Revisiting the Role of Aspirin for the Primary Prevention of Cardiovascular Disease

ABSTRACT: Aspirin is the cornerstone of the antithrombotic management of patients with established atherosclerotic cardiovascular disease, but major guidelines provide conflicting recommendations for its use in primary prevention. Findings from recent randomized trials totaling >47 000 patients called into question the net clinical benefits of aspirin in primary prevention for 3 key populations: patients with diabetes mellitus, community-dwelling elderly individuals, and patients without diabetes mellitus who are at intermediate risk for atherosclerotic events. In the context of increasing emphasis on the use of other treatments for primary prevention in patients with moderate-high future risk of developing atherosclerotic cardiovascular disease, the efficacy and safety of aspirin for primary prevention has become uncertain. Key unresolved questions regarding the role of aspirin in primary prevention include the optimal drug formulation, dosing schedule, weight-based dose selection, and interplay between sex and treatment response. In the current era, most patients without established atherosclerotic cardiovascular disease should not be prescribed aspirin. Rather, aggressive management of comorbidities tailored to the expected cardiovascular risk needs to be emphasized. In this context, informed shared decision making between clinicians and patients regarding the use of aspirin for primary prevention of cardiovascular events is a suitable and laudable approach. In this article, we revisit the role of aspirin for the primary prevention of cardiovascular diseases by critically reviewing the key scientific literature, highlight key areas of uncertainties for future research, and propose a decisional framework for clinicians to support prescription of aspirin in primary prevention.

Key Words: antiplatelets ★ aspirin ★ atherosclerotic cardiovascular diseases ★ cardiovascular diseases ★ primary prevention

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Both globally and in the United States, atherosclerotic cardiovascular disease (ASCVD) represents the leading cause of death and disability. Aspirin has been the cornerstone of the antithrombotic management of patients with ASCVD for >3 decades. It exerts its biological action mainly by inhibition of cyclooxygenase (COX)-1 activity, and consequently of thromboxane A₂ synthesis, leading to irreversible suppression of platelet activation and aggregation. Clinical practice guidelines recommend long-term aspirin therapy for the secondary prevention treatment of patients with established ASCVD but provide conflicting recommendations for primary prevention in patients with an increased risk of developing ASCVD (Table 1). Until recently, the supportive evidence underlying guidelines recommendations in favor of aspirin in primary prevention were based on meta-analyses of randomized controlled trials (RCT), or cost-utility analyses. Although this level of evidence can be sufficient to support low-grade recommendations, they do not comply with evidentiary standards to support a label indication. The US Food and Drug Administration voiced reservations with the use of data from studies that were not initially intended to be pooled to support primary prevention claims. Their position is echoed by the Center for Disease Control’s Million Hearts® Initiative, and by the National Heart, Lung, and Blood Institute.

The standards of care for the management of cardiovascular risk factors for patients without established ASCVD, including diabetes mellitus, lipids, hypertension, smoking cessation, and lifestyle interventions, have evolved substantially in the contemporary era. While the pivotal role of aspirin as a long-term secondary prevention therapy for patients with established ASCVD has not diminished over the past decades, findings from 3 large-scale RCTs including >47000 patients call into question its net clinical benefits when used for primary prevention in 3 key patient populations: patients with diabetes mellitus, community-dwelling elderly individuals, and patients without diabetes mellitus who are at intermediate risk for future atherosclerotic events. In this article, we revisit the role of aspirin in primary prevention, critically review the key scientific literature, highlight areas of uncertainties for future research, and propose a decisional framework for clinicians to support prescription of aspirin in primary prevention.

Contemporary Trials Evaluating Aspirin for Primary Prevention of ASCVD

Several meta-analyses of RCTs evaluating the role of aspirin in primary prevention have demonstrated significant benefits in the prevention of vascular events compared with placebo, mainly driven by lower rates of nonfatal myocardial infarctions. However, findings were inconsistent with respect to the effect of aspirin on all-cause mortality, and major bleeding event rates were invariably increased. A timeline of the major RCTs evaluating aspirin for the primary prevention of ASCVD is shown in Figure 1. In 2018, 3 large-scale RCTs have been published, including the ARRIVE trial (Aspirin to Reduce Risk of Initial Vascular Events), the ASCEND trial (A Study of Cardiovascular Events in Diabetes), and the ASPREE trial (Aspirin in Reducing Events in the Elderly).

