Aspirin Therapy for Primary Prevention: The Case for Continuing Prescribing to Patients at High Cardiovascular Risk—A Review

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Abstract

Current evidence supports the use of low-dose aspirin for secondary cardiovascular prevention. By contrast, the benefit-to-risk ratio of aspirin use in primary prevention is debated: three contemporary randomized control trials have been conflicting, and meta-analyses have concluded for an unclear clinical benefit, based on the consideration that the reduction in thromboembolic events is counterbalanced by increased bleeding. The primary prevention setting is, however, a heterogeneous mix of subjects at highly variable cardiovascular risk. One possible explanation for the uncertainty of data interpretation is the progressive reduction in risk of major adverse cardiovascular events (MACEs) in primary prevention that has accompanied global education programs, leading patients to smoke less, exercise more, and increasingly take lipid-lowering therapies. Based on a meta-regression of the benefits and harm of aspirin therapy in primary prevention as a function of the 10-year risk of MACE, we favor a nuanced approach still, however, based on the evaluation of cardiovascular risk, acknowledging differences between patients and emphasizing an individualized assessment of both benefits and harm. After optimal control of cardiovascular risk factors, and when patients are less than 70 years of age, clinicians should assess the risk of MACE and base decision on such stratification, considering the risk of bleeding and patient preferences. Clinicians would then advise the use of aspirin in primary prevention patients at the highest risk of MACE who do not have a prohibitive risk of bleeding, and in the majority of cases after initiation of properly titrated statin therapy.

Keywords

► aspirin
► primary cardiovascular prevention
► bleeding
► major acute cardiovascular events
► MACE
► benefit–risk balance

Introduction

The role of thrombosis in acute cardiovascular conditions and the evidence of aspirin’s ability to inhibit platelet aggregation have inspired large multicenter trials to test the cardiovascular benefit of aspirin in both primary and secondary prevention. After six inconclusive secondary prevention trials,1–6 a meta-analysis—the first one in the cardiovascular field—pooling data from over 10,000 patients with previous myocardial infarction (MI) provided initial evidence for a benefit, with a risk of reinfarction reduced by 21% compared with placebo.7,8 In 1983, a report from the Veterans Administration Cooperative Study on Aspirin in men with unstable angina showed a similar effect on death or acute MI in the setting of unstable angina,9 and soon after a Canadian study confirmed favorable effects in...
the same condition. Afterwards, the definitive Second International Study of Infarct Survival (ISIS-2) study demonstrated the clinical utility of aspirin in the acute MI setting, both alone and as an adjunct to fibrinolysis. Based on these and other results, included in the Antithrombotic Trialists’ Collaboration meta-analysis, low-dose aspirin (75–150 mg daily) is now more widely accepted and recommended for secondary cardiovascular prevention.

By contrast, the benefit-to-risk ratio associated with aspirin use in primary prevention is highly debated, as no trial has shown a clear prognostic benefit, particularly in the post-statin era. Indeed, the Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE) trial yielded inconclusive results, because of the inadequate statistical power to detect a moderate treatment effect in subjects at low cardiovascular risk, while the A Study of Cardiovascular Events in Diabetes (ASCEND) trial did establish the efficacy of low-dose aspirin in reducing risk of serious vascular events in a contemporary, well-treated population of subjects with diabetes mellitus, and the Aspirin in Reducing Events in the Elderly (ASPREE) study found that low-dose aspirin is not effective in improving disability-free survival in a population of healthy elderly individuals. The primary prevention setting is, however, a heterogeneous mix of subjects at highly variable cardiovascular risk. Primary prevention studies have either included or excluded patients with evidence of subclinical vascular disease, such as asymptomatic stenoses in various arterial districts or indirect signs of atherosclerotic disease, such as cardiac ischemia on provocative testing or reduced ankle-brachial index (ABI), suggesting the presence of peripheral arterial disease. Two recent meta-analyses have either included or excluded such patients, nonetheless concluding that aspirin does not confer a clear clinical benefit. Such conclusions are based on the consideration that the reduction in thromboembolic events is counterbalanced by an increased risk of bleeding.

One possible explanation for these results is the progressive reduction in risk of major adverse cardiovascular events (MACES) in primary prevention that has accompanied global education programs targeting patients to smoke less, exercise more, and increasingly to take lipid-lowering therapies. All of these important public health measures could lower the expected benefit from aspirin, while not similarly affecting the risk of bleeding.

