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SPECIAL ARTICLE

Aspirin for the Primary Prevention of Cardiovascular Disease: Time for a Platelet-Guided Approach

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ABSTRACT: Aspirin protects against atherothrombosis while increasing the risk of major bleeding. Although it is widely used to prevent cardiovascular disease (CVD), its benefit does not outweigh its risk for primary CVD prevention in large population settings. The recent United States Preventive Services Task Force guidelines on aspirin use to prevent CVD reflect this clinical tradeoff as well as the persistent struggle to define a population that would benefit from prophylactic aspirin therapy. Past clinical trials of primary CVD prevention with aspirin have not included consideration of a biomarker relevant to aspirin's mechanism of action, platelet inhibition. This approach is at odds with the paradigm used in other key areas of pharmacological CVD prevention, including antihypertensive and statin therapy, which combine cardiovascular risk assessment with the measurement of mechanistic biomarkers (eg, blood pressure and LDL [low-density lipoprotein]-cholesterol). Reliable methods for quantifying platelet activity, including light transmission aggregometry and platelet transcriptomics, exist and should be considered to identify individuals at elevated cardiovascular risk due to a hyperreactive platelet phenotype. Therefore, we propose a new, platelet-guided approach to the study of prophylactic aspirin therapy. We think that this new approach will reveal a population with hyperreactive platelets who will benefit most from primary CVD prevention with aspirin and usher in a new era of precision-guided antiplatelet therapy.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: aspirin ■ blood pressure ■ cardiovascular disease ■ cholesterol ■ risk factors

In October 2021, the United States Preventive Services Task Force (USPSTF) issued a draft statement updating its guidelines on the use of aspirin for the primary prevention of cardiovascular disease (CVD). The USPSTF recommends the following: (1) low-dose aspirin should not be initiated for primary prevention in individuals ages 60 years or older, and (2) initiation of low-dose aspirin should be considered on an individualized basis in adults aged 40 to 59 years with a 10-year CVD risk of ≥10%.[1] With the update, the USPSTF no longer recommends routine aspirin prescription for primary CVD prevention in any population, a position consistent with the most recent guidelines from the American College of Cardiology and American Heart Association,[2] and the European Society of Cardiology.[3] The shift reflects a longstanding struggle to identify a population in which aspirin's clinical benefit for primary CVD prevention exceeds its bleeding risk.

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THE CLINICAL DILEMMA

Aspirin has been widely used as an antipyretic and analgesic for centuries and became a staple of CVD prevention during the second half of the 20th century.[4] By irreversibly inhibiting COX-1 (cyclooxygenase-1), aspirin confers protection against platelet-mediated thrombotic events while increasing bleeding risk, setting up its clinical risk-benefit tradeoff. Low-dose aspirin therapy has net value in secondary CVD prevention, reducing the risk of cardiovascular (CV) events by 21% and all-cause mortality by 13% in individuals with preexisting CVD, although the same individuals have more than double the odds of severe bleeding.[5] However, despite the almost 30 million

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Nonstandard Abbreviations and Acronyms

COX-1	cyclooxygenase-1
CVD	cardiovascular disease
HOT	Hypertension Optimal Treatment Study
LTA	light transmission aggregometry
PRAX1	Platelet RNA and eXpression-1
TPT	Thrombosis Prevention Trial
USPSTF	United States Preventive Services Task Force

Highlights

- Aspirin is an antiplatelet therapy drug and has been shown to protect against atherothrombosis while increasing the risk of major bleeding.
- The recent United States Preventive Services Task Force guidelines on aspirin use to prevent cardiovascular disease reflect this clinical tradeoff as well as the persistent struggle to define a population that would benefit from prophylactic aspirin therapy.
- Reliable methods for quantifying platelet activity, including light transmission aggregometry and platelet transcriptomics, could be considered to identify individuals at elevated (platelet mediated) cardiovascular risk.
- Clinical studies are needed to investigate whether a platelet-guided precision-based medicine approach will identify individuals who will benefit (eg, benefit > risk) with aspirin for the prevention of a first heart attack or stroke.

