REVIEW ARTICLE

DRUG THERAPY

Low-Dose Aspirin for the Prevention of Atherothrombosis

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N Engl J Med 2005;353:2373-83.

Atherosclerosis, the major cause of ischemic coronary artery disease and cerebrovascular disease, is a chronic inflammatory disorder in which immune mechanisms interact with metabolic risk factors to initiate, propagate, and activate vascular lesions.[1] Arterial thrombosis, an acute complication that develops on the surface of a ruptured atheromatous plaque or as a consequence of endothelial erosion,[1] may cause myocardial infarction or ischemic stroke. Platelets are key cellular components of arterial occlusive thrombi and may participate in the development and progression of atheromatous plaques.[2] Platelets are also vital components of hemostasis, the physiologic process that arrests hemorrhage after tissue trauma and vascular injury. Although the adhesion and activation of platelets can be viewed as a repair-oriented response to sudden fissuring or rupture of an atheromatous plaque, uncontrolled progression of such a process through a series of self-sustaining amplification loops may lead to the intraluminal formation of thrombus, vascular occlusion, and transient ischemia or infarction. The ability of platelets to participate in both normal hemostasis and atherothrombosis depends on their adhesive properties and their capacity to become activated very quickly in response to various stimuli.[2]

Currently available antiplatelet drugs interfere with certain steps in the activation process by selectively blocking key platelet enzymes or receptors, reducing the risk of arterial thrombosis through mechanisms that cannot be dissociated from an increased risk of bleeding complications.[3] In particular, randomized trials indicate that low-dose aspirin can prevent arterial thrombosis under various circumstances, including first vascular events among low-risk, healthy subjects and recurrent vascular events among patients with known acute or chronic occlusive vascular disease.[3]

The aim of this review is to integrate our current understanding of the molecular mechanism of action of aspirin with the results of clinical trials and epidemiologic studies of aspirin as an antiplatelet agent, placing special emphasis on the benefits and risks in various patient populations.

PHARMACOKINETICS

Aspirin is rapidly absorbed in the stomach and upper small intestine, primarily by passive diffusion of nondissociated acetylsalicylic acid across gastrointestinal membranes. Plasma levels peak 30 to 40 minutes after the ingestion of uncoated aspirin. In contrast, it can take up to three or four hours for plasma levels to peak after the administration of enteric-coated formulations; thus, patients should chew these preparations if a rapid antiplatelet effect is required. Esterases hydrolyze aspirin in the gastrointestinal mucosa and the liver, forming salicylic acid.[4] The oral bioavailability of regular aspirin tablets is approximately 40 to 50 percent over a wide range of doses, but the bioavailability of enteric-coated tablets and sustained-release, microencapsulated preparations is

considerably lower.[4] Aspirin first comes into contact with platelets in the portal circulation, and as a consequence, platelets are exposed to substantially higher drug levels than are present in the systemic circulation.[4] Aspirin has a half-life of 15 to 20 minutes in plasma.

Despite the rapid clearance of aspirin from the circulation, its antiplatelet effect lasts for the life of a platelet owing to the permanent inactivation of a key platelet enzyme, an effect that can be reversed only through the generation of new platelets.[5] Thus, there is a complete dissociation between the pharmacokinetics and pharmacodynamics of aspirin, allowing the use of a once-a-day regimen for antiplatelet therapy despite the very short half-life of the drug.

MECHANISM OF ACTION

The best-characterized mechanism of action of aspirin occurs through permanent inactivation of the cyclooxygenase (COX) activity of prostaglandin H (PGH) synthase 1 and synthase 2, also referred to as COX-1 and COX-2, respectively[5] (Fig. 1). These

