The Aspirin Primary Prevention Conundrum

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ABSTRACT: In this review, the authors re-examine the role of aspirin in the primary prevention of cardiovascular disease. They discuss the history of the use of aspirin in primary prevention, the current guidelines, and the recent evidence surrounding aspirin use as primary prevention in special populations such as those with moderate cardiovascular risk, diabetes mellitus, and the elderly.

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HISTORY OF ASPIRIN USE

Aspirin is one of the most widely used drugs worldwide. The bark of the willow tree, from which aspirin is made, has been known to have analgesic and antipyretic properties since the times of the ancient Egyptians [1]. In 1897, Felix Hoffman synthesized acetylsalicylic acid by combining salicylic acid with acetic acid, thereby removing the potent nausea caused by pure salicylic acid and making aspirin a palatable drug. Craven [2] was the first to report on the cardiovascular effects of aspirin in 1950. He noted that aspirin prevented myocardial infarctions (MI) in his patients. In 1956, it was reported that aspirin may also prevent ischemic strokes [3].

Vane [3] reported that the mechanism of action of aspirin was prostaglandin production inhibition leading to its analgesic effects as well as its cardiovascular protective effects. For this discovery, he won the Nobel Prize in 1982. Aspirin's efficacy in the secondary prevention of major adverse cardiac events has been studied and proven [4].

For years, aspirin has also been used for primary prevention of cardiovascular disease; however, this treatment was based mainly on studies that were performed at a time when statins were not widely available. Recently, evidence is accumulating questioning the role of aspirin as primary prevention of cardiovascular disease [5,6].

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Evidence is accumulating against the routine use of aspirin for primary prevention of cardiovascular disease

THE HISTORY OF ASPIRIN AS PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE

One of the hallmark trials of aspirin in primary prevention was the Physicians Health Study published in 1989 [7]. This trial included over 22,000 healthy male physicians, with a mean age of 53 years. Participants were randomized into either the group receiving aspirin (325 mg every other day) or placebo. The trial was terminated early, after 5 years, when it was shown that, although there was no significant difference in the primary outcome, there was a significant decrease in the rates of MI (risk ratio [RR] 0.56, 95% confidence interval [95%CI] 0.45–0.70, $P < 0.00001$) among those in the aspirin arm of the trial. Further analyses demonstrated that this reduction was apparent only among those who were 50 years of age and older. However, there was a significant increase in all types of bleeding complications in those randomized to aspirin. In view of the large decrease in MI, it was suggested that aspirin therapy could be protective against coronary heart disease (CHD).

In 2005, a trial was performed with women, the Women's Health Study [8]. In this study, 39,876 healthy female health professionals, with a mean age of 55 years, were randomized to receive either 100 mg of aspirin or placebo with the primary endpoint of a first major cardiovascular event (nonfatal MI, nonfatal stroke, or death from cardiovascular causes). After a mean follow-up of 10 years, there was no difference in the primary endpoint of MI or death from a cardiovascular cause. However, there was a significantly lower rate of ischemic stroke in those in who were randomized to aspirin therapy (RR 0.76). This result was more pronounced in the group of women 65 years and older. Additional meta-analyses have demonstrated similar results with aspirin resulting in a 12% proportional risk reduction in major cardiovascular disease events mainly driven by the reduction in non-fatal MI. [9]

