

REVIEW TOPIC OF THE WEEK

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



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ABSTRACT

Inactivation of platelet cyclooxygenase (COX)-1 by low-dose aspirin leads to long-lasting suppression of thromboxane (TX) A₂ production and TXA₂-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)
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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) A₂ production and TXA₂-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., TXA₂/TP and adenosine diphosphate [ADP]/P2Y₁₂ 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 P2Y₁₂ blockers reduce this risk (12), are consistent with these pathophysiological concepts, and point to TXA₂ 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 P2Y₁₂ blockers in acute coronary syndromes (ACS) (12) suggest nonredundant, complementary roles of TXA₂ and ADP as amplifiers of platelet activation in coronary atherothrombosis.

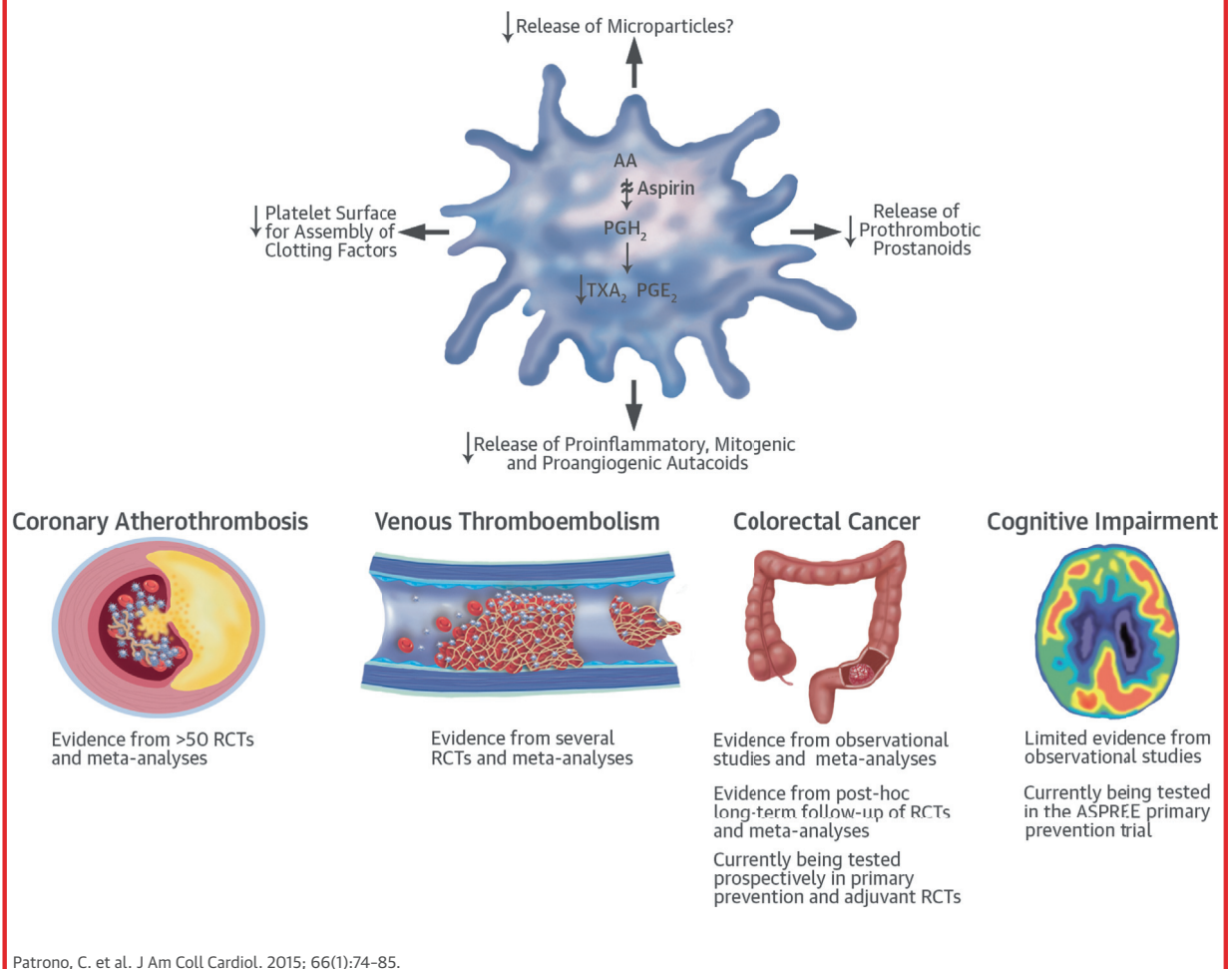
SECONDARY PREVENTION. Among patients with occlusive vascular disease, both individual studies (13) and meta-analyses of randomized trials of antiplatelet therapy (14) indicate that low-dose aspirin reduces the risk of a serious vascular event (nonfatal MI, nonfatal stroke, or death from vascular causes) 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

