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Antiplatelet Drugs*

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

Carlo Patrono, MD; Colin Baigent, MD; Jack Hirsh, MD, FCCP; and Gerald Roth, MD

This article about currently available antiplatelet drugs is part of the Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). It describes the mechanism of action, pharmacokinetics, and pharmacodynamics of aspirin, reversible cyclooxygenase inhibitors, thienopyridines, and integrin αIIbβ3 receptor antagonists. The relationships among dose, efficacy, and safety are thoroughly discussed, with a mechanistic overview of randomized clinical trials. The article does not provide specific management recommendations; however, it does highlight important practical aspects related to antiplatelet therapy, including the optimal dose of aspirin, the variable balance of benefits and hazards in different clinical settings, and the issue of interindividual variability in response to antiplatelet drugs.

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Platelets are vital components of normal hemostasis and key participants in atherothrombosis by virtue of their capacity to adhere to injured blood vessels and to accumulate at sites of injury.[1] Although platelet adhesion and activation can be viewed as a physiologic repair response to the sudden fissuring or rupture of an atherosclerotic plaque, uncontrolled progression of such a process through a series of self-sustaining amplification loops can lead to intraluminal thrombus formation, vascular occlusion, and transient ischemia or infarction. Currently available antiplatelet drugs interfere with some steps in the activation process, including adhesion, release, and/or aggregation,[1] and have a measurable impact on the risk of arterial thrombosis that cannot be dissociated from an increased risk of bleeding.[2]

In discussing antiplatelet drugs, it is important to appreciate that approximately 10^{11} platelets are produced each day under physiologic circumstances, a level of production that can increase up to 10-fold at

times of increased need.[3] Platelets are anucleate blood cells that form by fragmentation of megakaryocyte cytoplasm and have a maximum circulating life span of about 10 days in humans.[3] Platelets provide a circulating source of chemokines, cytokines, and growth factors, which are preformed and packaged in storage granules. Moreover, activated platelets can synthesize prostanoids (primarily, thromboxane [TX] A_2) from arachidonic acid released from membrane phospholipids through rapid coordinated activation of phospholipase(s), cyclooxygenase (COX)-1 and TX synthase (Fig 1). Newly formed platelets also express the inducible isoforms of COX (COX-2) and prostaglandin (PG) E synthase, and this phenomenon is markedly amplified in association with accelerated platelet regeneration.[4] Although activated platelets are not thought to synthesize proteins *de novo*, they can translate constitutive messenger RNAs into proteins, including interleukin-1β, over several hours.[5] Thus, platelets may play previously unrecognized roles in inflammation and vascular injury, and antiplatelet strategies may be expected to affect platelet-derived protein signals for inflammatory and/or proliferative responses.[1]

Negative modulation of platelet adhesion and aggregation is exerted by a variety of physiologic mechanisms, including endothelium-derived prostacyclin (PGI$_2$), nitric oxide, CD39/ecto-ADPase, and platelet endothelial cell adhesion molecule-1. Some drugs may interfere with these regulatory pathways, as exemplified by the dose-dependent inhibition of PGI$_2$ production by aspirin and other COX inhibitors.[2]

2.0 Aspirin and Other COX Inhibitors

Aspirin has been thoroughly evaluated as an antiplatelet drug[6] and was found to prevent vascular death by approximately 15% and nonfatal vascular events by about 30% in a metaanalysis of > 100 randomized trials in high-risk patients.[7]

