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Aspirin for the Primary Prevention of Cardiovascular Disease: In Need of Clarity

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Abstract Aspirin remains one of the most extensively studied cardiovascular medications in the history of medicine. However, despite multiple, well-designed, large randomized controlled trials evaluating the potential of aspirin to prevent cardiovascular events in individuals without known cardiovascular disease (CVD), the role of aspirin in primary prevention is currently unclear. The initial aspirin trials included largely low-risk individuals with primary outcomes mostly focused on myocardial infarction (MI) and stroke, and showed a significant reduction in these CVD outcomes, especially MI. The more recently conducted trials have focused on older, higher CVD risk populations with high rates of lipid-lowering and antihypertensive medications use. These studies have used broader CVD outcomes as their primary end points and have failed to show a significant benefit of aspirin therapy in primary prevention. The exact reasons for the lack of efficacy in these recent trials are unclear but may be related to low rate of atherothrombotic events relative to other CVD events in the populations studied. Four large randomized controlled trials are currently underway which should provide some clarity in determining the optimal use of aspirin in the primary prevention of CVD.

Keywords Aspirin · Primary prevention · Cardiovascular disease

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Introduction

Platelet activation and subsequent arterial thrombosis, triggered by atherosclerotic plaque rupture, has long been understood to be directly responsible for a substantial portion of cardiovascular disease (CVD) events and deaths, including the majority of myocardial infarctions (MIs) [1–3]. In addition to analgesic, anti-inflammatory, and anti-pyretic effects, acetylsalicylic acid (aspirin) inhibits platelet cyclooxygenase, particularly the cyclooxygenase-1 isozyme whose major product induces platelet aggregation [4]. The role of aspirin as an anti-platelet agent in the treatment of acute cardiovascular events as well as for secondary prevention of future CVD events has been well established [5–9].

However, despite ten well-designed randomized controlled trials (RCTs) that focused patients without known CVD [10••, 11–14, 15•, 16–18, 19••], the role of aspirin for the primary prevention of CVD is currently unclear. Recently, the United States Prevention Service Task Force (USPSTF) made available for comment a draft recommendation statement on the use of aspirin for the prevention CVD and cancer [20]. The statement recommends that adults aged 50–59 who have an estimated 10-year CVD risk of ≥10 % should consider taking a low dose aspirin. They also suggest individuals age 60–69 at increased CVD risk discuss the risks and benefits of ASA with their doctor. These recommendations have raised controversy given that lack of consensus on this topic. The aim of this review is to summarize the evidence on aspirin for primary

prevention, focusing on prior RCTs, review the most recent guidelines, and discuss potential future directions to determine the optimal use of aspirin for the primary prevention of CVD.

The First 6 RCTs: Clear Efficacy

From 1988–2005, six RCTs evaluated the potential of aspirin to reduce CVD events in individuals without known CVD (Table 1). The Physician's Health Study (PHS) randomized 22,071 US physicians using a 2 × 2 factorial design with 325 mg of aspirin every-other-day, beta carotene, and placebos [10••]. In PHS, a substantial 44 % relative risk reduction (relative risk 0.56, 95 % confidence interval [CI] 0.45–0.70) was seen for fatal and non-fatal MI in those taking aspirin alone compared to placebo. There was no reduction in CVD mortality though mortality rates were substantially lower than what the trial was powered to evaluate. The British Doctor's Trial randomized 5139 male physicians without known cardiovascular disease to either take 500 mg of aspirin daily or avoid aspirin in a 2:1 fashion and followed them over 6 years [11]. The study was not placebo controlled and ~20 % of the intervention group stopped aspirin due to potential side effects. The study showed significant reductions in TIAs by half in the aspirin group but no significant difference in rates of MI. However, given the smaller sample size, the significant rate of aspirin discontinuation, and the fact that the observed event rate of MI was less than predicted, the study was underpowered to evaluate many of its primary outcome measures.