CENTRAL ILLUSTRATION Platelet Inhibition by Low-Dose Aspirin

A wide repertoire of lipid and protein mediators, which may contribute to several clinical syndromes possibly responsive to low-dose aspirin therapy, are released upon platelet activation and aggregation. The figure illustrates inhibition of platelet prostanoid production by aspirin and its functional and clinical consequences. The lines of evidence supporting the protective effects of aspirin are summarized below each panel. AA = arachidonic acid; ASPREE = Aspirin in Reducing Events in the Elderly; RCT = randomized controlled trial(s); PGE₂ = prostaglandin E₂; PGH₂ = prostaglandin H₂; TXA₂ = thromboxane A₂.

trials may help assess the benefit/risk profile of low-dose aspirin in preventing multiple outcomes (including dementia and cancer) in approximately 50,000 participants at somewhat higher cardiovascular risk than in the earlier trials, because of diabetes mellitus (ASCEND [A Study of Cardiovascular Events in Diabetes] and ACCEPT-D [Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trials in Diabetes]) (22,23), advanced age (ASPREE [Aspirin in Reducing Events in the Elderly]) (24), or a number of risk factors (ARRIVE [Aspirin to Reduce Risk of Initial Vascular Events]) (25) (Table 2). In the meantime, clinical judgment, as well as adequate knowledge of the available data (Figure 2), may help

the doctor-patient relationship to reach a personalized therapeutic decision, after considering the different components of a complex equation that needs to incorporate the patient's preferences and values (15).

PREVENTION OF VENOUS THROMBOEMBOLISM

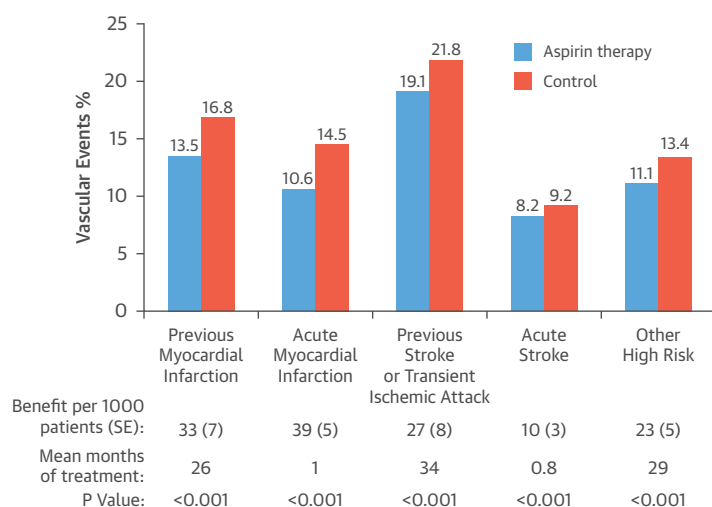
Several lines of evidence support the hypothesis that platelet activation in concert with neutrophil recruitment is involved in the initiation and propagation of deep vein thrombosis (6). The PEP (Pulmonary Embolism Prevention) trial has clearly shown

that short-term treatment with low-dose aspirin reduces the incidence of fatal pulmonary embolism and symptomatic nonfatal deep vein thrombosis or pulmonary embolism in patients with hip fracture (26). The results of the PEP trial are consistent with the meta-analysis performed by the Antiplatelet Trialists' Collaboration (27), and supersede the findings in most of the previous trials (13). Moreover, long-term treatment with low-dose aspirin, after oral anticoagulant agent discontinuation, has been shown to reduce the risk of recurrence by more than one-third in patients with a first unprovoked venous thromboembolism (VTE) (28). The postulated mechanisms underlying this protective effect of aspirin against VTE include acetylation of fibrinogen and other proteins in blood coagulation, resulting in more efficient fibrinolysis, and reduced thrombin generation at sites of vascular injury, possibly due to acetylation of prothrombin (6). However, there is no convincing evidence for fibrinogen or prothrombin acetylation being detectable in vivo after intake of low-dose aspirin (6). Although aspirin can acetylate a number of plasma proteins, enzymes, and DNA in vitro (29), this usually requires millimolar concentrations that are approximately 100 to 1,000 times higher than those achievable after oral dosing of low-dose aspirin (30). Consistent with this requirement, acetylation of serum albumin (31) and hemoglobin (32) in vivo was reported following chronic oral dosing with aspirin 3 to 6 g per day, that is, a 40-fold to 60-fold higher dose than a typical antiplatelet regimen. Therefore, the protective effect of low-dose aspirin against VTE may well reflect an important role of TXA₂-mediated amplification of platelet activation and aggregation in VTE, rather than non-COX-dependent mechanism(s) of action.