Americans who take aspirin to prevent a first CV event,[6] it is increasingly recognized that this preventive approach should be reassessed. As for the majority of individuals, the clinical risk-benefit tradeoff skews toward higher bleeding risk, and this is increasingly apparent with improved clinical management of other CV risk factors, including hypertension and hyperlipidemia. In those without preexisting CVD, aspirin yields only modest protection against CV events (0.41% absolute risk reduction) that does not outweigh the associated increased risk of major bleeding (0.47% absolute risk increase).[7] In the absence of broader evidence of aspirin's utility for primary CVD prevention, past trials have attempted to identify specific groups that would benefit from prophylactic aspirin use. Many trials were designed based on the assumption that aspirin's CV benefit increases and bleeding risk remains stable with increasing CV risk of the enrolled population. However, the point on the baseline CV risk spectrum at which aspirin's risk-benefit tradeoff becomes favorable remains unknown and is dependent upon bleeding risk (Figure 1). Meanwhile, atherosclerotic CVD is the leading cause of death in the United States, with an estimated 605 000 first heart attacks and 610 000 first strokes each year.[8]

STRATEGIES AND EVIDENCE

Past Randomized Trials

Initial trials of low-dose aspirin therapy for primary CVD prevention—including the Physicians' Health Study, TPT (Thrombosis Prevention Trial), HOT (Hypertension Optimal Treatment Study), and Primary Prevention Project (PPP)—suggested that aspirin conferred modest CV protection, particularly against nonfatal myocardial infarction, in individuals without established CVD.[9–12] Similarly, while the Women's Health Study did not show a reduction in its primary end point of major CV events with aspirin, it did suggest a modest benefit in women ages 65 years and older.[13] A meta-analysis of these early trials showed a 12 and 14% odds of reduction in CV events associated with aspirin therapy in women and men, respectively.[14,15] These CV risk reductions accompanied significant increases in major bleeding risk (68% and 72% in women and men, respectively). Given this clinical tradeoff and the assumption that aspirin's benefit increases with a patient's baseline CV risk, newer studies were designed in the mid to late 2000s to study primary preventive aspirin therapy in high-risk groups. ASCEND, ARRIVE, and ASPREE enrolled subjects with diabetes, subjects with multiple CVD risk factors and without diabetes, and the elderly, respectively.[16–18] Their results cast further doubt on aspirin's role in primary CV prevention, as ARRIVE and ASPREE did not show significant CV benefit with aspirin, and ASCEND demonstrated CV benefit

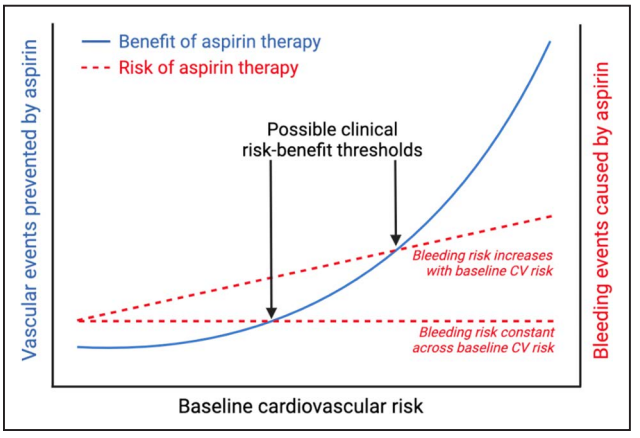

Figure 1. The clinical benefit and risk of aspirin therapy by baseline cardiovascular risk.
Past primary cardiovascular disease prevention trials of low-dose aspirin have attempted to characterize the clinical benefit (blue line) and risk (red dashed lines) of aspirin therapy by the baseline cardiovascular risks of enrolled populations. However, the clinical risk-benefit threshold, that is, the baseline cardiovascular risk at which the benefit of aspirin therapy exceeds the risk, remains unknown and is dependent upon bleeding risk. CV indicates cardiovascular.

that was counterbalanced by a substantial increase in the risk of major bleeding.[19] However, it is important to note that despite the intention of recent trials to study higher-risk primary prevention populations, the event rates in ASCEND, ARRIVE, and ASPREE were ≈1% per year, consistent with lower-risk populations. Thus, the power of these studies was lower than expected, and the translatability of these findings to higher-risk primary prevention populations is uncertain.

More recently, the use of a polypill (with 2 or more blood pressure–lowering drugs and a statin) with or without aspirin reduced CV events in participants with no known vascular disease.[19] The primary outcome composite of CV death, myocardial infarction, stroke, or arterial revascularization was significantly reduced by a fixed-dose combination strategy without aspirin by 32% and with aspirin by 47%.