2.1 Mechanism of Action of Aspirin

The best characterized mechanism of action of the drug is related to its capacity to inactivate permanently the COX activity of prostaglandin H-synthase-1 and -2 (also referred to as COX-1 and COX-2).[8–12] These isozymes catalyze the first committed step in prostanoid biosynthesis (*ie*, the conversion of arachidonic acid to PGH$_2$) [Fig 1]. PGH$_2$ is the immediate precursor of PGD$_2$, PGE$_2$, PGF$_{2\alpha}$, PGI$_2$, and TXA$_2$. COX-1 and COX-2 are homodimers of a ~ 72 kd monomeric unit. Each dimer has three independent folding units: an epidermal growth factor-like domain; a membrane-binding domain; and an enzy-
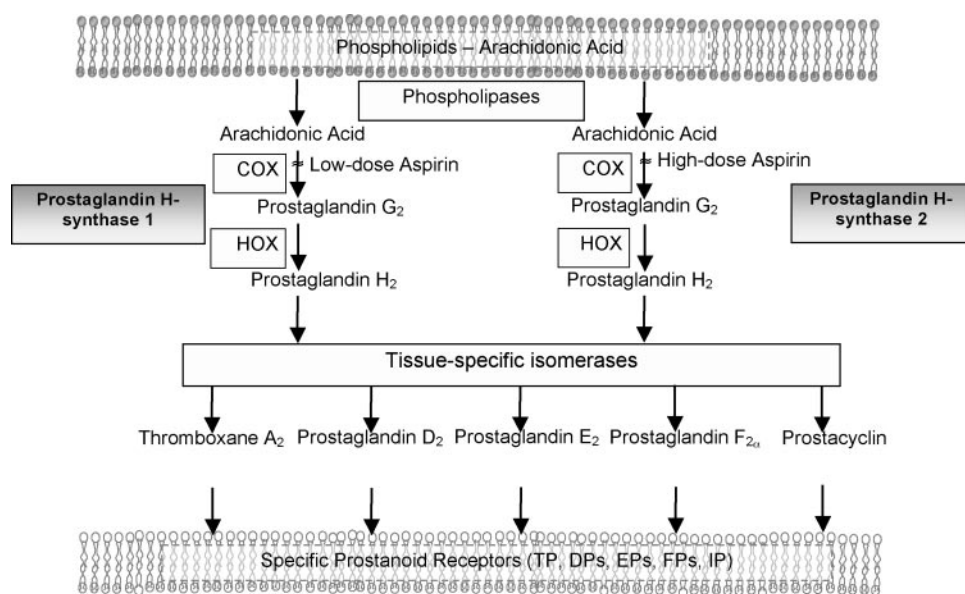
FIGURE 1. Arachidonic acid metabolism and mechanism of action of aspirin. Arachidonic acid, a 20-carbon fatty acid containing four double bonds, is liberated from the sn2 position in membrane phospholipids by several forms of phospholipase, which are activated by diverse stimuli. Arachidonic acid is converted by cytosolic PGH synthases, which have both COX and hydroperoxidase activity, to the unstable intermediate PGH$_2$. The synthases are colloquially termed *COXs* and exist in two forms, COX-1 and COX-2. Low-dose aspirin selectively inhibits COX-1, and high-dose aspirin inhibits COX-1 and COX-2. PGH$_2$ 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. DP = PGD$_2$ receptor; EP = PGE$_2$ receptor; FP = PGF$_{2\alpha}$ receptor; IP = prostacyclin receptor; TP = TX receptor.

matic domain.[12] Within the enzymatic domain, there is the peroxidase catalytic site and a separate, but adjacent site for COX activity at the apex of a narrow, hydrophobic channel.

The molecular mechanism of permanent inactivation of COX activity by aspirin is related to blockade of the COX channel as a consequence of acetylation of a strategically located serine residue (Ser529 in the human COX-1, Ser516 in the human COX-2) that prevents access of the substrate to the catalytic site of the enzyme.[13] The hydrophobic environment of the COX channel stabilizes the modified serine side-chain against hydrolysis.[13] Thus, inhibition of COX-1–dependent platelet function can be achieved with low doses of aspirin given once daily. In contrast, inhibition of COX-2–dependent pathophysiologic processes (*eg*, hyperalgesia and inflammation) requires larger doses of aspirin (probably because acetylation is determined by the oxidative state of the enzyme and is inhibited in cells with high peroxide tone)[14] and a much shorter dosing interval (because nucleated cells rapidly resynthesize the enzyme). Thus, there is an approximately 100-fold variation in daily doses of aspirin when used as an antiinflammatory rather than as an antiplatelet agent. Furthermore, the benefit/risk profile of the drug depends on the dose and indication because its GI toxicity is dose dependent (see below).

