in LDL without an increased risk of bleeding.[18]

Ongoing advances in healthcare have continuously affected primary prevention trials throughout the years of study and increases the difficulty of designing and conducting trials.[8] The benefits of treating comorbidities, new therapies, and access to healthcare has influenced the incidence rate and confounded the true benefit of daily aspirin therapy in primary prevention.[18] However, the combination of recent modern-day trials does provide meaningful information about the place of therapy for aspirin in primary prevention. These trials include patients in modern day healthcare systems, including the U.S and various parts of Europe, that that have effective management of comorbidities and access to healthcare resources. The results of these studies reflect outcomes that are more realistic of today's healthcare society versus the past where healthcare access and options were more limited. These studies suggest that treatment with aspirin may not be beneficial or needed in patients without prior CVD and managed comorbidities.

Results of these trials have influenced new recommendations from the AHA and ACC regarding primary prevention with the use of aspirin. In March 2019 the ACC/AHA Guideline on the Primary Prevention of CVD was released. This updated guideline now recommends that low-dose aspirin not be administered on a routine basis for primary prevention of ASCVD among adults >70, or for adults of any age who are at an increased risk of bleeding. The role for aspirin in primary prevention may be considered in select higher ASCVD adults aged 40-70 years who are not at increased bleeding risk.[19] Further studies will need to address different high-risk populations and other factors to truly determine the benefits and risks of aspirin therapy.

Aspirin is a widely available drug for the general public and improper use poses a risk to many consumers. Low dose aspirin is often marketed with the thought of being heart healthy and rarely associated with many of the serious side effects by the common

layperson. This poses a risk for patients who do not communicate or follow-up with a primary healthcare provider regularly as they may start potentially unnecessary therapy that increases the risk of bleeding events and hospitalization without offering benefit. Aspirin has been an extremely effective and affordable medication for decades and will likely continue to be used for secondary prevention of stroke and MI. However, in the setting of primary prevention without a history of CVD, the risk versus benefit of using aspirin needs to be weighed closely. Other effective treatments for comorbidities and risk factors should be considered to reduce the risk of CVD first. Patients and providers should be educated about the risks and benefits of aspirin therapy and patients should consult a healthcare provider when making the decision to use this medication.

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References

1. Soni, A. Aspirin Use among the Adult U.S. Noninstitutionalized Population, with and without Indicators of Heart Disease, 2005. Statistical Brief #179. July 2007. Agency for Healthcare Research and Quality, Rockville, Md. [cited 2019 Jan 4] Available from: https://meps.ahrq.gov/data_files/publications/st179/stat179.pdf
2. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the Early Management of Patients with Acute Ischemic Stroke. American Heart Association, American Stroke Association. *Circulation*. 2018. [cited 2019 Jan 24]. Available from: https://www.ahajournals.org/doi/pdf/10.1161/STR.0000000000000158
3. Amsterdam EA, Wenger NK, Brindis RG, et al. Guideline for the Management of Patients with Non–ST-Elevation Acute Coronary Syndromes. American Heart Association, American College of Cardiology. *Circulation.* 2014;130(25):344-426 [cited 2019 Jan 25]. Available from: https://www.ahajournals.org/doi/10.1161/CIR.0000000000000134
4. Primary, Secondary, and Tertiary Prevention. Institute for Work and Health. 2015 [cited 2019 Jan 30]. Available from: https://www.iwh.on.ca/what-researchers-mean-by/primary-secondary-and-tertiary-prevention
5. Collins R, Peto R, Hennekens C, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Antithrombotic Trialists' Collaboration. *Lancet*. 2009; 373(9678): 1849-1860. [cited 2019 Feb 7]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2715005/
6. Nansseu JR, Noubiap JJ. Aspirin for primary prevention of cardiovascular disease. *Thrombosis Journal.* 2015; 13 (38):1-10. [cited 2019 Feb 10]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4669607/pdf/12959_2015_Article_68.pdf
7. McNeil JJ, Wolfe R, Woods RL, et al. Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. The ASCEND Study Collaborative Group. *New England Journal of Medicine.* 2018; 379: 1529-39 [cited 2019 Jan 24] Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa1804988
8. Gaziano JM, Brotons C, Coppolecchia R, et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2018; 392(10152):1036-46. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31924-X/fulltext
9. McNeil JJ, Nelson MR, Woods RL, et al. Effect of Aspirin on All-Cause Mortality in the Healthy Elderly. *New England Journal of Medicine*. 2018; 379: 1519-28. [cited 2019 Jan 24] Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa1803955
10. McNeil JJ, Wolfe R, Woods RL, et al. Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly. *New England Journal of Medicine*. 2018; 379 (16): 1509-18. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30221597?dopt=Abstract
11. McNeil JJ, Woods RL, Nelson MR. Effect of Aspirin on Disability-free Survival in the Healthy Elderly. New England Journal of Medicine. 2018; 379(16):1499-508. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30221596?dopt=Abstract

12. Final Recommendation Statement: Aspirin Use to Prevent Cardiovascular Disease and Colorectal Cancer: Preventive Medication. U.S. Preventive Services Task Force. September 2017. [cited 2019 Jan 31] Available from: https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/aspirin-to-prevent-cardiovascular-disease-and-cance
13. Vandvik O, Lincoff M, Gore J, et al. Primary and Secondary Prevention of Cardiovascular Disease Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *CHEST*. 2012; 141(2):637-68. [cited 2019 Feb 4] Available from: https://journal.chestnet.org/article/S0012-3692(12)60134-2/pdf
14. Piepoli MF, Hoes AW, Agewall SA, et al. European Guidelines on cardiovascular disease prevention in clinical practice. *European Heart Journal*. 2016; 37(29): 2315-81 [cited 2019 Apr 2] Available from: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/CVD-Prevention-in-clinical-practice-European-Guidelines-on
15. Standards of Medical Care in Diabetes. American Diabetes Association. *Diabetes Care*. 2019; 42(1): S1-S194[cited 2019 Feb 5]. Available from: http://clinical.diabetesjournals.org/content/diaclin/early/2018/12/16/cd18-0105.full.pdf https://www.ncbi.nlm.nih.gov/pubmed/30221596?dopt=Abstract
16. Aspirin [package insert]. Mississauga, ON: Bayer Inc; 2014. Available from: https://www.bayer.ca/omr/online/aspirin-pm-en.pdf
17. Belch J, MacCuish A, Campbell I, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *British Medical Journal*. 2008. [cited 2019 Apr 7] Available from: https://www.bmj.com/content/bmj/337/bmj.a1840.full.pdf
18. Ridker PM. Should aspirin be used for primary prevention in the post-statin era? *New England Journal of Medicine*. 2018; 379:1572-74 [cited 2019 Feb 8] Available from: https://www.nejm.org/doi/full/10.1056/NEJMe1812000
19. Arnett DK, Blumenthal RS, Albert MA, et al. ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. *Journal of the American College of Cardiology* (2019). [cited 2019 Mar 18] Available from: http://www.onlinejacc.org/sites/default/files/additional_assets/guidelines/Prevention-Guidelines-Made-Simple.pdf