Results of aspirin trials are further confounded by evidence that the dose required for optimal CV prevention may be influenced by weight, body mass, and the drug formulation.[20,21] A meta-analysis of 10 aspirin primary prevention trials[20] found the effect of low-dose aspirin (75–100 mg) to reduce CV events attenuated with increasing weight. In contrast, higher doses (≥325 mg) of aspirin showed a reverse interaction with weight, reducing CV events only at larger body size and increased weights. Further confounding the results of many studies, both obesity and diabetes may affect an individual's response to aspirin,[22–24] and the enteric-coat of some aspirin formulations, which reduces gastrointestinal protection and impairs consistent absorption of the drug.[25–27]

In addition to platelet inhibition, low-dose aspirin may provide additional CV benefit via alternate mechanisms. Aspirin-triggered specialized lipid mediators can facilitate inflammation resolution (eg, the eicosanoids; prostaglandin, and leukotrienes),[28] and there is emerging evidence for their role in the suppression of vascular inflammation and reducing adverse CV events.[29–31]

Alternative Approaches to Primary CVD Prevention

The recent USPSTF update on aspirin use, which reflects the evidence to date and is in line with guidelines from major national and international heart societies, suggests either (1) aspirin should have no regular role in primary CVD prevention, or (2) we must adopt a new approach to identify individuals who will benefit from prophylactic aspirin use. Given aspirin's favorable antithrombotic properties, we advocate for the latter proposition and point to the paradigm guiding use of other primary CVD prevention therapies as a model for future aspirin use (Figure 2). Antihypertensives are recommended for primary CVD prevention when hypertension is diagnosed in conjunction with elevated CVD risk.[32] The dosing and number of antihypertensives are titrated to achieve a blood pressure goal, reflecting evidence that blood pressure level and CVD risk are directly correlated.[33] In short, the initiation and titration of antihypertensive therapy are guided by the measurement of a biomarker, blood pressure, with direct relevance to the medication's mechanism of action. While guidelines for primary CVD prevention with statins are more complex, they remain closely linked to a relevant biomarker, low-density lipoprotein-cholesterol (LDL-C). Indications for statin initiation emphasize LDL-C level, age, diabetes, or familial hypercholesterolemia, CVD risk, and other risk-enhancing factors.[34] Even when therapy is initiated absent an LDL-C trigger, the regimen may be guided by serial LDL-C measurements, reflecting evidence that the net value of LDL-C lowering increases with the degree of reduction.[35] Moreover, the favorable safety profile of statins means that they are typically of net value in individuals at even moderate CVD risk.

In contrast, guidelines directing the use of aspirin for primary CVD prevention do not consider a mechanism-related biomarker. This is as previous primary CVD prevention trials of aspirin therapy enrolled subjects based on age alone or age and CVD risk and did not use measures of platelet activity. The absence of a platelet biomarker in these trials is notable, as both the risk (excess bleeding) and benefit (protection against thrombosis) of aspirin reflect the drug's platelet-inhibitory effects. Though the measurement of platelet activity in response to $P2Y_{12}$ inhibition among individuals on dual antiplatelet therapy ($P2Y_{12}$ inhibitor and aspirin) did not improve clinical outcomes in prospective randomized secondary prevention trials, studies were limited by analyzing only ADP-induced platelet activity and small sample size with inadequate power.[36] We propose a different approaching—measuring the platelet phenotype at baseline to identify individuals at particular risk for platelet-mediated events, for example, MI and stroke. It stands to reason that adding this measurement of baseline platelet activity to traditional CV risk assessment may be the key to developing better aspirin use practices. This leads to the question of how best to measure platelet activity.

Characterizing Platelet Activity

Soon after the platelet's central role in hemostasis was recognized, methods for quantifying platelet function emerged. Early approaches included assessing platelet number, size, and morphology. Bleeding time was the first in vivo test of platelet function,[37,38] and though it remains useful in severe platelet dysfunction, its invasiveness and nonspecificity limit clinical application.[39] Thromboelastography and rotational thromboelastometry leverage viscoelastic dynamics to describe platelet activity and aspects of clot formation.[40] They are useful for tracking coagulopathy in liver transplantation and

