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REVIEW TOPIC OF THE WEEK

The Multifaceted Clinical Readouts of Platelet Inhibition by Low-Dose Aspirin

Carlo Patrono, MD

ABSTRACT

Inactivation of platelet cyclooxygenase (COX)-1 by low-dose aspirin leads to long-lasting suppression of thromboxane (TX) A_2 production and TXA_2-mediated platelet activation and aggregation. This effect is necessary and sufficient to explain aspirin's unique (among other COX-1 inhibitors) effectiveness in preventing atherothrombosis, as well as its shared (with other antiplatelet agents) bleeding liability. However, different mechanisms of action have been suggested to explain other beneficial effects of aspirin, such as prevention of venous thromboembolism, chemoprevention of colorectal (and other) cancers, and reduced risk of dementia. These mechanisms include acetylation of other proteins in blood coagulation, inhibition of COX-2 activity, and other COX-independent mechanisms. The intent of this review is to develop the concept that the multifaceted therapeutic effects of low-dose aspirin may reflect pleiotropic consequences of platelet inhibition on pathophysiological tissue repair processes. Furthermore, the clinical implications of this concept will be discussed in terms of current clinical practice and future research. (J Am Coll Cardiol 2015;66:74–85)

Marketed in 1899 as a prototypic analgesic, antipyretic, and anti-inflammatory agent, aspirin continues to attract research and debate related to its antiplatelet properties, which were discovered and developed by the medical-scientific community during the past 40 years (1). The best-characterized molecular mechanism of the action of aspirin as an antiplatelet drug is its permanent inactivation of a critical platelet protein, prostaglandin G/H-synthase 1 (also colloquially referred to as cyclooxygenase [COX]-1) (2). Inactivation of COX-1 by low-dose aspirin leads to long-lasting suppression of platelet thromboxane (TX) A_2 production and TXA_2-mediated platelet activation and aggregation (3,4). This effect is necessary and sufficient to explain aspirin's unique (among other COX-1 inhibitors) effectiveness in preventing atherothrombosis (5), as well as its shared (with other antiplatelet agents) bleeding liability. However, different mechanisms of action have been suggested to explain other beneficial effects of aspirin, such as prevention of venous thromboembolism (6), chemoprevention of colorectal (and other) cancer (7), and reduced risk of dementia (8). These mechanisms include acetylation of other proteins involved in blood coagulation (6), inhibition of COX-2 activity (7), and other COX-independent mechanisms (9).

The intent of this review is to develop the concept that the apparently heterogeneous therapeutic effects of low-dose aspirin may reflect the pleiotropic consequences of platelet COX-1 inhibition on pathophysiological tissue repair processes that participate in the healing response to vascular and mucosal injury (**Central Illustration**). Furthermore, the clinical implications of this concept will be discussed in terms of current clinical practice and future research.

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TREATMENT AND PREVENTION OF ATHEROTHROMBOSIS

Platelets participate in the development and progression of atheromatous plaques and are key cellular components of arterial occlusive thrombi (10). Adhesion and aggregation of platelets in response to fissuring or rupture of an atheromatous plaque can be viewed as a physiological repair response to an acute vascular lesion. Appropriate control mechanisms of thromboresistance (e.g., endothelial prostacyclin production) normally limit the spatial extent and duration of this platelet response. However, uncontrolled propagation and persistence of platelet activation through self-sustaining amplification loops (e.g., TXA_2/TP and adenosine diphosphate [ADP]/$P2Y_{12}$ interactions) may lead to intraluminal thrombus growth, vascular occlusion, and transient ischemia or infarction (10). The findings that structurally unrelated inhibitors of prostacyclin production (different classes of nonsteroidal anti-inflammatory drugs [NSAIDs]) increase the risk of major atherothrombotic complications, particularly myocardial infarction (MI) (11), whereas low-dose aspirin and $P2Y_{12}$ blockers reduce this risk (12), are consistent with these pathophysiological concepts, and point to TXA_2 and ADP as important mediators of atherothrombosis (10). Moreover, the dynamic nature of this process explains the effectiveness of low-dose aspirin in treating acute MI and acute ischemic stroke (**Figure 1**), by interfering with an important amplification loop of thrombus growth and new thrombus formation following pharmacological or mechanical reperfusion (5,10). Finally, the additive beneficial effects of low-dose aspirin and $P2Y_{12}$ blockers in acute coronary syndromes (ACS) (12) suggest nonredundant, complementary roles of TXA_2 and ADP as amplifiers of platelet activation in coronary atherothrombosis.

