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ROLE OF ASPIRIN IN PREVENTING CARDIOVASCULAR DISEASE. A SCIENTIFIC REVIEW OF CLINICAL TRIALS.

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ABSTRACT

Aspirin therapy is widely acknowledged as an effective treatment for preventing cardiovascular events that occur after a first incident. Current guidelines recognize the use of aspirin in

preventing cardiovascular events before they occur. This review provides an overview of the important trials involving the use of aspirin and their relevance to current guidelines. It also explores several aspects that can impact the effectiveness of aspirin therapy in preventing cardiovascular disease. We conducted a search on PubMed, covering the period from January 2016 to January 2022, to identify recent clinical studies and guidelines related to the use of aspirin for primary prevention of ASCVD. We limited the studies to randomized, controlled clinical trials. The available evidence strongly indicates that aspirin has a beneficial effect in preventing cardiovascular events in specific demographic groups, both for individuals who have already had such events (secondary prevention) and for those who have not yet experienced them (primary prevention). However, the way in which aspirin is currently being used in practice may not be ideal. As a cost-effective and uncomplicated preventive therapy for cardiovascular disease, the use of aspirin should be thoroughly evaluated in all adult patients at risk. Additional steps, such as patient education, are essential to guarantee its appropriate utilization.
Keywords- Anticoagulant, Aspirin, Cardiovascular, Bleeding risk

Introduction

Aspirin (ASA) is the most commonly prescribed antiplatelet agent. Although the evidence for efficacy of aspirin for secondary prevention of ischemic events in patients with established cardiovascular disease is strong, its role in primary prevention has been subject of controversies over the past decades. Cardiovascular disease (CVD) is a prime cause of mortality around the globe. The demographics of cardiovascular disease differ depending on the patient group. However, certain established risk factors have been found, including diabetes mellitus (DM), hypertension (HTN), obesity, dyslipidemia, and age. Statistics indicate that the occurrence of simultaneous diagnoses of diabetes mellitus (DM), hypertension, and dyslipidemia is consistently increasing among adults. This trend is prompting healthcare providers to reconsider the existing approach to cardiovascular (CV) care. There is a growing focus on tailoring risk reduction strategies to individuals in order to prevent both primary and secondary atherosclerotic cardiovascular disease (ASCVD) occurrences (1).

Although the benefit of aspirin in secondary prevention is well established, its net beneficial effect in persons without known cardiovascular disease is less certain. Because of a generally lower baseline risk, there will be less absolute benefit from aspirin in primary prevention for the same relative risk reduction. On the other hand, the adverse effects of aspirin appear unrelated to thrombotic risk, and hence there will be a lower ratio of benefit to risk for aspirin in primary, compared with secondary, prevention. Although the major effect of aspirin is thought to be in inhibiting thrombosis (2).

Randomized trials have proven that antiplatelet therapy (mainly with aspirin) is effective in reducing the risk of non-fatal myocardial infarction, non-fatal stroke or vascular death among patients with established arterial disease. When used for secondary prevention, the benefit from aspirin substantially outweighs possible harm of therapy. Recent controlled trials have also indicated a favourable riskbenefit ratio for aspirin in primary prevention among persons who are

at higher risk of coronary heart disease (CHD) and who are not at increased risk of bleeding complications (3).

Aim- This review article seeks to conduct a thorough analysis and offer opinion on the outcomes of recently published clinical trials on aspirin prompted prevention of cardiovascular disease. Additionally, it attempts to evaluate the 2019 ACC/AHA guideline recommendations about the use of aspirin for the primary prevention of ASCVD.

Materials and Method

A systematic literature search was performed utilizing the PubMed database to find pertinent publications published from January 2016 to January 2022, employing specific keywords. The selected timeline was intended to encompass literature produced from the introduction of the 2016 USPSTF [United States preventive services taskforce] guidelines to the 2022 ACC/AHA guidelines. The clinical trials identified were restricted to randomized, controlled trials that had a minimum of 100 outcome events. Once the articles were selected for inclusion, their citations were further examined for relevant literature. Additional publications were also reviewed by examining references of published articles, clinical trials, and guidelines.