Summary and Implications of the ARRIVE Trial: Aspirin in the Primary Prevention of ASCVD in Nondiabetic Patients at Moderate Risk of Cardiovascular Diseases

In the double-blind, multicenter, international ARRIVE trial, 12546 participants from 6 European countries and the United States, with an estimated 10% to 20% 10-year risk of developing coronary artery disease, were randomized to aspirin 100 mg daily vs placebo, and followed for an average of 5 years. The primary endpoint, defined as time to myocardial infarction, stroke, cardiovascular death, unstable angina, or transient ischemic attack, occurred in 269 (4.29%) participants in the aspirin group vs. 281 (4.48%) in the placebo group (hazard ratio [HR], 0.96; 95% CI, 0.81–1.13; P=0.6038). These results were consistent in prespecified subgroups, and there was no significant difference in the frequency of the individual components of the primary endpoint or in all-cause death. Gastro-intestinal bleeding events occurred in <1% of patients in each group and were predominantly mild but were more frequent for those assigned to aspirin (HR, 2.11; 95% CI, 1.36–3.28; P=0.0007). A major limitation of the ARRIVE trial was that the observed event rates were lower than anticipated, providing less power to detect a difference between the groups than originally planned. The primary composite endpoint was modified during the trial by adding transient ischemic attack and unstable angina as component endpoints, and the neutral results were consistent for both definitions of the primary endpoint. As such, the role of aspirin in primary prevention of cardiovascular events in patients with at least a moderate future risk of developing ASCVD remains uncertain.

Summary and Implications of the ASCEND Trial: Aspirin in the Primary Prevention of ASCVD in Diabetic Patients

In the ASCEND trial, conducted in the United Kingdom, 15480 patients ≥40 years old with diabetes mellitus without established ASCVD were randomized to aspirin 100 mg daily or placebo. After a mean follow-up of 7.4 years, the frequency of the primary endpoint (composite of nonfatal myocardial infarction, nonfatal stroke or
transient ischemic attack, or death from any vascular cause), was 8.5% with aspirin and 9.6% with placebo (HR, 0.88; 95% CI, 0.79–0.97; P=0.01). This salutary effect of aspirin came at the expense of more major bleeding events (rate ratio, 1.29; 95% CI, 1.09–1.52; P=0.003). Fatal and intracranial bleeding events were observed in <1% of participants with no significant between-group difference. Similarly to the ARRIVE trial, transient ischemic attack was added to the primary endpoint composite during the course of the trial, and only a non-significant trend was observed in favor of aspirin when transient ischemic attack was excluded from the primary endpoint (HR, 0.92; 95% CI, 0.82–1.03). The take-home message is that among patients with diabetes mellitus without established ASCVD, aspirin was associated with a modest decrease in the risk of ischemic events, but these findings were counterbalanced by an increased risk of major bleeding events.

### Table 1. Summary of Guidelines Recommendations for Aspirin in Primary Prevention of Atherosclerotic Cardiovascular Diseases