Cardiovascular disease, predominantly coronary artery disease (CAD) is the primary cause of morbidity and mortality in patients with diabetes mellitus [10]. Furthermore, it appears that patients with diabetes have hyper-reactive platelets with enhanced adhesion, activation, and aggregation compared with platelets of patients without diabetes [11,12]. This condition

makes this specific subgroup an important and noteworthy population that would seemingly benefit from anti-platelet therapy. One of the first studies to challenge the use of aspirin for diabetic patients without known coronary disease randomized 2539 patients with type 2 diabetes mellitus to either daily aspirin or placebo [13]. The rate of atherosclerotic events did not differ between the two groups (hazard ratio [HR] 0.80, 95% confidence interval [95%CI] 0.58–1.10, log-rank test $P = 0.16$), and there was no difference in mortality. However, there was a significant reduction in the combined endpoint of fatal coronary events and fatal cerebrovascular events that occurred in a small number of patients (1 patient in the aspirin group and 10 patients in the non-aspirin group [HR 0.10, 95%CI 0.01–0.79, $P = 0.0037$]). There was also no difference in the composite of hemorrhagic stroke and significant gastrointestinal bleeding between the aspirin and non-aspirin groups.

In 2014, Bayer Pharmaceuticals, the manufacturer of aspirin, proposed that the U.S. Food and Drug Administration (FDA) recommend the use of aspirin for primary prevention of MI and stroke. However, the FDA declined this recommendation citing the serious bleeding risks association with aspirin use [14]. This risk has been consistent throughout all trials with aspirin use, specifically those associated with hemorrhagic stroke and gastrointestinal bleeding [4,8,15].

Aspirin as primary prevention provides minimal cardiovascular protection in contemporary cohorts

Most of the aforementioned trials have been conducted on a patient population naïve to statin therapy and were completed in an era when cardio-preventative medicine was in its infancy. Thus, these studies are not representative of the contemporary patient, in which traditional cardiovascular risk factors such as smoking, hypertension, and dyslipidemia are better identified and managed. Since the use of statins, which have a prominent cardio-protective effect without the concerning bleeding side effects of aspirin, it is possible that the use of as aspirin as a cardiovascular protector would be minimized or stopped.

CURRENT GUIDELINES AND RECENT EVIDENCE

Over the years the guidelines have continuously reduced the use of aspirin a primary cardiovascular prevention. In 2019, the American College of Cardiology/American Heart Association (ACC/AHA) published updated Guidelines on the Primary Prevention of Cardiovascular Disease. They downgraded the recommendation for aspirin use as primary prevention. They recommended that low dose aspirin might be considered for the primary prevention of atherosclerotic cardiovascular disease (ASCVD) among select adults 40–70 years of age who are at higher risk for events but not at increased bleeding risk. Notably, they advocate against the use of low-dose aspirin routinely for the primary prevention of ASCVD among adults above 70 years of age as well as stating that low-dose aspirin should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding [16].

These guidelines are consistent with increasing contemporary data and three pivotal trials evaluating the role of aspirin in primary prevention of cardiovascular disease that were published in August 2018 [17-21] [Table 1]. These trials aimed to assess the use of aspirin in the modern cardio-preventative era and evaluate specific subgroups which might benefit most from a primary prevention strategy. The trials included patients with a baseline moderated cardiovascular risk (ARRIVE) [21], those with diabetes (ASCEND) [20], and the elderly (ASPREE) [17-19].

ARRIVE (ASPIRIN TO REDUCE RISK OF INITIAL VASCULAR EVENTS)

ARRIVE was a multi-center study that took place in seven countries and was funded by Bayer [21]. It aimed to evaluate the effect of aspirin in reducing cardiovascular events in patients at moderate cardiovascular risk. In this trial 12,546 patients were randomized to receive either aspirin (100 mg daily) or placebo. Patients were aged 55 years (men) and 60 years (women) or older and at an average cardiovascular risk based on specific risk factors including smoking, family history of cardiovascular disease, hypertension, and dyslipidemia. Patients with high risk of bleeding and those with diabetes were excluded. The median follow-up was 60 months and the primary endpoint was a composite outcome of time to first occurrence of cardiovascular death, MI, unstable angina, stroke, or transient ischemic attack. The mean age was 63, with a majority of male participants with a high prevalence of obesity, hypertension, and dyslipidemia. The mean ACC/AHA 10-year ASCVD risk score was 17%, demonstrat-