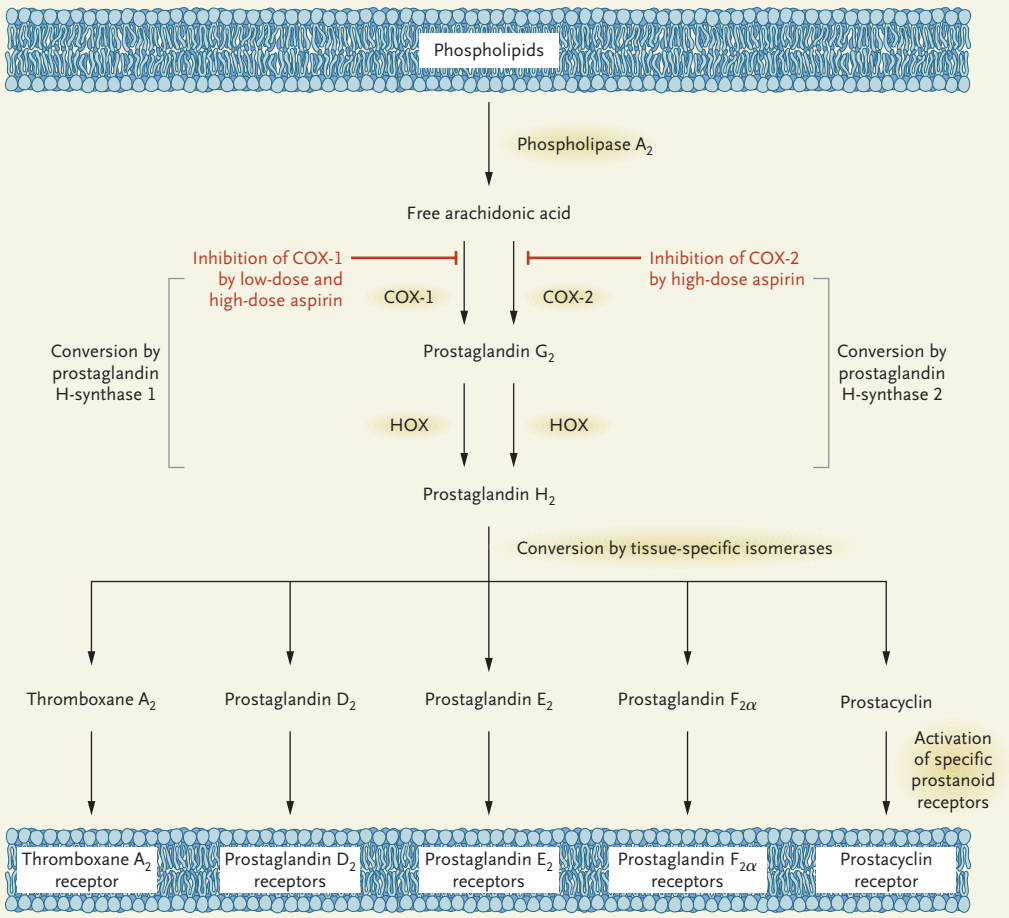

Figure 1. Mechanism of Action of Aspirin.

Arachidonic acid, a 20-carbon fatty acid containing four double bonds, is liberated from the *sn*2 position of membrane phospholipids by several forms of phospholipase A_2, which are activated by diverse stimuli. Arachidonic acid is converted by cytosolic prostaglandin H synthases, which have both cyclooxygenase and hydroperoxidase (HOX) activity, to the unstable intermediates prostaglandin G_2 and prostaglandin H_2, respectively. The synthases are colloquially termed cyclooxygenases and exist in two forms, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). Low-dose aspirin selectively inhibits COX-1, whereas high-dose aspirin inhibits both COX-1 and COX-2. Prostaglandin H_2 is converted by tissue-specific isomerases to multiple prostanoids. These bioactive lipids activate specific cell-membrane receptors of the superfamily of G-protein–coupled receptors, such as the thromboxane receptor, the prostaglandin D_2 receptors, the prostaglandin E_2 receptors, the prostaglandin $F_{2\alpha}$ receptors, and the prostacyclin receptor.

isozymes catalyze the first committed step in prostanoid biosynthesis — the conversion of arachidonic acid to PGH_2. PGH_2 is an unstable biosynthetic intermediate and a substrate for several downstream isomerases that generate at least five different bioactive prostanoids, including thromboxane A_2 (TXA_2) and prostacyclin (PGI_2). By diffusing through cell membranes, aspirin enters the COX channel, a narrow hydrophobic channel connecting the cell membrane to the catalytic pocket of the enzyme. Aspirin first binds to an arginine-120 residue, a common docking site for all nonsteroidal antiinflammatory drugs; it then acetylates a serine residue (serine 529 in human COX-1 and serine 516 in human COX-2) located in the narrowest section of the channel, thereby preventing arachidonic acid from gaining access to the COX catalytic site of the enzyme.[6] Higher levels of aspirin are needed to inhibit COX-2 than to inhibit COX-1.[7] These differences may account, at least in part, for the need to use considerably higher doses of aspirin to achieve analgesic and antiinflammatory effects, whereas antiplatelet effects can be obtained with daily doses as low as 30 mg.[3]

FUNCTIONAL CONSEQUENCES OF THE EXPRESSION AND INHIBITION OF CYCLOOXYGENASE

Although newly formed platelets express both COX-1 and COX-2,[8] mature platelets express only COX-1. In contrast, vascular endothelial cells express both COX-1 and COX-2. The latter is up-regulated in response to physiologic hemodynamics[9] and is the predominant source of PGI_2 in health[10] and disease.[11,12] Platelets and vascular endothelial cells process PGH_2 to produce primarily TXA_2 and PGI_2, respectively. TXA_2 is synthesized and released by platelets in response to a variety of stimuli (for example, collagen, thrombin, and adenosine diphosphate) and, in turn, induces irreversible platelet aggregation through its interaction with a G-protein–coupled receptor, the TXA_2 receptor.[13,14] Thus, TXA_2 provides a mechanism for amplifying the responses of platelets to diverse agonists. In addition, TXA_2 is a potent vasoconstrictor,[15] induces the proliferation of vascular smooth-muscle cells, and is proatherogenic.[16] In contrast, PGI_2 inhibits platelet aggregation in response to all agonists through its interaction with the PGI_2 receptor.[15] PGI_2 also induces vasodilation,[15] inhibits the proliferation of vascular smooth-muscle cells, protects the myocardium against oxidant stress, and is antiatherogenic.[16] Deletion of the gene encoding the PGI_2 receptor is associated with increased susceptibility to experimental thrombosis, thus supporting the importance of PGI_2 in vascular thromboresistance.[17]