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Recommendation</th>
<th>Level of Evidence</th>
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<tbody>
<tr>
<td>2019 American College of Cardiology/American Heart Association Guideline on the Primary Prevention of Cardiovascular Disease</td>
<td>Low-dose aspirin (75–100 mg/d orally) might be considered among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk</td>
<td>llb, A: weak recommendation; high-quality evidence from more than 1 RCT or meta-analyses of high-quality RCTs or 1 or more RCTs corroborated by high-quality registry studies</td>
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<tr>
<td></td>
<td>Low-dose aspirin (75–100 mg/d orally) should not be administered on a routine basis for the primary prevention of ASCVD among adults &gt;70 years of age</td>
<td>III, B-R: harm; moderate-quality evidence from 1 or more RCTs, or meta-analyses of moderate-quality RCTs</td>
</tr>
<tr>
<td></td>
<td>Low-dose aspirin (75–100 mg/d orally) 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, C-LD: harm; randomized or nonrandomized observational or registry studies with limitations of design or execution or meta-analyses of such studies or physiological or mechanistic studies in human subjects</td>
</tr>
<tr>
<td>American Diabetes Association Standards of Medical Care in Diabetes 2019</td>
<td>Aspirin 75–162 mg daily for patients with diabetes mellitus at increased cardiovascular risk (who do not have known CVD)</td>
<td>Class C: supportive evidence from poorly controlled or uncontrolled studies</td>
</tr>
<tr>
<td>US Preventive Services Task Force 2016 Recommendations for Primary Care Practice</td>
<td>Low-dose aspirin for adults 50–59 years old without CVD but with a ≥10% 10-year CVD risk</td>
<td>B: High certainty that the net benefit is moderate, or moderate certainty that the net benefit is moderate to substantial</td>
</tr>
<tr>
<td></td>
<td>Low-dose aspirin for adults 60–69 years old without CVD but with a ≥10% 10-year CVD risk</td>
<td>C: At least moderate certainty that the net benefit is small</td>
</tr>
<tr>
<td></td>
<td>No recommendation for patients &lt;50 or ≥70 years old without CVD</td>
<td>I: Current evidence is insufficient</td>
</tr>
<tr>
<td>European Society of Cardiology 2016 Guidelines on Cardiovascular Disease Prevention in Clinical Practice</td>
<td>Aspirin not recommended in individuals without CVD</td>
<td>III, B: Treatment not recommended, data derived from a single randomized clinical trial or large nonrandomized studies</td>
</tr>
<tr>
<td>American Heart Association Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women—2011 Update</td>
<td>Routine use of aspirin in healthy women &lt;65 years of age without CVD is not recommended to prevent myocardial infarction</td>
<td>III, C: Procedure/test not helpful or treatment has no proven benefit, procedure/test excess cost without benefit or harmful or treatment harmful to patients; based on expert opinion, case studies, or standard of care</td>
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<td></td>
<td>Aspirin therapy (75–325 mg/d) is reasonable to use in women with diabetes mellitus without known CVD unless contraindicated</td>
<td>llb, A: weight of evidence/opinion is in favor of usefulness/efficacy; limited evidence from single randomized trial or other nonrandomized studies</td>
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<tr>
<td></td>
<td>Aspirin therapy can be useful in women ≥65 y of age without known CVD (81 mg/d or 100 mg every other day) if blood pressure is controlled and benefit for ischemic stroke and myocardial infarction prevention is likely to outweigh risk of gastrointestinal bleeding and hemorrhagic stroke</td>
<td>llb, A: weight of evidence/opinion is in favor of usefulness/efficacy; limited evidence from single randomized trial or other nonrandomized studies</td>
</tr>
<tr>
<td></td>
<td>Aspirin (81 mg/d or 100 mg every other day) may be reasonable for women &lt;65 y without known CVD for ischemic stroke prevention</td>
<td>llb, B: usefulness/efficacy is less well established by evidence/opinion; limited evidence from single randomized trial or other nonrandomized studies</td>
</tr>
<tr>
<td>Canadian Cardiovascular Society Antithrombotic Guidelines</td>
<td>Aspirin not routinely recommended for patients without CVD</td>
<td>llb, B: use of aspirin is better established by evidence/opinion; limited evidence from single randomized trial or other nonrandomized studies</td>
</tr>
<tr>
<td></td>
<td>Aspirin 75–162 mg daily recommended for patients without CVD, if high vascular risk and low bleeding risk</td>
<td>llb, C: Conflict of evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment with the usefulness/efficacy less well established; consensus of opinion by experts and/or small studies, retrospective studies, and registries</td>
</tr>
</tbody>
</table>

ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; and RCT, randomized controlled trial.
Despite some limitations, the ASCEND trial provides high-quality evidence given the large sample size, the long length of follow-up, and the pragmatism of the trial eligibility criteria (only 5 inclusion and exclusion criteria altogether). However, the lack of significant benefit of aspirin observed using the original prespecified primary endpoint and the small magnitude of clinical effect (1.1% absolute risk reduction), indicate that aspirin does not have a definitive indication in primary prevention for patients with diabetes. In contrast, a shared decision-making approach involving clinicians and patients should be encouraged, in which the tradeoff between ischemic event reduction and increased bleeding risk with aspirin can be considered. According to the 2019 American Diabetes Association Standards of Medical Care in Diabetes, aspirin should be considered in certain cardiovascular risk categories. Modest relative risk reduction with aspirin in patients with diabetes translate into increasingly higher absolute reductions as the overall cardiovascular risk category increases, based on available risk calculators. Practical algorithms have been proposed to guide aspirin therapy use in primary prevention in patients with diabetes mellitus, incorporating an estimation of the ASCVD risk.