CHEMOPREVENTION OF COLORECTAL CANCER

Several lines of evidence support a chemopreventive effect of aspirin against some cancers, particularly of the GI tract (7,9). These include: 1) a large number of case-control and cohort studies that reported associations between aspirin use and reduced risk of colorectal (and other) cancers (33); 2) 4 randomized, placebo-controlled trials in subjects with sporadic colorectal adenomas and their meta-analysis (34) that demonstrated reduced risk of recurrence in aspirin-treated subjects; 3) a placebo-controlled, randomized clinical trial in patients with Lynch syndrome (hereditary nonpolyposis colon cancer), in whom aspirin reduced cancer incidence during long-term follow-up (35), but not during the scheduled

FIGURE 1 Absolute Effects of Antiplatelet Therapy With Low-Dose Aspirin on the Risk of Vascular Events (Nonfatal MI, Nonfatal Stroke, or Death From Vascular Causes) in 5 Groups of High-Risk Patients



The number needed to treat (NNT) ranged between 26 (acute myocardial infarction [MI]) to 100 (acute stroke) per month of treatment in the acute setting, and from 65 (previous MI) to 105 (previous stroke) per year of treatment in the secondary prevention setting. The figure is derived from an analysis of data from the Antithrombotic Trialists' Collaboration (14). Reproduced with permission from Patrono et al. (5).

treatment phase of the trial (36); and 4) a post-hoc, individual patient data meta-analysis of 51 randomized controlled trials of daily aspirin in prevention of vascular events that reported a 25% reduction in overall cancer incidence from 3 years onward (37). None of these individual lines of evidence can unequivocally establish a cause-and-effect relationship between exposure to aspirin and reduced risk of colorectal (and other) cancers. However, they are internally consistent and highly suggestive of a real treatment effect after a variable latency. In particular, the meta-analyses of cardiovascular trials (37-39) are mechanistically interesting because they suggest that the apparent chemopreventive effect of aspirin is detectable at daily doses as low as 75 mg (38) and is saturable at low doses; that is, much higher doses (e.g., 1,200 mg daily) are not more effective than lower doses (38). Moreover, reduced risk of developing colorectal cancer was also detected during long-term follow-up of healthy women treated with alternate-day 100 mg aspirin dosing versus placebo (40), and of high-risk men treated with a 75-mg controlled-release formulation of aspirin (38), developed to maximize cumulative inhibition of platelet COX-1 in the pre-hepatic circulation and minimize inhibition of COX-2 in the systemic vascular

TABLE 1 Guidelines on the Use of Aspirin in Primary Prevention

Organization (Year)	Recommendation	Class of Recommendation (Level of Evidence)
ESC WG on Thrombosis (2014)	We recommend that aspirin use in the primary prevention of acute MI and other atherothrombotic cardiovascular events in subjects of both sexes be guided by an assessment of the underlying cardiovascular risk.	I (B)
	We suggest that aspirin be considered in the primary prevention of cardiovascular disease in both sexes at a level of risk of major cardiovascular events (death, MI, and stroke) >2 per 100 subject-years, provided they have no clear evidence of increased risk of bleeding (gastrointestinal bleeding or peptic ulcer disease, no concurrent use of other medications that increase bleeding risk).	IIa (B)
ESC (2012)	Aspirin is not recommended in individuals without cardiovascular or cerebrovascular disease due to the increased risk of major bleeding.	III (B)
ACCP (2012)	We suggest low-dose aspirin (75–100 mg/day) in patients >50 years of age over no aspirin therapy.	2 (B)
USPSTF (2009)	The USPSTF recommends the use of aspirin for men 45 to 79 years of age when the potential benefit due to a reduction in myocardial infarctions outweighs the potential harm due to an increase in gastrointestinal hemorrhage.	A
	The USPSTF recommends the use of aspirin for women 55 to 79 years of age when the potential benefit of a reduction in ischemic strokes outweighs the potential harm of an increase in gastrointestinal hemorrhage.	A

ACCP = American College of Chest Physicians; ESC = European Society of Cardiology; MI = myocardial infarction; USPSTF = United States Preventive Services Task Force; WG = working group.

