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Aspirin in the Primary Prevention of Cardiovascular Disease

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Abstract

For decades, people have prophylactically used aspirin (ASA), or acetylsalicylic acid, to mitigate their risk for cardiovascular disease (CVD). The role of ASA as a means of secondary prevention for CVD is well established, however there are conflicting schools of thought as to whether or not it should be used as primary prophylaxis. While this indication has been studied for more than 30-years, questions remain pertaining to the risk of bleeding that is associated with ASA usage, which ranges from mild epistaxis to life threatening hemorrhage.[1] Lifestyle and behavioral factors play a large role in a person's CVD risk, however individuals are often resistant to making said changes and instead prefer to use medications in hopes that they will have the same protective effects as altering daily habits. Thus, this paper will provide a summary of the six current literature articles that addresses the issue of prophylactic ASA as a means of primary CVD prevention in adults over the age of 40 with modifiable risk factors.

Key words: Aspirin, Cardiovascular Disease

Highlights

- ASA has a questionable role in the primary prevention in CVD
- Platelet aggregation analysis should be utilized when possible
- USPSTF states ASA for CVD prevention in persons with risks should be individualized

Methods

In the US, CVD related death is among 1 of the leading causes of mortality.[2] Many lifestyle factors contribute to a person's cardiovascular health status, which include but are not limited to a healthy diet, regular exercise, not smoking and limited alcohol intake.[1] Genetics are also known to play a role, especially when it comes to a person's degree of platelet aggregability, of which an overabundance of may lead to the formation of an athlerosclerotic plaque.[3] Poor performance in all these combined factors may lead to CVD. CVD is a broad term that encompasses a variety of deadly pathologies such as myocardial infarction, stroke, and cardiac arrest. While modifying one's behavioral determinants of health is the most effective means to mitigate cardiovascular risk, several medications have been proposed as an adjunctive therapy. ASA is among these. Though there is an abundance of evidence supporting the use of ASA as secondary CVD prevention, there have been decades of debate as to whether or not it has a role as a primary prophylaxis.[1]

When determining if ASA should be used as a means of primary prevention for CVD, it is important for one to understand its mechanism of action. ASA is an antiplatelet therapy drug. At low doses, it irreversibly inhibits the cyclooxygenase 1 (COX-1) enzyme. When used at higher doses, it also inhibits the cyclooxygenase 2 (COX-2) enzyme. Inhibition of COX-1 primarily prevents platelet aggregation and thus the formation of an athlerosclerotic plaque. The COX-1 enzyme also works to produce prostaglandins that protect the gastrointestinal (GI) mucosa. Thus, inhibition of COX-1 can damage the mucosa, and consequently place a person at increased risk for a GI bleed. In determining if aspirin is indicated for a particular patient, one must individually weigh the benefit of its protective effects against formation of an athlerosclerotic plaque to its risk of GI bleeding.[3]

This paper will provide a review of the six current literature articles pertaining to the use of ASA as a means of primary prevention for CVD in persons over the age of 40 with modifiable risk factors. Its goal is to enlighten practitioners on the topic of prophylactic ASA usage and help them determine whether or not such therapy may be indicated for the patient sitting in their office.

This review was conducted by searching Primo, PubMed and ProQuest Education. The following terms were used in the search: aspirin primary prevention, aspirin risks, and cardiovascular lifestyle changes. A total of 6 articles were selected and used for the purpose of this review.

Results

The first article selected for this literature review is titled *Aspirin for Primary Prevention—Time to Rethink Our Approach* by Berger et al.[3] In this article, the authors explore the rationale behind the decision to use ASA prophylactically based on measurable outcomes. Many commonly prescribed preventive medications are deemed efficacious based on quantifiable factors which are routinely monitored. The use of statins in the treatment of hyperlipidemia is based on a person's measured cholesterol levels; the use of anti-hypertensive medications in the treatment of hypertension is based on a person's measured blood pressure. However ASA is not prescribed on the basis of one's measurable degree of platelet aggregation, which is how it works as a protective agent against athlerosclerotic plaque formation. To measure platelet aggregability, a clinician would be required to utilize light transmission aggregometry or platelet genetic signature. By determining a person's platelet function, a superior culprit to base the decision of prophylactically prescribing ASA is obtained. This is especially true when it is contrasted to using cardiovascular risk calculators, which is the present

method utilized to guide the decision of prescribing prophylactic ASA. Risk calculators cannot fully account for the profound impact of a person's behavioral habits. For instance, as one starts to exercise, stops smoking and eats healthier foods, their cardiovascular risk declines independent of their usage of ASA. Presently, both light transmission aggregometry and platelet genetic signature are costly and impractical to use in an office setting. Nonetheless, Berger et al suggests that these methods are the most superior, objective means to use when deciding if prophylactic ASA is indicated.[3]

The 3 most of the most commonly cited studies that evaluate the use of ASA in the primary prevention of CVD for persons at risk are *The Aspirin to Reduce Risk of Initial Vascular Events* (ARRIVE) trial by Gaziano et al[1], *A Study of Cardiovascular Events in Diabetes* (ASCEND) trial by Bowman et al[4] and *Aspirin in Reducing Events in the Elderly* (ASPREE) trial by McNeil et al.[5] A brief summary of the findings of each of these studies will be further discussed and are shown in Table 1.