**Summary and Implications of the ASPREE Trial: Aspirin in Primary Prevention in Community-Dwelling Elderly Patients**

In the ASPREE trial, 19,114 participants from Australia or the United States aged ≥70 years old (≥65 years old for Hispanic and African American patients within the United States) without life-limiting chronic illness, dementia, physical disability or documented cardiovascular or cerebrovascular disease, were randomized to aspirin 100 mg daily or placebo. After a median follow-up of 4.7 years, the trial was stopped prematurely based on futility. The primary endpoint of disability-free survival (survival free from dementia or persistent physical disability) occurred in 21.5 per 1000 patient-years in the aspirin group and 21.2 per 1000 patient-years in the placebo group (HR, 1.01; 95% CI, 0.92–1.11; P=0.79), with significantly more major bleeding events with aspirin (8.6 vs. 6.2 per 1000 patient-years; HR, 1.38, 95% CI, 1.18–1.62; P<0.001). The incidence rate of cardiovascular disease was also similar between study groups. Although the latter cardiovascular endpoint was not specified as the primary endpoint, it remains unlikely that the trial missed a significant beneficial effect of aspirin to prevent major adverse cardiovascular events, given ASPREE’s large sample size and the consistency of the results among the relevant prespecified subgroups. A higher risk of all-cause mortality was observed with aspirin, mainly driven by cancer-related mortality, although this signal disappeared after statistical correction for multiple comparisons. In summary, the ASPREE trial did not show any benefit of aspirin in terms of disability-free survival in elderly patients without documented cardiovascular disease but demonstrated higher major bleeding rates and a signal for higher all-cause mortality. These findings thus call into question the use of aspirin in primary prevention.
in community-dwelling elderly patients in the contemporary era.

A summary of the ARRIVE, ASCEND, and ASPREE trials are provided in Table 2. An updated meta-analysis including these 3 trials did not demonstrate significant survival benefits with aspirin in primary prevention (risk ratio, 0.98; 95% CI, 0.93–1.02; P=0.30), and confirmed the heightened risks of major bleeding (risk ratio, 1.47; 95% CI, 1.31–1.65; P<0.0001).31 These findings were consistent among trials including high-risk and diabetic patients.31

**Key Residual Questions**

**Tailoring Aspirin Dosing and Formulation**

Whether testing higher doses of aspirin in primary prevention would uncover significant cardiovascular benefits in the current era remains uncertain. The proportional dose-relationship of aspirin to define bleeding risk is well established, but the clinical equipoise surrounding aspirin dosing has been reflected by the variability of clinical practice patterns.32 Prior post hoc analyses of RCTs, meta-analyses, and a single, short-term RCT of low-dose vs high-dose aspirin (CURRENT-OASIS 7) have not definitively established the efficacy and safety profiles of different aspirin dosing regimens in secondary prevention.4,33,34

Mechanistic knowledge of the pharmacodynamic targets of aspirin can contribute to explain the heightened thrombotic risk occasionally observed with higher doses. Doses in the lower range (75–162 mg) are sufficient to saturate COX-1 acetylation, leading to maximal thromboxane A2 suppression required for adequate platelet inhibition. Increasing the dose over this range does not provide incremental pharmacodynamic advantage through this pathway, but rather augments dose-dependent COX-2 inhibition, leading to suppression of prostacyclin synthesis. This prostaglandin has established platelet aggregation inhibition and vasodilatory properties, potentially underpinning a paradoxical prothrombotic effect of aspirin with higher doses.

Inter-individual variability of COX-1 recovery following once-daily aspirin administration, with some patients having faster thromboxane B2 renormalization during the 12- to 24-hour period after administration, can be counteracted by twice-daily regimens.35

