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Aspirin

Eric H. Awtry, MD; Joseph Loscalzo, MD, PhD

Salicylates, in the form of willow bark, were used as an analgesic during the time of Hippocrates, and their antipyretic effects have been recognized for more than 200 years.¹ Acetylsalicylic acid, or aspirin, was introduced in the late 1890s² and has been used to treat a variety of inflammatory conditions; however, the antiplatelet activity of this agent was not recognized until almost 70 years later.³ Recent advances in our understanding of the central role of platelets in the pathophysiology of cardiovascular disease have spurred in-depth investigations into the mechanisms of action of aspirin and the clinical utility of this agent in the treatment of common cardiovascular disorders.

Mechanism of Action

Aspirin exerts its effect primarily by interfering with the biosynthesis of cyclic prostanoids, ie, thromboxane A₂ (TXA₂), prostacyclin, and other prostaglandins. These prostanoids are generated by the enzymatically catalyzed oxidation of arachidonic acid, which is itself derived from membrane phospholipids⁴ (Figure). Arachidonic acid is metabolized by the enzyme prostaglandin (PG) H-synthase, which, through its cyclooxygenase (COX) and peroxidase activities, results in the production of PGG₂ and PGH₂, respectively. PGH₂ is then modified by specific synthases, thus producing prostaglandins D₂, E₂, F_{2α}, I₂ (prostacyclin), and TXA₂, all of which mediate specific cellular functions.

PGH-synthase, also referred to as COX, exists in 2 isoforms that have significant homology of their amino acid sequences.⁵ A single amino acid substitution in the catalytic site of the enzyme confers selectivity to inhibitors of the COX isoforms.^{6,7} The first isoform (COX-1) is constitutively expressed in the endoplasmic reticulum of most cells (including platelets)⁸ and results in the synthesis of homeostatic prostaglandins responsible for normal cellular functions, including gastric mucosal protection, maintenance of renal blood flow, and regulation of platelet activation and aggregation.⁴ The second isoform (COX-2) is not routinely present in most mammalian cells but, rather, is rapidly inducible by inflammatory stimuli and growth factors and results in the production of prostaglandins that contribute to the inflammatory response.^{9,10}

Aspirin imparts its primary antithrombotic effects through the inhibition of PGH-synthase/COX by the irreversible acetylation of a specific serine moiety (serine 530 of COX-1

and serine 516 of COX-2)^{11,12} and is ≈170-fold more potent in inhibiting COX-1 than COX-2.¹³ In the presence of aspirin, COX-1 is completely inactivated, whereas COX-2 converts arachidonic acid not to PGH₂, but to 15-*R*-hydroxyeicosatetraenoic acid (15-*R*-HETE).¹⁴ The end result is that neither affected isoform is capable of converting arachidonic acid to PGH₂, a necessary step in the production of prostanoids. The resultant decreased production of prostaglandins and TXA₂ likely accounts for the therapeutic effects, as well as the toxicities, of aspirin. From a cardiovascular standpoint, it is principally the antithrombotic effect of aspirin that results in its clinical utility. Platelet production of TXA₂ in response to a variety of stimuli (including collagen, thrombin, and ADP) results in the amplification of the platelet aggregation response and in vasoconstriction.^{15,16} Conversely, vascular endothelial cell production of prostacyclin results in inhibition of platelet aggregation and induces vasodilation. Aspirin-induced inhibition of TXA₂ and PGI₂ has opposing effects on hemostasis; however, the available data suggest that the potentially prothrombotic effects of PGI₂ inhibition are not clinically relevant and that the antithrombotic effects of TXA₂ inhibition predominate.¹⁷ This may, in part, be a result of the ability of vascular endothelial cells to regenerate new COX and thus recover normal function,¹⁸ whereas COX inhibition in platelets is irreversible owing to the limited mRNA pool and protein synthesis in these anuclear cells.

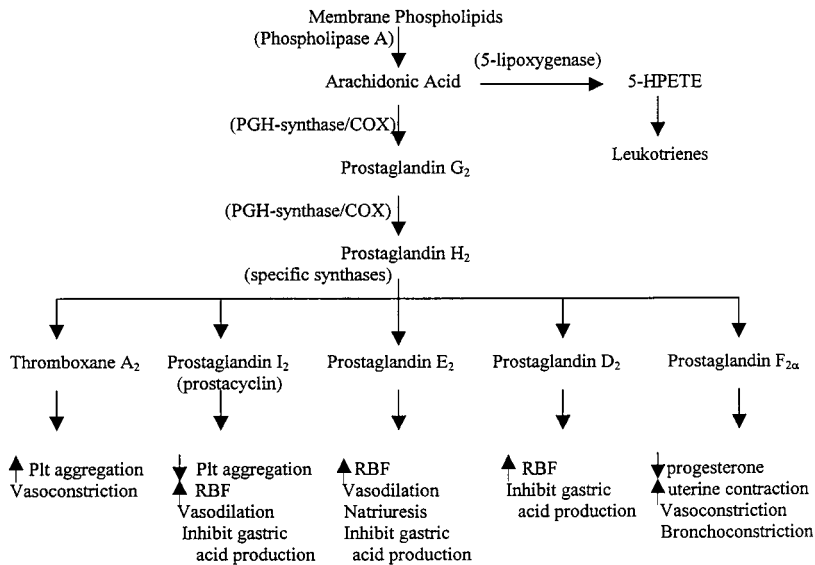
Other mechanisms for platelet inhibition by aspirin have been proposed. For example, aspirin facilitates the inhibition of platelet activation by neutrophils, an effect that appears to be mediated by a nitric oxide (NO)/cGMP-dependent process,¹⁹ and inhibition of prostacyclin synthesis in endothelial cells enhances NO production.²⁰ In addition to its antithrombotic effects, other mechanisms may contribute to the clinical benefits of aspirin in the treatment of cardiovascular disorders. Aspirin may help to decrease the progression of atherosclerosis by protecting LDL from oxidative modification²¹ and also improves endothelial dysfunction in atherosclerotic vessels.²² Several mechanisms have been proposed to explain these benefits, all of which center on the potential role of aspirin as an antioxidant. Salicylate has been shown to be an inhibitor of the cytokine-dependent induction of NOS-II gene expression,^{23,24} perhaps through a mechanism involving nuclear factor-κB activation, an effect that would tend to decrease the nitrosative stress that accompanies cytokine