ARRIVE is a large-scale study that evaluates the efficacy of ASA as a means of primary prevention for cardiovascular events in persons with a 10-20% 10-year risk of coronary heart disease who did not have a history of cardiovascular events or bleeding. The ARRIVE trial takes place over seven years and men over the age of 55 and women over the age of 60 are continually enrolled from seven countries. Eligible candidates receive either a 100mg dose daily aspirin or placebo. The primary endpoint is the time to the first occurrence of a cardiovascular event, which included myocardial infarction, unstable angina, stroke, or transient ischaemic attack, or death. The primary finding of the study is that despite the presence of cardiovascular risk factors, such as hypertension, hyperlipidemia and smoking, the use of ASA in the treatment group did not mitigate the incidence of myocardial infarction, unstable angina, stroke, or transient ischaemic

attack, or death. There was however a decrease in cardiovascular related deaths in the treatment group. Thus, a conclusion is drawn that on a global scale, the benefits and risks of a prophylactic ASA should be individually weighed for each patient.[1]

The ASCEND trial by Bowman et al evaluates the effectiveness of a 100mg ASA in the primary prevention of CVD in persons who have diabetes mellitus (DM)[4]. The primary efficacy outcome is the time to first vascular event or death from vascular disease. The primary safety outcome is the first bleeding event. The trial demonstrates that while ASA has great benefits in mitigating primary CVD in persons with diabetes mellitus, this is counterbalanced by its associated bleeding hazard. Thus, while persons with diabetes mellitus are not resistant to the beneficial effects of ASA and benefit from its vascular protection, the bleeding risk it poses limits a universal recommendation for its prophylactic use[4].

The ASPREE trial by McNeil et al[5] assesses the usage of prophylactic ASA in the elderly. Given that the elderly are at increased risk for both CVD and bleeding with certain ethnic populations at increased risk, the ASPREE trial seeks to evaluate the role of ASA in Non-Black or Non-Hispanics over the age of 70 and Blacks and Hispanics over the age of 65 who do not have CVD. Healthy in the context of the ASPREE trial is defined as being free of the following: coronary heart disease, overt cerebrovascular disease, atrial fibrillation, a clinical diagnosis of dementia, clinically significant physical disability, and/or high risk of bleeding or anemia. The trial does not exclude participants with hypertension, dislipidemia, chronic kidney disease, diabetes mellitus, obesity or smoking. Specific trial endpoints are defined as time to acute coronary syndrome or a major hemorrhagic event[5]. The ASPREE trial demonstrated that in the elderly, ASA's risk of bleeding outweighs its cardiovascular benefits and thus recommends against its prophylactic use in said population.

The 5th article evaluated is *The International Polycap Study-3 (TIPS-3)* by Joseph et al; this study compares the efficacy of polypill therapy versus a combination of polypill therapy with ASA in reducing the incidence of cardiovascular events in persons without CVD who are at moderate risk.[6] The study is a double-blind, randomized controlled trial. Polypill therapy in this context includes the use of atenolol, ramipril, hydrochlorothiazide, and a statin. Participants are first assigned to either receive polypill therapy or placebo. Within these 2 groups, they are further assigned to receive ASA or a placebo. Time to major CVD is the primary outcome of the study. The study concludes that polypill therapy with ASA over an average of 4.6 years leads to 31% decrease in cardiovascular events. In the 5731 participants who received ASA alone versus placebo, a 14% reduction in incidence of death due to a cardiovascular cause was observed in the ASA alone group. In the 2850 participants who received polypill plus ASA versus double placebo, a 31% reduction in incidence of death from cardiovascular cause is observed in the polypill plus ASA group. The most common reported adverse events in those who received polypill therapy with ASA was hypotension, dizziness, and cough. In this group, these adverse events were more prevalent than bleeding. Thus, the findings of this study demonstrate that while ASA does increase a person's risk of bleeding, other side effects are more prevalent.[6] It should be noted that the study does not make a specific recommendation on whether or not ASA should be used prophylactically, as this is not its intent.

