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.

KEY WORDS: aspirin, cardiovascular disease, primary prevention

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].

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 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

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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 atherothrombotic events did not differ between the two groups (hazard ratio [HRR] 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 associated 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].

Most of the aforementioned trials have been conducted on a patient population naïve to statin therapy and were completed in an era when cardio-preventive 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 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 atherothrombotic 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 moderate 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-

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

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<tbody>
<tr>
<td>Study cohort</td>
<td>Moderate cardiovascular risk (10-20% estimated 10-year risk of CHD)</td>
<td>Diabetes (no cardiovascular disease)</td>
<td>Healthy elderly (no cardiovascular disease, dementia, or disability)</td>
</tr>
<tr>
<td>Follow-up duration (years)</td>
<td>12,546</td>
<td>15,480</td>
<td>19,114</td>
</tr>
<tr>
<td>PRIMARY ENDPOINT</td>
<td>Composite of MI, stroke, cardiovascular death, UA, TIA</td>
<td>Composite of MI, stroke or TIA, cardiovascular death</td>
<td>3-Arms: All-cause mortality, Dementia, Significant disability</td>
</tr>
<tr>
<td>RESULTS</td>
<td>No significant difference in the primary endpoint between groups</td>
<td>Slightly lower incidence of primary endpoint in the aspirin group</td>
<td>Trial terminated early, increased all-cause mortality</td>
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<td>BLEEDING RISK</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
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<td>CONCLUSION</td>
<td>Aspirin not effective for primary prevention</td>
<td>Minimal incremental benefit of aspirin</td>
<td>Aspirin not effective for primary prevention</td>
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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 com-
pared 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.

ASCEND (A STUDY OF CARDIOVASCULAR EVENTS IN DIABETES)
ASCEND was an international multi-center trial that random-
ized 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 received 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 surpris-
ingly 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 cardiovas-
cular disease and thus mortality driven
by cancer, and not cardiovascular dis-
eease, could be anticipated. The authors warn that these results
should be interpreted cautiously.

The results of these contemporary trials are relatively nega-
tive regarding aspirin use for primary prevention of cardiovas-
cular 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 differ-
ence 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 isch-
emic 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 signifi-
cantly 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 indis-
criminately 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 signifi-
cantly 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 therapeutical 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 Ondorana tornota. 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 chemotactic attractant 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