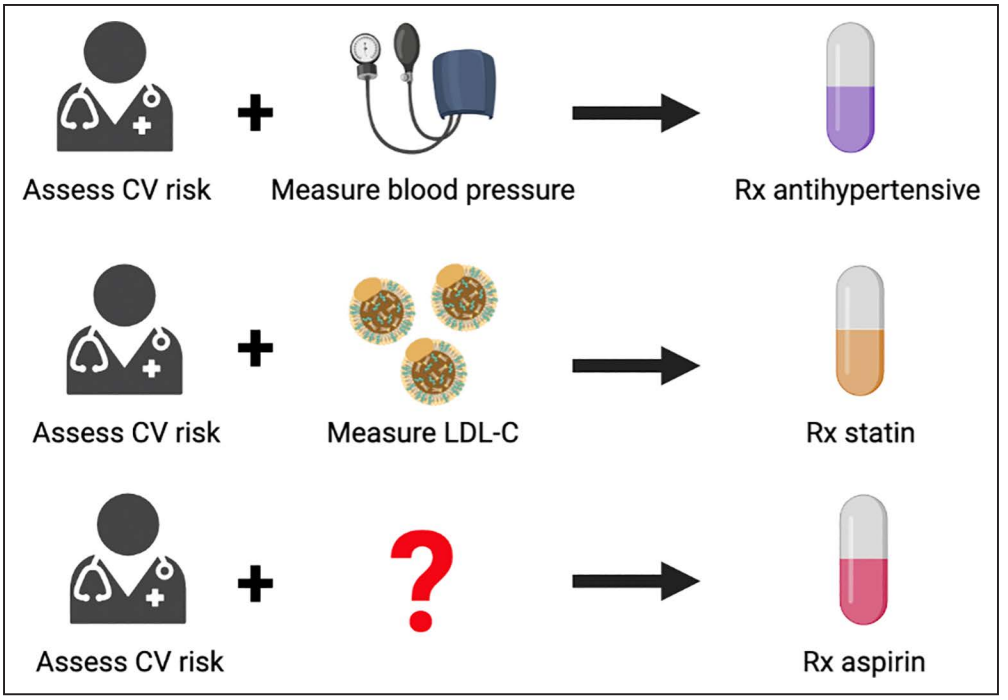

Figure 2. Approaches to pharmacological primary cardiovascular disease prevention.
Primary preventive antihypertensive and statin therapy are prescribed after a cardiovascular risk assessment and the measurement of a biomarker related to the drug class's primary mechanism of action. In contrast, primary preventive aspirin therapy is prescribed after cardiovascular risk assessment alone and is not guided by any related biomarker. CV indicates cardiovascular; and LDL-C, low-density lipoprotein cholesterol.

trauma,[41,42] but do not confer a nuanced description of platelet activity nor are they sensitive to aspirin-mediated platelet inhibition.[43] The platelet function analyzer and the cone and plate(let) analyzer are other functional in-vitro assays but lack the specificity required for antiplatelet therapy personalization.[44,45] Circulating platelet biomarkers (eg, sCD40L, P-selectin, TxB2, βTG, PF4) have been proposed as biologic markers of platelet activity. However, the association between circulating platelet biomarkers and platelet-mediated events are inconsistent—likely arising from differences in blood collection, including tube anticoagulant, time to centrifugation, tourniquet use, etc.[46–49] Most recently, flow cytometry and immunoassays have facilitated the measurement of key soluble and on-platelet markers of platelet activation and platelet-leukocyte interaction.[50,51] These methods are increasingly being used in clinical research, although they seem to have the greatest utility in acute disease, for example, acute coronary syndromes, with limited data describing their use in populations without CVD.[47,52]

Light Transmission Aggregometry

Light transmission aggregometry (LTA), introduced in the 1960s, remains the gold standard for the clinical assessment of platelet activity.[53,54] In LTA, platelet aggregation is measured in response to stimulation with platelet agonists (Figure 3A). The technique can be performed with different stimuli at varying concentrations, thereby comprehensively characterizing platelet activity. Clinically, LTA in response to high-dose agonists is used to assess hematologic disorders of platelet dysfunction (Figure 3B). In contrast, LTA with low-dose agonists can identify individuals with a hyperreactive platelet phenotype, although the use of this technique is currently limited to research settings. The use of low-dose agonists in LTA yields a bimodal distribution of platelet aggregation, with most individuals exhibiting low aggregation while a small minority have a hyperreactive response, with aggregation above 60% (Figure 3C).[55–57] The hyperreactive response is consistent across multiple agonist classes, is reproducible over time,[55,57] and we suggest is a proxy for an activated platelet phenotype. Indeed, high platelet aggregation at baseline and following inhibition with aspirin is associated with adverse CV outcomes.[58,59] Ongoing work is validating the association between platelet hyperreactivity and incident CV events. Data from our group and others suggest that individuals with hyperreactive platelets are at increased CV risk; inconsistencies to date in these data are partially attributable to inter-study methodological heterogeneity (including differences in preanalytical sample preparation) that can be minimized by standardization of technique in specialized centers. We propose that individuals with a hyperreactive platelet phenotype on LTA are likely to benefit most from platelet-directed therapies for primary CVD prevention.