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The production of prostaglandins from arachidonic acid and their physiological effects. HPETE indicates hydroperoxyeicosatetraenoic acid; PG, prostaglandin; Plt, platelet; and RBF, renal blood flow.

elaboration. Aspirin can also directly scavenge hydroxyl radicals to form the 2,3- and 2,5-dihydroxybenzoate derivatives, which themselves serve as markers of oxidative stress²⁵ and quench oxy-radical flux,²⁶ and can acetylate the ϵ -amino groups of lysine residues in proteins,²⁷ which prevents their oxidation.²⁸ This antioxidant effect on proteins may be important in limiting both lipoprotein oxidation and fibrinogen oxidation; in the latter case, oxidation enhances fibrin formation,^{27,29} and lysine acetylation enhances fibrinolysis.³⁰ It is likely through this combination of effects that aspirin reduces the inflammatory response in patients with coronary artery disease.³¹

Pharmacology/Pharmacokinetics

Aspirin is rapidly absorbed in the upper gastrointestinal (GI) tract and results in a measurable inhibition of platelet function within 60 minutes.^{17,32} This antiplatelet effect is associated with prolongation of the bleeding time and inhibition of TXA₂-dependent platelet aggregation.³³ These effects occur even before acetylsalicylic acid is detectable in the peripheral blood, owing to the exposure of platelets to aspirin in the portal circulation.³⁴ Enteric coating of aspirin significantly delays its absorption.³⁵ The plasma half-life of aspirin is only 20 minutes; however, because platelets cannot generate new COX, the effects of aspirin last for the duration of the life of the platelet (\approx 10 days). After a single dose of aspirin, platelet COX activity recovers by \approx 10% per day as a function of platelet turnover.³⁶ Although it may take 10 days for the total platelet population to be renewed, and thus restore normal COX activity, it has been shown that if as little as 20% of platelets have normal COX activity, hemostasis may be normal.^{37,38}

The dose of aspirin required to obtain adequate platelet inhibition has been studied extensively. A single dose of 100 mg of aspirin effectively abolishes the production of TXA₂ in normal individuals, as well as in patients with atherosclerotic disease.^{39,40} Single doses below 100 mg result in a dose-dependent effect on TXA₂ production; the effect of repeated

daily doses is cumulative, although >24 hours may be required to achieve maximal COX inhibition.^{38,39,41} Therapeutic benefit in a variety of cardiovascular diseases has been demonstrated with doses of 30 to 1500 mg/d; higher doses do not appear to be more effective but may increase the risk of GI side effects.^{17,42} Low-dose aspirin or controlled-release preparations may result in somewhat preferential inhibition of platelet COX over endothelial COX.^{33,40,43} This differential effect has theoretical advantages in that intact endothelial PGI₂ production may enhance the antithrombotic effects of aspirin; however, the clinical importance of maintaining normal PGI₂ production remains undetermined.

Aspirin in Coronary Artery Disease

Acute Therapy

Acute Myocardial Infarction

The importance of platelets and thrombosis in the pathophysiology of acute coronary syndromes is well established. Although early studies of the use of aspirin as an antithrombotic agent in the acute treatment of myocardial infarction (MI) yielded conflicting results, the Second International Study of Infarct Survival (ISIS-2)⁴⁴ has since unequivocally established the benefit of aspirin in this setting. In this trial, 17 187 patients presenting within 24 hours of the onset of a suspected acute MI (AMI) were randomized to receive intravenous streptokinase (1.5 MU), 162.5 mg of aspirin daily for 30 days, both, or neither. At the end of 5 weeks, patients receiving aspirin therapy alone had a highly significant 23% reduction in vascular mortality and a nearly 50% reduction in the risk of nonfatal reinfarction and nonfatal stroke. This benefit occurred irrespective of whether heparin was given. These reductions translate into the avoidance of \approx 25 deaths and 10 to 15 nonfatal reinfarctions or strokes by treating 1000 patients with aspirin for 1 month. Additionally, there was no increase in major bleeding complications (including no increase in cerebral hemorrhage or need for transfusion) with

TABLE 1. Benefit of Aspirin in Unstable Angina

Reference	No. of Patients	Dose, mg	Duration of Treatment	% Death or Nonfatal MI			% Mortality		
				Aspirin	Control	% Reduction (P)	Aspirin	Control	% Reduction (P)
VA Cooperative Study ⁵³	1266	325 QD	12 wk	5.0	10.1	51 (0.0005)	1.6	3.3	51 (0.054)
Canadian Multicenter Trial ⁵⁴	555	325 QID	24 mo	8.6	17.0	51 (0.008)	3.0	11.7	71 (0.004)
Thérout et al ⁵⁵	479	325 BID	6 d	3.3	12.0	72 (0.01)	0.0	1.7	...
RISC ^{52,56,57*}	796	75 QD	5 d	2.5	5.8	57 (0.033)	0.25	0.25	0 (NS)
			6 mo	8.9	19.0	53 (<0.0001)	2.0	3.8	47 (NS)
			12 mo	11.0	21.4	49 (0.0001)	2.8	4.5	38 (NS)

*Included patients with unstable angina and non-Q-wave infarctions. Results were similar in both groups.

aspirin therapy, and the mortality benefit was maintained after 10 years of follow-up.⁴⁵