The 6th article reviewed is titled *Platelet Responses to Pharmacological and Physiological Interventions in Middle-Aged Men with Different Habitual Physical Activity Levels*, written by Lundberg et al.[7] This study assesses the pharmacological response to dual antiplatelet therapy in men who are at varying levels of physical fitness. The intent of this study is to compare the platelet response in untrained, moderately-trained and well trained middle aged

men. Aside from physical activity levels, the study subjects were equivocal in terms of their cardiovascular risk factors and were otherwise healthy. It concludes that dual antiplatelet therapy has a more potent effect on decreasing platelet aggregation via prostacyclin inhibition in well-trained men compared to moderately-trained and untrained men.

Discussion

The six articles used for the purpose of this literature review all draw to a similar conclusion- while the prophylactic role of ASA in preventing CVD should be individualized for each patient, its risks generally tend to outweigh its benefits.

The study by Berger et al highlights that prior to determining whether or not ASA should be used prophylactically for a patient, the use of light transmission aggregometry or one's platelet genetic signature should be used to determine their specific degree of platelet aggregability, which can in turn help determine if the benefits outweigh the risk for a specific patient.[3] This highlights a very important point, as a clinician should be aware of how ASA will biochemically affect a specific patient based on that patient's unique physiologic variations. Regardless of a person's modifiable and nonmodifiable risks, their response to a medication will vary, as no two people are the same. Likewise humans are dynamic, and the changes they make may impact their physiologic response to certain therapies, as was suggested by the study by Lundberg et al.[7] Therefore, there should be measurable endpoints that a clinician routinely monitors in order to determine whether prophylactic ASA is indicated. Further research is needed to determine the precise values for these specific indications.

The ARRIVE trial assigns participants to either a 100mg dose of ASA or placebo.[1] A drawback to the study is that enrolled participants are followed until their last contact, and so it is difficult to determine the long-term outcomes of prophylactic ASA given the varying time frame

each participant participated in the study**.** Enrolled participants also have a large degree of varying comorbidities; these comorbidities are not weighed against the incidence of a cardiovascular event in either the treatment or placebo groups. Thus, while the study recommends that the use of ASA for each patient be individualized based on individual risk factors, not determining which specific risk factors increase a person's risk most for a cardiovascular event makes it difficult for a clinician to practically apply this recommendation. Given the large degree of variance in the comorbidities a person can have that increases their cardiovascular risks, a measurable standard should be established for each person to help predict whether or not using ASA will lead to its risks outweighing its benefits. Other limitations of this study are that aside from smoking cigarettes, lifestyle modifications and behaviors were not recorded or tracked. Lifestyle behaviors contribute to a person's risk, however this risk is dynamic based on the changes that a person makes.[3] Therefore a more convincing recommendation could have been made by the ARRIVE trial had there been more thorough evaluation of these dynamic variables.

In the ASCEND trial, the role of ASA in persons with DM is evaluated.[4] Diabetes mellitus increases a person's risk of CVD and is consequently the largest cause of morbidity and mortality in this population.[8] Thus, given this known risk, it is important to assess how ASA can help mitigate it. Diabetes mellitus is often the endpoint of poor diet, low activity levels, obesity and the respective interactions of these modifiable variables with a person's genetics. While diabetes mellitus can be managed and controlled with medications, there is no cure due to irreversible beta cell failure associated with its pathophysiology.[8] While DM is a risk factor for CVD, the impact it has on cardiovascular health is modifiable to a variable degree. In determining whether or not ASA can be of benefit to this patient population who do not have

known vascular disease, it is important to consider the mechanism of how action of ASA mitigates the pathophysiological implications of DM. Diabetic vascular disease can be divided into microvascular and macrovascular disease, with the former primarily causing a thickening of the capillary basement membrane and the latter accelerating atherosclerosis in large vessels.[9] The pathogenesis of atherosclerosis acceleration is unclear; thus further research is needed to determine the role of an antiplatelet aggregant in the prevention of this etiology.

Elderly persons with comorbidities are both at an increased risk of bleeding and CVD. The ASPREE trial demonstrates that the risk of bleeding in this population specifically outweighs its benefits.[5] This suggests that the risks to benefits ratio of ASA changes as a person ages; what at one age may be beneficial in preventing CVD can later pose greater bleeding threats. Thus, if a person is prescribed a daily ASA, their bleeding risk should be routinely assessed. This can be a time consuming and costly task for both the practitioner and the patient, especially given the lack of a feasible means to accurately do so. Thus, a clinician will likely be forced to rely on their own discretion in making this choice, which is very subjective by nature.

The main argument against using ASA prophylactically pertains to it increasing a person's risk of bleeding, which is demonstrated by multiple trials. However there are other reported side effects of ASA that patients experience which may be more predominant than bleeding, such as hypotension, dizziness, and cough.[6] Depending on a person's comorbidities, these more reported side effects cause the risks to outweigh the benefits in lieu of the increased risk of bleeding. It should also be noted that hypotension and dizziness can increase a person's risk of bleeding related to an increase in the incidence of falls. Falls in persons who have an increased bleeding risk are more likely to suffer from a lethal bleed. Thus, there may be an

indirect correlation here which leads to an increase in a person's morbidity and mortality associated with ASA usage.