Reflecting this diminution of anticipated benefit, guidelines for the use of aspirin in primary prevention have shifted over time and range from “do not use,” as described in the 2016 European Society of Cardiology (ESC) recommendations, to “consider for those at high cardiovascular risk who are not at high bleeding risks” as described in the 2019 American College of Cardiology/American Heart Association (ACC/AHA) Clinical Practice Guidelines for Prevention (Table 1). The authors here favor the more nuanced approach of the ACC/AHA, which acknowledges differences between patients and emphasizes an individualized assessment of both benefits and risks. For example, the latter North American guidelines suggest that low-dose aspirin might be considered in primary prevention of cardiovascular disease.

Table 1 Recommendations from main recent guidelines on cardiovascular prevention

<table>
<thead>
<tr>
<th>Guideline, year [ref.]</th>
<th>Recommendation</th>
<th>Class</th>
<th>LOE</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>American College of Chest Physicians CVD prevention, 2012</td>
<td>Low-dose aspirin (75–100 mg/d) in patients aged &gt; 50 years [is recommended] over no aspirin therapy</td>
<td>2B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESC Primary CVD prevention, 2016</td>
<td>Antiplatelet therapy (e.g., with aspirin) is not recommended for people with DM who do not have CVD</td>
<td>III</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>ESC Primary CVD prevention, 2016</td>
<td>Antiplatelet therapy is not recommended in individuals without CVD due to the increased risk of major bleeding</td>
<td>III</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>ACC/AHA Primary CVD prevention, 2019</td>
<td>Low-dose aspirin (75–100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk</td>
<td>IIb</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>ACC/AHA Primary CVD prevention, 2019</td>
<td>Low-dose aspirin (75–100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults &gt; 70 years of age</td>
<td>III</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>ACC/AHA Primary CVD prevention, 2019</td>
<td>Low-dose aspirin (75–100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding</td>
<td>III</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>ESC Guidelines on diabetes, 2019</td>
<td>In patients with DM at high/very high risk, aspirin (75–100 mg/d) may be considered in primary prevention in the absence of clear contraindications</td>
<td>IIb</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>ESC Guidelines on diabetes, 2019</td>
<td>In patients with DM at moderate CV risk, aspirin for primary prevention is not recommended</td>
<td>III</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>ESC Guidelines on diabetes, 2019</td>
<td>When low-dose aspirin is used, proton-pump inhibitors should be considered to prevent gastrointestinal bleeding</td>
<td>IIa</td>
<td>A</td>
<td></td>
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</table>

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; DM, diabetes mellitus; ESC, European Society of Cardiology; LOE, level of evidence.
among adults aged 40 to 70 years with higher cardiovascular risk and with no increased bleeding risk, while aspirin should not be prescribed on a routine basis to primary prevention patients aged >70 years or among those of any age at increased risk of bleeding (►Table 1).

We here discuss evidence from the three latest trials published in 2018 and provide further rationale for a decisional strategy based on risk stratification. We then propose an algorithm that could be used in clinical practice to assist physicians in deciding whether or not an individual patient should consider use of aspirin in primary prevention.

The ARRIVE, ASCEND, and ASPREE Trials

ARRIVE: Aspirin for Nondiabetic Patients

The ARRIVE trial\(^{14}\) was a randomized, double-blind, placebo-controlled, multicenter study enrolling men ≥55 years and women ≥60 years with a predicted moderate cardiovascular risk (10-year risk of MACE 10–20%). Patients at high risk of bleeding were excluded, as well as those with diabetes. Patients (n = 12,546) were randomized in a 1:1 ratio to aspirin 100 mg daily or placebo. Over a median of 60-month follow-up, there was no significant difference in the occurrence of the primary endpoint (a composite of time to first MI, stroke, cardiovascular death, unstable angina, or transient ischemic attack): hazard ratio (HR) 0.96, 95% confidence interval (CI) 0.81 to 1.13 (p = 0.604). Similarly, the incidence rates of both fatal and nonfatal MI were not significantly different. With respect to safety, gastrointestinal (GI) bleeding events were more frequent in the aspirin than in the placebo groups (HR 2.11, 95% CI 1.36–3.28; p < 0.001), although these events were predominantly mild. The incidence of serious adverse events was similar in both treatment groups (20.19% in the aspirin group vs. 20.89% in the placebo group).\(^ {14} \)

Although designed to represent an “intermediate risk” population, the observed incidence rates for MACE in ARRIVE were significantly lower (4%) than anticipated. As such, we believe the negative benefit-to-risk ratio observed in ARRIVE is informative for contemporary “low-risk” patients, but may not be generalized to those at higher risk.