Discussion

In 2013, the American College of Cardiology (ACC) introduced a web-based and mobile application tool to calculate the likelihood of experiencing an ischemic stroke or myocardial infarction (MI) during a 10-year period for individuals between the ages of 40 and 79. The purpose of this tool wss to assist in making informed decisions on the prevention of atherosclerotic cardiovascular disease (ASCVD) (4). The ACC tool utilizes age, sex, race, blood pressure, cholesterol levels, history of diabetes mellitus, smoking status, and treatment for hypertension to compute the risk. It is important to mention that the ACC tool has the potential to either overstate or underestimate the level of risk for certain racial groups. This tool was employed as a reference in previously published guidelines outlining the utilization of antiplatelet medicines, such as aspirin, for the primary prevention of ASCVD (5).

Previous recommendations for the use of aspirinin primary prevention

The 2018 guidelines from the American Diabetes Association (ADA) suggest that men and women with type 1 or type 2 diabetes who are 50 years or older and have at least one additional risk factor for cardiovascular disease (CVD), such as a family history of early CVD, high blood pressure, abnormal lipid levels, smoking, or albuminuria, may benefit from aspirin therapy (1). Recently conducted clinical trials have examined the safety and effectiveness of low-dose aspirin for preventing cardiovascular disease in persons who have not yet experienced any symptoms. These trials have revealed that in certain individuals who were previously considered suitable candidates for aspirin therapy, the potential risks of taking aspirin may exceed the benefits. In

March 2019, the ACC and American Heart Association published a joint recommendation called the ACC/AHA recommendation on the Primary Prevention of Cardiovascular Disease (2). In the 2019 and 2020 Standards of Medical Care, the ADA has retained their previous stance on the use of aspirin for primary prevention. Nevertheless, there is a strong focus on restricting the use of aspirin to patients who are at a high risk and engaging in a collaborative decision-making process with patients after thoroughly evaluating the potential risks and benefits (6). The European Society of Cardiology (ESC) recently issued comparable recommendations for the use of aspirin in primary prevention among patients with DM. They advise the use of aspirin for individuals at high or very high risk of cardiovascular events, while discouraging its use for those at moderate risk (6).

Recent clinical trials affecting updated recommendations

In 2018, three randomized trials were conducted to evaluate the effectiveness and safety of aspirin for primary prevention. These trials were named ARRIVE, ASCEND, and ASPREE, and they were placebo-controlled. These trials were distinctive because they encompassed populations that are frequently excluded from clinical trials, such as the elderly, individuals with diabetes mellitus, and those at a heightened risk for atherosclerotic cardiovascular disease (ASCVD)(7,8,9). Each of the three clinical studies assessed the effectiveness of a 100 mg dose of aspirin in preventing primary cardiovascular events in patients who were deemed to have an elevated cardiovascular risk based on their initial characteristics. The ARRIVE investigation was a global, multicenter, randomized, double-blind, placebo-controlled trial conducted in individuals who were deemed to have a moderate cardiovascular risk by the investigators due to the presence of certain cardiovascular risk factors. This study examined the main measure of effectiveness in both the intent-to-treat (ITT) and per-protocol population. The per-protocol analysis consisted of patients who adhered to the study drug at a minimum of 60% throughout the whole clinical trial. ASCEND was a clinical research that followed a double-blind, randomized, controlled design. The experiment included patients who were at least 40 years old and had either type 1 or type 2 diabetes mellitus. These patients did not have a clear reason to use aspirin, as indicated by previous studies. Prior to enrolling patients in the trial, a two-month run-in phase was conducted to guarantee adherence. This phase was single-blind, meaning that the patients were not aware of the treatment they were receiving. ASPREE was a clinical trial conducted on older people living in the community who did not have a known history of ASCVD, dementia, or physical handicap. The experiment was randomized, double-blind, and placebo-controlled. The period of follow-up varied, with a median of 4.7 years in the ASPREE study and a mean of 7.4 years in the ASCEND study (7,10).

