Indian Heart Journal 71 (2019) 113–117

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Review Article

Aspirin for primary prevention: Is this the end of the road?

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ARTICLE INFO

Article history:
Received 20 December 2018
Accepted 15 April 2019
Available online 2 May 2019

Keywords:
Aspirin
Primary prevention
MI-bleed trade-off

ABSTRACT

Aspirin is one of the oldest and most commonly used cardiovascular drugs. Despite there being high-quality evidence supporting the use of aspirin for patients with known cardiovascular disease, a definitive consensus regarding its use for patients at risk for cardiovascular disease (and without established cardiovascular disease) has never been reached. Many randomized control trials have produced conflicting results, and consequently, society guidelines have issued differing recommendations. Three major trials were published in 2018, which supplement the existing data on aspirin's role in primary prevention and provide further guidance on this contentious issue. This article reviews the history of aspirin through the last two decades, with special emphasis on these new trials.

1. Introduction

Aspirin remains one of the wonder drugs in the field of cardiology. The use of salicylates (derived naturally from plants) as pain relievers has been described since the times of first documented medical writings.[1] Credit for the synthesis of acetylsalicylic acid (ASA), as we know it today, goes to Dr. Felix Hoffman, who in 1897, first described its chemical formulation.[2] The antithrombotic effects of aspirin were described by Lawrence Craven, and decades later, this laid the foundation for the use of aspirin in prevention of myocardial infarction (MI) and other cardiovascular events.[3] Aspirin is the cornerstone of modern day therapy for patients who have suffered a major cardiovascular event (i.e., secondary prevention).[4]

Unlike its established role in secondary prevention, the status of aspirin for primary prevention has remained an area of intense debate. One of the first randomized controlled trials which described a positive role for aspirin in MI prevention in young healthy adults was the Physicians Health Study Research Group, which showed a reduction in the risk of MI without an effect on the risk of stroke or death.[5] A similar study was conducted in healthy women which suggested a different effect of aspirin in women compared with men when used for cardiovascular prevention.[6] The Women Health Study Group suggested that aspirin use in healthy women reduced the rate of stroke while causing no reduction in the risk of MI. Since then, numerous trials and meta-analyses have been published; none of which have been able to put this debate to rest. This is reflected in the discordance between the guidelines issued by different organizations over the years and even by the same organizations from time to time (Table 1).

This question has again been brought to the fore by the recent publication of 3 major trials on the role of aspirin in primary prevention. In this review, we summarize the major trials and guidelines which looked at aspirin's role in primary prevention over the last 2 decades. In addition, we discuss the three recently published trials.

2. Journey of aspirin over the past two decades

The first decade of the 21st century saw guidelines from two major Societies. The ADA guidelines in 2003[7] were followed by the AHA guidelines in 2007[8]; both of which gave a go-ahead to the use of aspirin for primary prevention in patients with diabetes (Table 1). These guidelines, however, were not based on any major trials conducted in the diabetic population. Results were drawn mainly from trials conducted in healthy populations,[6,9] or in

Abbreviations: ASA, Acetylsalicylic Acid; MI, Myocardial Infarction; ADA, American Diabetes Association; AHA, American Heart Association; HR, Hazard Ratio; CI, Confidence Interval; MACE, Major Adverse Cardiac Events; ESC, European Society of Cardiology; FDA, Food and Drug Administration; USPSTF, United States Preventive Services Task Force; NNT, Number Needed to Treat; NNH, Number Needed to Harm.

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[1] These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

https://doi.org/10.1016/j.ihj.2019.04.001

Table 1
Guidelines on role of aspirin for primary prevention by various organizations over the last 20 years.

Guideline-releasing body	Year	Recommendation on aspirin for primary prevention	Statement
ADA[7]	2003	Use in diabetics	Recommended use of low-dose aspirin (75–100 mg) for diabetic patients who were considered to be at high risk.
AHA[8]	2007	Use in diabetics	Recommended aspirin therapy (75–162 mg/day) as a primary prevention strategy in those with diabetes at increased cardiovascular risk, including those >40 years of age and with additional risk factors (family history of cardiovascular disease (CVD), hypertension, smoking, dyslipidemia, or albuminuria).
ESC[19]	2013	Do not use	Recommended against the use of aspirin for primary prevention of cardiovascular diseases in general. Its use in diabetic population was to be considered on individual basis as per these guidelines.
FDA[20]	2014	Do not use	Stated that the benefits associated with the use of aspirin for prevention of MI and stroke in patients who did not suffer from cardiovascular disease was doubtful at best and was associated with increased bleeding risk. It advised against the use of aspirin in similar settings.
USPSTF[21]	2016	Use in specific population	Recommended the use of aspirin for primary prevention in select group of individuals—use of aspirin for primary prevention in people aged 50–59 years with a ≥10% 10 year CVD risk, with a life expectancy of ≥10 years, who were willing to take aspirin for ≥10 years, and who were not at an increased risk of bleeding (Class B recommendation). Use of aspirin in similar group of patients except those aged 60–69 years (Class C recommendation).