In the past decade, thrombolytic therapy has become the cornerstone of medical management of AMI.^{46,47} Aspirin, however, remains an important adjunctive therapy. In ISIS-2,⁴⁴ administration of streptokinase alone was associated with a 25% reduction in vascular deaths, and the effect of aspirin therapy was additive (42% reduction in vascular mortality with combined aspirin and streptokinase therapy). Additionally, an excess of nonfatal reinfarctions was seen in the first several days after treatment with streptokinase alone, likely as a result of plasmin-induced platelet activation; this increase was entirely prevented by the concomitant use of aspirin. Compared with aspirin as an adjunct to thrombolysis, heparin appears to be associated with a higher early patency rate of the infarct-related artery, although aspirin was associated with a trend toward a decreased 7-day reocclusion rate.⁴⁸ The addition of heparin to aspirin does not clearly decrease mortality or reinfarction and is associated with an increase in bleeding complications.^{49,50} A meta-analysis of 32 trials using aspirin as adjunctive therapy to thrombolysis demonstrated significantly decreased reocclusion rates (11% versus 25%) and recurrent ischemic events (25% versus 41%) with aspirin therapy.⁵¹

Unstable Angina and Acute Non-ST-Segment-Elevation MI

Several studies have clearly demonstrated a beneficial role for aspirin in the treatment of unstable angina (Table 1).^{52–55} Despite instituting aspirin therapy at various doses (75 to 1300 mg/d) and differing intervals after a patient's initial presentation (<24 hours to <8 days), these trials have consistently demonstrated a significant decrease in the incidence of death or death and nonfatal MI. Additionally, in the Research Group on Instability in Coronary Artery Disease in Southeast Sweden (RISC) trial,⁵⁶ treatment with aspirin (75 mg/d) decreased the progression to severe angina necessitating cardiac catheterization by 40% at 3 months (10.8% versus 18.1%) and 29% at 12 months (20.8% versus 29.2%). Low-dose aspirin (75 mg/d) has also been shown to decrease the risk of MI or death in patients with asymptomatic ischemia on treadmill testing after an episode of unstable angina or a non-Q-wave MI.⁵⁷ A review of ≈4000 patients with unstable angina treated with aspirin or placebo demonstrated a 5% absolute risk reduction in nonfatal stroke or MI

or vascular death (9% versus 14%)⁴²; this corresponds to 50 vascular events avoided per 1000 patients treated with aspirin for 6 months.

Aspirin has been compared with heparin as both alternative and adjunctive therapy in the setting of unstable angina. In the RISC trial,⁵⁶ treatment with heparin alone provided no significant benefit for the incidence of MI and death, although the significant delay in instituting heparin therapy likely contributed to this finding (average delay 33 hours). Aspirin therapy was significantly better than heparin; however, the combination of aspirin and heparin produced the greatest benefit. Other studies have demonstrated a greater benefit of heparin over aspirin therapy^{55,58,59} and a potential increase in bleeding complications with combination therapy.⁵⁵ In a recent meta-analysis, the addition of heparin to aspirin therapy in unstable angina and non-Q-wave MI resulted in a nonsignificant 33% decrease in the risk of MI or death compared with aspirin alone; this benefit occurred without an increase in bleeding complications.⁶⁰ In addition, therapy with aspirin may prevent the early reactivation of angina observed after discontinuation of heparin therapy.⁶¹

Secondary Prevention

After MI

There have been 6 large, randomized trials that used aspirin alone as long-term treatment after an AMI,^{62–67} and all but 1 of these⁶² demonstrated a trend toward decreased mortality with aspirin therapy. The results of these trials and 139 others that evaluated the long-term use of aspirin in a wide range of patients were reviewed in a meta-analysis by the Antiplatelet Trialists in 1994.⁴² This analysis comprised ≈100 000 patients, 70 000 of whom were considered "high-risk patients" by virtue of a prior history of AMI, unstable angina, stable angina, prior percutaneous or surgical coronary revascularization, stroke, transient ischemic attack (TIA), atrial fibrillation, valvular heart disease, or peripheral vascular disease. Overall, among these high-risk patients, aspirin reduced the risk of nonfatal MI by approximately one-third, the risk of nonfatal stroke by one-third, and the risk of vascular death by one-sixth.

Among ≈20 000 of these patients with a prior history of MI, aspirin therapy decreased the risk of vascular events over an average 2-year treatment period from 17.1% to 13.5%, corresponding to an absolute decrease of 36 events per 1000 patients treated. Among 11 000 patients with a prior stroke or

TABLE 2. Studies of Aspirin for Primary Prevention of Cardiovascular Events

Reference	No. of Patients	Dose, mg	Length of Follow-up	Total Mortality, RR (95% CI)	Nonfatal MI, RR (95% CI)	Stroke, RR (95% CI)
Physicians' Health Study ⁶¹	22 071	325	5 y	0.96 (0.80–1.14)	0.59 (0.47–0.74)	1.22 (0.93–1.60)
Peto et al ⁶²	5139	500	6 y	0.89*	0.97*	1.15 (0.75–1.50)
Thrombosis Prevention Trial ⁸⁴	5085	75	6.4 y	1.06 (0.88–1.28)	0.68 (0.52–0.88)	0.98 (0.65–1.45)
Manson et al ^{†88}	87 678	Varied	5.4 y	0.86 (0.72–1.03)	0.68 (0.49–0.93)	0.99 (0.71–1.36)

RR is for aspirin vs nonaspirin groups.

*Result not statistically significant; CIs not available.

†RRs for subgroup taking up to 6 aspirin per week vs nonaspirin group.

TIA, aspirin therapy was associated with an event rate of 18.4% compared with a rate of 22.2% in control subjects (3-year decrease in absolute event rate of 38 events per 1000 patients). In other high-risk patients, the benefit was somewhat less but still significant: the 1-year benefit in this group was \approx 20 events per 1000 patients treated with aspirin.

These results clearly demonstrate a significant treatment effect of aspirin when given as secondary prevention in patients with underlying cardiovascular disease. Additionally, the results were significant in all groups irrespective of age, gender, or the presence of hypertension or diabetes. A wide range of dosing regimens was evaluated in this trial (most frequently 75 to 325 mg/d), and these regimens were equally effective. Given the effectiveness of a dose of 162.5 mg/d in the ISIS-2 trial⁴⁴ and the higher incidence of GI side effects when aspirin is used chronically at higher doses (see below), it seems reasonable to begin treatment with a dose of 160 to 325 mg and continue chronic treatment with 75 to 160 mg/d in patients with coronary artery disease.