Table 1. Contemporary trials evaluating the use of aspirin for primary prevention in different patient populations

	ARRIVE [21]	ASCEND [20]	ASPREE [17-19]
Population	Moderate cardiovascular risk (10–20% estimated 10-year risk of CHD)	Diabetes (no cardiovascular disease)	Healthy elderly (no cardiovascular disease, dementia, or disability)
Study cohort	12,546	15,480	19,114
Follow-up duration (years)	5	7.4	5
Primary endpoint	Composite of MI, stoke, cardiovascular death, UA, TIA	Composite of MI, stroke or TIA, cardiovascular death	3 Arms: All-cause mortality Dementia Significant disability
Results	No significant difference in the primary endpoint between groups	Slightly lower incidence of primary endpoint in the aspirin group	Trial terminated early, increased all-cause mortality
Bleeding risk	Increased	Increased	Increased
Conclusion	Aspirin not effective for primary prevention	Minimal incremental benefit of aspirin	Aspirin not effective for primary prevention

CHD = coronary heart disease, MI = myocardial infarction, TIA = transient ischemic attack, UA = unstable angina

ing moderate cardiovascular risk. Of note, almost half of the patients were on statin therapy and almost two-thirds received anti-hypertensive therapy.

There was no significant difference in the primary endpoint between the two arms (269 patients in the aspirin group compared with 281 patients in the placebo group). Gastrointestinal bleeding occurred in 0.97% of patients in the aspirin group vs. 0.46% in the placebo group (HR 2.11, $P = 0.0007$). The investigators noted a lower risk of MI among those taking aspirin compared with placebo, although the difference was not significant. What was significant was the lower than expected event rate in this trial, thus making this trial underpowered. The ARRIVE results suggest that aspirin is not effective as primary prevention in those at moderate risk of CHD.

Aspirin has continuously been associated with a significantly increased risk of bleeding

ASCEND (A STUDY OF CARDIOVASCULAR EVENTS IN DIABETES)

ASCEND was an international multi-center trial that randomized 15,480 participants with diabetes mellitus and no known cardiovascular disease upon trial entry to low-dose daily aspirin and placebo. Most patients were not smokers at the time of the trial, were under hypertensive treatment, and there was a high prevalence of statin use (≈75%) [20]. After a mean follow-up time of 7.4 years, severe cardiovascular events (non-fatal MI, stroke, transient ischemic attack, and death from vascular causes) occurred in a significantly lower percentage of the aspirin group (odds ratio [OR], 0.88, $P = 0.01$). As expected, this was at the expense of a statistically significant increase in major bleeding in the aspirin group (OR 1.29, $P = 0.003$). The number needed to treat was 91 in order to prevent a severe vascular event, whereas the number needed to harm was 112. As a large proportion of patients recieved lipid lowering and anti-hypertensive therapy, and most were not smokers, this study showed that the incremental benefit of aspirin to other cardio-preventative interventions is minimal.

ASPREE (ASPIRIN IN REDUCING EVENTS IN THE ELDERLY)

ASPREE evaluated the use of aspirin for primary prevention of cardiovascular disease in the elderly, a subgroup that has been traditionally under investigated and often neglected from studies. The results of this trial, although of the same cohort, were published as three different publications [17-19]. The trial included 19,114 healthy adult patients (most above 70 years of age). These patients were free from cardiovascular disease, dementia, and disability at trial entry. The primary endpoint was a composite of death, dementia, or permanent physical disability. The trial was terminated at a median of 4.7 years of follow-up after a determination was made that there would be no benefit with continued aspirin use regarding the primary endpoint. Compared with a placebo, aspirin did not improve disability-free survival or reduce major adverse cardiovascular events. Aspirin was associated with a significant increase in major bleeding, which was attributed to excess intracranial and upper gastrointestinal bleeding (HR 1.38; 95%CI 1.18–1.62, $P < 0.001$). In contrast to previous trial results, aspirin was surprisingly associated with an increase in all-cause mortality (HR 1.14; 95%CI 1.01–1.29). This was attributed to excess cancer mortality. There was no increase in any specific type of cancer. There was a population bias as the trial included healthy adults free of cardiovascular disease and thus mortality driven by cancer, and not cardiovascular disease, could be anticipated. The authors warn that these results should be interpreted cautiously.