Human platelets and vascular endothelial cells process PGH_2 to produce primarily TXA_2 and PGI_2, respectively.[11] TXA_2 induces platelet aggregation and vasoconstriction, whereas PGI_2 inhibits platelet aggregation and induces vasodilation.[11] Whereas TXA_2 is largely a COX-1–derived product (mostly from platelets) and thus highly sensitive to aspirin inhibition, vascular PGI_2 can derive both from COX-1 and, to a greater extent even under physiologic conditions, from COX-2.[16] COX-1–dependent PGI_2 production occurs transiently in response to agonist stimulation (*eg*, bradykinin)[15] and is sensitive to aspirin inhibition. COX-2–mediated PGI_2 production occurs long term in response to laminar shear stress[17] and is largely insensitive to aspirin inhibition at conventional antiplatelet doses. This may explain the substantial residual COX-2–dependent PGI_2 biosynthesis *in vivo* at daily doses of aspirin in the range of 30 to 100 mg,[18] despite transient suppression of COX-1–dependent PGI_2 release.[15] It is not established that more profound suppression of PGI_2 formation by higher doses of aspirin is sufficient to initiate or predispose to thrombosis. However, two lines of evidence suggest that PGI_2 is thromboprotective. The first is the observation that mice lacking the PGI_2 receptor had increased susceptibility to experimental thrombosis.[19] The second is the observation of the cardiovascular toxicity associated with

COX-2 inhibitors[20] that also supports the concept of PGI_2 acting as an important mechanism of thromboresistance in the setting of inadequate inhibition of platelet TXA_2 biosynthesis.[21]

2.2 Pharmacokinetics

Aspirin is rapidly absorbed in the stomach and upper intestine. Peak plasma levels occur 30 to 40 min after aspirin ingestion, and inhibition of platelet function is evident by 1 h. In contrast, it can take up to 3 to 4 h to reach peak plasma levels after administration of enteric-coated aspirin. If only enteric-coated tablets are available, and a rapid effect is required, the tablets should be chewed. The oral bioavailability of regular aspirin tablets is approximately 40 to 50% over a wide range of doses.[22] A considerably lower bioavailability has been reported for enteric-coated tablets and sustained-release, microencapsulated preparations.[22] Lower bioavailability of some enteric-coated preparations and poor absorption from the higher pH environment of the small intestine may result in inadequate platelet inhibition, particularly in heavier subjects.[23] Both a controlled-release formulation[15] and a transdermal patch[24] with negligible systemic bioavailability have been developed in an attempt to achieve selective inhibition of platelet TXA_2 production without suppressing systemic PGI_2 synthesis. The former was used successfully in the Thrombosis Prevention Trial (see below), but it remains unknown whether there is any advantage to the controlled-release formulation *vis-à-vis* plain aspirin.

The plasma concentration of aspirin decays with a half-life of 15 to 20 min. Despite the rapid clearance of aspirin from the circulation, the platelet-inhibitory effect lasts for the life span of the platelet[25] because aspirin irreversibly inactivates platelet COX-1.[8,9] Aspirin also acetylates the enzyme in megakaryocytes before new platelets are released into the circulation.[10,26–28] The mean life span of human platelets is approximately 8 to 10 days. Therefore, about 10 to 12% of circulating platelets are replaced every 24 h.[29,30] However, the recovery of TXA_2 biosynthesis *in vivo* following prolonged aspirin administration is somewhat faster than predicted by the rate of platelet turnover,[18] possibly because of the nonlinear relationship between inhibition of platelet COX-1 activity and inhibition of TXA_2 biosynthesis *in vivo*[31] (Fig 2).