Although TXA_2 is a prostanoid largely derived from COX-1 (mostly from platelets) and its biosynthesis is highly sensitive to inhibition by aspirin,[18,19] vascular PGI_2 is derived predominantly from COX-2[10-12] and is less susceptible to inhibition by low doses of aspirin.[19] Aspirin induces a long-lasting functional defect in platelets that can be detected clinically as a prolonged bleeding time.[20] In contrast, low-dose aspirin has no measurable effects on PGI_2-dependent vascular functions; thus, it does not increase blood pressure,[21] impair renal function,[22] or interfere with the antihypertensive effects of diuretics and angiotensin-converting–enzyme (ACE) inhibitors.[23]

Although other mechanisms have been proposed,[3] inhibition of platelet COX-1 is sufficient to explain the antithrombotic effects of low-dose aspirin. This does not necessarily imply that a single mediator, TXA_2, is responsible for the one quarter of major vascular events that can be prevented by low-dose aspirin in high-risk patients, because inhibition of platelet activation at sites of vascular injury may have indirect consequences, such as reducing the release of inflammatory cytokines,[24] oxygen radicals,[25] growth factors,[26] and other proteins.[27] Moreover, reduced release of these diverse platelet products may contribute, at least in part, to interference with other disease processes in which the efficacy and safety of low-dose aspirin are currently being investigated. In fact, the efficacy of once-a-day regimens of low-dose aspirin in preventing the recurrence of colorectal adenoma[28,29] is consistent with the hypothesis that activated platelets induce the up-regulation of COX-2 in one or more types of cells involved in early intestinal carcinogenesis.[30]

CLINICAL PHARMACOLOGY OF THE INHIBITION OF PLATELET CYCLOOXYGENASE

The effects of aspirin on the activity of platelet COX-1 have been characterized through measurements of serum thromboxane B_2 (TXB_2)[18,31] and urinary metabolites of TXB_2.[19] Three important features of these effects should be emphasized: the cumulative nature of the inactivation of platelet COX-1 with repeated daily doses of aspirin,[18,31] the saturability of this effect,[18,32] and the selectivity for

COX-1 at low doses.[18,31] Thus, the daily administration of 30 mg of aspirin results in virtually complete suppression of platelet TXA_2 production after one week[18] through a cumulative process of fractional acetylation of roughly 50 percent of unacetylated platelet COX-1 by successive daily doses of aspirin.[31] The practical implication of this finding is that typical regimens of 75 to 100 mg of aspirin per day clearly exceed the minimal effective dose required for a full pharmacodynamic effect, thus accommodating some degree of interindividual variability in drug response. There is no evidence that the pharmacodynamics of platelet inhibition by aspirin is any different in women than in men.[18,31]

Because the maximal biosynthetic capacity of human platelets[33] (Fig. 2A) is several thousand times as high as the basal rate of TXA_2 biosynthesis in healthy subjects[34] (Fig. 2B), the relationship between the inhibition of platelet COX-1 activity and TXA_2 biosynthesis in vivo is strikingly nonlinear[35] (Fig. 2C). The inhibition of platelet COX-1 attains functional relevance when the maximal capacity to generate TXA_2 is reduced by at least 95 percent.[35,36]

The relative COX-1 selectivity of low-dose aspirin most likely accounts for the substantial residual COX-2–dependent PGI_2 biosynthesis in vivo at daily doses in the range of 20 to 80 mg,[19] despite transient suppression of COX-1–dependent release of PGI_2.[37] More profound suppression of PGI_2 formation by higher doses of aspirin, as a function of the dose-dependent inhibition of COX-2, might be expected to attenuate the antithrombotic efficacy of the drug. However, there is limited direct evidence supporting this possibility.[38-40]

Permanent inactivation of platelet COX-1 by aspirin may lead to bleeding complications as well as the prevention of arterial thrombosis. At least two distinct COX-1–dependent mechanisms contribute to the increased risk of upper gastrointestinal bleeding associated with aspirin therapy: the inhibition of TXA_2-mediated platelet aggregation and the impairment of PGE_2- and PGI_2-mediated cytoprotection in the gastrointestinal mucosa.[3] Whereas the former effect is independent of a dose in excess of 30 mg daily, the latter effect is clearly dose-dependent. Inhibition of platelet function may largely account for the twofold increase in the risk of upper gastrointestinal bleeding associated with daily doses of aspirin in the range of 75 to 100 mg, inasmuch as a similar relative risk is associated with other drugs that interfere with primary hemostasis but do not affect COX-dependent cytoprotection.[41] Dose-dependent inhibition of cytoprotection by higher doses of aspirin amplifies the risk of bleeding and perforation by causing new mucosal lesions or aggravating existing ones and increases the risk by a factor of 4 to 10 at analgesic doses. The use of an antisecretory agent (especially a proton-pump