After Revascularization

Percutaneous revascularization with balloon angioplasty or intracoronary stenting results in local vascular trauma, with exposure of the subendothelium to the vascular space. This highly thrombogenic milieu predisposes to intraluminal thrombus development with either abrupt closure or subacute thrombosis of the vessel in 3.5% to 8.6% of procedures.^{68–70} Several studies have demonstrated a significant decrease in acute complications of angioplasty with the combination of aspirin and dipyridamole,⁷¹ although this combination provides little additional benefit over aspirin alone.⁷² Compared with aspirin alone or a regimen of aspirin plus warfarin, the combination of ticlopidine (500 mg/d for 1 month) and aspirin (325 mg/d) in patients undergoing intracoronary stent placement significantly decreases the 30-day combined end point of death, target-vessel revascularization, angiographic thrombosis, or MI (relative risk [RR] 0.15 for combined therapy versus aspirin alone).⁷³ This benefit is seen irrespective of whether the stent deployment is felt to be “successful” with a low risk for thrombosis⁷³ or if high-risk markers for stent thrombosis are present.⁷⁴

Coronary artery bypass surgery with saphenous vein grafts is associated with a 5% to 15% graft occlusion rate during the first postoperative month,^{75,76} which is largely related to thrombosis at the anastomotic site as a result of endothelial disruption and vessel damage.⁷⁷ When given in the immediate postoperative period, aspirin clearly decreases the rate of

early thrombotic graft occlusion by \approx 50%, and continued aspirin therapy for 1 year further decreases the rate of occlusive events.^{75,76} Preoperative administration of aspirin is associated with increased bleeding complications but offers no additional benefit in early graft patency compared with providing aspirin 6 hours after surgery.⁷⁸ Although there does not appear to be additional benefit of aspirin with regard to long-term graft patency after 1 year of therapy,⁷⁹ continued aspirin therapy is required for secondary prevention of vascular events in these patients. Treatment with ticlopidine or sulfinpyrazone also improves early graft patency; however, these agents have not been shown to be better than aspirin.⁸⁰

Primary Prevention

In light of the benefit of aspirin in the treatment of acute cardiovascular disease and in the secondary prevention of recurrent events, enthusiasm has developed for the evaluation of aspirin as a primary preventive measure (Table 2). There have been 2 large, randomized trials of aspirin for the primary prevention of cardiovascular events that enrolled male physicians without prior MI and with a low incidence of prior cardiovascular disease (eg, TIA or angina).^{81,82} The Physicians' Health Study randomized 22 071 subjects between the ages of 40 and 84 years to treatment with aspirin (325 mg every other day) or placebo.⁸¹ The study was stopped prematurely after an average follow-up of 5 years owing to a highly significant 44% reduction in the risk of MI in the aspirin-treated group (0.26% per year versus 0.44% per year), an effect that was limited to participants over the age of 50 years. Nonetheless, there was no decrease in cardiovascular mortality. Additionally, there was a nonsignificant increase in hemorrhagic stroke (RR 2.14) and a significant increase in GI bleeding requiring transfusion. The British Physicians' Study enrolled 5139 subjects and also demonstrated no difference in cardiovascular mortality after 6 years of aspirin therapy (500 mg/d).⁸² Importantly, this trial showed no significant difference in the incidence of MI but a significant increase in disabling strokes. Combined analyses of these results demonstrated a significant 33% treatment-related reduction in nonfatal MI but still failed to show a decrease in mortality and demonstrated a borderline increase in hemorrhagic strokes and a nonsignificant increase in all strokes.^{42,83}

These 2 trials studied a population of patients who have a very low risk for cardiovascular events. Individuals at higher risk for the development of cardiovascular events (based on their risk factor profile) were enrolled in the Thrombosis Prevention Trial⁸⁴ and randomized to aspirin (75 mg/d),

warfarin (average dose 4.1 mg/d), both, or neither. After >6 years of follow-up, there was a 20% reduction in ischemic heart disease events (cardiac death, fatal or nonfatal MI) in the aspirin-treated groups. This difference was almost entirely accounted for by a 32% reduction in nonfatal events, without a significant effect on mortality. In contrast, warfarin therapy resulted in a 21% reduction in ischemic events, mostly as a result of a 39% reduction in fatal events. Neither of these therapies alone resulted in an increase in the total number of strokes. The combination of aspirin and warfarin produced the greatest reduction in ischemic events (34%) but was also associated with an increase in hemorrhagic and fatal strokes.

Patients with chronic stable angina have a significant risk of developing subsequent cardiovascular events,⁸⁵ and several studies have demonstrated a beneficial effect of aspirin in this group of patients. In the Physician's Health Study, patients who had chronic stable angina and received aspirin had an 87% reduction in the risk of MI compared with their counterparts who received placebo.⁸⁶ Similarly, in the Swedish Angina Pectoris Aspirin Trial, 2035 patients with chronic stable angina but without prior MI who received aspirin (75 mg/d) had a 34% decrease in the combined risk of MI and sudden death.⁸⁷ The risk of stroke, however, was increased by aspirin use in both studies.

No randomized data are available regarding the use of aspirin for the primary prevention of cardiovascular disease in women. However, in a prospective cohort study of 87 678 US nurses, the use of up to 6 aspirin per week did not alter the risk of cardiovascular death, stroke, or important vascular events.⁸⁸ The risk of first MI was significantly reduced (RR 0.68), although this beneficial effect was limited to women over the age of 50 years. These findings are consistent with the results of primary prevention trials in men; however, definitive recommendations await the results of the ongoing Women's Health Study.⁸⁹

In summary, the primary prevention trials demonstrate that aspirin therapy does not decrease cardiovascular mortality but significantly decreases the risk of nonfatal MI. There does not appear to be a consistent effect on the incidence of stroke, although there is a trend toward an increase in stroke risk. Additionally, there is an increase in nonfatal bleeding. The absolute benefit of aspirin therapy clearly increases as the risk of cardiovascular events increases in the treatment group (Table 3). Therefore, in patients with a relatively low risk of developing cardiovascular disease, the risk of prophylactic aspirin therapy may be outweighed by the risk of hemorrhagic complications. Conversely, in patients believed to be at high risk, the benefits of therapy, specifically a decrease in the development of MI, may outweigh the risk of hemorrhagic complications, and prophylactic therapy may be warranted.