The effects that ASA has on a person is dependent on their unique physiology, which includes the degree of their physical fitness. In the study by Lundberg et al[7], the effects of ASA, both the potential good and bad, are amplified in those who exercise regularly. This suggests that in athletic individuals, ASA has a greater antiplatelet effect and greater risk of bleeding. The primary goal of this study is not to assess the use of ASA as a means of primary prevention for CVD, however it provides a valuable comparison of the physiologic response a person has to antiplatelet therapy given their degree of physical fitness. Thus, specific and modifiable lifestyle behaviors impact a person's response to antiplatelet therapy. The study consists of 42 males aged 52 ± 1 year, which is a small population to serve as a basis for a universal recommendation. Still, like the ASPREE trial[5], the findings in the study by Lundberg et al[7] suggest again that a person's response to ASA is a dynamic process; in persons with CVD risk factors, attention should be given to maximizing modifiable risk factors. Still, there is insufficient evidence to determine the physical fitness level at which the use of ASA will be therapeutic and its benefits will outweigh its risk.

As it stands, there is no general consensus for use of ASA as prophylaxis in the primary prevention of CVD in adults older than 40 with risk factors. The risk of bleeding is a large concern, and prophylactic ASA should be avoided in select populations, such as potentially well trained athletes and elderly.[5,7] Certainly the clinician should consider how ASA physiologically alters the patient before them in order to most precisely weigh its specific benefit versus risk profile for the patient before them. While there have been proposed means by which to do this,

further research is needed to determine specific parameters. There is no doubt, however, that ASA can be cardiovascular protective in those with risk factors.

As of April 22, 2022, The US Preventive Services Task Force (USPSTF) updated their 2016 recommendation to conclude with moderate certainty that there is a small benefit to the prophylactic use of low-dose ASA for CVD primary prevention in adults 40 to 59-years-old with a 10% or greater 10-year CVD risk and that this recommendation should be individualized; a patient who is not at an increased risk of bleeding will have a greater benefit from ASA usage (C recommendation).[2] Given the high degree of morbidity and mortality associated with CVD, there is a need for a clinician to prioritize mitigating a person's chance of CVD acquisition, especially in those who are at risk due to both modifiable and non-modifiable risk factors. This update from the 2016 USPSTF recommendation highlights a national recognition of the urgency of the matter, and will hopefully make way for further research to develop pertaining to this topic.

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Table 1: Brief Summary of Findings in: *The Aspirin to Reduce Risk of Initial Vascular Events, A Study of Cardiovascular Events in Diabetes,* and *Aspirin in Reducing Events in the Elderly*

Study	Objective	Inclusion Criteria	Exclusion Criteria	Procedure	Findings
Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE)	Address the benefit of a daily 100 mg enteric coated ASA for prophylaxis against stroke, myocardial infarction and cardiovascular conditions in non-diabetic patients who are at risk	Males over 55 and females over 60 with at least 3 of the following risk factors: high total cholesterol, currently smoking, low HDL cholesterol, hypertension, taking anti-hypertensive therapy & positive family history for CVD	History of a vascular event, currently on antiplatelet therapy, high risk for GI bleed, diabetic	Participants receive a 100mg enteric coated ASA or placebo and are followed until last point of contact with key variables collected every 6 months	ASA lowers the risk of CVD in enrolled participants. There is an increased risk of bleeding, which is mild
A Study of Cardiovascular Events in Diabetes (ASCEND)	To determine if a daily100 mg ASA prevents cancer and CVD in diabetic persons without arterial disease	Men and women over 40 who have diabetes	Clear indications or contraindications to ASA, comorbid predominant life threatening illness	Participants receive a 100mg ASA or placebo and complete routine 6 month adverse effect questionnaires. At ~ 2.5 years, blood and urine samples are collected	There is a 12% reduction in major adverse cardiovascular events in the treatment versus placebo group; conversely there is a 29% increase in major bleeding events in the placebo group compared to the treatment group, primarily GI bleeding
Aspirin in Reducing Events in the Elderly (ASPREE)	To determine if low dose ASA increases the lifespan expectancy in an otherwise healthy elderly person	Non-Black or Non-Hispanic men and women over 70 (or hispanic or blacks over the age of 65) without:	History of coronary heart disease, cerebrovascular disease, atrial fibrillation, dementia, significant physical disability, high bleeding risk, anemia, regular use of another anticoagulant other than ASA, hypertension, medical indication or contraindication for ASA, presence of a comorbidity that would likely result in death in the next 5 years	Participants receive either an enteric coated ASA or placebo with annual adherence assessments	Use of a low dose ASA does not significantly decrease CVD events and results in an increase in intracranial hemorrhage