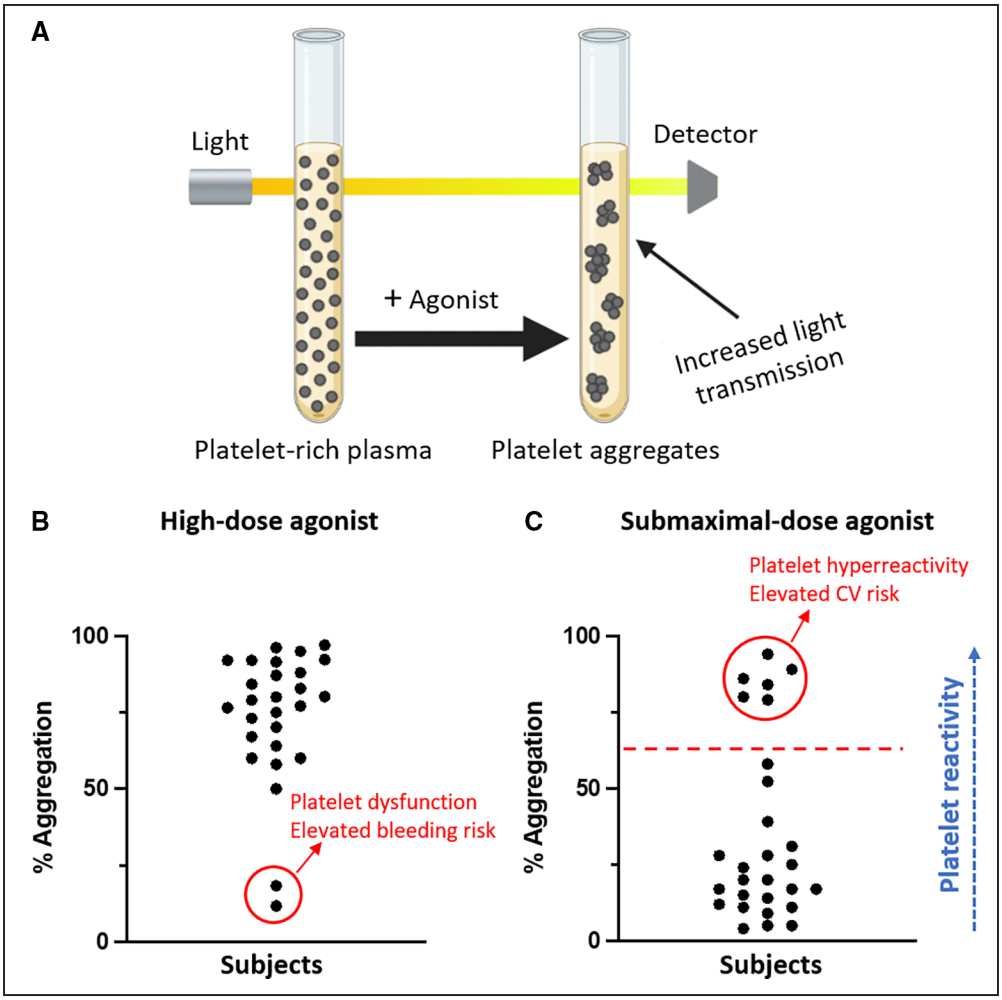

Figure 3. Characteristics of light transmission aggregometry (LTA).
A, Introduction of an agonist into platelet-rich plasma induces platelet aggregation, increasing light transmission through the suspension. Aggregation extent can be quantified using a calibrated light detection system. **B**, LTA with high-dose agonists is used clinically to diagnose hematologic disorders of platelet dysfunction (eg, minimal aggregation despite stimulation with a high-dose agonist). **C**, LTA with submaximal-dose agonists can be used to identify individuals with a hyperreactive platelet phenotype, a subgroup that may receive net value from low-dose aspirin therapy.