ADA, American Diabetes Association; AHA, American Heart Association; ESC, European Society of Cardiology; FDA, Food and Drug Administration; USPSTF, United States Preventive Services Task Force.

hypertensives,[10] or situations where aspirin was being used for secondary prevention.[11] These recommendations were influenced by several studies which suggested that the risk of cardiovascular events among diabetics was similar to those who had previously suffered a myocardial infarction.[12] However, data reported in subsequent years indicated that diabetes conferred only a modest increase in risk.[13]

Major trials performed in the diabetic population were published in 2008. The first of these was the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) study[14]; in which, more than 2500 diabetic patients were randomized. There was a 20% reduction in the primary outcome (composite of fatal or nonfatal ischemic heart disease, fatal or nonfatal stroke, and peripheral arterial disease), which was not statistically significant. Although aspirin managed to reduce fatal coronary and cerebrovascular events, there was no reduction in nonfatal events. There was no significant difference in the composite of bleeding outcomes. Overall, low-dose aspirin did not reduce the risk of cardiovascular events.

The second trial involving a diabetic population (with an ankle-brachial index (ABI) <1.0) was the prevention of progression of arterial disease and diabetes (POPADAD) study.[15] Despite following up patients for seven years, this trial failed to show any benefit of aspirin. Bleeding outcomes were also similar and were not affected by the use of aspirin.

One of the landmark publications concerning aspirin's role in primary prevention was the antithrombotic trialists' (ATT) collaboration meta-analysis in 2009.[16] They reviewed 6 major primary prevention trials, including about 95,000 patients. There was a 12% relative reduction in the primary composite outcome with aspirin (0.51% vs 0.57% per year, $p = 0.0001$), which was primarily driven by a significant reduction in nonfatal MIs (0.18% vs 0.23% per year, $p < 0.0001$). The stroke and vascular mortality rates did not differ. Rates of major GI and extracranial bleeding were significantly increased by aspirin (0.10% vs 0.07%, $p < 0.0001$). They concluded that the net benefit of aspirin could not be ascertained in view of the advantageous effects on thrombotic events being counter balanced by an increase in the major bleeding event rates.

A couple of years later, a trial similar to the POPADAD study was published, where role of aspirin was tested in people with low ABI; except here, instead of diabetics, the general population was screened.[17] After a mean follow-up of more than 8 years and studying close to 29,000 patients without preexisting cardiovascular disease, it was seen that the use of aspirin did not reduce the number of vascular events (composite of initial fatal or nonfatal coronary event or stroke or revascularization). Aspirin increased the rate of major hemorrhage resulting in hospitalization, although not by a statistically significant margin.

During the same period, another study which looked at the role of aspirin for primary prevention in the general population was the Japanese Primary Prevention Project[18] This study recruited elderly patients (>60 years) with ≥1 cardiovascular risk factors. More than 6 years of follow-up of more than 14,000 patients showed that low-dose aspirin (100 g/day) did not reduce the primary outcome (composite of cardiovascular death, nonfatal stroke or nonfatal MI) (hazard ratio [HR], 0.94, 95% confidence interval [CI] 0.77-1.15). In fact, aspirin significantly increased the risk of extracranial hemorrhage requiring transfusion or hospitalization (HR 1.85, 95% confidence interval [CI] 1.22–2.81).