SECONDARY PREVENTION. Among patients with occlusive vascular disease, both individual studies (13) and meta-analyses of randomized trials of antiplatelet therapy (14) indicate that low-dose aspirin reduces the risk of a serious vascular event (nonfatal MI, nonfatal stroke, or death from vascular causes) by approximately one-fourth. Therefore, among a wide range of patients with symptomatic vascular disease, in whom the annual risk of a serious vascular event ranges between 4% and 8%, low-dose aspirin may prevent approximately 10 to 20 fatal and nonfatal ischemic events for every 1,000 patients treated for 1 year (number needed to treat [NNT]: 50 to 100) (5) (**Figure 1**). This substantial benefit is obtained at the expense of causing 1 to 2 major extracranial (mostly gastrointestinal [GI]) bleeding complications per 1,000 patients (number needed to harm [NNH]: 500 to 1,000) and 1 to 2 hemorrhagic strokes per 10,000 patients (NNH: 5,000 to 10,000) (5). Therefore, for most high-risk patients taking low-dose aspirin, the number in whom a serious vascular event would be avoided clearly outweighs the number with a major bleeding complication, unless an individual patient has increased susceptibility to bleeding due to advanced age, a history of GI bleeding, or concomitant treatment with NSAIDs or anticoagulant agents (5).

PRIMARY PREVENTION. Among asymptomatic subjects without a prior vascular event, the balance of benefits and risks of long-term antiplatelet therapy with low-dose aspirin is substantially uncertain because the risks without aspirin, and hence the absolute benefits of antiplatelet prophylaxis, are at least an order of magnitude lower than in secondary prevention (15). On the basis of a meta-analysis of individual participant data from 6 primary prevention trials of aspirin in approximately 90,000 subjects at average low vascular risk, the Antithrombotic Trialists' Collaboration has shown that, irrespective of age or sex, the absolute reduction in serious vascular events (largely, nonfatal MI) would be only about twice as large as the absolute increase in nonfatal GI bleeding (16). Moreover, the predicted 5-year absolute effects of allocation to aspirin in different categories of 5-year coronary risk (from <5% to >10%) would yield a relatively constant ratio between the calculated NNH (from 1,000 to 100, respectively) and NNT values (from 500 to 50, respectively) (16). This is not surprising, inasmuch as the main risk factors for coronary events were also associated with hemorrhagic events, although for most the associations were slightly weaker for bleeding than for ischemic events (16). Thus, trying to identify a threshold risk level above which recommending aspirin is expected to produce substantially more benefit than harm in asymptomatic subjects (17) is probably a Sisyphean exercise, as a patient at high ischemic risk because of a cluster of cardiovascular risk factors is very unlikely to be at low risk of bleeding. The current uncertainty is reflected by conflicting guidelines on the use of aspirin in primary prevention (**Table 1**) (17–20), as well as by its heterogeneous regulatory status in different countries (12). This may result in about 1 in 10 patients receiving inappropriate aspirin therapy for primary prevention, with significant practice-level variations (21). Four ongoing primary prevention

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)
ADP = adenosine diphosphate
COX = cyclooxygenase
GI = gastrointestinal
MI = myocardial infarction
NNH = number needed to harm
NNT = number needed to treat
NSAID = nonsteroidal anti-inflammatory drug
PPI = proton pump inhibitor
TX = thromboxane
VTE = venous thromboembolism