Aspirin for Primary Prevention—Time to Rethink Our Approach
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Over the past decades, the medical community has witnessed a significant improvement in cardiovascular disease (CVD) outcomes. Nonetheless, CVD remains a leading cause of morbidity and mortality globally. Prevention strategies must address all aspects of a patient’s lifestyle habits, including healthy nutrition, physical activity, smoking cessation, and stress reduction. When an individual’s risk is sufficiently high, pharmacologic therapy is often considered to reduce CVD risk as part of a shared decision-making process for optimal CVD prevention.

Aspirin is a cornerstone of antiplatelet therapy for the secondary prevention of CVD, but its role in primary prevention remains uncertain. Over the past several decades, there has been great interest to identify individuals for whom the clinical benefit of aspirin for the prevention of a first heart attack or stroke (primary prevention) exceeds the risk of bleeding. Meta-analyses of early primary prevention trials of aspirin suggested a modest benefit of low-dose aspirin in the prevention of first heart attack or stroke at the cost of excess major bleeding. In fact, the number needed to treat to prevent a single cardiovascular event was comparable to the number needed to harm by causing 1 major bleeding event. Thus, early guidelines recommended low-dose aspirin only for individuals with high CVD risk when the benefit would exceed the risk. Over time, larger trials investigating the benefit vs risk of low-dose aspirin were designed in individuals with higher CVD risk, including older adults, individuals with diabetes, and individuals with subclinical CVD. Despite the enrollment of individuals with higher risk, the results were consistent: the clinical benefit of aspirin was marginal and, in most individuals, the benefit was offset by the excess risk of bleeding.

Based on cumulative data, the US Preventive Services Task Force (USPSTF) updated its 2016 recommendations on the use of aspirin for the primary prevention of CVD. The 2022 USPSTF recommendations suggest that the decision to initiate low-dose aspirin for the primary prevention of CVD in adults ages 40 to 59 years who have a 10% or greater 10-year CVD risk should be an individual one (C statement), and recommends against initiating low-dose aspirin use for the primary prevention of CVD in adults aged 60 years or older (D statement). While the new USPSTF recommendations have some distinguishing features from the 2016 recommendations, including changing the age ranges and statement grades on aspirin use, and stating that the evidence is inadequate that low-dose aspirin use reduces colorectal cancer incidence and mortality, the overall message and recommendations are largely consistent with regard to individualized decision-making. Both the 2016 and 2021 recommendations remind us that the clinical benefit of low-dose aspirin for primary prevention is marginal and must be carefully balanced against the well-known excess risk of major bleeding.

Consistent with the USPSTF approach, other guidelines recommend a tailored decision-making process between the patient and the health care professional based on the potential benefit vs risk. The American College of Cardiology and American Heart Association recommend that low-dose aspirin use (75 to 100 mg/d) might be considered for the primary prevention of atherosclerotic CVD among select adults ages 40 to 70 years at higher CVD risk but not at increased risk of bleeding. Low-dose aspirin use is not recommended on a routine basis for primary prevention of CVD in adults older than 70 years, or among adults of any age who are at increased risk of bleeding. The European Society of Cardiology suggests that among individuals at very high CVD risk, low-dose aspirin may be considered for primary prevention. The American Academy of Family Physicians supports the 2016 USPSTF recommendation on aspirin use.

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A personalized approach toward aspirin use for patients at elevated cardiovascular risk has been based on the ability to accurately estimate the risk of future cardiovascular events. While many tools exist to calculate the risk of a cardiovascular event, risk calculators tend to overestimate risk for populations in which cardiovascular risk is declining. Assessing cardiovascular risk is even more complex because risk is not static. If individuals adopt healthier lifestyles, quit smoking, or improve their lipid levels or blood pressure, the future risk of a cardiovascular event declines. New ways to identify groups at increased cardiovascular risk, beyond the use of conventional risk factors and current estimation models, are required and warrant investigation.

A precision medicine approach holds promise to improve the identification of individuals who may benefit from the use of aspirin for primary prevention of CVD (Figure). Pharmacologic therapy traditionally used for primary prevention consists of lipid-lowering therapy with statins, blood pressure-lowering therapy, glucose-lowering therapy, and antiplatelet therapy with aspirin.

Traditionally, statins are recommended for the primary prevention of CVD in individuals with elevated low-density lipoprotein cholesterol levels or those determined to be at sufficient CVD risk.
after a patient-clinician risk discussion. Among adults with elevated blood pressure, pharmacologic therapy is used when blood pressure is sufficiently high, with blood pressure targets guided by background CVD risk. In contrast, aspirin is not considered in individuals based on their platelet activity. However, if clinicians were able to identify individuals based on their increased platelet activity (eg, the target of antiplatelet therapy) and an individual’s likelihood of experiencing a platelet-mediated event, use of antiplatelet therapy and aspirin for the prevention of a first heart attack or stroke should be possible.

Light transmission aggregometry is the accepted standard for measuring platelet function and is consistently used by hematologists to identify individuals with dysfunctional platelets and those at risk for bleeding. In the past 2 decades, we have learned that platelet aggregation in response to submaximal agonist stimulation can reproducibly identify individuals with a hyperreactive platelet phenotype. Owing to the cost, time, and complexity of measuring platelet aggregation, large-scale clinical measurement of platelet aggregation remains problematic and is susceptible to ex vivo perturbations. To avoid some of these limitations, platelet transcriptome profiling is increasingly being explored to provide clinical insight into a patient’s platelet phenotype. Individuals with a hyperreactive platelet phenotype and those at risk for platelet-mediated diseases exhibit specific patterns of the platelet transcriptome. Ongoing work is investigating a platelet genetic signature to identify individuals with a hyperreactive platelet phenotype and those at risk for platelet-mediated diseases. I believe that understanding these genetic patterns of platelet hyperactivity will ultimately guide the choice of optimal antiplatelet therapies to prevent cardiovascular events.

Future study of aspirin for CVD prevention will require novel designs. Instead of identifying individuals’ global CVD risk using traditional risk factors (eg, age, hypertension, diabetes, hyperlipidemia), the individual patient’s platelet phenotype could be considered for the initiation of platelet targeting therapy, including aspirin. Because individuals with increased platelet activity are at greater cardiovascular risk and because aspirin decreases platelet activity, measuring platelet activity or the platelet transcriptome in individuals without CVD may help to identify a high-risk group that would benefit from preventive aspirin therapy. Moreover, bleeding risk is increased in individuals with low platelet activity. Thus, an understanding of patients’ platelet phenotype may increase the potential for benefit with antiplatelet therapy, while reducing the potential for harm. The Figure highlights a proposed conceptual framework for how to investigate the benefit vs risk of aspirin in individuals based on their baseline platelet phenotype. Adequately designed trials could provide definitive evidence to test this approach.

ARTICLE INFORMATION
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