2.3 Issues Concerning the Antithrombotic Effects of Aspirin

A number of issues related to the clinical efficacy of aspirin continue to be debated. These include the following: (1) the optimal dose of aspirin in order to
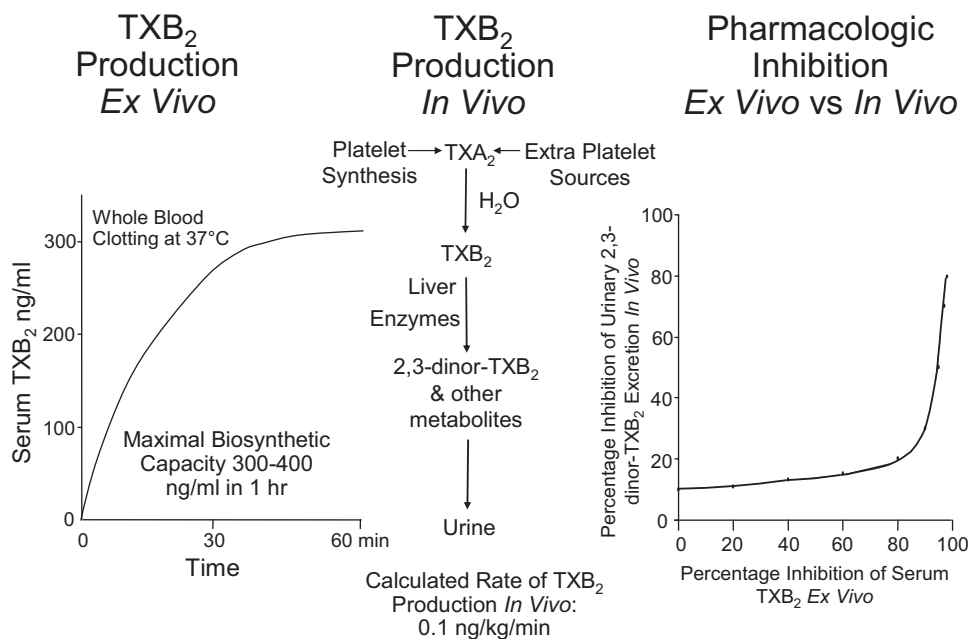
FIGURE 2. Maximal capacity of human platelets to synthesize TXB_2, rate of TXB_2 production in healthy subjects, and relationship between the inhibition of platelet COX activity and TXB_2 biosynthesis *in vivo*. *Left panel:* The level of TXB_2 production stimulated by endogenous thrombin during whole-blood clotting at 37°C.[62] *Center panel:* The metabolic fate of 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. *Right panel:* The nonlinear relationship between inhibition of serum TXB_2 measured *ex vivo* and the reduction in the excretion of TX metabolite measured *in vivo*.[31]

maximize efficacy and minimize toxicity; (2) the suggestion that part of the antithrombotic effect of aspirin is unrelated to inhibition of platelet TXA_2; and (3) the possibility that some patients may be aspirin "resistant."

2.3.1 The Optimal Dose of Aspirin: Well-designed, placebo-controlled randomized trials have shown that aspirin is an effective antithrombotic agent when used long term in doses ranging from 50 to 100 mg/d, and there is a suggestion that it is effective in doses as low as 30 mg/d.[6,7] Aspirin, 75 mg/d, was shown to be effective in reducing the risk of acute myocardial infarction (MI) or death in patients with unstable angina[32] and chronic stable angina,[33] as well as in reducing stroke or death in patients with transient cerebral ischemia[34] and the risk of postoperative stroke after carotid endarterectomy.[35] In the European Stroke Prevention Study (ESPS)-2, aspirin 25 mg bid was effective in reducing the risks of stroke and of the composite outcome stroke or death in patients with prior stroke or transient ischemic attack (TIA).[36] Moreover, in the European Collaboration on Low-Dose Aspirin in Polycythemia vera Trial,[37] aspirin, 100 mg/d, was effective in preventing thrombotic complications in patients with polycythemia vera, despite a higher-than-normal platelet count.

The lowest effective dose of aspirin for these various indications is shown in Table 1.

The clinical effects of different doses of aspirin have been compared directly in a relatively small number of randomized trials.[38–43] In the United Kingdom TIA study,[41] no difference in efficacy was found between 300 and 1,200 mg/d of aspirin (see below). In a study of 3,131 patients after a TIA or minor ischemic stroke, aspirin in a dose of 30 mg/d was compared with a dose of 283 mg/d, and the

Table 1—*Vascular Disorders for Which Aspirin Has Been Shown To Be Effective and Lowest Effective Dose (Section 2.3.1)*

Disorder	Lowest Effective Daily Dose, mg
TIA and ischemic stroke*	50
Men at high cardiovascular risk	75
Hypertension	75
Stable angina	75
Unstable angina*	75
Severe carotid artery stenosis*	75
Polycythemia vera	100
Acute MI	160
Acute ischemic stroke*	160

*Higher doses have been tested in other trials and were not found to confer any greater risk reduction.

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hazard ratio for the group receiving the lower dose was 0.91 (95% confidence interval [CI], 0.76 to 1.09).[42] The Acetylsalicylic Acid and Carotid Endarterectomy Trial reported that the risk of stroke, MI, or death within 3 months of carotid endarterectomy is significantly lower for patients taking 81 or 325 mg/d aspirin than for those taking 650 or 1,300 mg (6.2% vs 8.4%; p = 0.03).[43] Thus, there is no convincing evidence from randomized studies that have compared different doses of aspirin that higher doses are more effective in reducing the risk of serious vascular events. In fact, both this limited set of randomized comparisons and the indirect comparisons reported in the overview of the Antithrombotic Trialists' (ATT) Collaboration (Table 2) are compatible with the reverse (ie, blunting of the antithrombotic effect at higher doses of aspirin, consistent with dose-dependent inhibition of PGI_2). Such inhibition of PGI_2 may be a potential mechanism by which COX-2 inhibitors produce an excess risk of MI (see below).