Cardiovascular Outcomes

The primary outcome of each trial was a composite of CV endpoints, with the exception of the ASPREE study, in which CV endpoints were a secondary outcome. Ultimately, ASCEND was the only trial to find a reduction in the primary composite endpoint of serious vascularevents, defined

as MI, nonfatal stroke, transient ischemic attack (TIA), or death from vascular cause in the aspirin group compared to placebo in patients with DM [658 events, 8.5% (Aspirin) vs. 743 events, 9.6% (placebo). This benefit was demonstrated primarily in the first 5 years of therapy. Aspirin use was also associated with a significant reduction in the composite of any serious vascular event or revascularization, a predefined secondary end point [833, 10.8% (Aspirin) vs. 936, 12.1% (placebo)]. Conversely, ARRIVE and ASPREE found no significant differences in the composite CV endpoints between groups. Further, there were no subgroups in which aspirin use was favored for the primary CV outcome in the ASCEND or ASPREE trials. Subgroup analysis of ARRIVE was consistent with the overall findings, except for those who fell within the lowest CV risk quartile, defined as an ASCVD risk of 10.5% or lower, in whom aspirin was favored in the ITT population (11,12,13,14).

Aspirin was not found to significantly reduce the incidence of any of the individual components of the composite CV endpoints in either the ASCEND or ASPREE trials. However, in the ARRIVE trial, aspirin use was associated with a significantly lower incidence of MI and non-fatal MI in the per-protocol group. Across all three studies, no statistically significant difference was seen in stroke incidence in patients receiving aspirin therapy compared to placebo.

Bleeding Outcomes

The ARRIVE trial monitored bleeding events according to the Global Use of Strategies to Open Coronary Arteries (GUSTO) criteria, which grades hemorrhagic events as mild, moderate or severe. In the ARRIVE trial, the occurrence of gastrointestinal (GI) bleeding was significantly higher in the intervention ver- sus placebo group. Most instances of GI bleeding were graded as mild according to GUSTO criteria. Of note, investigators acknowledged that there was a higher incidence of bleeding and adverse events considered to be clinically relevant, such as GI bleeding and epistaxis, in the aspirin group compared to placebo.

The ASCEND and ASPREE trials utilized a composite bleeding endpoint to analyze bleeding events. In the ASCEND trial, patients who received aspirin experienced a significantly higher rate of major bleeding, defined as a composite of intracranial hemorrhage, sight-threatening bleeding in the eye, GI bleeding, or any other serious bleeding. GI bleeding was the most common bleeding event, and the incidence was more common in patients receiving aspirin compared to placebo. A 5-year vascular risk was calculated at baseline for each patient based on age, sex, smoking status, systolic blood pressure, BMI, duration of DM, A1C and assignment to intervention group. Patients were classified as having less than 5%, 5 to 10%, or greater than 10% 5-year risk of a serious vascular event. Ultimately, there was no clear evidence that vascular score had a significant impact on serious vascular events or major bleeding (13,14).

In ASPREE, aspirin use was associated with a significant increase in major hemorrhage, defined as a composite of hemorrhagic stroke, symptomatic intracranial bleeding, or clinically significant extracranial bleeding. Bleeding events were noted to occur at progressively increasing rates throughout the duration of the trial, inferring that the risk of bleeding is maintained throughout the duration of aspirin use (15).

New updated guidelines

Recent guideline recommendations for using low-dose aspirin for primary prevention of stroke and MI are available from theADA, ESC and ACC/AHA. In March 2019, the ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease was published. Compared to previous recommendations, the ACC/AHA guideline is reflective of the new evidence demonstrating limited benefit of aspirin for primary prevention of ASCVD and a significant increased risk of major bleeding. As a result, fewer patients are recommended to receive aspirin therapy than previously recommended by the USPSTF (16).