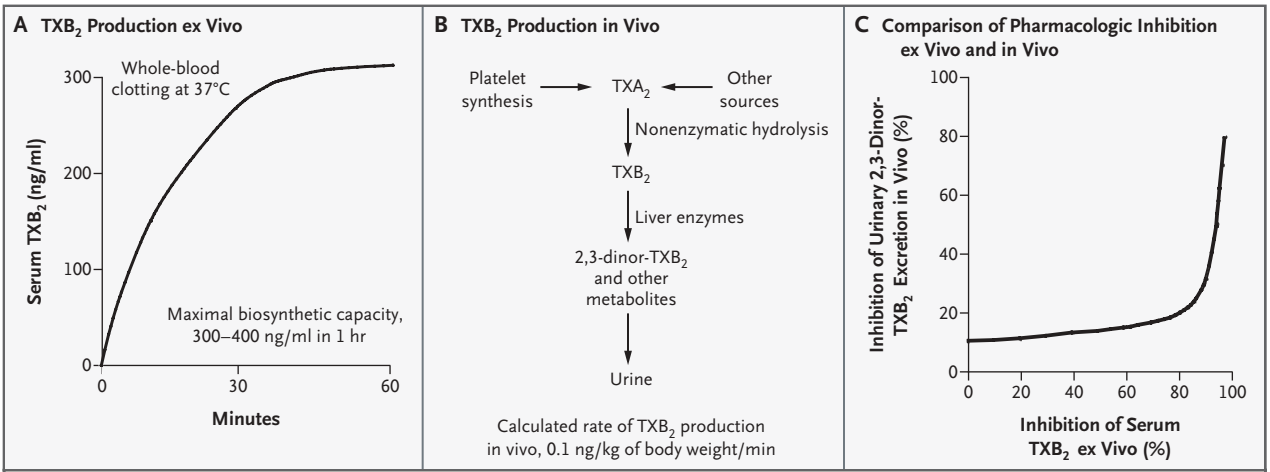

Figure 2. Maximal Capacity of Human Platelets to Synthesize Thromboxane B_2 (TXB_2) (Panel A), Rate of TXB_2 Production in Healthy Subjects (Panel B), and Nonlinear Relationship between the Inhibition of Platelet Cyclooxygenase Activity and TXB_2 Biosynthesis in Vivo (Panel C).

Panel A depicts the level of TXB_2 production stimulated by endogenous thrombin during whole-blood clotting at 37°C and is based on data from Patrono et al.[33] Panel B shows the metabolic fate of thromboxane A_2 (TXA_2) in vivo and the calculated rate of its production in healthy subjects on the basis of TXB_2 infusions and measurement of its major urinary metabolite.[34] Panel C depicts the nonlinear relationship between the inhibition of serum TXB_2 measured ex vivo and the reduction in the excretion of thromboxane metabolites measured in vivo.[35]

inhibitor) was associated with a reduced risk of upper gastrointestinal bleeding in patients taking aspirin in a case–control study,[42] but no adequately sized placebo-controlled, randomized trial has examined the protective effects of acid-antisecretory therapy in patients treated with 75 to 100 mg of aspirin daily.

DRUG INTERACTIONS

In contrast to treatment with the vast majority of COX inhibitors,[43] low-dose aspirin therapy (75 mg daily) does not affect blood-pressure control or the need for antihypertensive therapy in patients with intensively treated hypertension.[21] This observation is consistent with the absence of an effect of low-dose aspirin on renal prostaglandin synthesis.[18,22] In humans, renal synthesis of prostaglandins is dependent on constitutively expressed COX-2.[43] The suggestion that the benefit of ACE inhibitors after acute myocardial infarction may be reduced by aspirin[44] is not supported by the results of a large meta-analysis of myocardial infarction trials.[45] Similarly, no negative interaction occurs between ACE inhibition and the cardioprotection afforded by low-dose aspirin in patients with hypertension,[46] and a meta-analysis of six long-term randomized trials comparing an ACE inhibitor with placebo did not show that aspirin use abrogated the benefits of ACE inhibitors.[47] Thus, it appears that ACE inhibitors are beneficial irrespective of aspirin use.[47]

A pharmacodynamic interaction that potentially interferes with the antiplatelet effect of aspirin is related to the two-step mechanism of COX-1 inactivation.[6] Concomitant administration of reversible COX-1 inhibitors, such as ibuprofen[48] and naproxen,[49] may prevent the irreversible acetylation of platelet COX-1 by low-dose aspirin. This is due to competition between these drugs and aspirin for a common docking site within the COX-1 channel (arginine 120); aspirin binds this site with weak affinity before the acetylation of serine 529.[6] This pharmacodynamic interaction does not occur with coxibs or traditional nonsteroidal antiinflammatory drugs (NSAIDs) such as diclofenac that have some degree of COX-2 selectivity.[48] Whether this interaction attenuates or abrogates the cardioprotective benefit of low-dose aspirin is uncertain.[50,51]

Low-dose aspirin therapy can cause upper gastrointestinal bleeding.[3] In two large trials, subgroup analyses suggested that aspirin may attenuate the gastrointestinal safety of selective COX-2 inhibitors, as compared with traditional NSAIDs.[52,53] However, this potential interaction needs to be assessed further in studies that compare selective COX-2 inhibitors with traditional NSAIDs in patients who are receiving aspirin.