ASCEND: Aspirin for Diabetic Patients

Patients with diabetes mellitus have a substantially higher risk of a first atherothrombotic event compared with nondiabetic subjects. Yet, clinical trials with aspirin in this setting have proven inconclusive.\(^ {24} \)

The ASCEND trial\(^ {15}\) enrolled 15,480 patients aged ≥40 years, with any form of diabetes but no symptomatic cardiovascular disease at baseline. These patients were randomized to aspirin 100 mg daily or placebo, as well as to omega-3 fatty acids versus placebo. Mean age was 63 years, 63% were male, and 94% had type 2 diabetes, with median disease duration of 7 years. Other cardiovascular risk factors often coexisted, with 62% of patients affected by hypertension, 75% being on statins, and a mean body mass index in the obese range. The primary efficacy outcome was a composite of nonfatal MI, nonhemorrhagic stroke, transient ischemic attack, or cardiovascular death, whereas the primary safety outcome was major bleeding. Over a mean follow-up duration of 7.4 years, the primary efficacy endpoint occurred in a lower percentage of participants in the aspirin group than in the placebo group (rate ratio [RR] 0.88, 95% CI 0.79–0.97; p = 0.01). Major bleeding events, however, occurred more frequently in the aspirin group (RR 1.29, 95% CI 1.09–1.52; p = 0.003), with most of the excess being GI bleeding and other extracranial bleeding.\(^ {15} \)

There were no patient subgroups in which benefits clearly numerically outweighed risk, including in the highest risk subgroups; however, as in ARRIVE, overall risk was low to moderate, with only 17.2% of patients having a 5-year risk exceeding 10%.\(^ {15} \)

ASPREE: Aspirin for Elderly Fit Individuals

The ASPREE trial\(^ {16–18} \) was a randomized, placebo-controlled trial performed in Australia and the United States to investigate whether giving aspirin to healthy, community-dwelling older adults would prolong life free from dementia and physical disability. The trial included subjects aged ≥70 years (or ≥65 years among blacks and Hispanics from the United States), free from life-limiting illness, and with no documented vascular disease. A high bleeding risk was an exclusion criterion. Following a run-in phase to exclude patients with unsatisfactory compliance to treatment, 19,114 subjects were enrolled and randomized in a 1:1 ratio to aspirin or placebo. The median age was 74 years, 56% were women, 11% had diabetes, and another 11% had been on aspirin before. The trial was terminated after a median of 4.7-year follow-up, providing no evidence of benefit from aspirin with regard to the primary endpoint, which was a composite of death, onset of dementia, and persistent physical disability (HR 1.01, 95% CI 0.92–1.11; p = 0.79). There was a trend toward increased mortality among patients on aspirin (HR 1.14, 95% CI 1.01–1.29), largely because of a higher incidence of cancer-related death, not achieving statistical significance when accounting for the multiplicity of secondary endpoints analyzed. This finding for cancer is inconsistent with prior reports. With regard to cardiovascular disease, findings from ASPREE were neutral for incident events (HR 0.95, 95% CI 0.83–1.08) with a consistent increase in major hemorrhage (HR 1.38, 95% CI 1.18–1.62; p < 0.001). These data thus affirm that aspirin does not confer a net benefit among healthy elderly patients.\(^ {16–18} \)

**Toward an Approach Based on Risk Stratification**

The results from the three latest trials, summarized in ►Table 2, have been pooled together with previous studies. After the observation that no individual trial has ever shown a mortality benefit from aspirin,\(^ {13} \) a meta-analysis limited to those unlikely to have underlying atherosclerosis found that aspirin does not reduce all-cause or cardiovascular mortality, but only the risk of MI, while increasing the risk of bleeding.\(^ {20} \) Another recent meta-analysis used a broader definition of primary prevention (“participants without known preexisting cardiovascular disease”),\(^ {21} \) and thus included trials with asymptomatic atherosclerotic disease, such as the Prevention of Progression of Arterial Disease and Diabetes (POPADAD)\(^ {25} \)
and Aspirin for Asymptomatic Atherosclerosis trials. While confirming the absence of benefit on all-cause mortality and the increased risk of major bleeding, this meta-analysis concluded for a benefit from aspirin in terms of a composite cardiovascular endpoint, as well as MI and ischemic stroke, leading the authors to conclude that “this information may inform discussions with patients about aspirin for primary prevention of cardiovascular events and bleeding.”

