EDITORIAL

Aspirin for Primary Prevention
Clinical Considerations in 2019

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Reducing platelet activity with aspirin and other antiplatelet agents is an important factor in the prevention and management of atherothrombotic vascular events.[1] For this indication, aspirin has both beneficial and potentially harmful effects; it can diminish or reverse thrombus formation (eg, in the setting of acute myocardial infarction or stroke), but it also increases the risk of bleeding.

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The antiplatelet effects of aspirin led to trials involving patients with acute events, such as stroke and myocardial infarction. For instance, in the Second International Study of Infarct Survival (ISIS-2),[2] which included 17 187 patients with acute myocardial infarction, aspirin reduced the risk of serious vascular events, including death, around the time of the acute event. This beneficial effect occurs over days, and there is little or no bleeding risk during that short duration. Subsequent secondary prevention trials involving patients with cardiovascular disease (CVD) also demonstrated clear benefits of aspirin in reducing the risk of vascular events. Several hundred secondary prevention trials have been conducted, and data from these studies (287 studies with approximately 212 000 patients) were pooled in the first Antithrombotic Trialists' Collaboration meta-analysis published in 2002.[3] Results demonstrated a 22% relative reduction (2.5% absolute risk reduction) in important vascular events associated with aspirin use, which outweighed the increased bleeding risk (0.42% absolute risk increase).

It has also clearly been demonstrated that aspirin can reduce the risk of events following vascular procedures, such as stent placement, and that this reduction outweighs the risk of bleeding. For this reason, most guidelines are in general agreement in recommending aspirin as therapy after acute vascular events, for secondary prevention, and at the time of certain vascular procedures.

The next logical question was whether aspirin could be effective in primary prevention. However, there are many challenges in conducting primary prevention trials. The CVD event rates are much lower than in the setting of acute treatment, secondary prevention, and after certain vascular procedures. For this reason, study populations need to be larger and the study duration must be longer. Further, it is easier to maintain medication adherence among patients with known disease who are concerned about preventing a subsequent event and are taking other medications. Accordingly, there are fewer primary prevention trials than secondary prevention trials, and they have had varied results.

The Physicians' Health Study was the first to show that chronic aspirin use could prevent a first myocardial infarction.[4] Pooled estimates from the first 6 studies of aspirin for primary prevention indicated a 12% relative reduction (0.06% absolute risk reduction) in first CVD events in contrast to the 22% relative reduction seen in secondary prevention.[5] Another meta-analysis demonstrated a greater effect in first CVD events in the initial 3 years of these trials.[6] This finding may reflect decreasing adherence with aspirin over the longer duration of the primary prevention trials.

Unlike acute treatment and secondary prevention, aspirin use for primary prevention involves a similar magnitude of vascular events prevented and bleeding events caused, especially among the lower-risk patients included in most primary prevention trials. Thus, guidelines on aspirin use for primary prevention do not all agree. The European Society of Cardiology does not recommend aspirin for primary prevention,[7] whereas the US Preventive Services Task Force (USPSTF) recommends aspirin after considering the effects of aspirin on vascular events and bleeding, as well as the longer-term potential effects in reduction of risk of colorectal cancer, and recommends aspirin for primary prevention based on a patient's risk of future vascular disease, bleeding events, and longevity as well as personal preferences.[8]

Three 2018 trials were designed to fill gaps in knowledge involving treatment of patients who have been less represented in previous trials. These included A Study of Cardiovascular Events in Diabetes (ASCEND) trial for patients with diabetes (N = 15 480),[9] the Aspirin for Reducing Events in the Elderly (ASPREE) trial for older patients (N = 19 114),[10-12] and the Aspirin to Reduce Risks of Initial Vascular Events (ARRIVE) trial for patients at higher CVD risk based on multiple risk factors (N = 12 546).[13]

In this issue of *JAMA*, Zheng and Roddick[14] report findings from a meta-analysis in which the data from these new trials were combined with data from 10 previous primary prevention trials, resulting in a total of 164 225 participants with 1 050 511 participant-years of follow-up. This meta-analysis demonstrates that the estimated risks and benefits of aspirin for primary prevention were not materially altered with the addition of the 3 recent trials, despite the challenges in conducting trials in the current setting of aggressive preventive strategies, such as use of statins. Aspirin use, compared with no aspirin, was associated with significant reductions in the composite cardiovascular outcome of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke (57.1 per 10 000 participant-years with aspirin and 61.4 per