ASPIRIN RESISTANCE

The term "aspirin resistance" has been used to describe the inability of aspirin to produce a measurable response on ex vivo tests of platelet function, to inhibit TXA_2 biosynthesis in vivo, or to protect individual patients from thrombotic complications.[54] Similar phenomena have been described for clopidogrel, which is a thienopyridine with a totally different mechanism of action from that of aspirin.[55] The term "resistance" does not describe the mechanisms underlying interindividual variability in response to aspirin or clopidogrel. In fact, it is potentially misleading, implying that something can be measured that has a direct bearing on clinical efficacy and that, depending on the results, may lead to a change in antiplatelet therapy. However, the relevance to in vivo platelet activation of the various ex vivo functional indexes of platelet capacity is largely unknown.[54,56] Moreover, the correlations between results of different tests of aspirin responsiveness are poor.[57] Thus, we think that the term "resistance" should be abandoned. Rather, the distinct factors that contribute to interindividual variability in response to aspirin or clopidogrel should be explored.[55] For aspirin, these include the pharmacodynamic interaction with reversible COX-1 inhibitors,[48,49] as noted above, as well as the role of extraplatelet sources of TXA_2 production in different clinical settings.[58,59]

As with any drug used to prevent atherothrombosis, vascular events are frequent among patients treated with aspirin or other antiplatelet drugs, and this phenomenon is sometimes described as treatment failure. Given the multifactorial nature of atherothrombosis, it is not surprising that less than a quarter of all vascular complications typically can be prevented through the use of any one strategy. There is no scientific basis for changing antiplatelet therapy in the face of such treatment failure, since we cannot be sure whether a second vascular event in the same patient will share the same components of the causal mechanism that led to the first. Moreover, we have no convincing evidence that changing therapy is a more effective strategy than maintaining an evidence-based antiplatelet regimen. Increased awareness of factors that may in-

terfere with the desired antiplatelet effects of aspirin or clopidogrel,[55] particularly avoidable drug interactions, may result in better patient care than requesting unnecessary tests of platelet function. In fact, no test of platelet function is currently recommended to assess the antiplatelet effects of aspirin or clopidogrel in individual patients.[3,56,60]

EFFICACY AND SAFETY OF LOW-DOSE ASPIRIN IN THE PREVENTION AND TREATMENT OF ATHEROTHROMBOSIS IN HIGH-RISK PATIENTS

The efficacy and safety of aspirin have been evaluated in several populations, ranging from apparently healthy persons at low risk to patients presenting with an acute myocardial infarction or an acute ischemic stroke. Among patients with occlusive vascular disease, both individual studies[3] and a meta-analysis of trials of antiplatelet therapy[38] indicate that aspirin and other antiplatelet drugs reduce the risk of a serious vascular event (nonfatal myocardial infarction, nonfatal stroke, or death from vascular causes) by approximately 25 percent. This figure represents a composite of a 34 percent reduction in the rate of nonfatal myocardial infarction, a 25 percent reduction in the rate of nonfatal stroke, and a reduction by one sixth in the rate of death from a vascular or unknown cause.[3,38] Since each of these proportional reductions applies similarly to all categories of patients with vascular disease, the absolute benefits of aspirin in individual patients can be estimated by reducing the estimated absolute risk of nonfatal myocardial infarction by one third, the risk of nonfatal stroke by one fourth, and the risk of death from vascular causes by one sixth.[3,38] Thus, among a wide range of patients with vascular disease, in whom the annual risk of a serious vascular event ranges from 4 to 8 percent, aspirin typically prevents at least 10 to 20 fatal and nonfatal vascular events for every 1000 patients treated for one year (Fig. 3).[3,38]

Observational studies[61] and a meta-analysis of randomized clinical trials in high-risk patients[38] have demonstrated that long-term therapy with low-dose aspirin approximately doubles the risk of major extracranial (mostly, upper gastrointestinal) bleeding. In middle-aged patients, this corresponds to an estimated absolute excess of approximately 1 to 2 major bleeding complications per 1000 patients treated with low-dose aspirin for one year.[3,38,61] Moreover, there is an absolute excess of hemorrhagic strokes of 1 to 2 per 10,000 patients.[38] Therefore, for most high-risk patients taking low-dose aspirin, the number in which a serious vascular event would be avoided clearly outweighs the number with a major bleeding episode, unless a given patient has increased susceptibility to bleeding owing to advanced age, a history of ulcer, or concomitant treatment with other drugs interfering