The antithrombotic effects of a range of doses of aspirin also have been compared with an untreated control group in a number of thrombotic vascular disorders. The doses have varied between 50 and 1,500 mg/d. Aspirin has been shown to be effective in the following conditions: unstable angina in which the incidence of acute MI or death was significantly reduced in four separate studies using daily doses of 75 mg,[32] 325 mg,[44] 650 mg,[45] and 1,300 mg[46]; stable angina in which a dose of 75 mg/d reduced the incidence of acute MI or sudden death[33]; aortocoronary bypass surgery in which the incidence of early occlusion was similarly reduced with daily doses of 100 mg,[47] 325 mg,[48] 975 mg,[49] and 1,200 mg[49]; thromboprophylaxis of patients with prosthetic heart valves who also received warfarin in whom the incidence of systemic embolism was reduced with daily doses of 100 mg,[50] 500 mg,[51] and 1,500 mg[52,53]; thromboprophylaxis of patients with arterial venous shunts undergoing long-term hemodialysis in whom a dose of 160 mg/d was shown to be effective[54]; acute MI in which a dose of 162.5 mg/d reduced early

(35-day) mortality as well as nonfatal reinfarction and stroke[55]; transient cerebral ischemia in which doses between 50 and 1,200 mg/d were effective[34,36,41,56–58]; acute ischemic stroke in which doses of 160 to 300 mg/d were effective in reducing early mortality and stroke recurrence[59,60]; and polycythemia vera in which 100 mg,[37] but not 900 mg,[61] was effective in reducing fatal and nonfatal vascular events.

Thus, aspirin is an effective antithrombotic agent in doses between 50 and 1,500 mg/d. It is also possible from the results of the Dutch TIA study that 30 mg/d is effective.[42] There is no evidence that low doses (50 to 100 mg/d) are less effective than high doses (650 to 1,500 mg/d) and, in fact, the opposite may be true. These clinical findings are consistent with saturability of platelet COX-1 inactivation at doses as low as 30 mg/d.[62]

There is evidence, however, that doses of approximately 300 mg/d produce fewer GI side effects than doses of approximately 1,200 mg/d.[41] There is also some evidence that a dose of 30 mg/d produces fewer side effects than 300 mg/d.[42] The Clopidogrel in Unstable Angina To Prevent Recurrent Events (CURE) investigators have retrospectively investigated the relationship between the aspirin dose (the CURE protocol recommended 75 to 325 mg/d) and risk of major bleeding.[63] This study was a randomized comparison of clopidogrel with placebo on a "background" of aspirin therapy. Patients with acute coronary syndromes receiving aspirin, ≤ 100 mg/d, had the lowest rate of major or life-threatening bleeding complications both in the placebo (1.9%) and in the clopidogrel (3%) arms of the trial. Bleeding risks increased with increasing aspirin dose with or without clopidogrel.[63]

In summary, the saturability of the antiplatelet effect of aspirin at low doses, the lack of dose-response relationship in clinical studies evaluating its antithrombotic effects, and the dose dependence of its side effects all support the use of as low a dose of aspirin as has been found to be effective in the treatment of various thromboembolic disorders (Table 1). Use of the lowest effective dose of aspirin (50 to 100 mg/d for long-term treatment) is currently the most appropriate strategy to maximize its efficacy and minimize its toxicity.[6]

2.3.2 Effects of Aspirin Not Related to TXA_2: Aspirin has been reported to have effects on hemostasis that are unrelated to its ability to inactivate platelet COX-1. These include dose-dependent inhibition of platelet function,[64–68] enhancement of fibrinolysis,[69–71] and suppression of plasma coagulation.[72–75]

In contrast to the saturable and well-characterized (nanomolar aspirin concentration, rapid time course, physiologic conditions, single serine modification)

Table 2—Indirect Comparison of Aspirin Doses Reducing Vascular Events in High-Risk Patients (Section 2.3.1)*

Aspirin Dose, mg/d	No. of Trials	No. of Patients	Odds Reduction
500–1,500	34	22,451	19 ± 3%
160–325	19	26,513	26 ± 3%
75–150	12	6,776	32 ± 6%
< 75	3	3,655	13 ± 8%