The results of these contemporary trials are relatively negative regarding aspirin use for primary prevention of cardiovascular disease. In light of these data, a large systematic review of 15 randomized controlled trials, over a 30-year period and including the trials mentioned previously, examined the clinical outcomes for aspirin as primary prevention. There was no difference between the control group and the aspirin group in regard to fatal outcomes. While aspirin did reduce nonfatal ischemic events (nonfatal MI (RR 0.82; 95%CI 0.72–0.94), transient ischemic attack (RR 0.79, 95%CI 0.71–0.89), and ischemic stroke (RR 0.87, 95%CI 0.79–0.95). It was also associated with a significantly higher risk of major bleeding (RR 1.5, 95%CI 1.33–1.69), intracranial bleeding (RR 1.32, 95%CI 1.12–1.55), and major gastrointestinal bleeding (RR 1.52, 95%CI 1.34–1.73) [22].

CONCLUSIONS

In contemporary practice, aspirin is no longer prescribed indiscriminately for primary prevention of cardiovascular disease as recommended in the 2019 ACC/AHA guidelines on Primary Prevention of Cardiovascular Disease. The incremental benefit for prophylactic aspirin on top of treatment of cardiovascular risk factors is small, if any, and this comes at the cost of a significant increase in the risk of bleeding. These results highlight the important of individualising patient management and should affect contemporary clinical practice.

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Capsule

A frog-derived immunomodulatory peptide promotes cutaneous wound healing by regulating cellular response

Wound healing-promoting peptides exhibit excellent therapeutic potential in regenerative medicine. However, amphibian-derived wound healing-promoting peptides and their mechanism of action remain to be further elucidated. **He** et al. characterized a wound healing-promoting peptide, Ot-WHP, derived from Chinese concave-eared frog *Odorrana tormota*. It efficiently promoted wound healing in a mouse model of full-thickness wounds. Ot-WHP significantly increased the number of neutrophils in wounds, and modestly promoted neutrophil phagocytosis and phorbol myristate acetate (PMA)-induced neutrophil extracellular trap formation. Ot-WHP also significantly increased the number of macrophages in wound sites, and directly induced chemokine, cytokine, and growth factor production in macrophages by activating mitogen-activated protein kinases (MAPKs) and nuclear factor-κB (NF-κB) signaling pathways. Of note, Ot-WHP did not act as a chemoattractant for neutrophils and macrophages, suggesting its chemotactic activity depends on inducing chemoattractant production in macrophages. Besides, Ot-WHP directly promoted keratinocyte migration by enhancing integrin expression and cell adhesion. In addition, Ot-WHP significantly enhanced the cross-talk between macrophages and keratinocytes/fibroblasts by promoting keratinocyte/fibroblast proliferation, and fibroblast-to-myofibroblast transition despite having no direct effects on keratinocyte/fibroblast proliferation, and fibroblast differentiation. Collectively, Ot-WHP directly elicited the production of regulatory factors in macrophages, consequently initiated and accelerated the inflammatory phase by recruiting neutrophils and macrophages to wounds, and in turn enhanced the cross-talk between macrophages and keratinocytes/fibroblasts, additionally promoted keratinocyte migration, and finally promoted cutaneous wound healing. These findings provide a promising immunomodulator for acute wound management and new clues for understanding the mechanism of action of amphibian-derived wound healing-promoting peptides.

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Eitan Israeli

"Use the talents you possess, for the woods would be a very silent place if no birds sang except the best"

Henry van Dyke (1852–1933), poet