Platelet Transcriptomics

Platelet transcriptomic analysis, facilitated by RNA-sequencing (RNA-seq), is increasingly used to gain insight into platelet biology and phenotype.[60,61] Though platelets are anucleate, they retain mRNA and translational machinery from their megakaryocyte precursors. Recent studies have revealed that the platelet transcriptome is reproducible over time in healthy individuals,[62] can be used to characterize platelet hyperreactivity,[61,63–66] and is significantly altered at disease onset and progression.[57,67–69] Current research has defined platelet RNA signatures characteristic of (1) platelet hyperreactivity,[57,67,70–73] (2) CVD prevalence and severity,[57,67–69] and (3) incident platelet-mediated atherothrombotic events.[68,69] The utility of platelet transcriptome profiling and CV risk was highlighted by the results of the PRAX1 (Platelet RNA and eXpression-1) Study, which investigated the impact of race on the platelet transcriptome and platelet activity.[71] In 2013, Edelstein et al[71] reported increased platelet aggregation and calcium mobilization induced by the PAR4 (thrombin receptor) in self-identified black subjects. By unbiased platelet transcriptome profiling, miR-376c levels were found to be reduced and a miR-376c target gene, *PCTP* (encoding phosphatidylcholine transfer protein), increased in black subjects. The PRAX1 study was to the first demonstrate a functional contribution of the platelet transcriptome to race-associated platelet hyperreactivity. Despite the potential clinical significance of these findings to facilitate a personalized approach to reduce platelet hyperactivity and subsequent CV risk, these seminal findings still require validation in external cohorts, and prospective studies demonstrating how this information can influence clinical CV risk reduction practices.

Relevant to the development of a diagnostic tool to identify those at high risk of CV events, platelet aggregation responses have been shown to be heritable in both the Framingham Heart Study[74] and the Genetic Study of Atherosclerotic Risk,[75] and GWAS studies have identified specific loci that regulate platelet activation responses.[76,77] Despite the identification of various platelet phenotype-genotype relationships, for example polymorphism of the alpha2, thromboxane receptor, GPVI, GPIb-V-IX, PAR1, $P2Y_{12}$, and $P2Y_1$ genes[78–80] the link between functional genetic variations and CV risk is under investigation.[81,82]

Despite the application of platelet transcriptomics to CVD and platelet-mediated events, the current literature raises the intriguing possibility that the platelet transcriptome could be harnessed to identify those with hyperreactive platelets and those at increased risk of a CV event. The clinical consequences of these findings, particularly in the era of personalized medicine, calls for a consequential shift when studying antiplatelet therapies to improve patient outcomes.

A NEW APPROACH TO GUIDE ASPIRIN USE IN PRIMARY CVD PREVENTION

Platelets drive CVD pathogenesis and are the primary target of aspirin therapy. Aspirin confers its clinical benefit by inhibiting platelet activity, thereby decreasing platelet-mediated thrombotic events. However, by the same mechanism, aspirin induces harm by increasing major bleeding. Since platelet activity is central to aspirin's risk-benefit tradeoff, it should be considered to guide aspirin therapy. In contrast to prior studies that enrolled individuals based only upon their CV risk using nonspecific markers (eg, age, hypertension, diabetes), we propose a new, platelet-centric approach to investigating the net value of aspirin therapy in primary CVD prevention. Specifically, we propose identifying individuals with hyperreactive platelets using aggregometry and/or an aspirin-responsive platelet hyperreactivity RNA signature. Next, individuals with hyperreactive platelets should be randomized to either low-dose aspirin therapy or placebo, with each treatment group