Four additional prospective trials followed over the next ~15 years. The first two, the Thrombosis Prevention Trial (TPT) and Hypertension Optimal Treatment (HOT) Trial, targeted populations at greater risk of CVD. The 2 × 2 factorial design TPT trial examined the benefit of warfarin and aspirin in primary prevention on 5499 men aged 45–69 years who were at high risk for coronary heart disease, and found a 20 % relative risk reduction for all ischemic heart disease, mostly attributed to a 32 % relative risk reduction in non-fatal coronary events with aspirin [12]. The HOT trial examined the potential benefits of lowering blood pressure and use of aspirin in 18,790 hypertensive men and women. The trial demonstrated a relative risk reduction in major cardiovascular events by 15 %, with a significant 36 % risk reduction for MI [13]. Neither TPT or the HOT trial showed a significant difference in mortality, though again, the trials were not powered to adequately evaluate those outcomes. The Primary Prevention Project (PPP) examined the effect of vitamin E and aspirin in 4495 men and women with 1+ major cardiac risk factor, and showed a 44 % relative risk reduction in cardiovascular death and 33 % relative risk reduction in total cardiovascular events in the aspirin group [14]. Finally, the Women's Health Study (WHS) randomized 39,876 female health professionals without known CVD or major illnesses to either 100 mg of aspirin or placebo every-other-day [15•]. No significant decrease in the rate of overall cardiovascular events or MI was noted in the intervention group. However, the study included women at very low risk for CVD events (the rate of the primary outcome of major CVD events—non-fatal MI, non-fatal stroke, or CVD death—was <3 % over 10 years). When stratified by age in WHS, women over 65 did have a significant reduction in major CVD events (hazard ratio [HR] 0.74 (95 % CI, 0.59–0.92)), including a reduction in non-fatal myocardial infarction (HR 0.66 [95 % CI, 0.44–0.97]). Unlike previous studies, a 17 % decrease in the risk of stroke was noted as well (HR 0.83 [95 % CI, 0.69–0.99]).

In 2006, a meta-analysis was performed using the first six RCTs, comparing benefits and risks by sex [21]. Pooled results showed a 12 % reduction in cardiovascular events and 17 % reduction in strokes among studied women. Men were shown to have a 14 % reduction in cardiovascular events and a 32 % reduction in MI. There was a significant increase in risk of bleeding in both women and men as well (odds ratio 1.68 [95 % CI, 1.13–2.52] in women, odds ratio 1.72 [96 % CI, 1.35–2.20] in men). Based on these data, in 2009, the USPSTF published tailored recommendations for men and women [22]. The guidelines assumed a 32 % reduction in CHD in men and a 17 % reduction in stroke in women as well as a varying risk in the rate of gastrointestinal bleeding with aspirin use according to age. Aspirin was encouraged for women 55 to 79 years old whose risk for stroke outweighed

Table 1 Aspirin in primary prevention of cardiovascular disease—six initial prospective randomized trials

Trial	Number	Gender	Primary end point	Hazard ratio
BDT	5139	100 % male	Major cardiovascular events	0.98 (0.81–1.19)
PHS	22,071	100 % male	Fatal and non-fatal MI	0.56 (0.45–0.70)
HOTT	18,790	53 % male	Major cardiovascular events	0.85 (0.73–0.99)
TPT	5085	100 % male	Ischemic heart disease (sum of fatal and non-fatal MI and coronary death)	0.80 (0.64–0.99)
PPP	4495	58 % female	Combined end point of cardiovascular death, non-fatal MI and stroke	0.71 (0.48–1.04)
WHS	39,876	100 % female	Major cardiovascular events	0.91 (0.80–1.03)

BDT British Doctors Trial, *PHS* Physician's Health Study, *HOT* Hypertension Optimal Treat Trial, *TPT* Thrombosis Prevention Trial, *PPP* Primary Prevention Project, *WHS* Women's Health Study

their risk for gastrointestinal bleeding. Men 45 to 79 years old whose risk for MI outweighed that of gastrointestinal bleeding were also encouraged to take aspirin. Guidelines from the American Heart Association (AHA) have followed a similar absolute risk-based approach to the use of aspirin. The 2002 guidelines for primary prevention of CVD and stroke recommended that men with a ≥10 % 10-year risk of CHD consider taking a daily aspirin [23]. A 2011 update to the AHA guidelines for CVD prevention for women recommended aspirin use for women with a ≥10 % 10-year CVD risk [24].