*Data are from Lindemann et al[5]/2001.

inhibition of COX-1 by aspirin,[13,62,76] the putative mechanisms underpinning the non-PG effects of aspirin on hemostasis are dose dependent and less clearly defined. For example, inhibition of shear-induced platelet aggregation depends on the level of aspirin provided, and enhanced fibrinolysis due to N-acetylation of lysyl residues of fibrinogen is seen *in vivo* with high doses of aspirin (650 mg bid)[69] and proceeds more rapidly *in vitro* under nonphysiologic alkaline conditions.[77] Aspirin suppresses plasma coagulation through several mechanisms. The first, initially described in 1943 by Link et al and confirmed by others,[72,73] is caused by an antivitamin K effect of aspirin. It requires very high doses of aspirin and does not contribute to the antithrombotic effect of aspirin when the drug is used in doses up to 1,500 mg/d. The second is platelet dependent and is characterized by inhibition of thrombin generation in a whole blood system.[74,75] A single dose of 500 mg depresses the rate of thrombin generation, whereas repeated daily dosing with 300 mg of aspirin reduces the total amount of thrombin formed.[78] An interaction with platelet phospholipids, which is blunted in hypercholesterolemia, has been proposed to explain the effects of aspirin on thrombin generation.[78] It is possible (but unproven) that this effect occurs as a consequence of impaired platelet coagulant activity secondary to inhibition of TX-dependent platelet aggregation. It is unknown whether lower doses of aspirin are able to produce this effect. This sort of *in vitro* effect has been shown for other platelet inhibitors, such as glycoprotein (GP)-IIb/IIIa antagonists (see below). Furthermore, high-dose aspirin can cause abnormal coagulation *in vitro* by direct acetylation of one or more clotting factors. This can be demonstrated in platelet-poor plasma and, thus, is not related to platelet inhibition or vitamin K antagonism.

Additional studies in both animal models and human subjects have reported antithrombotic effects of aspirin that may occur, at least in part, through mechanisms unrelated to inactivation of platelet COX-1. In animal models, Buchanan et al[66] and Hanson et al[64] reported that optimal antithrombotic activity of aspirin required doses in excess of those required to inhibit TXA_2. In clinical studies, the results of a subgroup analysis of the North American Symptomatic Carotid Endarterectomy Trial study[79] suggested that aspirin in doses of ≥ 650 mg/d might be more effective than ≤ 325 mg/d for the prevention of perioperative stroke in patients having carotid artery surgery.[80] This retrospective observation was refuted by a second prospective study, the Acetylsalicylic Acid and Carotid Endarterectomy Trial,[43] which tested the hypothesis that the wide area of collagen exposed by endarterectomy is a sufficiently strong stimulus to platelet aggregation to require a larger dose of aspirin. Approximately 3,000 patients scheduled for carotid endarterectomy were randomly assigned 81, 325, 650, or 1,300 mg/d aspirin, started before surgery and continued for 3 months. The combined rate of stroke, MI, or death at 3 months was significantly (p = 0.03) lower in the low-dose groups (6.2%) than in the high-dose groups (8.4%) [primary analysis]. There were no significant differences between the 81-mg and 325-mg groups or between the 650-mg and 1,300-mg groups in any of the secondary analyses of the data.[43]

A subgroup analysis of the Physicians' Health Study,[81] based on *post hoc* measurements of baseline plasma C-reactive protein performed in 543 apparently healthy men who subsequently had MI, stroke, or venous thrombosis, and in 543 study participants who did not report vascular complications, has found that the reduction in the risk of a first MI associated with the use of aspirin (325 mg on alternate days) appears to be directly related to the level of C-reactive protein, raising the possibility of antiinflammatory as well as antiplatelet effects of the drug in cardiovascular prophylaxis.[82] This hypothesis is unlikely to be correct because, as noted above, the antiinflammatory effects of aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs) are largely related to their capacity to inhibit COX-2 activity induced in response to inflammatory cytokines,[12] as these clinical effects can be fully reproduced by highly selective COX-2 inhibitors (coxibs) in patients with rheumatoid arthritis.[83] As shown in Table 3, the dose and time dependence of the effects of aspirin on nucleated inflammatory cells expressing COX-2 vs anucleated platelets expressing COX-1 are markedly different, thus making a clinically relevant antiinflammatory effect of the drug at 325 mg every