Aspirin in Cerebrovascular Disease

Acute Therapy

Two large, randomized trials of aspirin use in the setting of an acute, ischemic stroke have recently been reported (Table 4).^{90,91} Combined, these trials enrolled >40 000 patients within 48 hours of the onset of neurological symptoms and

TABLE 3. Gradient of Benefit in Trials of Aspirin Therapy

Indication for Therapy	Magnitude of Benefit
Treatment of AMI	24 deaths/1000 patients treated for 5 wk
Treatment of unstable angina	50 events/1000 patients treated for 6 mo
Secondary prevention	
After MI	36 events/1000 patients treated for 2 y
After CVA/TIA	38 events/1000 patients treated for 2 y
Primary prevention	
In patients with angina	51 events/1000 patients treated for 4 y
In "high-risk" patients	5 events/1000 men treated for 1 y
In "low-risk" patients	4 events/1000 men treated for 5 y

CVA indicates cerebrovascular accident.

"High-risk" refers to patients in the top 20% of risk based on their risk factor profile.⁸⁴ "Low-risk" refers to patients with minimal risk factors for atherosclerotic cardiovascular disease.

demonstrated a significant decrease in the risk of recurrent stroke and in the combined incidence of death or nonfatal stroke (Table 4). Importantly, there was no significant increase in hemorrhagic stroke. These results correspond to a reduction of 10 deaths or recurrent strokes per 1000 patients after 2 to 4 weeks of aspirin therapy. These trials also demonstrated a trend toward a decreased incidence of death or significant disability (dependence) at 4 weeks of follow-up. The addition of heparin (5000 or 12 500 IU subcutaneously, twice a day) to aspirin yielded no further benefit but increased bleeding complications.⁹⁰ In addition, heparin therapy alone effected no difference in the rate of death or recurrent stroke but resulted in a significant increase in hemorrhagic strokes and major noncerebral bleeding.

Secondary and Primary Prevention

There are conflicting results from individual trials regarding the effectiveness of aspirin in the secondary prevention of cerebrovascular events.⁹²⁻⁹⁵ Included in the Antiplatelet Trialists' review were 12 randomized trials of >10 000 patients with a prior stroke or TIA.⁴² Most of these patients were treated with aspirin (50 to 1500 mg/d), although some received other antiplatelet agents, either alone or in combination with aspirin. Overall, there was a highly significant 17% reduction in the risk of nonfatal stroke and of all vascular events (nonfatal stroke or MI or vascular death) in patients treated for a mean of 33 months. This effect was similar whether the patient presented with a TIA or a completed stroke and resulted in a reduction of 37 vascular events per 1000 patients treated. Similar results have been reported in 3 subsequent trials.⁹⁶⁻⁹⁸ In a recent meta-analysis of 10 randomized trials comprising 9172 patients with cerebrovascular disease who were given prolonged aspirin administration, aspirin resulted in a significant 13% reduction in the risk of subsequent stroke compared with placebo.⁹⁹

Overall, data regarding the use of aspirin for the primary prevention of strokes in patients at high risk are not encouraging. In the British Physicians' Study,⁸² aspirin therapy significantly decreased the incidence of TIA (15.9% versus 27.5%; $P<0.05$) but did not decrease the risk of stroke and in fact increased the risk of disabling stroke (19.1% versus

TABLE 4. Trials of Aspirin Therapy in Acute Ischemic Stroke

End Point	Chinese Acute Stroke Trial ⁹¹			International Stroke Trial ⁹⁰		
	Aspirin	No Aspirin	2P	Aspirin	No Aspirin	2P
Death	3.3	3.9	0.04	9.0	9.4	NS
Death and nonfatal CVA	5.3	5.9	0.03	11.3	12.4	<0.05
Recurrent CVA	1.6	2.1	0.01	2.8	3.9	<0.001
Hemorrhagic CVA	1.1	0.9	NS	0.9	0.8	NS
Death or dependence	30.5	31.6	0.08	62.2	63.5	0.07

CVA indicates cerebrovascular accident. Values are percentages (except for 2P values).

In the International Stroke Trial, follow-up was at 2 weeks except for "death or dependence," which was evaluated at 6 months. In the Chinese Acute Stroke Trial, follow-up was at 4 weeks.

7.4%; $P < 0.05$). Similarly, an increased risk of stroke, primarily of the hemorrhagic type, was noted in the Physicians' Health Study.⁸¹ In a small study of asymptomatic patients with carotid bruits and $\geq 50\%$ stenosis of a carotid artery, aspirin failed to prevent subsequent cerebrovascular events.¹⁰⁰ Four placebo-controlled trials have evaluated aspirin for the prevention of stroke in patients with atrial fibrillation^{101–104} and, when their data are combined, demonstrate a small but significant reduction in risk.¹⁰⁵ However, except in the very-low-risk patient (age < 65 years with no other cardiovascular disease), the reduction in stroke risk is much greater with warfarin therapy in trials that directly compare the 2 agents (68% versus 12%).^{101,103,105–107}

The ideal dose of aspirin for the prevention of future vascular events in patients with TIAs or minor stroke has been the subject of much debate,^{108,109} although several trials have demonstrated increased bleeding complications with higher doses.^{95,98} In the meta-analysis mentioned above, the beneficial effect of aspirin on the incidence of recurrent stroke occurred irrespective of dose (50 to 1500 mg/d).⁹⁹ Additionally, in a large group of patients undergoing carotid endarterectomy, low-dose aspirin (81 or 325 mg/d) was associated with a lower risk of stroke, MI, or death compared with high-dose regimens (650 or 1300 mg/d).^{110,111} Thus, as is the case with coronary artery disease, a low-dose aspirin regimen appears appropriate for secondary prevention of cerebrovascular disease.