The Recent four RCTs: Efficacy Unclear

From 2008–2014, four additional RCTs have been published that evaluated aspirin for primary prevention in individuals presumed to be at high CVD risk (Table 2). The Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial included 1276 adults with diabetes and an abnormal ankle-brachial index suggestive of peripheral arterial disease [16]. Despite a study population of individuals at high CVD risk, there was no difference in the primary cardiovascular end points with the use of 100 mg aspirin daily over a mean follow-up of ~6 years (HR 0.98; 95 % CI, 0.76 to 1.26). The Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial also evaluated a high-risk population, including 2539 individuals with type II diabetes but without known CVD [17]. Over a median follow-up of 4.4 years, there was no difference in the primary end-point of total atherosclerotic events (HR 0.80; 95 % CI, 0.58–1.10). Both the POPADAD and JPAD trials suffered from difficulties in recruitment and lower than expected event rates and subsequently were underpowered to evaluate their primary end points.

In 2010, the Aspirin for Asymptomatic Atherosclerosis (AAA) trial screened individuals without known CVD for a low ankle-brachial index (ABI) as a proxy for atherosclerosis [18]. Over a mean follow-up of 8.2 (1.6) years, 3350 men and women were followed on either 100 mg of aspirin daily or placebo. The primary end point was a composite of fatal or non-fatal coronary event or stroke as well as revascularization. Despite the long duration of follow-up and adequate event rate, there was no difference in the primary end point (HR 1.03; 95 % CI, 0.84–1.27). Most recently, the Japanese Primary Prevention Project (JPPP) with aspirin evaluated the effect of 100 mg of aspirin daily on the composite end point of non-fatal MI or stroke or CVD death [19••]. Patients included in the study were age 60–85 and had to have at least one risk factor (hyperlipidemia, hypertension, or diabetes). In 14,464 men and women followed for ~5 years, there was no difference in the primary end point (HR 0.94; 95 % CI, 0.77–1.15). There was a significant reduction in non-fatal MI (HR 0.53; 95 % CI, 0.31–0.091) but also a significant increase in the risk of serious extra-cranial hemorrhage (HR 1.85; 95 % CI, 1.22–2.81).

A meta-analysis encompassing the first nine aforementioned published RCTs demonstrated a small benefit in terms of CVD risk reduction, with a significant 10 % reduction in CVD events and a 20 % reduction in non-fatal MI with the use of aspirin but no significant CVD mortality benefit [25]. However, this benefit came at the cost of a virtually equivalent increase in the risk of bleeding, with a calculated number-needed-to-treat (NNT) to prevent a single CVD event of 120 versus a number-needed-to-harm (NNH) for a significant bleed of 73. Based on these data, the European Society of Cardiology updated guidelines on cardiovascular prevention in 2012 did not endorse the use of aspirin for primary prevention due to lack of clear efficacy and a significant increase in major bleeding [26]. Neither the AHA nor the USPSTF have officially updated their guidelines for aspirin use based on these recent studies, though the USPSTF did recently make available a draft recommendation statement on the use of aspirin for the prevention CVD and cancer [20]. The recent lifestyle and cholesterol guidelines from the American College of Cardiology (ACC) and the AHA did not address the use of aspirin for primary prevention of CVD [27, 28].