endothelium (41). Although several mechanisms of action could explain a chemopreventive effect of high-dose aspirin (9), including inhibition of COX-2 in the GI mucosa and its downstream effects on cellular proliferation, apoptosis, and angiogenesis (9), any effects of low-dose aspirin administered once daily or every other day on nucleated cellular targets would be more difficult to reconcile with its pharmacokinetics (very short half-life) and pharmacodynamics (relatively selective inhibition of platelet COX-1) (5,13). These considerations led us to suggest that inhibition of platelet activation at sites of deep GI mucosal lesions could be the primary mechanism of action of low-dose aspirin, acting upstream of platelet-driven COX-2 expression in adjacent nucleated cells of the intestinal mucosa during the early stages of colorectal carcinogenesis (42,43). Direct

evidence of COX-2 induction in human colon cancer cells by platelet-derived mediators has been reported (44). Moreover, platelet activation and aggregation by circulating cancer cells is hypothesized to protect tumor cells from natural killer cell-mediated lysis (45). Therefore, platelet inhibition may also help to explain the apparent reduced risk of cancer metastases in cardiovascular trials of low-dose aspirin (46). Finally, antiplatelet therapy with aspirin and clopidogrel inhibits or delays immune-mediated hepatocarcinogenesis and improves survival in a mouse model of chronic hepatitis B (47).

Additional evidence for the chemopreventive effects of aspirin is being sought prospectively in ongoing primary prevention trials (Table 2). Moreover, several adjuvant trials of various low-dose aspirin regimens have been initiated recently in

TABLE 2 Ongoing Randomized Trials of Low-Dose Aspirin for Primary Prevention

Study (Ref. #)	Regimen(s)	Treatment Duration	N	Eligibility	Primary Endpoint	End Date
ACCEPT-D (23)	Aspirin 100 mg versus open control; simvastatin for all	5 yrs	5,170	Diabetes, no CVD	CV death, nonfatal stroke, nonfatal MI, other CV hospitalization	2015
ARRIVE (25)	Aspirin 100 mg versus placebo	5 yrs	~12,000	10–20% estimated 10-yr risk of CHD	MI, stroke, CV death, unstable angina, TIA	2016
ASPREE (24)	Aspirin 100 mg versus placebo	5 yrs	~19,000	Elderly, no diabetes or CVD	Death, dementia or significant disability	2017
ASCEND (22)	Aspirin 100 mg versus placebo (ω3FA vs. placebo)	7.5 yrs	~15,000	Diabetes, no CVD	MI, stroke or TIA, or CV death	2018

ACCEPT-D = Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trials in Diabetes; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASCEND = A Study of Cardiovascular Events in Diabetes; ASPREE = ASPIrin in Reducing Events in the Elderly; CHD = coronary heart disease; CV = cardiovascular; CVD = cardiovascular disease; FA = fatty acids; MI = myocardial infarction; TIA = transient ischemic attack.

patients with newly diagnosed cancers, including colorectal, gastroesophageal, breast, and prostate cancer (Table 3).

PREVENTION OF VASCULAR DEMENTIA

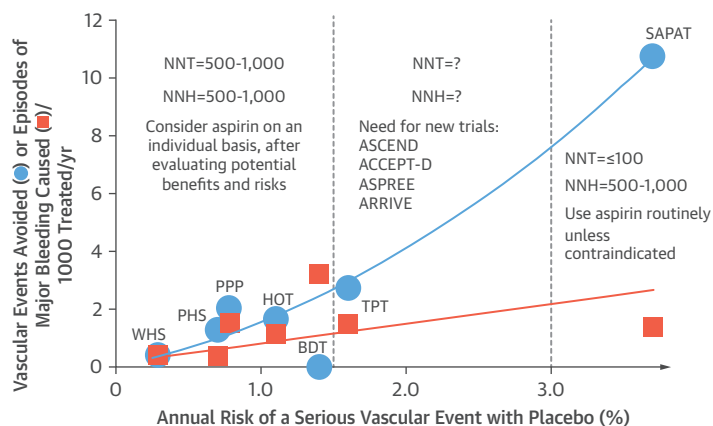
Enhanced TXA₂ biosynthesis in the chronic phase after stroke is associated with the presence of post-stroke dementia (48). Low-dose aspirin therapy has been shown to reduce the risk of ischemic stroke (5,13), and there is observational evidence of its potential to reduce the rate of cognitive decline in the elderly (8,24,49). It has recently been revealed that platelets can behave as innate inflammatory cells in immune responses with roles in leukocyte recruitment (50), migration into tissues, release of cytotoxic mediators, and in tissue remodeling following injury (51). This proinflammatory platelet function involves both complex formation with circulating leukocytes and the secretion of soluble factors (Figure 3) (50,51). Therefore, an anti-inflammatory effect of low-dose aspirin that could contribute to reduced neurodegeneration does not necessarily require inhibition of COX-2 in inflammatory cells, as would occur with high daily doses of aspirin or other NSAIDs (52), but may simply reflect its antiplatelet action. Moreover, aspirin-triggered lipoxins (a family of eicosanoids generated by interactions between 5-lipoxygenase and aspirin-acetylated COX-2) have been suggested to play a role in attenuating brain inflammation by stimulating alternative activation of microglia (53). However, although discovered 20 years ago (54), the actual biosynthesis of these compounds in vivo remains elusive.