Drawing evidence from the ATT collaboration meta-analysis and these subsequent trials, the ESC, in 2013, recommended against the use of aspirin for primary prevention of cardiovascular diseases.[19] Along the same lines, a year later, the Food and Drug Administration (FDA) released an advisory against the use of aspirin in similar settings (Table 1).[20]

The pendulum-like swing in the advisories regarding aspirin continued, with the United States Preventive Services Task Force (USPSTF) recommending the use of aspirin for primary prevention in a select group of individuals in 2016 (Table 1).[21] This was based on meta-analyses conducted especially for the USPSTF evaluating the benefits[22] and harm[23] resulting from the use of aspirin for primary prevention. These suggested a beneficial effect of aspirin on MI prevention at low (100 mg) dose, along with a simultaneous increase in the risk of major gastrointestinal bleeding. The fact that the USPSTF looked at the role of aspirin in preventing both cardiovascular disease outcomes as well as prevention of cancers may have contributed to its favorable recommendation.

A 10-year follow-up of the original JPAD study[14] was published in 2017.[24] Building on the previous results, no beneficial effect of low-dose aspirin in reduction of cardiovascular events (HR 1.14; 95% CI 0.91–1.42) was found even after 10 years. Gastrointestinal (GI) bleeding was increased significantly (2% vs 0.9%, $p = 0.03$) with no significant effect on rates of haemorrhagic stroke.

A timeline of the role of ASA in primary prevention is presented in Fig. 1.

3. Aspirin in 2018

Two major trials were discussed at the ESC Congress, 2018, and were simultaneously published.[25,26] Compared with most of the