Applying the Data and Future Directions: Finding Clarity

How can the results of the first six RCTs be reconciled with the results of the four recent RCTs? There are several potential explanations. Differences in sample size, patient populations,

Table 2 Aspirin in primary prevention of cardiovascular disease—four recent prospective trials

Trial	Number	Gender	Primary end point	Hazard ratio
POPADAD	1276	56 % female	Fatal and non-fatal MI or stroke	0.98 (0.76–1.26)
JPAD	2539	55 % male	Any atherosclerotic event	0.80 (0.58–1.10)
AAA	3350	72 % female	Fatal or non-fatal coronary event, stroke or coronary revascularization	1.03 (0.84–1.27)
JPPP	14,464	58 % female	CVD death, non-fatal MI or stroke	0.94 (0.77–1.15)

POPADAD The Prevention of Progression of Arterial Disease And Diabetes, *JPAD* Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes, *AAA* The Aspirin for Asymptomatic Atherosclerosis trial, *JPPP* The Japanese Primary Prevention Project

study design, and aspirin dosage may all have played a role in producing variable results among the different trials. Potentially, a more important difference is that the initial trials focused on MI and stroke at a time when traditional CVD risk factors were less optimally controlled while the recent trials have focused on broader CVD outcomes in patients with high rates of use of preventive CVD medications.

From the standpoint of pathophysiology, aspirin should largely just be beneficial for those individuals destined to otherwise experience an event that involves arterial thrombosis. A number of factors may have led to a decrease over the past couple of decades in the number of atherothrombotic events relative to other cardiovascular events. The initial aspirin trials occurred at a time when cholesterol and blood pressure were not as well controlled as they were at the time of the most recent four aspirin trials [29, 30]. Utilization of statin therapy was infrequent during the first six trials, whereas given the high-risk nature of the individuals included in the recent four trials, statin therapy was present in the majority of patients in those trials. Both statin therapy as well as improved blood pressure control have been associated with a substantial reduction in MI [31, 32]. Having a patient population with well controlled CHD risk factors may have removed the "low-hanging fruit" that was present in previous aspirin trials. To support this concept, prior data has shown the rate of MI has declined significantly over the past two decades, largely due to a decline in STEMI [33], which is almost universally an atherothrombotic event. This decline in CHD has largely been attributed to better control of CHD risk factors [34]. Recent data from a large electronic health record database of ~1.9 million adults showed that the majority (66 %) of all initial CVD events were not myocardial infarction or stroke [35]. Additionally, older individuals in that database were even less likely to suffer an MI or stroke as there initial event. Given that the four recent trials included older individuals compared to the first six trials, it may be that the populations studied were at high CVD risk, but not necessarily high risk for an atherothrombotic event.

As an example, in the JPPP aspirin trial, aspirin reduced the rate of non-fatal MI by 47 %, but this did not significantly influence the primary outcome as non-fatal MIs represented only a small portion of the total CVD events (207 total events in the placebo group, 56 fatal CVD events, and 38 [18 % of total CVD events] were non-fatal MI) [19••]. Conversely, in PHS, the sample size was 1.5 times higher compared to JPPP, but there were 5.6 times more non-fatal MIs (213 in the placebo group) over a similar follow-up duration of ~5 years [10••]. It seems plausible that aspirin may have not lost its efficacy for preventing atherothrombotic events over time, but rather it has recently been studied in patient populations with low rates of the type of CVD events it is capable of preventing.

There is hope for clarity in regard to the risks and benefits of aspirin for primary CVD prevention in the modern era of medicine with four trials currently underway. The Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE) trial has enrolled 12,000 patients with moderate CVD risk, a group not studied in previous trials [36]. The Aspirin in Reducing Events in the Elderly (ASPREE) trial has 15,000 patients over 70 years old without known CVD enrolled, a group also not included in previous studies [37]. To better determine what, if any benefit, aspirin plays in primary prevention of CVD in diabetic patients, the ongoing ASCEND trial (A Study of Cardiovascular Events in Diabetes) has enrolled over 15,000 patients with plans to complete the study within the next couple of years [38]. Additionally, ACCEPT-D (Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes) has a planned enrollment of 5170 patients, evaluating the preventative benefit of aspirin + statin versus aspirin alone [39]. While none of these trials will address the benefit of aspirin in a mixed clinical population with no-to-few cardiovascular risk factors, they should