The hypothesis that low-dose aspirin may prevent or reduce the rate of cognitive decline in the elderly has not been previously tested in a randomized clinical trial having dementia as the primary endpoint. The ASPREE trial is a double-blind, randomized, placebo-controlled primary prevention trial with an average follow-up of 5 years, designed to assess whether daily active treatment of oral 100 mg enteric-coated aspirin will extend the duration of disability-free and dementia-free life in healthy U.S. participants 65 years of age and older for African Americans and Hispanics and 70 years of age and older for Caucasians and other minority groups (24).

OPTIMIZING LOW-DOSE ASPIRIN THERAPY

A sizeable proportion of patients with a clear indication to be treated with low-dose aspirin do not receive the drug for a variety of reasons (55), or are inadequately treated because of less than optimal dose, dosing interval, or concomitant medications.

FIGURE 2 Benefits and Risks of Low-Dose Aspirin in Primary Prevention Trials



The numbers of vascular events avoided and episodes of major bleeding caused per 1,000 patients treated with aspirin per year are plotted from the results of individual placebo-controlled trials of aspirin in different patient populations characterized by various degrees of cardiovascular risk, as noted on the abscissa. Number needed to treat (NNT) and number needed to harm (NNH) values are given for subjects in 3 categories of risk on the basis of the presence or absence of randomized controlled trials. Modified with permission from Patrono et al. (5). ACCEP-D = Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trials in Diabetes; ASCEND = A Study of Cardiovascular Events in Diabetes; ARRIVE = Aspirin to Reduce Risk of Initial Vascular Events; ASPREE = Aspirin in Reducing Events in the Elderly; BDT = British Doctors Trial; HOT = Hypertension Optimal Treatment Study; PHS = Physicians' Health Study; PPP = Primary Prevention Project; SAPAT = Swedish Angina Pectoris Aspirin Trial; TPT = Thrombosis Prevention Trial; WHS = Women's Health Study.

The following is a list of practical issues that need to be addressed in order to optimize antiplatelet therapy with low-dose aspirin (Table 4).

1. Are we using the optimal dose of aspirin? Though current treatment guidelines recommend a range of daily doses, the generally accepted aspirin dose is 75, 81, or 100 mg, depending on the available commercial formulations of the drug in different countries. Because even 75 mg is at least twice as high as the lowest dose necessary and sufficient to fully inhibit platelet COX-1 activity upon repeated daily dosing (3), there are no material differences in the antiplatelet effects of doses ranging between 75 mg and 100 mg. However, enteric coating may somewhat delay and reduce aspirin absorption and impair its pharmacodynamic effect in some subjects (56).

The "optimal" dose of aspirin was the subject of a heated debate in the past, with several groups advocating the requirement of somewhat higher doses (e.g., 325 to 650 mg daily) in patients with cerebrovascular disease or ACS (13). This issue has been settled by randomized comparisons of higher versus lower doses in patients with cerebrovascular disease

TABLE 3 Ongoing Randomized Trials of Aspirin Versus Placebo in High-Risk Cancer Patients

Study	Regimen(s)	Treatment Duration	N	Eligibility	Primary Endpoint	End Date
AspECT	Aspirin 300 mg versus placebo	8 yrs	2,500	Barrett's esophagus	Death/adenocarcinoma or high-grade metaplasia	2017
seAFood	Aspirin 300 mg versus placebo (EPA versus placebo)	1 yr	904	Multiple adenomas at BCSP	≥1 adenoma at 1-yr screen	NA
ASCOLT	Aspirin 200 mg versus placebo	3 yrs	2,660	Dukes C or high-risk Dukes B cancer	5-yr disease-free survival	2022
Add-Aspirin	Aspirin 100 mg versus aspirin 300 mg versus placebo	5 yrs	9,920	CRC, breast, gastroesophageal, prostate cancer	Disease-free survival (death for gastroesophageal)	2025