As with other CV guidelines, modulation of modifiable ASCVD risk factors, including HTN, DM, dyslipidemia, and smoking, should be prioritized in all patients. Lifestyle modifications and the use of medications that have proven safe and effective for primary prevention, namely statins, should be first line therapy. In patients, 40–70 years of age, who are at high risk of ASCVD, and are unable to control these ASCVD risk factors despite optimal therapy, low-dose aspirin (75–100 mg daily) may be indicated. However, this remains a Class IIb (weak) recommendation, and should be considered on a case by case basis. Special consideration must be given to both bleeding risk, as well as presence of CV risk-enhancing factors, such as an elevated coronary artery calcium (CAC) score or family history of premature ASCVD. The inability to control CV risk factors with traditional therapy may provide a compelling argument to initiate low-dose aspirin therapy. Use of aspirin by an individual patient should be considered after a provider-patient discussion of risk versus benefit of therapy.

Per ACC/AHA recommendations, aspirin therapy should be used with caution in patients greater than 70 years of age, as evidence demonstrates that the risk of bleeding outweighs the benefit of ASCVD prevention. Furthermore, aspirin therapy should be avoided for the use of primary prevention in any patient considered to be at an increased risk of bleeding. Pertinent risk factors for bleeding include, but are not limited to, age greater than 70 years, previous or current history of major bleeding, GI bleed, peptic ulcer disease (PUD), thrombocytopenia, coagulopathy, and CKD (17). Concurrent use of medications that increase bleeding risk, such as non-steroidal anti-inflammatory drugs (NSAIDs), steroids, and anticoagulants may also place the patient at an increased risk of bleeding.

Discussion

These three notable clinical trials have questioned previous guidelines for the use of aspirin for primary prevention of ASCVD and shed new light on aspirin use, especially in patients who are considered to have a higher risk of ASCVD. Ultimately, the benefit of primary ASCVD prevention was not demonstrated across study populations, and was outweighed by the increased bleeding observed. These findings indicate that aspirin is likely not appropriate for primary prevention in a majority of patients due to its lack of efficacy and accompanying risks (11, 12,13).

The only trial to show a statistically significant reduction in composite CV events was ASCEND. However, no individual components of the composite outcome were significantly reduced with

aspirin use. Further, this reduction in CV risk was accompanied by increased bleeding events. Patients who received aspirin for the duration of this study experi- enced a 12% reduction in the risk of serious vascular events, and a 29% increase in the risk of major bleeding compared to placebo. Based on trial data, the number needed to treat (NNT) for the primary CV outcome over 7.4 years is 91, while the number needed to harm (NNH) for major bleeding is 112. While aspirin did demonstrate efficacy in reducing CV events in this patient population, this benefit is accompanied witha significant bleeding risk, primarily GI bleeding (17,18).

Contrary to ASCEND, the ARRIVE and ASPREE trials did not demonstrate a significant reduction in CV events with aspirin use compared to placebo. However, there was a significant reduction in fatal or non-fatal MI with aspirin use compared to placebo in the per-protocol group in the ARRIVE trial, although only a small number of events occurred. There were no significant differences between intervention and placebo groups in the per-protocol population that could have contributed to this difference. In the per-protocol group, compliance was self- reported by patients, which may have led to an overestimate in compliance rates. However, this is typically seen in clinical practice, and does accurately mimic a standard patient population, making the results generalizable. Interestingly, due to the lower than expected event rate, the original primary efficacy endpoints were changed, becoming time-driven versus event-driven. The follow-up study period was also extended in an attempt to capture increased CV events. The low event rate may be contributed to many factors, including exclusion of patients considered to be at high risk of CV events such asthose with DM, or concomitant use of cardioprotective medications(18).

Aspirin use was not associated with a decreased incidence of stroke in any of the trials. Further, aspirin use did not reduce CV death or all-cause mortality. However, ASPREE demonstrated a significant increase in all-cause mortality with aspirin use. These findings are consistent with a 2009 meta-analysis performed by the Antithrombotic Trialists' (ATT) Collaboration, which found that aspirin use for primary prevention did not significantly impact the incidence of stroke or vascular mortality.