<table>
<thead>
<tr>
<th>Study population</th>
<th>ARRIVE</th>
<th>ASCEND</th>
<th>ASPREE</th>
</tr>
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<tbody>
<tr>
<td>Men ≥55 years and 2–4 risk factors; women ≥60 years and ≥3 risk factors from Europe and the United States</td>
<td>≥40 years old with type I or type II diabetes mellitus without known cardiovascular disease from the United Kingdom</td>
<td>≥70 years old (≥5 years for Hispanic and African American patients) in Australia or the United States without life-limiting chronic illness, dementia, physical disability or documented cardiovascular or cerebrovascular disease</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>63.9 (mean)</td>
<td>63.3 (mean)</td>
<td>74 years (median)</td>
</tr>
<tr>
<td>Sample size</td>
<td>12 546 patients</td>
<td>15 480 patients</td>
<td>19 114 patients</td>
</tr>
<tr>
<td>Median follow-up time, y</td>
<td>5</td>
<td>7.4</td>
<td>4.7</td>
</tr>
<tr>
<td>Study interventions</td>
<td>Enteric-coated aspirin 100 mg daily versus placebo</td>
<td>Enteric-coated aspirin 100 mg daily versus placebo</td>
<td>Enteric-coated aspirin 100 mg daily versus placebo</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Composite of time to myocardial infarction, stroke, cardiovascular death, unstable angina, or transient ischemic attack</td>
<td>Serious vascular event (composite of nonfatal myocardial infarction, nonfatal stroke (excluding confirmed intracranial hemorrhage) or transient ischemic attack, or death from any vascular cause (excluding confirmed intracranial hemorrhage)</td>
<td>Disability-free survival, defined as survival free from dementia or persistent physical disability</td>
</tr>
<tr>
<td>Results:</td>
<td>Aspirin versus placebo: 4.3% versus 4.5%; hazard ratio, 0.96 (95% CI, 0.81–1.13; P=0.6038)</td>
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<tr>
<td>All-cause mortality</td>
<td>Aspirin, 2.6%; placebo, 2.6%; hazard ratio, 0.99 (95% CI, 0.80–1.24; P=0.9459)</td>
<td>Aspirin, 9.7%; placebo, 10.2%; rate ratio, 0.94 (95% CI, 0.85–1.04)</td>
<td>Aspirin, 12.7 per 100 patient-year; placebo, 12.1 per 100 patient-year (P=0.79)</td>
</tr>
<tr>
<td>Bleeding endpoints</td>
<td>Gastrointestinal bleeding events</td>
<td>Major bleeding events</td>
<td>Major hemorrhagic events</td>
</tr>
<tr>
<td>Aspirin: 0.97%; placebo: 0.46%; hazard ratio, 2.11 (95% CI, 1.36–3.28; P=0.0007)</td>
<td>Aspirin: 4.1%; placebo: 3.2%; rate ratio, 1.29 (95% CI, 1.09–1.52)</td>
<td>Aspirin: 8.6 per 1000 person-year; placebo: 6.2 per 1000 person-year; hazard ratio, 1.38 (95% CI, 1.18–1.62)</td>
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</table>

ARRIVE indicates Aspirin to Reduce Risk of Initial Vascular Events; ASCEND, A Study of Cardiovascular Events in Diabetes; and ASPREE, Aspirin in Reducing Events in the Elderly.
A dose-escalating pharmacodynamic study suggested that twice-daily aspirin administration was associated with better platelet inhibition than increasing the once daily dose in patients with diabetes mellitus.36 Owing to aspirin pseudoresistance observed in patients with diabetes mellitus, partly explained by accelerated thrombopoiesis and platelet turnover, its net clinical benefits might improve with dosing regimens different from once-daily administration in this population.29 The potential benefits of extended-release formulations or of twice-daily administration remains to be studied in phase III trials in patients with diabetes mellitus and in those with faster COX-1 recovery (Table 3).

Furthermore, enteric-coated aspirin was used in the ARRIVE, ASCEND, and ASPREE trials, but recent pharmacodynamic and pharmacokinetic insights have shown that half of patients with diabetes mellitus are nonresponders to this formulation.37 This proportion is significantly reduced if plain aspirin or a modified-release lipid-based aspirin formulations are used.37 This observation was mediated by lower absorption with enteric-coated aspirin, translating into decreased bioavailability. In the absence of definitive evidence for bleeding risk mitigation with enteric-coated aspirin, the use of this formulation in the recent large-scale trials might have led to suboptimal bioavailability of the drug, undermining the evaluation of the full potential of aspirin to prevent ASCVD, especially in participants with diabetes mellitus.