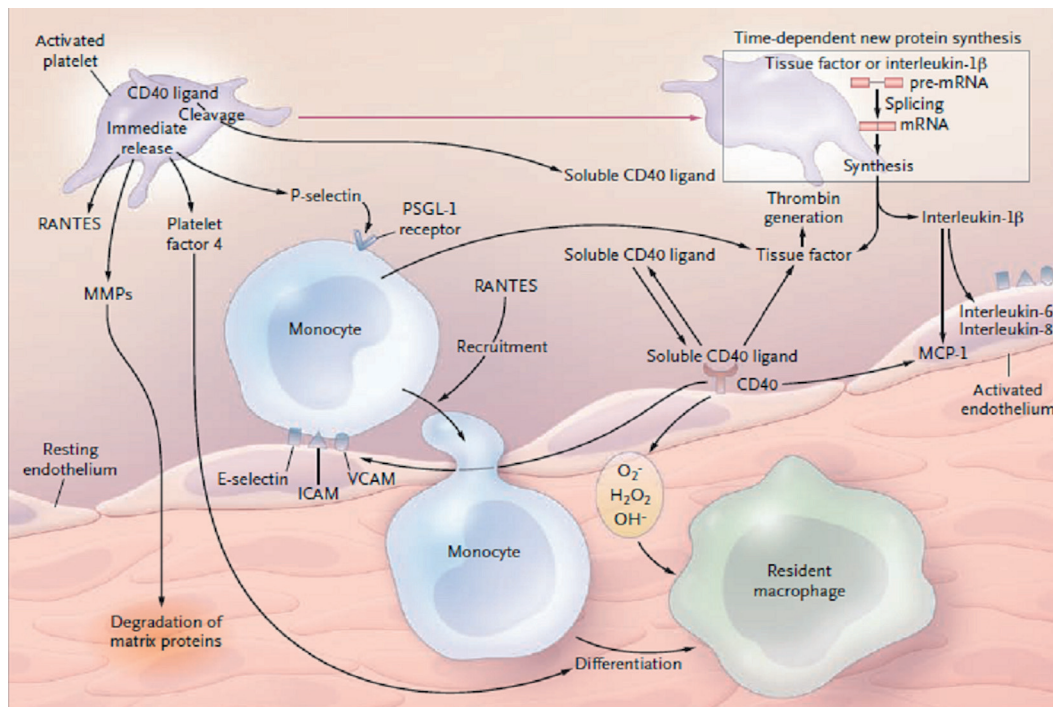
ASCOLT = Aspirin for Dukes C and High Risk Dukes B Colorectal Cancers; AspECT = Aspirin and Esomeprazole Chemoprevention Trial; BCSP = bowel cancer screening program; CRC = colorectal cancer; EPA = eicosapentaenoic acid; NA = not available; seAFood = Systematic Evaluation of Aspirin and Fish Oil.

(57,58) and in ACS (59), showing no evidence of superiority of higher versus lower doses, and in fact demonstrating that lower doses may be more effective than higher doses in the setting of carotid endarterectomy (58). The “aspirin wars” (60) are over, and there is only one winner, that is, low-dose aspirin. Using a 3-fold to 4-fold excess of the fully effective dose would not be considered an acceptable practice for any other drug treatment. Except for a loading dose in the setting of ACS or acute ischemic stroke, prescribing aspirin 325 mg daily for long-term treatment would not produce any additional benefit, while exposing the patient to unnecessary GI damage and undue bleeding complications, as well as to potential negative interactions with angiotensin-converting enzyme inhibitors (13) and ticagrelor, a reversible P2Y₁₂ blocker (61). It should be noted that in both the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction 38) (62) and PLATO (Platelet Inhibition and Patient Outcomes) (61) trials of improved P2Y₁₂ blockade in ACS, there was significant geographical variation in aspirin dosing, with North American patients receiving high-dose aspirin more frequently than patients from other places. Thus, in the PLATO trial, 54% of U.S. patients took a median aspirin dose ≥300 mg/day as compared to 2% in the rest of the world (63). Interestingly, the lowest risk of cardiovascular death, MI, or stroke with ticagrelor compared with clopidogrel was associated with a low maintenance dose of concomitant aspirin (63). Although the 2014 American Heart Association/American College of Cardiology Non-ST Elevation-Acute Coronary Syndromes guideline states that “the lower dose is favored and all patients treated with ticagrelor should receive only 81 mg per day,” as mandated by

the Food and Drug Administration, the summary of recommendations table for antiplatelet therapy lists the aspirin maintenance dose as 81 mg/day to 325 mg/day (64). It is perhaps time for members of guideline committees to come to terms with the available evidence and stop recommending such a wide dose range, in the interest of patients' safety.