Adverse Effects

The inhibition of prostaglandin synthesis is responsible for the anti-inflammatory effects of aspirin but also results in the alteration of normally protective prostaglandin functions with potentially serious consequences, including gastric ulcers,

renal failure, and impaired platelet function with resultant hemorrhagic complications. These side effects and others will be discussed next.

GI Toxicity

Aspirin-induced inhibition of COX results in loss of the cytoprotective effects of PGE₂ on the gastric mucosa. This mechanism likely accounts in part for the more frequent development of GI side effects in the aspirin-treated patients in most trials.^{93,95,97,112} Minor GI symptoms (including nausea, vomiting, heartburn, and indigestion) have been reported in 5.2% to 40% of patients treated with aspirin versus 0.7% to 34% of patients taking placebo,^{52,54,62,81,95} peptic ulcers in 0.8% to 2.6% of aspirin-treated patients versus 0% to 1.2% with placebo,^{81,82,93} and major GI bleeding (melena requiring transfusion or hematemesis) in $< 1\%$ of patients in both groups.^{53,81,84,87,90} Minor bleeding episodes (epistaxis, hematuria, melena not requiring therapy, and bruising) occur frequently in patients taking aspirin and are significantly more common than among their placebo-treated counterparts.^{84,104,113} In the United Kingdom Transient Ischaemic Attack (UK-TIA) trial,⁹⁵ the incidence of GI symptoms was not only significantly higher in the aspirin-treated group than in the placebo group, but GI symptoms were significantly more frequent in the high-dose (1200 mg/d) than in the low-dose (300 mg/d) aspirin groups ($2P < 0.001$ for both comparisons). An overview of randomized trials of aspirin therapy similarly found that GI toxicity (both major and minor) was dose related with daily doses between 30 and 1300 mg.¹¹² Nonetheless, even low doses of aspirin (50 to 75 mg/d) are not free from side effects, may still be associated with increased GI bleeding,^{97,104,113} and frequently precipitate the discontinuation of therapy.^{52,56}

TABLE 5. Recommendations for Aspirin Use

Clinical Indication	Recommended Dose
For treatment of	Initial therapy: 160–325 mg
AMI	Subsequent daily dose: 75–160 mg
Acute thromboembolic stroke	
Unstable angina	
Secondary prevention after MI, stroke, or TIA and in patients with chronic stable angina	Daily therapy with 160–325 mg
Primary prevention	No clear indication at this time. Consider therapy with 75–160 mg/d in patients believed to be at high risk for development of cardiovascular disease.

Hemorrhagic Stroke

Several studies have suggested an increase in the risk of hemorrhagic stroke in patients treated with aspirin in the setting of an AMI⁴⁴ or acute ischemic stroke,^{90,91} as well as when aspirin is used for the primary⁸¹ or secondary⁹⁷ prevention of cardiovascular events. A recent meta-analysis of 16 trials comprising 55 462 patients treated with aspirin or control therapy demonstrated a significant increase in hemorrhagic strokes (RR 1.84; $P < 0.001$) despite a decrease in ischemic strokes, total strokes, and MI.¹¹⁴ This relative risk translated into an absolute increase of 12 hemorrhagic strokes per 10 000 patients treated with aspirin.

Other Side Effects

The use of nonaspirin inhibitors of COX (nonsteroidal anti-inflammatory drugs [NSAIDs]) may be associated with an increased risk of renal insufficiency and worsening of hypertension control owing to inhibition of renal vasodilatory prostaglandins.^{115,116} Aspirin is a relatively weak inhibitor of renal prostaglandin synthesis and does not significantly affect renal function or blood pressure control when used at the low to moderate doses suggested for the treatment of cardiovascular disease.¹¹⁷ However, at high doses (1500 mg/d), aspirin can significantly reduce renal sodium excretion in patients with heart failure.¹¹⁸ Aspirin has been reported to counteract the systemic arterial vasodilatory effects and attenuate the mortality benefit of ACE inhibition by enalapril in patients with congestive heart failure.^{119–121} A similar loss of efficacy was not seen in a post hoc analysis of the Captopril and Thrombolysis Study.¹²² A recent review of the literature in this regard suggests that low-dose aspirin (≤ 100 mg/d) has very little interaction with the effects of ACE inhibitors, whereas higher doses may attenuate the benefit of these agents in patients with hypertension or congestive heart failure.¹²³

A small percentage of people, most of whom have preexisting asthmatic disease, suffer from aspirin intolerance or sensitivity. Administration of aspirin to these persons results in the development of bronchoconstriction, rhinitis, and/or urticaria.¹²⁴ The mechanism of this sensitivity is not known but likely results from the inhibition of COX and possibly from abnormal leukotriene production.¹²⁵ Aspirin sensitivity can result in severe respiratory decompensation; however, most patients can be safely desensitized by the gradual administration of increasing doses of aspirin.

Making a Safer Aspirin

Attempts have been made to decrease the gastric toxicity of aspirin by pharmacological manipulation. Sustained-release⁴³ and topical formulations¹²⁶ have been demonstrated to produce relatively selective inhibition of platelet TXA₂ production with minimal effects on vascular and gastric prostanoids and thus may have less gastrototoxicity. Enteric-coated aspirin tablets may be less gastrototoxic as a result of decreased gastric irritation. In a small endoscopic study of asymptomatic patients undergoing long-term aspirin therapy,¹²⁷ gastric mucosal erosions were noted in 90% of patients treated with regular aspirin compared with 60% of patients receiving enteric-coated aspirin. Additionally, GI blood loss has been

shown to be less with enteric-coated aspirin than with the noncoated formulation.¹²⁸ Nonetheless, because the mechanism of action of enteric-coated aspirin still leads to the systemic inhibition of COX, coated aspirin is associated with significant gastric toxicity compared with placebo¹²⁷ and results in a similar risk of upper GI bleeding compared with regular, uncoated aspirin.¹²⁹

Regular aspirin is rapidly absorbed from the acid environment of the stomach. Enteric coating of aspirin results in its release into the alkaline environment of the small bowel, where it is hydrolyzed. As a result, enteric-coated aspirin has lower bioavailability than regular aspirin.¹³⁰ Nonetheless, the antiplatelet effects of full-dose (>300 mg) enteric-coated aspirin are similar to those of uncoated formulations.^{130,131} However, the efficacy of low-dose (<100 mg) enteric-coated preparations has not been clearly established, and it is possible that such doses may result in inadequate platelet inhibition. Thus, if coated aspirin is prescribed, larger doses may be necessary to obtain the desired antiplatelet effect.