With respect to bleeding outcomes, all three trials demonstrated a significantly higher incidence of bleeding events with aspirin use, primarily GI bleeding. In the trials which demonstrated increased bleeding with aspirin, GI bleeds were by far the most common. However, these bleeding events carry a relatively low risk of mortality, weighing into the risk vs. benefit decision of starting aspirin to prevent a potentially fatal ASCVD event. Further, the number of bleeding events were small across trials when compared to CV events observed. This further demonstrates the need for individualizing aspirin therapy and weighing the relatively low bleeding events versus the potential to prevent a serious CV event (20).

In 2019, a meta-analysis evaluating CV events and bleeding outcomes associated with aspirin use for primary prevention across 13 trials, including the three discussed in this review article, was published. The analysis-combined data from a total of 164,225 patients. Ultimately, aspirin use resulted in a statistically significant reduction in the composite CV out- come of CV death, nonfatal MI, and nonfatal stroke compared to placebo. However, aspirin use was also associated with an increased risk of major bleeding events when compared to placebo. Similarly, a case control analysis comparing low dose aspirin and placebo showed increased risk of non-fatal upper and

lower GI bleed in patients receiving aspirin for primary prevention of CV disease (21). These analyses demonstrate a delicate balance of risk versus benefit when considering the use of aspirin for primary prevention.

Suggestions

Recently published studies demonstrate that many individuals take aspirin without first discussing with their healthcare provi der, which places patients at an increased risk of adverse effects and drug–drug interactions. Aspirin is easily accessible to all patients as it is available as an over-the-counter (OTC) product, that can be purchased without a prescription. A report utilizing data from the 2017 National Health Interview Survey (NHIS) assessed aspirin use among a sample of 14,328 patients over the age of 40 without CV disease (11). Researchers found that 23.4% of patients reported taking daily aspirin for primary prevention of CV disease. Of these patients, 22.8% did so without a physician recommendation. Furthermore, nearly half of adults aged 70 years or older, without diagnosed CV disease, reported taking aspirin for primary prevention. The results of this survey highlight the overuse of aspirin for primary prevention of ASCVD in the general population and the need for proper evaluation of aspirin therapy by healthcare providers in those patients receiving aspirin for primary prevention of ASCVD.
Despite it being available OTC, unsolicited aspirin use may result in significant health risks, especially in those already deemed to have high bleeding risk. Aspirin use by individual patients is difficult to track using medical informatics, as aspirin use is not currently available through most insurer databases as there is no pharmacy benefit plan associated with its use. Further, aspirin is often initiated by patients without consultation with a healthcare provider.

Aspirin use should be limited in primary prevention given not only its increased risk of bleeding events, but perhaps more importantly, its limited proven efficacy in preventing CV events and CV mortality. Per the 2019 ACC/AHA recommendations, aspirin should only be considered in patients at high CV risk, defined as 10-year ASCVD risk $\geq$ 20%, who cannot adequately control CV risk factors such as blood pressure, blood glucose, hemoglobin A1C, smoking cessation, and/or cholesterol levels with lifestyle modifications and pharmacotherapy interventions. Modulation of modifiable ASCVD risk factors and treatment of comorbidities linked to ASCVD should be prioritized before initiation of aspirin. Those who are on optimal therapy for these comorbid conditions and continue to remain at high CV risk should be considered candidates for aspirin therapy in the absence of risk factors for bleeding (6). For patients not at high risk, this deci-sion must be made collaboratively between the patient and provider. Thus, the recommendations leave much room for patient-specific decision making and clinical judgment. The 2019 ACC/AHA guideline recommends consideration be given to risk-enhancing factors such as family history of premature CHD, cigarette smoking, and, if measured, CAC score, elevated high-sensitivity C-reactive protein, elevated lipoprotein (a), elevated apolipoprotein B, and ankle brachial index < 0.9 (12). Taking these recommendations into considera-tion, only a small number of patients are likely to be appro- priate candidates for aspirin therapy. Ultimately, aspirin should be considered a last-line therapy for primary prevention.