2. Is a 24-h dosing interval suitable for all? Historically, the dosing interval for aspirin administration has moved from 6 h (65) to up to 48 h (66,67), with the appreciation that the duration of aspirin's antiplatelet effect was not dependent on the drug's half-life, but on the rate of platelet turnover (68). However, the standard once-daily regimen may not provide maximal platelet inhibition throughout the 24-h dosing interval in all patients. Incomplete inhibition of platelet COX-1 activity has been described in association with obesity (69-71), diabetes mellitus (70,72-74), essential thrombocythemia (75), and coronary artery bypass surgery (76). In aspirin-treated healthy subjects, negligible recovery of platelet COX-1 activity is detectable for 24 to 48 h after low-dose aspirin administration (3,77). This finding most likely reflects COX-1 acetylation of bone marrow megakaryocytes by aspirin (3,77,78). Reduced systemic bioavailability of low-dose aspirin, as seen in association with some enteric-coated formulations (56,69), may be responsible for reduced acetylation of platelet and megakaryocyte COX-1, resulting in time-dependent recovery of platelet TXA₂ production during the 24-h dosing interval. Accelerated platelet turnover, as characterized in a fraction of the diabetic population (70) and in the vast majority of patients with essential thrombocythemia (79), may limit the duration of the antiplatelet effect of low-dose aspirin and require twice-daily dosing for sustained COX-1 suppression throughout the dosing interval (70,79-81). A twice-daily regimen

FIGURE 3 Platelet-Derived Mediators of the Inflammatory Response



Activated platelets release inflammatory and mitogenic substances into the microenvironment, primarily altering the chemotactic, adhesive, and proteolytic properties of the endothelium. Pre-formed platelet mediators, stored in α -granules, can be released immediately after platelet activation through a process of exocytosis triggered by increased intracellular calcium levels. Activated platelets are also capable of time-dependent synthesis of protein mediators, such as tissue factor and interleukin-1 β . CD40 ligand is stored in the cytoplasm of resting platelets and rapidly presents on the surface after platelet activation. After cleavage, to generate a soluble, functional fragment (soluble CD40 ligand), the mediator is released into the extracellular environment, inducing inflammatory responses in the endothelium by binding CD40 on endothelial cells. P-selectin is released from platelet granules and binds to the P-selectin glycoprotein ligand 1 (PSGL-1) receptor on monocytes, enhancing the adhesion of the monocytes to vascular-cell adhesion molecule (VCAM) 1 and the other adhesins expressed on activated endothelial cells and inducing the production of tissue factor by monocytes. Activated platelets also release chemokines that trigger the recruitment of monocytes (e.g., regulated on activation normal T-cell expressed and secreted [RANTES]) or promote the differentiation of monocytes into macrophages (e.g., platelet factor 4), as well as matrix-degrading enzymes such as matrix metalloproteinase (MMP) 2 or 9. Interleukin-1 β is a major mediator of platelet-induced activation of endothelial cells, causing enhanced chemokine release and up-regulation of endothelial adhesion molecules to promote the adhesion of neutrophils and monocytes to the endothelium. H_2O_2 = hydrogen peroxide; ICAM = intracellular adhesion molecule; mRNA = messenger RNA; MCP = monocyte chemoattractant protein; O_2^- = superoxide anion; OH^- = hydroxyl radical. Reproduced with permission from Davi and Patrono (10).

of low-dose aspirin administration is currently considered in a personalized approach to antiplatelet therapy in patients with myeloproliferative neoplasms (82).

3. Do we need to worry about aspirin resistance? If we define “resistance” in classical pharmacological terms, that is, as the failure of aspirin intake to fully inactivate platelet COX-1 (83), then aspirin resistance is either a very rare phenomenon (56,77) or does not exist. A relatively large study of 400 healthy volunteers failed to identify a single case of true drug resistance (56). “Pseudo-resistance,” reflecting delayed and reduced drug absorption, may complicate

enteric-coated, but not immediate-release aspirin administration (56). Noncompliance and/or drug-drug interactions with some traditional NSAIDs, that is, ibuprofen (84,85) and naproxen (86-88), are likely to be responsible for many reports of aspirin “resistance” in the published data, and should be carefully considered in order to ensure persistent platelet inhibition by low-dose aspirin. Both noncompliance and drug-drug interactions can be easily assessed by serum TXB_2 measurements performed before and 24 h after a witnessed aspirin intake (77). Increasing the dose of aspirin will not improve platelet inhibition if the patient is not taking aspirin or is on