The dissociation of the effects of the different COX enzymes (COX-1 and COX-2) has stimulated the production of agents that preferentially inhibit COX-2 and allow for the inhibition of inflammatory prostaglandins while leaving homeostatic prostaglandins relatively intact. Several new NSAIDs have been shown to have relative COX-2 selectivity^{132–134} and appear to be associated with fewer gastric side effects.^{7,135,136} The therapeutic antithrombotic effects and the toxic gastric effects of aspirin are both mediated through the inhibition of COX-1; therefore, dissociation of these effects is not feasible. However, coadministration of aspirin with the synthetic PGE₂ analog misoprostol allows for the complete inhibition of TXA₂ synthesis in platelets while maintaining gastric protection. This approach decreases the risk of gastric ulceration, erosion, and hemorrhage in dogs.^{137,138} Furthermore, in a randomized trial in healthy volunteers given anti-inflammatory doses of aspirin (3900 mg/d), cotreatment with 200 mg of misoprostol twice daily significantly reduced endoscopically documented gastric and duodenal mucosal injury ($P < 0.006$).¹³⁹

Other novel methods of improving the safety profile of aspirin are being developed. Animal models suggest that the intragastric administration of aspirin stimulates the release of NO, which decreases gastric acid secretion and increases cytoprotection, thus limiting gastric mucosal damage.¹⁴⁰ Furthermore, compared with regular aspirin, the administration of NO-releasing derivatives of aspirin has no topical gastric irritating effects, does not worsen stress-induced gastric ulceration, and protects against toxic gastric injury.^{141–143} This marked improvement in gastric toxicity occurs with these agents despite the equivalent inhibition of COX and equipotent or enhanced antithrombotic activity compared with aspirin.¹⁴³ The clinical safety and efficacy of these agents remain to be determined.

Comparison With Other Antiplatelet Agents

Despite aspirin's demonstrated effectiveness in treating and preventing atherosclerotic disease, it produces only partial inhibition of platelet aggregation, and therefore it is a relatively weak antiplatelet agent. Additionally, a minority of

patients appear to be relatively resistant to the antiplatelet effects of aspirin, even when it is administered in large doses.¹⁴⁴ Platelet aggregation studies have demonstrated incomplete inhibition of aggregation in 25% of patients with prior ischemic stroke who were receiving long-term aspirin therapy (minimum dose 325 mg/d).¹⁴⁵ Some patients demonstrate improved platelet inhibition at higher aspirin doses; however, 8% of patients taking 1300 mg of aspirin per day may still be aspirin resistant.¹⁴⁵ The mechanism of this decreased efficacy of aspirin in some patients is not well understood but may reflect the limited potency of aspirin as an inhibitor of COX-2, the expression of which has recently been demonstrated in human platelets.¹⁴⁶

Aspirin does not completely inhibit TXA₂ synthesis,⁴¹ and other non-TXA₂-dependent activators of platelet aggregation (eg, thrombin, ADP, and collagen) can bypass the aspirin-inhibitory effect and result in thrombosis. Newer agents that interrupt these other pathways or interfere with the glycoprotein IIb/IIIa receptor, the final common pathway in platelet aggregation, may prove to be more effective antithrombotic agents.¹⁴⁷ Several other antiplatelet agents have therefore been used for the treatment of thrombotic cardiovascular disease and have been compared with aspirin in randomized clinical trials.

In the Antiplatelet Trialists' overview, several antithrombotic regimens were evaluated, including aspirin, ticlopidine, or sulfapyrazone alone or the combination of aspirin plus dipyridamole.⁴² Direct and indirect comparisons of the effectiveness of these regimens demonstrated no significant difference in vascular events, although the numbers of patients enrolled in trials that directly compared agents were low.

Ticlopidine and Clopidogrel

Ticlopidine and clopidogrel are thienopyridine derivatives that inhibit ADP-induced binding of fibrinogen to platelets, a process necessary for platelet aggregation.¹⁴⁸ In randomized trials of patients with recent stroke or TIA, ticlopidine (250 mg twice daily) has demonstrated a significant 23.3% reduction in the combined incidence of stroke, MI, or vascular death compared with placebo (11.3% per year versus 14.8% per year with placebo; $P=0.02$),¹⁴⁹ as well as a 21% lower risk of stroke (10% versus 13%; $P=0.024$) and a 12% reduction in the combined risk of death and nonfatal stroke (17% versus 19%; $P=0.048$) compared with aspirin (650 mg twice daily).¹⁵⁰ However, ticlopidine therapy resulted in severe neutropenia in $\approx 1\%$ of patients.

The Clopidogrel versus Aspirin in Patients at Risk for Ischemic Events (CAPRIE) study compared the efficacy of aspirin (325 mg/d) with clopidogrel (75 mg/d) for reducing the combined incidence of ischemic stroke, MI, or vascular death in 19 185 patients with a recent stroke or MI or with symptomatic peripheral arterial disease.¹⁵¹ After an average follow-up of almost 2 years, clopidogrel demonstrated a significant 8.7% benefit over aspirin (5.32% versus 5.83%; $P=0.043$). Adverse events were not significantly different between the agents, and neutropenia was rare (0.1%) with clopidogrel.