While tailoring clinical decision making to the individual patient is paramount to clinical practice, too much ambiguity in the guideline recommendations may lead to vastly different interpretations of the expert recommendations, and thus inconsistencies in care. A major barrier with implementing these recommendations are that the risk of bleeding and ASCVD are often highly correlated, meaning patients with a high CV risk tend to also have a high bleeding risk. It is evident that the 10-year ASCVD risk score alone is not suffi- cient to predict benefit from aspirin for primary prevention; thus, there exists a need for developing a new risk stratifica- tion tool which also accounts for bleeding risk.

An aspirin bleeding risk calculator, developed by Selak andcolleagues, aims to help clinicians quantify a patient's bleedingrisk, by presenting the estimated number of major bleeds causedversus cardiovascular events prevented by aspirin in the next fiveyears (21). This tool evaluates gender, age, ethnicity, deprivation, smoking status, relevant clinical history, systolic blood pressure,cholesterol and medication use within the last 6 months. Thiscalculator is not appropriate for patients less than 30 years orgreater than 75 years, patients with a history of CVD, heart failure, renal insufficiency, or patients currently receiving aspirin therapy. Additionally, this tool was developed and studied in New Zealand, thus its generalizability to the US population isyet to be determined. However, it may be a useful tool in helping clinicians more clearly identify patients who would benefit fromaspirin therapy.

While updated guideline recommendations note that aspirin should not be initiated for primary prevention in indi- viduals greater than 70 years of age, evidence is not clear as to whether aspirin should be discontinued upon age 70 in those already receiving therapy. Individuals greater than 70 years ofage are at an increased bleeding risk, and results from theASPREE trial revealed bleeding complications were increased in those receiving aspirin. Furthermore, aspirin was associatedwith an increase in all-cause mortality. For this reason, aspirin should be used with caution for primary prevention in this agegroup, and serious consideration should be given to disconti- nuing aspirin for primary prevention.

Inappropriate aspirin use increases the risk of adverse events, including major or serious bleeding, and drug–drug interactions. Recent clinical trials demonstrate minimal benefit of ASCVD prevention with aspirin use, and given that bleedingrisks may outweigh the CV benefit, a decreased number of patients than previously thought will be deemed candidates for aspirin therapy. Recent data and guidelines support de- escalation of aspirin therapy for primary prevention, limiting its use to patients at higher risk for ASCVD events. Further,aspirin de-escalation should be considered in those at a highbleeding risk, especially in patients coprescribed an anticoagulant. Therefore, it is crucial that ASCVD risk and aspirin use be discussed between patients and healthcare professionals frequently. We suggest that clinicians add a question aboutregular aspirin use and rationale to their medication histories. Inappropriate aspirin use may also be addressed by health systems through patient electronic health records, proper med- ication reconciliation, and attempts at de-escalation whether through face-to-face encounters or mailed information. When approached by healthcare providers, patients may be confused due to mixed messages about benefits and risks in the media. Community pharmacists can place signs or placards near theaspirin stock encouraging a dialogue. Pharmacists, with their trusting patient relationships and accessibility, are uniquely positioned to

impact aspirin use ensuring optimal benefit-to- risk for primary prevention.

Conclusion

Aspirin is commonly prescribed among middle and older-aged adults, however, there is still potential to optimise use of it and other antithrombotics in those with existing cardiovascular disease. Most aspirin prescriptions are for those without previous cardiovascular disease. Although prescribing is targeted at those with higher cardiovascular risk, prescribers should reconsider starting aspirin for primary prevention for patients where risks are likely to outweigh benefits, and whether current users should continue on aspirin.

With rapidly evolving novel antithrombotic and preventive therapies, our ability to modify cardiovascular risk factors has improved. With that, the role of aspirin in both primary and secondary prevention in the modern era also continues to evolve.

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