**Interplay Between Body Weight and Treatment Effect**

Emerging evidence suggests that the anti-platelet activity of aspirin is influenced by body weight. Findings from a recent meta-analysis including more than 100,000 patients with established ASCVD from 9 previous aspirin clinical trials suggested that patients weighing ≥70 kg did not derive benefit with low-dose (≤100 mg daily) aspirin (HR, 0.95; 95% CI, 0.86–1.04; P for interaction=0.0072), that patients weighing <70 kg did not derive benefits with doses of aspirin ≥300 to 325 mg (P for interaction=0.017), and that a putative dose-response relationship with higher doses of aspirin demonstrating greater benefit with increasing body weight may be present.42 The results of this meta-analysis suggest that the efficacy of aspirin to prevent cardiovascular events may vary according to body weight (and likely drug exposure) and that a more personalized approach to aspirin dosing could be helpful. The apparent interaction between aspirin dose and body weight observed in the meta-analysis contrasts with the results from the ASCEND trial, which suggested that only patients with weighting ≥70 kg or with a body mass index ≥30 seemed to benefit from low-dose aspirin. Body mass index was not an effect modifier in the ASPREE and the ARRIVE trials. Because none of the findings regarding body weight and aspirin treatment effect were the results of a priori hypotheses before the development of the datasets, they can only be considered as hypothesis testing.

<table>
<thead>
<tr>
<th>Areas of Uncertainty</th>
<th>Rationale</th>
<th>Proposed Potential Study</th>
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</thead>
<tbody>
<tr>
<td><strong>Optimal drug formulation</strong></td>
<td>Increased platelet turnover in patients with diabetes mellitus Interindividual variability of cyclooxygenase-1 recovery can be overcome by twice-daily aspirin</td>
<td>Randomized trial comparing twice-daily aspirin and/or extended-release formulation to placebo, preferably in patients with diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>In patients with diabetes mellitus, the number of nonresponders is significantly higher with enteric-coated aspirin compared with other formulations Definitive evidence for bleeding risk mitigation with enteric-coated aspirin is lacking</td>
<td>Randomized trial comparing plain aspirin and/or modified-release lipid-based aspirin to placebo, preferably in patients with diabetes mellitus</td>
</tr>
<tr>
<td><strong>Interplay between body weight and aspirin dosing</strong></td>
<td>A meta-analysis of randomized trials suggests an interaction between body weight and treatment response according to the dose of aspirin In ASCEND, only patients weighing ≥70 kg benefited significantly from low-dose aspirin</td>
<td>Randomized trial comparing a weight-based aspirin dosing strategy versus placebo, in which randomization is stratified by weight</td>
</tr>
<tr>
<td><strong>Decision support tools</strong></td>
<td>Tools to predict the net clinical benefit of aspirin in primary prevention of ASCVD are lacking</td>
<td>Derivation and external validation of risk prediction scores to identify patients for trial inclusion who are predicted to be the most likely to derive net positive benefits from aspirin</td>
</tr>
<tr>
<td><strong>Interaction between sex and aspirin</strong></td>
<td>Evidence suggests that aspirin reduces the risk of myocardial infarction only in men, and the risk of ischemic strokes only in women</td>
<td>Randomized trial of aspirin in primary prevention stratified by sex, with both strata sufficiently powered to detect a significant treatment effect</td>
</tr>
<tr>
<td><strong>Cancer chemoprevention</strong></td>
<td>The US Preventive Services Task Force recommends aspirin for the prevention of colorectal cancer, and family history of gastrointestinal cancer has been advocated as a variable to take into account in the risk/benefit assessment for aspirin prescription</td>
<td>Randomized trials specifically evaluating the effect of aspirin on cancer-related endpoints. The ADD-ASPIRIN trial (URL: <a href="https://www.clinicaltrials.gov">https://www.clinicaltrials.gov</a>; unique identifier: NCT02804815) is currently ongoing to address this question</td>
</tr>
</tbody>
</table>

ADD-ASPIRIN indicates A Trial Assessing the Effects of Aspirin on Disease Recurrence and Survival After Primary Therapy in Common Non Metastatic Solid Tumours; ASCEND, A Study of Cardiovascular Events in Diabetes; and ASCVD, atherosclerotic cardiovascular disease.
Interplay Between Sex and Response to Aspirin