1000 participant-years with no aspirin) (hazard ratio [HR], 0.89 [95% credible interval, 0.84-0.95]; absolute risk reduction, 0.38% [95% CI, 0.20%-0.55%]; number needed to treat, 265). Aspirin use also was associated with an increased risk of major bleeding events compared with no aspirin (23.1 per 10 000 participant-years with aspirin and 16.4 per 10 000 participant-years with no aspirin) (HR, 1.43 [95% credible interval, 1.30-1.56]; absolute risk increase, 0.47% [95% CI, 0.34%-0.62%]; number needed to harm, 210).

In an exploratory analysis, Zheng and Roddick found no overall association between aspirin use and incident cancer or cancer mortality. This finding is consistent with previous studies that did not detect an effect of aspirin on reduction in risk of total cancer until much longer follow-up.[15] Also, there was no significant difference in all-cause mortality or CVD mortality associated with aspirin use.

The meta-analysis was well conducted. Both fixed-and random-effects models were presented in supplemental tables, and the results were similar to the initial results. One limitation is that the analysis was not a pooled analysis based on individual patient data, such as the analysis conducted by the Antithrombotic Trialists collaboration,[3,5] thereby limiting the ability to examine some subgroups and account for some differences in the outcomes. However, in the past, the overall results for the primary effects of aspirin were similar regardless of the type of meta-analysis conducted.

How does the new information from the 3 recently published trials and the meta-analysis by Zheng and Roddick add to the current understanding about aspirin for primary prevention? The best estimates for the effects of aspirin on CVD events and bleeding have not materially changed after the results of the 2018 trials. These recent trials provide important data for older individuals, patients with diabetes, and patients with multiple risk factors, and may contribute meaningfully to the effect of aspirin use on cancer after longer follow-up.

The similarity of the number needed to treat (265) and the number needed to harm (210) has been the rationale for some guidelines that recommend not using aspirin for primary prevention and waiting to initiate aspirin until there is manifest CVD disease (secondary prevention) when the separation between benefit and risk is more clear. On the other hand, the USPSTF recommends improving the benefit-to-harm ratio for aspirin in primary prevention by estimating future risks of vascular and bleeding events, by understanding longevity as an indicator of the potential longer-term benefits of aspirin for colorectal cancer prevention, and by carefully discussing patient preferences regarding vascular and bleeding events.[8] The meta-analysis by Zheng and Roddick demonstrates that the estimates for aspirin preventing vascular events and for increasing bleeding risk that support this USPSTF approach are largely unchanged after the addition of the new trials.

A personalized approach toward aspirin use for patients above a certain threshold of CVD risk is predicated on the ability to accurately estimate the risk of future events. CVD risk calculators tend to overestimate risk for populations in which CV risk is declining, such as in the United States and Europe. Further, risk is not static. If patients stop smoking, achieve better control of lipids and blood pressure, or adopt healthier lifestyles, the future risk of CVD events declines. Other guidelines, such as guidelines for lipid and blood pressure management, also advocate the use of risk estimation in tailoring therapy. Perhaps new genetic markers and risk estimators derived from artificial intelligence approaches will help refine risk assessment. Because weighing the risks and benefits of aspirin in primary prevention is complicated, it should involve a shared decision-making discussion between the patient and the clinician.

The meta-analysis by Zheng and Roddick demonstrates a general consistency of the newer studies with the previous studies of aspirin for primary prevention of cardiovascular events. When applying these results to an individual patient, clinicians must consider other interventions in addition to aspirin, such as smoking cessation and control of blood pressure and lipid levels, to lower risk. In places of the world in which CVD risk is rising or where other preventive strategies, such as statins, are less available, aspirin as a low-cost intervention may have a more important role. Aspirin remains an important medication for acute management of vascular events; for use after certain procedures; for secondary prevention; and, after careful selection of the right patients, for primary prevention.

ARTICLE INFORMATION

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