**When then, if ever, to Prescribe Aspirin in the Setting of Primary Prevention?**

In 2014, a Consensus Document from the ESC Working Group on Thrombosis proposed a therapeutic algorithm based on risk stratification. According to this document, aspirin should not be prescribed for primary prevention when the estimated 10-year risk of MACE is <10%, while it could be considered when the risk was 10 to 20%, especially when the bleeding risk was not increased. Family history of GI cancer would further support aspirin prescription. Aspirin therapy was more frequently in the aspirin group (RR 1.29, 95% CI 1.09–1.52; p = 0.003), and other extracranial bleeding

<table>
<thead>
<tr>
<th>Study (ref.)</th>
<th>Study design</th>
<th>Inclusion criteria</th>
<th>Patient n, median FU</th>
<th>Aspirin vs. placebo: efficacy</th>
<th>Aspirin vs. placebo: safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARRIVE14</td>
<td>Randomized, double-blind, placebo-controlled, multicenter study (Germany, Italy, Ireland, Poland, Spain, U.K., U.S.)</td>
<td>Patients ≥55 years (M) or 60 years (W), estimated moderate CV risk</td>
<td>12,546 patients, 5 years</td>
<td>No significant differences in: composite of time to first MI, stroke, cardiovascular death, unstable angina, or transient ischemic attack: HR 0.96, 95% CI 0.81–1.13, p = 0.60; fatal or nonfatal MI: HR 0.85, 95% CI 0.64–1.11, p = 0.233</td>
<td>GI bleeding (usually mild) more frequent in the aspirin group (HR 2.11, 95% CI 1.36–3.28; p &lt; 0.001); similar incidence of serious adverse events in both arms</td>
</tr>
<tr>
<td>ASCEND15</td>
<td>Randomized, double-blind, placebo-controlled, multicenter study (U.K.)</td>
<td>Patients ≥40 years diagnosed with diabetes mellitus (any type), no known CV disease, no clear indication for antiplatelet therapy</td>
<td>15,480 patients, 7.4 years</td>
<td>Serious vascular events less frequent in the aspirin group than in the placebo group (RR 0.88, 95% CI 0.79–0.97, p = 0.01) Similar incidence of GI cancer (RR 0.99, 95% CI 0.80–1.24) or any cancer (RR 1.01, 95% CI 0.92–1.11)</td>
<td>Major bleeding more frequent in the aspirin group (RR 1.29, 95% CI 1.09–1.52; p = 0.003), ++ GI and other extracranial bleeding</td>
</tr>
<tr>
<td>ASPREE16–18</td>
<td>Randomized, double-blind, placebo-controlled, multicenter study (Australia, U.S.)</td>
<td>Subjects aged ≥70 years (or ≥65 years if blacks or Hispanics in the U.S.), no cardiovascular disease, dementia, or physical disability</td>
<td>19,114 patients, 4.7 years</td>
<td>No significant differences in: composite of death, dementia, or persistent physical disability (HR 1.01, 95% CI 0.92–1.11, p = 0.79); CV disease: HR 0.95, 95% CI 0.83–1.08. Higher risk of death from any cause (but formal comparison not possible)</td>
<td>Higher rate of major hemorrhage in the aspirin group (HR 1.38, 95% CI 1.18–1.62, p &lt; 0.001)</td>
</tr>
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</table>

Abbreviations: CI, confidence interval; CV, cardiovascular; FU, follow-up; GI, gastrointestinal; HR, hazard ratio; MI, myocardial infarction; RR, relative risk.
thromboembolic events was balanced by an increase in risk of bleeding complications in patients with low risk of MACE, whereas patients with higher risk seemed to derive a net benefit from aspirin. As arbitrary cut-points useful for clinical decisions, the 10 and 20% values of 10-year risk of MACE were selected, with an area of uncertainty in patients with a 10-year risk of 10 to 20%. Additionally, the authors proposed to consider patient’s bleeding risk and the possible beneficial effect of aspirin toward the development of GI cancer, particularly colorectal cancer, since epidemiologic evidence indicates that regular and long-term use of aspirin is associated with a lower incidence of colorectal and other types of cancer.28