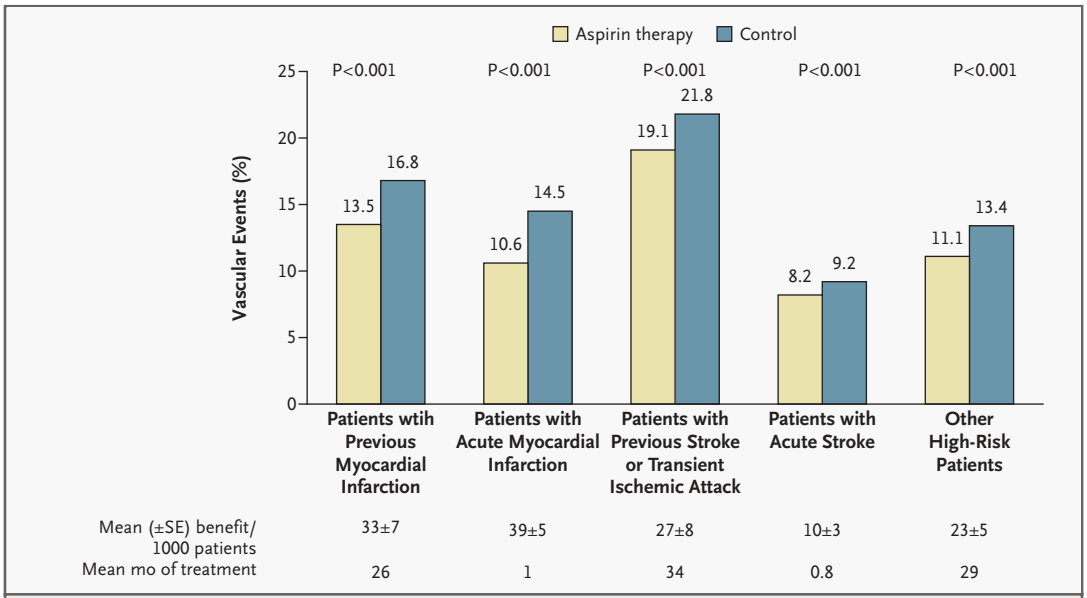

Figure 3. Absolute Effects of Antiplatelet Therapy with Aspirin on the Risk of Vascular Events (Nonfatal Myocardial Infarction, Nonfatal Stroke, or Death from Vascular Causes) in Five Groups of High-Risk Patients.

The figure is based on an analysis of data from the Antithrombotic Trialists' Collaboration.[38]

with primary hemostasis or gastrointestinal cytoprotection.

Such a favorable risk–benefit ratio of low-dose aspirin in high-risk patients has resulted in level 1 recommendations,[60] and the Food and Drug Administration has approved aspirin for patients at high risk for occlusive vascular disease. Despite such a recommendation, aspirin use appears to be less than optimal, according to cardiovascular registries[62,63] and a recent survey.[64] A history of adverse reactions to aspirin is a common reason for avoiding long-term use in high-risk patients. In a double-blind, placebo-controlled, randomized study of 150 patients using low-dose (80 mg daily) aspirin with upper gastrointestinal symptoms, treatment with a proton-pump inhibitor significantly reduced the rate of heartburn, but not other aspirin-associated symptoms.[65] In addition to causing gastrointestinal intolerance, aspirin is an infrequent cause of unpredictable hypersensitivity reactions, often referred to as "aspirin allergy."[66] Proper classification of patients who are allergic to aspirin and early referral of such patients to allergy services for potential desensitization may allow continued use of this lifesaving drug.[66]

Thus, aspirin is recommended in all clinical conditions in which antiplatelet prophylaxis has a favorable risk–benefit profile.[3,60] Given the potential of aspirin to cause dose-dependent impairment of gastric cytoprotection and endothelial thromboresistance, physicians are encouraged to use the lowest dose of aspirin shown to be effective in each clinical setting[67-74] (Table 1). The available evidence supports the use of daily doses of aspirin in the range of 75 to 100 mg for the long-term prevention of serious vascular events in high-risk patients. The use of a once-a-day regimen is preferable to the use of an every-other-day regimen because of interindividual variability in the platelet turnover rate, which represents an important determinant of the extent and duration of platelet inhibition on repeated dosing with low-dose aspirin.[31] In clinical settings in which an immediate antithrombotic effect is required (such as in the presence of acute coronary syndromes or acute ischemic stroke), a loading dose of 160 to 200 mg should be given at the time of diagnosis to ensure rapid and complete inhibition of thromboxane-dependent platelet aggregation.[3]