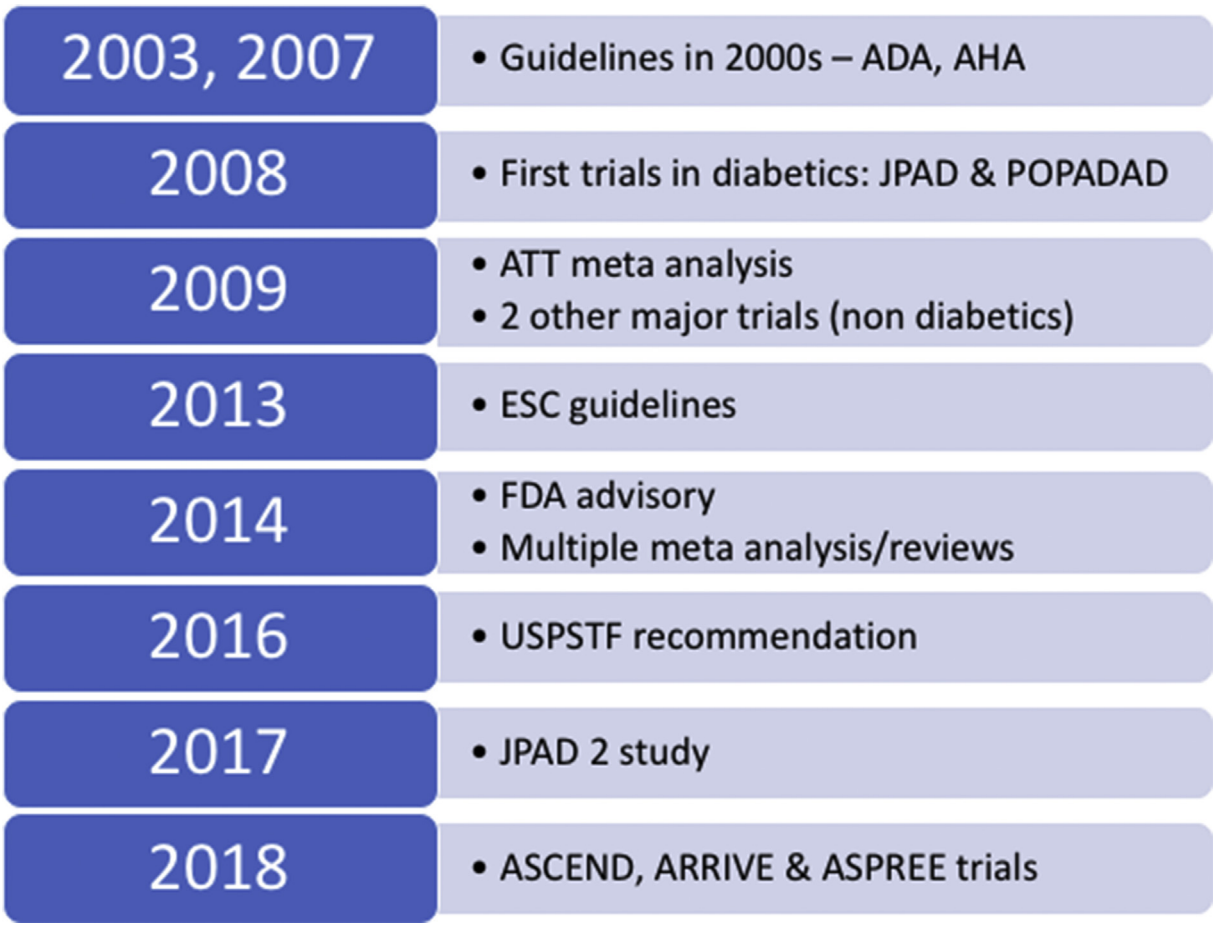

Fig. 1. Timeline of the role of ASA in primary prevention. ADA, American Diabetes Association; AHA, American Heart Association; ESC, European Society of Cardiology; FDA, Food and Drug Administration; USPSTF, United States Preventive Services Task Force; JPAD, Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; ATT, antithrombotic trialists; POPADAD, prevention of progression of arterial disease and diabetes.

previous studies which included patients at a low baseline risk for developing cardiovascular disease, these trials included populations at moderate risk.

A study of cardiovascular events in diabetes (ASCEND)[25] was a randomized, parallel-group, 2x2 factorial trial conducted in the United Kingdom, which recruited more than 15,000 diabetics aged ≥40 years without any cardiovascular disease at baseline, and followed them up for a mean of 7.4 years. There was a significant reduction in the cardiovascular event rate which came at the cost of increased bleeding. The primary efficacy outcome, occurrence of the first serious vascular event (MI, stroke or transient ischemic attack, or death from any vascular cause, excluding any confirmed intracranial hemorrhage), was significantly reduced by aspirin (rate ratio, 0.88; 95% CI, 0.79–0.97). This was associated with a simultaneous increase in the primary safety outcome, the first major bleeding event (intracranial hemorrhage, sight-threatening bleeding event in the eye, gastrointestinal bleeding, or other serious bleeding)—rate ratio, 1.29; 95% CI, 1.09–1.52. Among the secondary outcomes, there was no reduction in the incidence of GI cancer. The absolute risk reduction was 1.1% compared with the absolute increase in bleeding events by 0.9%. Therefore, for every 1000 such patients treated with aspirin for 7.4 years, 11 serious vascular events would be prevented, at the cost of 9 major bleeds: number needed to treat of 91 and number needed to harm of 112.

In exploratory landmark analyses performed at varying time points during follow-up, it was found that most of the benefit due to aspirin accrued within the first 5 years of its use, with attenuation of benefit beyond that (HR of 0.74 at 3 years vs 1.02 at 7 years). However, a similar reduction was not seen in the major bleeding rates (HR of 1.32 at 3 years vs 1.29 at 7 years). In addition, the effect of aspirin did not appear to be modulated by baseline cardiovascular risk. Although the total number of cardiovascular events prevented increased as baseline risk increased, this was accompanied by an equivalent increase in the bleeding events (number of events per 5000 person-years in the aspirin group in average 10-year risk groups of <5%, 5–10%, >10%: benefit rate of 6.1 ± 4.2, 13.4 ± 6.3, 11.3 ± 14.3 vs major bleeding rate of 2.8 ± 2.6, 8.9 ± 3.2, 9.6 ± 7.5, respectively). There was no reduction in all-cause mortality with aspirin use.

In contrast to ASCEND, the use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE) study[26] excluded diabetic patients and those at high risk of bleeding. More than 12,000 patients were randomized and followed up for a median of 60 months. The primary outcome (composite of time to first occurrence of cardiovascular death, MI, unstable angina, stroke, or transient ischemic attack) was not significantly different between the two groups (HR 0.96; 95% CI 0.81–1.13). None of its components were significantly different in the two arms as per the intention to treat analysis. However, the risk of MI was significantly reduced by aspirin in the per-protocol analysis (HR 0.53, 95% CI 0.36–0.79). Similar to ASCEND, the ARRIVE also showed no mortality reduction, and most of the benefit due to aspirin occurred early on and reduced over time. Despite the exclusion of patients at high bleeding risk, the rate of

gastrointestinal bleeding was higher with the use of aspirin (HR 2.11; 95% CI 1.36–3.28).