TABLE 4 Optimizing Low-Dose Aspirin Therapy

Suggested Action	Evidence (Ref. #)	Clinical Implication
1. Use the lowest effective dose (i.e., 75–100 mg daily)	(13,57–59)	Maximize clinical efficacy; minimize gastrointestinal toxicity and drug-drug interactions
2. Consider bid dosing in patients with type-2 diabetes mellitus and essential thrombocythemia	(70,79–81)	Ensure persistent inhibition of platelet function throughout the dosing interval; clinical relevance remains untested
3a. Prefer non-enteric-coated formulations in obese patients	(54,69)	Improve extent and duration of platelet inhibition
b. Improve compliance	(77)	Avoid misclassification of “resistance”
c. Avoid concomitant administration of ibuprofen and naproxen.	(84–88)	Avoid interference with the antiplatelet effect of low-dose aspirin
4a. Avoid concomitant administration of gastrotoxic medications (nonsteroidal anti-inflammatory drugs and high-dose corticosteroids)	(93)	Improve gastrointestinal safety
b. Consider proton pump inhibitors in high-risk patients	(89–91)	Improve gastrointestinal safety
Consider eradication in <i>H. pylori</i> -positive patients		

concomitant NSAID medication. However, improving the patient’s motivation, stopping NSAID therapy (if acceptable), or switching to an NSAID that does not interfere with the antiplatelet action of aspirin (e.g., celecoxib or diclofenac) (84,85) will likely increase the extent and duration of platelet inhibition by a standard low-dose aspirin regimen. Similarly, doubling the dose of aspirin administered once daily does not prolong the duration of its antiplatelet effect in diabetic or thrombocytopenic patients with faster recovery of platelet COX-1 during the 24-h dosing interval (70,79), while increasing dosing frequency (e.g., twice a day) results in persistent suppression of COX-1 activity throughout the dosing interval (70,79).

4. Can we reduce aspirin-associated GI bleeding hazard? Both H_2 receptor antagonists and proton pump inhibitors (PPIs) reduce gastric acid secretion, thus allowing gastric erosions and ulcers to heal (89). Although PPIs have been shown effective in reducing the risk of developing gastric and/or duodenal ulcers associated with long-term use of low-dose aspirin in elderly patients (90), no large randomized clinical trials of PPI cotherapy have been completed using upper GI bleeding as the primary endpoint. Although it would be reasonable to expect that PPIs reduce upper GI bleeding, they would not be effective in reducing lower GI bleeding (91) and may actually increase the risk of small bowel mucosal damage (92). The HEAT (*Helicobacter* Eradication Aspirin Trial) trial is currently testing the hypothesis that a 1-week course of *H. pylori* eradication in 10,000 *H. pylori*-positive patients using low-dose aspirin will halve the incidence of subsequent peptic ulcer bleeding that results in hospitalization. Avoidance of concomitant gastrotoxic medications (e.g., NSAIDs or high-dose oral corticosteroids) may somewhat reduce the risk of upper GI bleeding associated with low-dose aspirin (93).

CONCLUSIONS

The knowledge about low-dose aspirin as an antiplatelet agent has evolved considerably over the past 30 years. Its benefit/risk profile in secondary prevention is clearly favorable, and efforts should be made to ensure that all patients with symptomatic cardiovascular or cerebrovascular disease do take low-dose aspirin regularly (55). However, the balance of potential benefits and risks is substantially uncertain in primary prevention, and efforts should be made to avoid inappropriate over-prescription of low-dose aspirin (21) until the results of ongoing trials become available. In addition to rapidly becoming the cornerstone of antithrombotic therapy, and maintaining such a role in the face of newer antiplatelet agents, low-dose aspirin has been instrumental in elucidating the contribution of platelet-derived prostanoids to atherothrombosis and VTE. The same investigative approach is currently being used to dissect out the role of platelet-derived lipid and protein mediators in intestinal carcinogenesis (43,52) and age-related cognitive decline (24). If both the cardiovascular and noncardiovascular effects of low-dose aspirin are due to its antiplatelet properties, this raises the question as to whether other antiplatelet drugs may share the same spectrum of beneficial effects discussed in this review. The shorter duration of P2Y₁₂ inhibitor trials may limit the detectability of an anticancer effect, but this remains to be explored in a meta-analysis of these trials. Another interesting research question that needs to be addressed in the appropriate experimental setting is whether the ADP-P2Y₁₂, TXA₂-TP, and thrombin-PAR-1 pathways of platelet activation differentially modulate the release of specific proinflammatory and proangiogenic mediators. The translational axis leading to combined antiplatelet therapy for cancer and/or dementia prevention would

then close the loop back to clinical investigation. Finally, an appreciation that the most important clinical effects of low-dose aspirin can be explained by its unique antiplatelet properties is also useful in clinical practice because it allows concentration on those strategies that can realistically maximize its efficacy and minimize its bleeding complications.

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