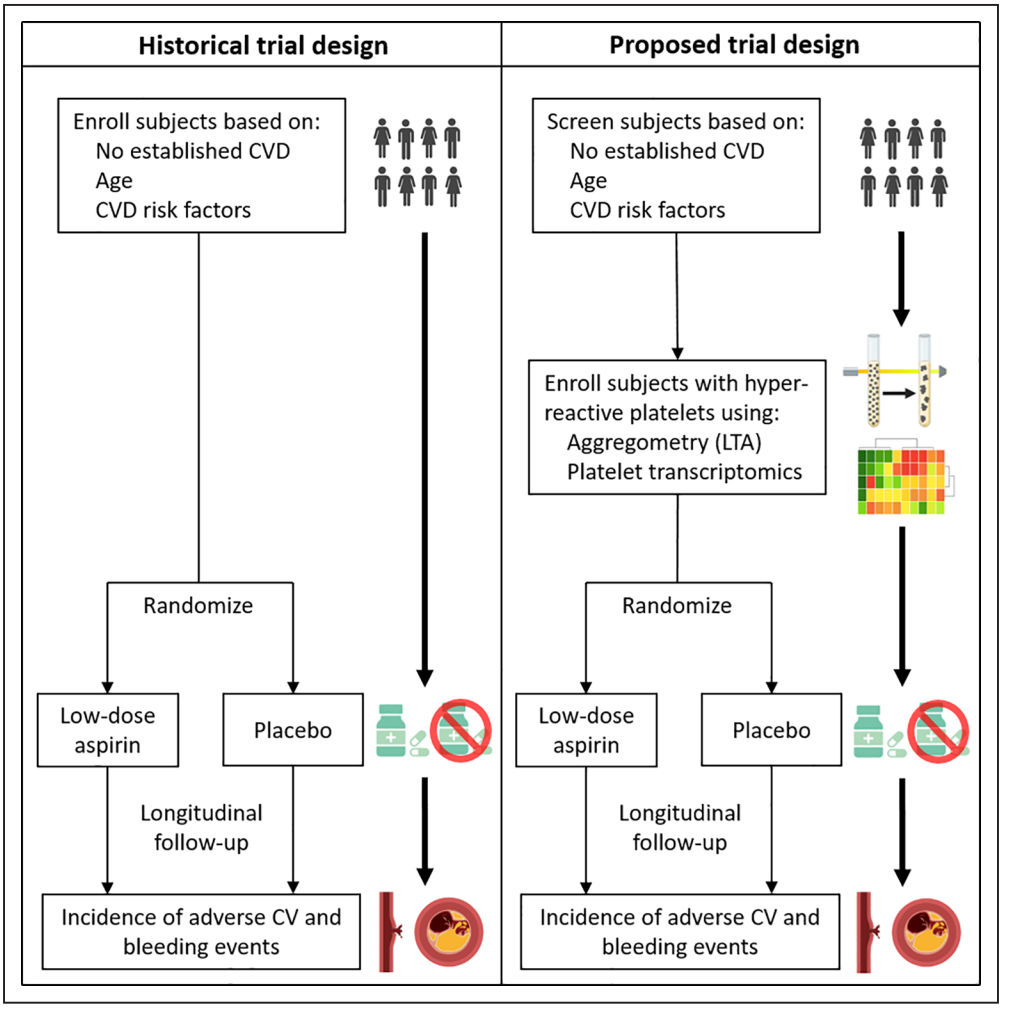

Figure 4. Aspirin primary prevention trials: past and future.
Historical and proposed designs of trials evaluating low-dose aspirin for primary cardiovascular disease prevention. CV indicates cardiovascular; and LTA, light transmission aggregometry.