Dipyridamole

Dipyridamole is a pyrimidopyrimidine derivative that inhibits cyclic nucleotide phosphodiesterases and blocks the uptake of adenosine, resulting in a reduction in platelet cytosolic calcium and subsequent inhibition of platelet activation.¹⁵² Initial studies demonstrated no significant benefit of adding dipyridamole to aspirin for the secondary prevention of stroke⁹⁴ or recurrent MI.¹⁵³ The European Stroke Prevention-2 trial randomized 6602 patients with prior minor stroke or TIA to treatment with aspirin (50 mg/d), dipyridamole (400 mg/d), both, or neither. After 2 years of follow-up, the 2 agents alone were found to be equally effective in reducing the risk of stroke (RR reductions: 18% with aspirin, $P=0.013$; 16% with dipyridamole, $P=0.039$) and stroke or death combined (RR reductions: 13% with aspirin, $P=0.016$; 15% with dipyridamole, $P=0.015$) compared with placebo.¹⁰⁴ Furthermore, the benefits were additive with combination therapy (RR reductions: 37% for stroke, $P<0.001$; 24% for combined end point, $P<0.001$). A recent review of 15 randomized trials suggests that the addition of dipyridamole to aspirin will reduce the risk of vascular events by an additional 15% over the effects of aspirin alone.⁹⁹

Glycoprotein IIb/IIIa Inhibitors

Irrespective of the activating stimulus, the final common pathway of platelet activation involves exposure and activation of glycoprotein IIb/IIIa, the platelet fibrinogen receptor. Inhibitors of this receptor, including monoclonal antibodies and peptide- and nonpeptide-derived agents, have been studied extensively in various settings. When added to standard antiplatelet therapy with aspirin (325 mg) and intravenous heparin in patients undergoing percutaneous revascularization, the monoclonal antibody c7E3 (abciximab) reduced the risk of ischemic complications (death, nonfatal MI, unplanned revascularization procedures, or refractory angina) by 35% (8.3% versus 12.8% with placebo; $P=0.008$) in patients undergoing high-risk angioplasty (unstable angina, evolving AMI, or high-risk coronary morphology)¹⁵⁴ and by 56% (5.2% versus 11.7% with placebo; $P<0.001$) in patients undergoing urgent or elective percutaneous revascularization.¹⁵⁵ A similar reduction in the risk of early ischemic events was demonstrated with tirofiban, a synthetic, nonpeptide IIb/IIIa inhibitor, after high-risk coronary angioplasty¹⁵⁶ and with abciximab after intracoronary stenting.¹⁵⁷

The benefit of platelet inhibition in patients with unstable angina has been assessed recently by monitoring troponin T release, which serves as a surrogate marker for thrombus formation. Patients with refractory unstable angina and elevated troponin T levels were shown to constitute a high-risk subgroup who particularly benefited from antiplatelet therapy with abciximab.¹⁵⁸ When added to treatment with intravenous heparin in patients with unstable angina, treatment with intravenous eptifibatid (integrelin), a peptide IIb/IIIa inhibitor, decreased the incidence and duration of ischemic episodes noted on 24-hour ECG monitoring compared with aspirin therapy.¹⁵⁹ In patients with unstable angina or non-Q-wave MI, the addition of tirofiban to aspirin therapy (325 mg/d) reduced the composite end point of death, MI, or refractory ischemia by 32% after 48 hours of therapy (3.8%

versus 5.6% with heparin; $P=0.01$)¹⁶⁰; however, at 30 days, the difference was no longer significant. In a group of patients with more severe unstable angina and a higher proportion of non-Q-wave MI, treatment with aspirin plus tirofiban resulted in an increase in mortality compared with a regimen of aspirin plus intravenous heparin (mortality rate of 4.6% versus 1.1% at 7 days; $P=0.012$).¹⁶¹ However, the addition of tirofiban to a regimen of aspirin plus heparin decreased the composite end point of death, MI, or refractory ischemia at 7 days by 32% (12.9% versus 17.9%; $P=0.004$). This benefit persisted, although to a smaller degree, at 30 days and at 6 months after treatment.

Taken together, these trials demonstrate a significant benefit of glycoprotein IIb/IIIa inhibitors when administered in addition to usual aspirin therapy in patients with unstable coronary syndromes and after percutaneous revascularization. Although initial studies were complicated by increased rates of bleeding,¹⁵⁴ with adjusted heparin dosing, the expected bleeding rate is not different from that with standard heparin and aspirin therapy.^{155,160,161}

Conclusions

Aspirin clearly decreases mortality and reinfarction when given as short-term therapy for AMI, when given to patients with unstable angina, and when given as long-term secondary preventive therapy in a wide range of patients with established cardiovascular disease. Despite the strength of the data in this regard, studies suggest that aspirin remains underused for both the treatment of acute coronary syndromes^{162,163} and for secondary prevention of recurrent events.^{164–166} More than 10% of patients suffering an AMI do not receive aspirin therapy despite the absence of contraindications,¹⁶² and 20% to 50% of postinfarction patients may not be taking aspirin on an ongoing basis.^{164,165} The statistics are even worse in the elderly population: almost 30% of Medicare patients hospitalized for unstable angina are not treated with aspirin in the short term,¹⁶³ and as many as 80% of nursing home patients with a prior history of MI may not be given aspirin.¹⁶⁶ Nonetheless, its use in these settings should be the accepted standard unless absolute contraindications exist. The dose of aspirin should always be the lowest dose that is known to be effective (ie, 160 to 325 mg for acute treatment of cardiovascular events and 75 to 160 mg/d for primary and secondary prevention) because higher doses result in higher rates of complications. The role of aspirin in primary prevention is less clear. In patients felt to be at high risk of a future cardiac event owing to the presence of significant risk factors, prophylactic aspirin should be considered but weighed against the risk of potential complications. In patients at low risk of cardiac events, the risk of hemorrhagic complications may outweigh the benefits of therapy, and the current data do not support the use of prophylactic aspirin therapy in this setting. As newer aspirin regimens are developed that have improved safety profiles, the risk/benefit ratio may change to support the use of aspirin as primary prevention in a broader range of patients. Other antithrombotic agents, especially the glycoprotein IIb/IIIa inhibitors, which are capable of more complete platelet inhibition, are likely to play an increasingly greater role in the treatment of cardiovascular diseases;

however, given its relative safety and extremely low cost, aspirin will continue to be an important agent in the treatment and prevention of cardiovascular diseases for the foreseeable future.

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