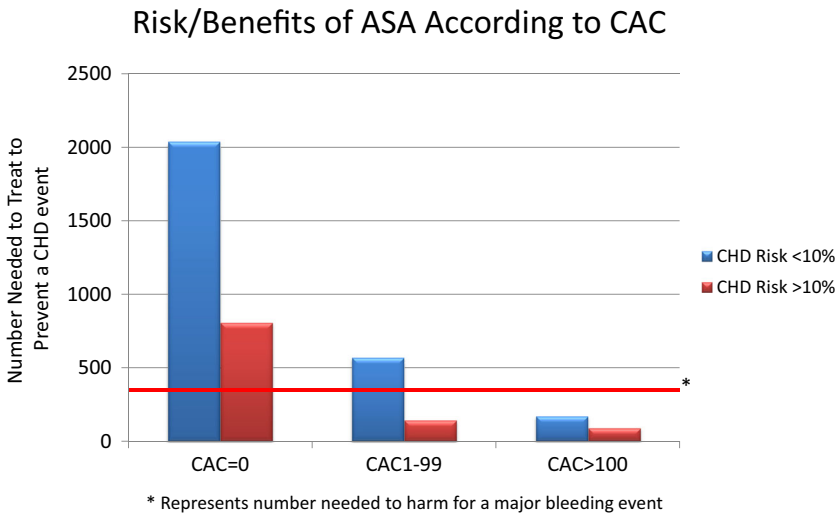

Fig. 1 The risks and benefits of aspirin in 4229 MESA participants stratified by coronary artery calcium score and CHD risk [40•]

help decide if these particular populations at-risk for CVD show sufficient benefit to warrant recommendation for aspirin despite the increased bleeding risk. It is important to note that any benefit or harm from aspirin therapy (even if small in magnitude) is important from a public health stand point as the population attributable benefit or risk could still be high given the large number of individuals currently using aspirin for primary CVD prevention.

An alternative approach that may be helpful in determining an individual's benefit, or lack thereof, from aspirin therapy is personalizing risk assessment with a coronary artery calcium (CAC) score. A recent paper hypothesized that CAC scoring could be used to determine which individuals are most and least likely to benefit from aspirin therapy [40•]. Using data from the Multi-Ethnic Study of Atherosclerosis (MESA), the study estimated the risks and benefits of aspirin in participants stratified by CAC score at baseline of the study. The study showed that individuals with significant plaque in their arteries (coronary artery calcium score ≥100) were estimated to be two to four times more likely to prevent a heart attack with aspirin use than to have a major bleed secondary to aspirin. Conversely, MESA participants with no calcified plaque (coronary artery calcium score = 0) were estimated to be two to four times more likely to suffer a major bleed from aspirin use than to prevent a heart attack with aspirin. These findings were independent of qualification for aspirin by AHA guidelines (Fig. 1).

Conclusions

Despite a large amount of data, the role of aspirin in primary prevention is currently unclear. Similar to the patient-provider discussion recommended by the recent ACC/AHA cholesterol guidelines [28], a thorough patient-provider discussion concerning the risks and benefits of aspirin is warranted for individuals without known CVD. A more personalized risk assessment using CAC may be beneficial in determining the likelihood of benefit from aspirin but further research is needed before such an approach can be strongly recommended. Fortunately, the results of the four large RCTs that currently underway should be available in the next 2–3 years. Hopefully, they will provide clarity in determining the optimal use of aspirin in the primary prevention of CVD.

Compliance with Ethical Standards

Conflict of Interest Michael D. Miedema, Joseph Huguelet, and Salim S. Virani declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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