How the sex-based biologic differences in the pharmacodynamic response to aspirin should affect the patterns of prescription is another key unresolved issue. In their guidelines for the prevention of cardiovascular diseases in women, the American Heart Association established specific recommendations for aspirin in primary prevention targeted toward women (Table 1). Even if low-dose aspirin suppresses the direct COX-1 activation pathway similarly between both genders, a meta-analysis of 6 RCTs suggested that aspirin reduced the risk of myocardial infarction only in men, and the risk of ischemic strokes only in women, while the effect on mortality was neutral for both men and women. Aspirin increased significantly the risk of bleeding for both genders. This meta-analysis is limited by the fact that 3 of the included trials only involved men, and 1 only involved women, implying that male men and women populations included in the pooled analysis were not comparable. In the Women’s Health Study, the only trial focusing exclusively on women (n=39,876), the rates of major cardiovascular events was similar between those who were randomized to aspirin 100 mg on alternate days and placebo, but aspirin was associated with a significant relative 17% risk reduction in strokes. In the ARRIVE, ASCEND, or ASPREE trials, there was no significant interaction between sex and treatment effect of aspirin. Collectively, in the absence of trial in which randomization was stratified by sex, the available evidence does not support a sex-based personalization of aspirin therapy in primary prevention of ASCVD.

CONCLUSION

The positioning of aspirin as a treatment option for the primary prevention of cardiovascular events has been informed by the recent results of 3 large-scale RCTs that collectively question its role for the treatment of patients without established ASCVD. A decisional framework for clinicians to support prescription of aspirin in primary prevention is presented in Figure 2. Key unresolved questions regarding the role of aspirin in primary prevention include the optimal drug formulation, dosing schedule, weight-based dose selection, and interplay between sex and treatment response. Given the desire expressed by regulatory authorities to explore the use of real-world data sources in RCTs, creative approaches are needed in future trials of aspirin in primary prevention. For example, evaluation of the validity and utility of risk calculators derived from real-world data could be conducted to enable their use to inform modeling of eligibility criteria. In the current era, most patients without established ASCVD should not be prescribed aspirin in the absence of established evidence for definitive risk reduction and of decision support tools to tailor patient selection according to

Predicting Future Cardiovascular and Bleeding Risk in the Primary Prevention Population

Results from both the ARRIVE and ASCEND trials demonstrate the difficulties with accurately predicting the risk of future ischemic cardiovascular events in patients without established ASCVD, given that event rates were lower than expected, similarly to previous trials evaluating cardiometabolic therapies. Over the past decade, the management of known cardiovascular risk factors has evolved considerably based on several developments in the risk stratification and treatment of dyslipidemia, hypertension, and diabetes, accounting for the overestimation of the risk of ASCVD using available tools. This current landscape lead the ACC/AHA to move away from recommending the use of a specific risk threshold based on the validated pooled cohort equations in the decision to prescribe aspirin in primary prevention. Rather, the guidelines encourage clinicians to weigh the totality of the available evidence in their decision to prescribe aspirin in primary prevention, which includes traditional comorbidities in addition to risk-enhancing factors.

Longitudinal prediction risk scores have been derived and validated to inform the choice of dual antiplatelet therapy duration in secondary prevention. However, tools to predict the risk/benefit ratio of aspirin in primary prevention of ASCVD are lacking. Risk tables have been developed to estimate bleeding off-aspirin in a cohort of 359,166 patients without cardiovascular disease, but they do not inform on the bleeding risk on aspirin treatment. In the era of precision medicine, development of decision support tools leveraging real-world data reflecting patients treated in routine practice more accurately than the more narrowly defined clinical trial populations is desirable to inform net clinical benefits of aspirin initiation in primary prevention. This real-world data can incorporate multisource technologies including electronic health records and digital mobile health applications. Recently, a risk score incorporating 17 variables was developed and internally validated to predict bleeding risk in a cohort of 385,191 patients without cardiovascular disease in New Zealand. However, the effect of this score for clinical practice is limited because it does not inform on the expected ischemic benefits, its generalizability in the US population is unknown, and it does not apply to patients with diabetes, which were excluded from the development cohort.

Globally generating. Dedicated trials focusing on a personalized approach with the use of aspirin tailored to body weight are required. Results from the ADAPTABLE trial (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-Term Effectiveness) that is evaluating low-dose (81 mg) vs. high-dose (325 mg) aspirin for patients with established ASCVD should provide more definitive evidence regarding optimization of aspirin dose but targeted only toward secondary prevention.
the expected net clinical benefits. Rather, aggressive management of comorbidities tailored to the expected cardiovascular risk needs to be emphasized. Informed shared decision making between clinicians and patients regarding the use of aspirin for primary prevention of cardiovascular events is a suitable and laudable approach going forward.\textsuperscript{11}

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