The same trends of risk of MACE and bleeding events as a function of 10-year MACE risk are observed in an updated meta-regression including the three latest trials, which either fell below the 10% threshold (6.8 and 8.3% in the ARRIVE and ASPREE trials, respectively)14,16-18 or just above the same threshold (10.2% in the ASCEND trial)15—see - Fig. 1A and - Supplementary Table S1 (available in the online version). The new trials diminish—but do not eliminate—the significance of the relationship of MACEs versus baseline cardiovascular risk, and the separation of the regression lines depicting the benefit (reduction in MACE) and the risk (increased bleeding) as a function of cardiovascular risk. It should be acknowledged that the trend of MACE risk is driven by the Early Treatment Diabetic Retinopathy Study (ETDRS),29 which included patients either in primary or secondary prevention, and statistical significance is lost when this trial is excluded ( Fig. 1B). It should further be noted that the net benefit from aspirin appears different in the only two trials above the 20% risk threshold, that is, the ETDRS29 and POPADAD trials.25 Last, clinicians must recognize that trials have been heterogeneous in many aspects over time, including the much more intensive control of cardiovascular risk factors and use of statins in the most recent trials. Despite these issues, the presentation of data in - Fig. 1 continues to suggest that there may be a net benefit from aspirin among those at the very highest levels of risk in primary prevention, as is clearly proven in secondary prevention, provided that conditions of high bleeding risk are excluded.

A potential consequent decision algorithm addressing the use of aspirin in primary prevention is presented in - Fig. 2, and this is broadly similar to that recently endorsed by the ACC and AHA.23 Importantly, this algorithm only considers prophylactic aspirin among those who are less than 70 years of age for whom optimal control of other risk factors, in particular cholesterol and blood pressure, has already been achieved.

The use of risk thresholds preferably requires the use of American-based score systems (preferably the Atherosclerotic Cardiovascular Disease Score, which estimates the 10-year risk of heart disease or stroke)30 even in the European setting, since the European Systematic Coronary Risk Evaluation risk charts yield only the risk of fatal atherosclerotic cardiovascular events; the use of this last algorithm would require somewhat imprecise conversion factors to estimate the incidence of MACE.22 Additionally, it is important to note that current risk scores seem to overestimate the risk of MACE in contemporary patient cohorts.31 For these reasons, the 10 and 20% values should be considered as reference points more than fixed thresholds. For patients aged less than 70 years, the 20% threshold in primary prevention would appear particularly justified, as it is the level of risk observed in current practice in secondary prevention, as in the COMPASS trial, where aspirin is the accepted standard of care.32 This level of risk is about half of the risk that patients with stable angina had.
almost three decades ago. This is also the approximate level of risk attributable to primary prevention with evidence of significant atherosclerosis, such as an ABI of < 0.9 or evidence of carotid artery plaques or coronary plaques by imaging techniques, now also available noninvasively, or with moderate/high levels of calcium score (>100 Agatston units). Finally, all patients must be thoroughly informed about the risks and potential benefits from therapy.

It should be noted that no reliable predictors of bleeding exist, and data suggest that cardiovascular risk factors are also risk factors for bleeding. This would reduce the proportion of individuals that would derive a benefit from aspirin by prevention of cardiovascular events. On the other hand, the proposed approach derives from three considerations:

1. Although we recognize that risk factors for bleeding largely overlap with cardiovascular risk factors, still the slope of the relationship between the burden of risk factors and MACE appears somewhat steeper than the relationship between the same burden and major bleeding events. The purpose of the approach is indeed to provide some evidence to this point.
2. Extracranial bleeding events, particularly in the case of GI bleeding, are usually less serious than MIs or ischemic strokes, and a proper net clinical benefit analysis attributing prognostic weights to nonfatal events, can only amplify the difference between benefit and risk. Clinical judgment on the relative risks of cardiovascular events and GI bleeding may be supported by the use of a dedicated risk calculator, as proposed by Lanas et al. (3) Additionally, it is important to remind that most GI bleeding events can be prevented through a more widespread use of proton-pump inhibitors, which may be cost-effective also in primary cardiovascular prevention.

Conclusion
Given current trial evidence, aspirin remains effective in secondary prevention, but should no longer be recommended for all primary prevention patients, and now probably only for a minority of them. Contemporary trial evidence also indicates that the first pharmacologic step in primary prevention beyond diet, exercise, and smoking cessation should be prescription of a statin, as benefits of this approach are clear and risks exceptionally low and reversible. Nonetheless, with regard to aspirin, we believe a nuanced approach in primary prevention similar to that recently proposed by the ACC/AHA is the best path forward. After optimal control of cardiovascular risk factors, involving in most patients properly titrated statin therapy, and when patients are less than 70 years of age, clinicians should assess cardiovascular risk. When that risk is high and when bleeding risk is not prohibitive, aspirin treatment should be considered, taking into account patients' preferences.

Conflict of Interest
R.D.C. declares having received fees and honoraria from Bayer related to the topic. A.A. and P.M.R. have no conflict of interest to disclose.

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