Table 3—Dose and Time Dependence of the Effects of Aspirin on Platelets and Inflammatory Cells (Section 2.3.2)

Cellular Target	Enzyme	Single Dose,* mg	Duration of Prostanoid Suppression, h	Cumulative Effects Upon Repeated Dosing	Daily Dose,† mg
Platelets	COX-1	100	24–48	Yes	50–81
Inflammatory cells	COX-2	≥ 650	3–4	No	3,000–5,000

*Dose causing full suppression of prostanoid formation and/or clinically detectable functional effect after single dosing.
†Range of doses shown clinically effective in long-term trials of cardiovascular protection or rheumatoid arthritis.

other day pharmacologically implausible. Finally, aspirin has been reported to modify the way in which neutrophils and platelets[84] or erythrocytes and platelets[85,86] interact, to protect endothelial cells from oxidative stress,[87] and to improve endothelial dysfunction in atherosclerotic patients.[88] However, neither the molecular mechanism(s) nor the dose dependence of these effects have been clearly established. Although improved endothelial dysfunction could reflect an antiinflammatory effect of aspirin of relevance to atherogenesis, it should be emphasized that the hypothesis has never been tested by an appropriately sized controlled prospective study.

All of the evidence detailed above suggesting dose-dependent effects for aspirin is indirect and inconsistent with the failure to show a dose effect in randomized clinical trials and in the ATT overview analysis.[7] This failure to show a dose effect is the critical point of the discussion because it correlates with the saturability of the aspirin effect on platelet COX-1. For example, in studies with purified enzyme and with isolated platelets, nanomolar concentrations of aspirin will completely block PG synthesis within 20 min after exposure.[89] Higher concentrations and longer exposures will not alter the inhibitory effect of aspirin on PG synthesis because of this saturable quality. Exactly the same feature (maximal effect at low doses, absence of dose effect) is seen in clinical trials with aspirin as an antithrombotic agent. When one raises the dose of aspirin in this situation, no further or additional effect can be appreciated because the critical event has already taken place, namely, maximal inhibition of platelet TX synthesis. Thus, the consistency of dose requirements and saturability of the effects of aspirin in acetylating the platelet enzyme,[8] inhibiting TXA_2 production,[25,62] and preventing atherothrombotic complications[6,7] constitutes the best evidence that aspirin prevents thrombosis through inhibition of TXA_2 production. It is likely, therefore, that any of the potential effects of aspirin on other determinants of arterial thrombosis are much less important than the inhibition of platelet COX-1 activity.

2.3.3 Aspirin "Resistance": The term *aspirin resistance* has been used to describe a number of different phenomena, including the inability of aspirin to (1) protect individuals from thrombotic complications, (2) cause a prolongation of the bleeding time, (3) reduce TXA_2 production, or (4) produce a typical effect on one or more *in vitro* tests of platelet function.[90] From a therapeutic standpoint, it is important to establish whether aspirin resistance can be overcome by increasing the dose of aspirin, but unfortunately very few data bear directly on this

issue. The fact that some patients may experience recurrent vascular events despite long-term aspirin therapy should be properly labeled as *treatment failure* rather than aspirin resistance. Treatment failure is a common phenomenon occurring with all drugs (*eg*, lipid-lowering or antihypertensive drugs). Given the multifactorial nature of atherothrombosis and the possibility that platelet-mediated thrombosis may not be responsible for all vascular events, it is not surprising that only a fraction (usually one fourth to one third) of all vascular complications can be prevented by any single preventive strategy.