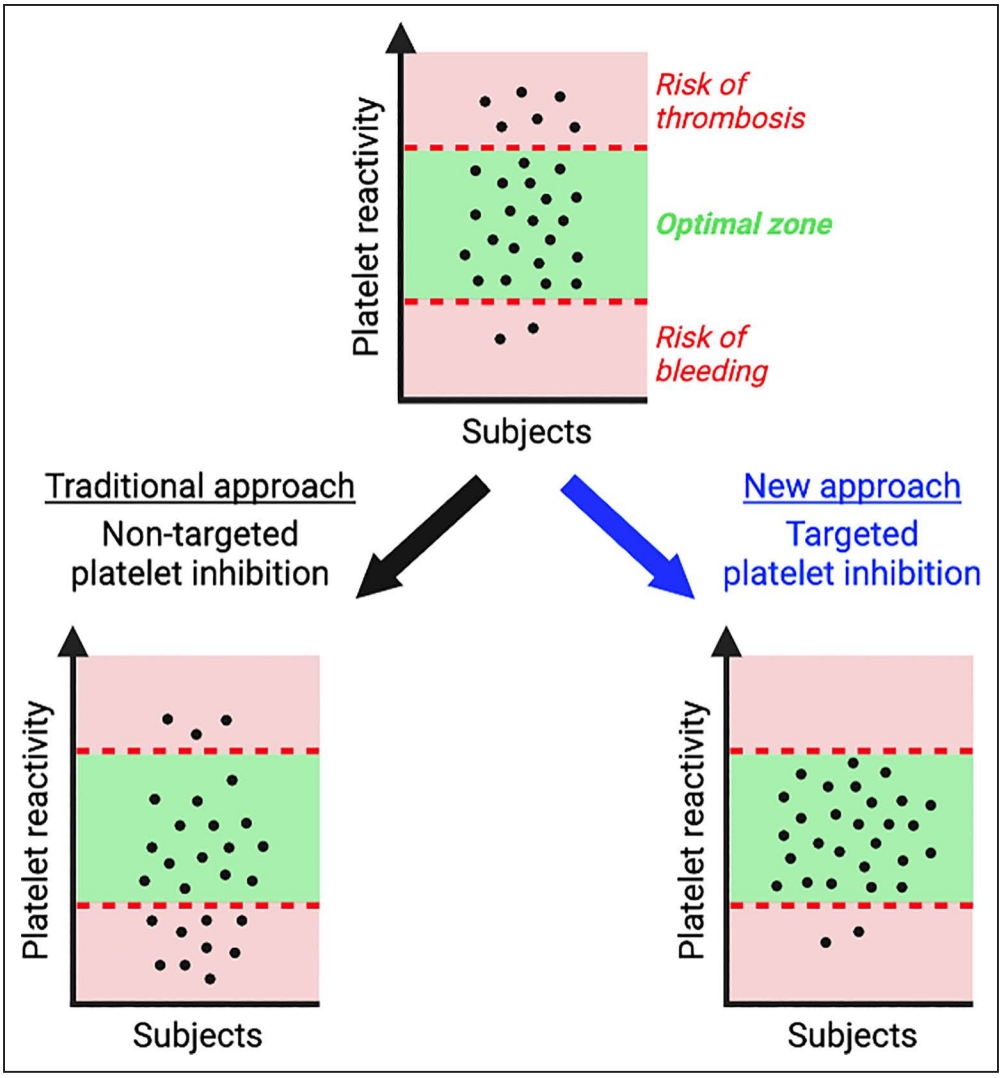

Figure 5. Platelet-guided aspirin therapy.
The traditional approach to aspirin therapy involves suppressing platelet activity in a nontargeted manner, which likely unnecessarily increases bleeding risk without conferring vascular benefit in individuals with an optimal or hyporeactive platelet phenotype at baseline. We propose a new, targeted approach to aspirin therapy in which use is limited to individuals with a hyperreactive platelet phenotype who are most likely to receive maximum vascular benefit and minimal bleeding risk from platelet inhibition.

followed longitudinally for incident adverse CV and bleeding events (Figure 4).

We think that applying a platelet-guided approach to the clinical study of aspirin will finally reveal a population with a hyperreactive platelet phenotype that receives net value (benefit >> risk) from primary prevention with aspirin therapy. Elevated platelet activity predisposes to thrombosis whereas over-inhibition predisposes to bleeding. Intuitively, improving aspirin use practices in primary CVD prevention requires identifying individuals whose platelet phenotype positions them to benefit from pharmacological platelet inhibition (Figure 5). Such prescriptive nuance is likely necessary to maximize efficacy versus safety. Should this platelet-guided approach prove clinically beneficial and cost-effective for directing primary preventive aspirin use, further study across diverse patient cohorts and with different antiplatelet medications will usher in a new era of precision-guided antiplatelet therapy.

CONCLUSIONS

The new USPSTF recommendations are important as guidelines for clinical decision-making and a formalized reflection of the multi-decade struggle to define the role of aspirin in primary CVD prevention. Traditional platelet-agnostic trial design methods have repeatedly failed to refine clinical practice while the burden of CVD is persistent. Thus, a new model for the study of aspirin in primary CVD prevention is needed. A platelet-focused approach appears prudent given the centrality of platelets in CVD pathogenesis, thrombosis, and hemostasis, aspirin's well-characterized antiplatelet mechanism, and the successful adoption of biomarker-led approaches in other

areas of CVD prevention. Shifting to this new model will require well-designed trials to prospectively investigate the associations between baseline platelet phenotype, CV risk factors, low-dose aspirin therapy, and longitudinal clinical outcomes. We are optimistic that, in the near future, we will use precision-guided antiplatelet therapy for the prevention of a first heart attack or stroke.

ARTICLE INFORMATION

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Disclosures

None.

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