EFFICACY AND SAFETY OF LOW-DOSE ASPIRIN IN LOW-RISK SUBJECTS

In contrast to the clear benefits of low-dose aspirin on the risk of myocardial infarction, stroke, and death from vascular causes among high-risk patients with known occlusive vascular disease, its effects in low-risk persons are less clear. A meta-analysis of five primary-prevention trials[21,75-78] indicated that aspirin reduces the risk of myocardial infarction by approximately 30 percent (which is similar to the benefit associated with secondary prevention) but has no significant effect on the risk of stroke.[79] More recently, the results of the aspirin component of the Women's Health Study, which compared 100 mg of aspirin every other day with placebo in approximately 40,000 apparently healthy women, were reported.[80] The results were surprising because they appeared to contrast with the results of earlier trials, in which the majority of participants had been men. Aspirin reduced the risk of stroke by 17 percent (95 percent confidence interval, 1 to 31 percent; P=0.04), but there was no significant reduction in the risk of myocardial infarction (relative risk, 1.02; 95 percent confidence interval, 0.84 to 1.25). However, in secondary-prevention trials, the effects of aspirin on the risk of major coronary events and strokes were similar in men and women.[81] The reasons for this apparent discrepancy remain unclear,[82] and further research is needed to clarify this issue.

Whereas the benefits of aspirin exceed the risks of bleeding in most patients with clinically overt arterial disease, the risk–benefit ratio is marginal in low-risk populations. As shown in Figure 4, whereas the risk of a vascular event was almost 4 percent per year among patients with ischemic heart disease in the Swedish Angina Pectoris Aspirin Trial,[67]

Table 1. High-Risk Disorders for Which Aspirin Has Been Shown to Be Effective and Lowest Effective Daily Dose.

Disorder	Lowest Effective Daily Dose*
	mg
Chronic stable angina[67]	75
Polycythemia vera[68]	100
Unstable angina[69]	75
Acute myocardial infarction[70]	160
Transient ischemic attack and ischemic stroke[71]	50
Severe carotid artery stenosis[72]	75
Acute ischemic stroke[73]	160
Atrial fibrillation[74]	325

* The lowest effective daily dose is the lowest daily aspirin dose for which direct randomized evidence of effectiveness is available.

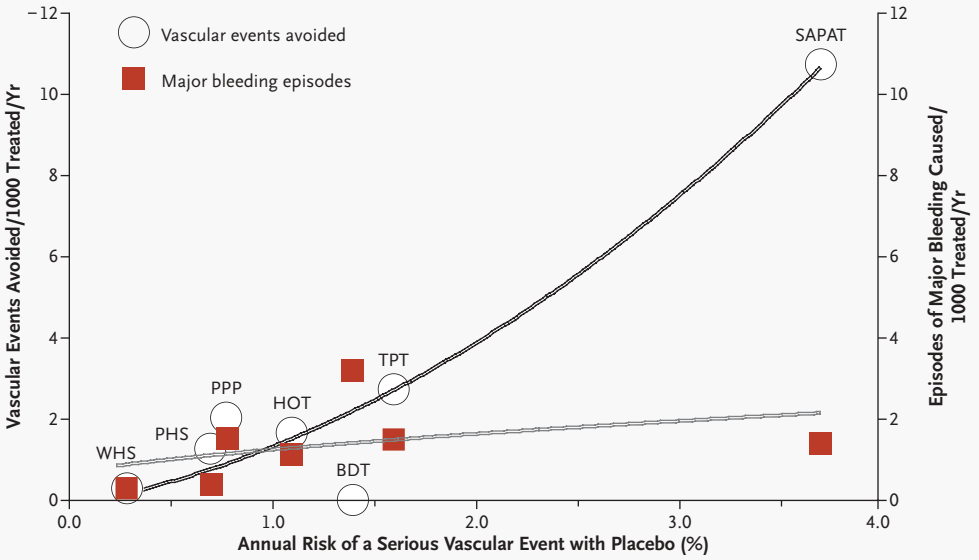

Figure 4. Benefits and Risks of Low-Dose Aspirin in Primary-Prevention Trials.

The numbers of vascular events avoided and episodes of major bleeding caused per 1000 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. WHS denotes Women's Health Study, PHS Physicians' Health Study, PPP Primary Prevention Project, HOT Hypertension Optimal Treatment Study, BDT British Doctors Trial, TPT Thrombosis Prevention Trial, and SAPAT Swedish Angina Pectoris Aspirin Trial. Data are modified from Patrono et al.[60]

the average annual risk was much lower (0.3 to 1.6 percent per year) in six primary-prevention trials involving mostly asymptomatic subjects. The benefit of aspirin did not clearly outweigh the harm within this range of cardiovascular risk. In these primary-prevention trials, few subjects exceeded the threshold for aspirin prophylaxis recommended by the American Heart Association — a risk of coronary heart disease of 1 percent per year.[83] It is worth remembering that these trials included few people older than 70 years of age, in whom the predicted risk of coronary heart disease and stroke rises steeply and who are the dominant demographic group at elevated risk (i.e., the risk exceeds 1 percent per year). The lack of randomized trials involving older people makes it difficult to assess whether any possible benefits of aspirin would exceed the known risks of upper gastrointestinal bleeding in this age group.[84] As illustrated in Figure 5, the risk of such complications increases sharply among people 70 years of age or older. This risk is further increased by a history of gastrointestinal disturbances (Fig. 5) and by concomitant use of nonsteroidal antiinflammatory drugs (data not shown). Although there seems to be a general agreement among gastroenterologists that proton-pump inhibitors should be prescribed to high-risk patients taking low-dose aspirin,[85] such a strategy has not been widely adopted because of a lack of definitive evidence to support it.