This study was limited by lower than expected event rates (17.3% vs <10%) and low compliance rates (evidenced by a significant difference between intention to treat vs per-protocol analysis). The primary composite outcome was modified during the study (to include transient ischemic events and unstable angina). The intention was to account for patients whose need for aspirin changed from primary prevention to secondary prevention because of occurrence of any of these events. This did not have an impact on the final analysis, and the results of the original end point were similar to those obtained from the redefined end point.

Other than the inclusion criteria differences, ARRIVE differs from ASCEND with respect to the components of the primary outcome, a larger number of cardiovascular events, and fewer bleeding events.

In the elderly (≥70 years age), the utility of aspirin for primary prevention was studied in the aspirin in reducing events in the elderly (ASPREE) trial in more than 19,000 patients over a median of 4.7 years.[27–29] There was no difference in the primary outcome (composite of death, dementia, or persistent physical disability). Neither any of the secondary outcomes (individual parameters which constituted the primary composite) nor the rate of cardiovascular disease was different between the two groups.

Surprisingly, the all-cause mortality was increased (although this was not statistically not significant) in the aspirin group. Majority of these additional deaths in the aspirin arm were cancer-related deaths (1.6 extra deaths per 1000 person years). The rate of major hemorrhage was significantly increased with aspirin (HR 1.38; 95% CI, 1.18–1.62). There were 2.4 extra serious bleeding events per 1000 person years of exposure.

4. Weight-adjusted aspirin dosing

Recent data suggest that there may be a significant interaction between aspirin dose and body weight on the beneficial and harmful effects of aspirin.[30] In a meta-analysis involving more than 117,000 patients spread across ten primary prevention studies, it was found that low-dose aspirin (75–100 mg) benefits patients weighing less than 70 kg, whereas the higher dose aspirin is more beneficial in heavier patients. The notion that one dose fits all notion may not hold true for aspirin, in the light of these results. This has given rise to an interesting hypothesis of weight-based dosing of aspirin which is likely to influence how similar studies using aspirin will be planned in the future. The interaction of body weight with aspirin dosing: a patient-centric trial assessing benefits and long-term effectiveness (ADAPTABLE) is an ongoing trial of secondary prevention which is testing different doses of aspirin (81 mg vs 325 mg) and will possibly shed some more light on this issue.[31]

5. Aspirin for primary prevention: the end of the road?

Most patients, particularly those living in low and middle income countries, currently do not receive treatments with proven benefits.[32] Aspirin has a neutral, if not adverse, benefit-risk trade-off when used for primary prevention and, therefore, should not be a priority in this setting. This adverse benefit-risk trade-off is reflected in recent trends indicating a reduction in the use of aspirin for primary prevention in the United States.[33]

Another consideration which should guide aspirin use for primary prevention is patient preference. In general, major cardiovascular events are weighed against major bleeding events when assessing the benefit-risk trade-off with aspirin. However, patients may place greater value over preventing cardiovascular events than incurring bleeding, or vice versa. Studies exploring patient preference regarding the use of oral anticoagulants for stroke prevention in AF suggest that patients' preferences vary depending on the trade-off between the risk of stroke and risk of bleeding.[34] The 'concept of loss aversion', that is, a preference to avoid loss over gaining benefits, suggests that patients are likely to avoid risk of a bleed (especially a disabling intracranial bleed), over prevention of a potential future MI.[35] Nevertheless, patient preference may depend on other considerations such as cost and cultural attitudes. These are best addressed in the doctor-patient conversations before making a decision regarding the use of aspirin for primary prevention.

Finally, another unanswered question is about the potential for prevention of aspirin-induced bleeding. In the ASCEND study, GI bleeds were the most common major bleeds (41.3%), and only one-fourth of the patients were on proton pump inhibitors (PPIs). There is supporting evidence for reduction in peptic ulcer disease and its complications by the use of PPIs.[36] However, the wide spread use of PPIs comes with its own set of disadvantages, most prominent being the nephrotoxicity.[37] Whether an increased use of PPIs would have led to a beneficial decrease in major bleeding in the setting of primary prevention by aspirin is speculative.

The deidentified data of the ASCEND trial will be soon be released for meta-analysis by the ATT collaboration group, and given that all the 3 recent studies are concordant, it is likely that the lack of benefit of aspirin for primary prevention will be reinforced, and become incorporated into guidelines. For now, it is best to avoid the use of aspirin routinely for primary prevention.

Grant support

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

All authors have none to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2019.04.001.

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