FUTURE DIRECTIONS

There are several potential strategies for improving the ability of antiplatelet therapy to prevent atherothrombosis. One important aim is to ensure the appropriately wide use of aspirin (or some other effective antiplatelet regimen) among high-risk patients with vascular disease. Several surveys[62-64] have indicated that many patients who may benefit do not routinely receive low-dose aspirin; considerable efforts are needed to improve these statistics. In some groups of patients, however, low rates of aspirin use reflect the lack of convincing evidence of its efficacy and safety; thus, there is a need for additional placebo-controlled trials in these groups. For example, the ongoing A Study of Cardiovascular Events in Diabetes should provide valuable information about the efficacy and safety of aspirin in people with diabetes with no history of vascular

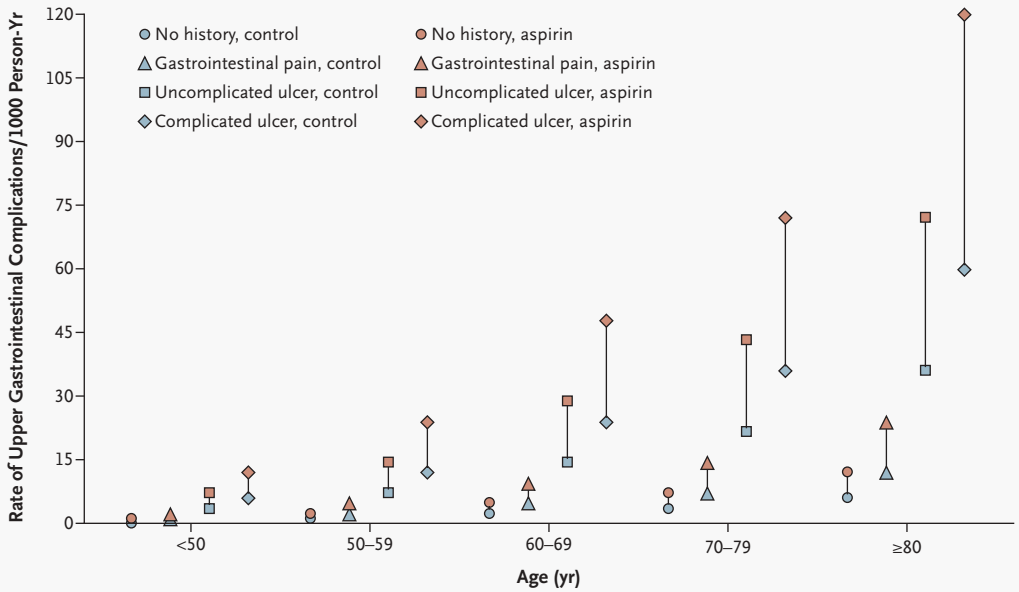

Figure 5. Estimated Rates of Upper Gastrointestinal Complications in Men, According to Age and the Presence or Absence of a History of Such Complications and Regular Treatment with Low-Dose Aspirin.

The solid lines connecting each pair of blue and red symbols depict the absolute excess of complications related to aspirin therapy. Data are from García Rodríguez et al.[61] and unpublished results from S. Hernandez-Díaz and L.A. García Rodríguez.

events, and the Aspirin in Reducing Events in the Elderly study should provide such information about patients older than 70 years of age.[86]

In high-risk patients who are already taking aspirin, it is reasonable to ask whether an alternative antithrombotic regimen might be more effective than aspirin. Although clopidogrel may be marginally more effective than aspirin in certain high-risk groups,[87] adding a second antithrombotic agent (either an antiplatelet or an anticoagulant) to aspirin is likely to result in much larger reductions in risk than switching from aspirin to an alternative agent. Although there is already some evidence from randomized trials to support the use of this strategy,[71,88,89] more information is needed on its efficacy and safety in different high-risk groups.

Supported by a grant (project 005033) from the Commission of the European Communities.

Dr. Patrono reports having received consulting fees from Bayer and NiCox and lecture fees from Sanofi, Bayer, and Eli Lilly; Dr. García Rodríguez, lecture fees from Bayer and grant support from Pfizer; Dr. Landolfi, lecture fees from Aventis and Bayer Italia; and Drs. Baigent and Patrono, grant support from Bayer and Merck.

We are indebted to Dr. Angel Lanas for reviewing and discussing several aspects of this article, to Dr. Patricia Kearney for assistance with the analyses included in Figure 3, to Dr. Roberto Marchioli for drafting the original version of Figure 4, and to Daniela Basilico for editorial assistance.

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