It has been reported that a variable proportion (up to one fourth) of patients with cerebrovascular disease only achieve partial inhibition of platelet aggregation at initial testing, and some (up to one third) seem to develop resistance to aspirin over time, even with increasing doses.[91–93] The results of these long-term studies carried out by Helgason et al are at variance with those of a short-term study of Weksler et al,[94] showing that aspirin, 40 mg/d, inhibited platelet aggregation and TXA_2 formation as effectively as higher doses of aspirin in patients who had recent cerebral ischemia. Variable platelet responses to aspirin have also been described in patients with peripheral arterial disease[95] and with ischemic heart disease.[96–98] In the Buchanan and Brister study,[96] aspirin nonresponders were identified on the basis of bleeding time measurements. Approximately 40% of patients undergoing elective coronary artery bypass grafting showed no prolongation of bleeding time in response to aspirin. This finding was associated with increased platelet adhesion and 12-HETE synthesis.[96] In contrast, repeated measurements of platelet aggregation performed over 24 months of placebo-controlled treatment by Berglund and Wallentin[99] demonstrated that 100 patients with unstable coronary artery disease randomized to receive aspirin, 75 mg/d, in the Research Group on Instability in Coronary Artery Disease in Southeast Sweden study[32] had consistently reduced platelet aggregation without attenuation during long-term treatment. Based on measurements of platelet aggregation in response to arachidonate and adenosine diphosphate (ADP), 5% and 24% of patients with stable cardiovascular disease who were receiving aspirin (325 mg/d for ≥ 7 days) were defined as resistant and semiresponders, respectively.[97] Using a variety of techniques, including conventional aggregometry, shear stress-induced activation, and the expression of platelet surface receptors, Sane et al[98] recently reported that 57% of a group of 88 patients with documented heart failure who had been treated with aspirin, 325 mg/d, for ≥ 1 month showed aspirin nonresponsiveness. Overall, the majority of these studies were characterized by the following major

limitations: (1) biochemical or witnessed verification of patient's adherence to the prescribed therapy were absent; (2) there was a single measurement of any given test; (3) intrasubject and intersubject variability and stability of the assay over time were usually not reported; (4) the criteria to define the normal vs the aspirin-resistant range and the assay conditions differed among studies; (5) doses of aspirin were heterogeneous, ranging from 75 to 1,300 mg; and (6) none of these studies were properly controlled.

Lack of biochemical assessment of compliance is a major issue for the majority of studies assessing platelet function in response to aspirin, and this aspect is crucial in studies investigating aspirin unresponsiveness. Interestingly, a recent study[100] in 190 patients with a history of MI compared arachidonate-induced platelet aggregation in patients while receiving their usual aspirin therapy, after 7 days of withdrawal, and 24 h after a single witnessed intake of aspirin of 325 mg. Although 9% of the patients who declared having taken their usual therapy failed to show inhibition of platelet aggregation, this percentage dropped to < 1% (1 patient of 190) after a witnessed dose.[100] Furthermore, this single patient admitted NSAID intake 12 h before testing. Similar results were reported in the study by Lev et al,[101] where after a witnessed dose of 325 mg of aspirin, the mean of arachidonic acid-induced light transmission aggregometry became < 20% (the established limit to define resistance) in formerly resistant patients. Other studies have reported up to 40% noncompliance with long-term aspirin use.[102] It is therefore clear that questionnaires cannot be a reliable parameter to assess the compliance to any given treatment, including aspirin, and that studies not relying on salicylate measurements or serum TXB_2 have a major, intrinsic bias, seriously hampering the interpretation of results. Furthermore, the few studies directly comparing different functional assays failed to find any significant agreement between tests, generating the disappointing conclusion that aspirin nonresponsiveness may be highly test specific.

Several relatively small studies (n = 39 to 180) of stroke patients[103–105] have suggested that aspirin resistance may contribute to treatment failure (ie, recurrent ischemic events while on antiplatelet therapy) and that doses higher than 500 mg may be more effective than lower doses in limiting this phenomenon. The uncontrolled nature and small sample size of these studies make it difficult to interpret the results. As noted above, a much larger database failed to substantiate a dose-dependent effect of aspirin in stroke prevention,[7] an effect that one would theoreti-

cally expect if aspirin resistance could be overcome at least in part by increasing the daily dose of the drug.

Gum et al[106] reported that 5% of 326 stable cardiovascular patients were aspirin resistant based on the results of platelet aggregation induced by ADP and arachidonic acid. The aspirin-resistant group had an increased risk of death, MI, or cerebrovascular accident during almost 2 years of follow-up. There were, however, relatively few events in this study, and the rationale for the particular definition of aspirin resistance is uncertain.

Among a wide range of patients with vascular disease in whom the annual rate of serious vascular events ranges from 40 to 80 per 1,000, aspirin typically prevents at least 10 to 20 fatal and nonfatal vascular events for every 1,000 patients treated for 1 year.[6] Thus, 30 to 60 vascular events are expected to occur for every 1,000 patients treated with low-dose aspirin for 1 year not because of resistance, but because of the multifactorial nature of atherothrombosis. Thus, we do not agree with the definition given by Wang et al,[107] whereby "in its broadest sense, resistance refers to the continued occurrence of ischemic events despite adequate antiplatelet therapy and compliance." Indeed, as suggested by Hennekens et al,[108] "given the multiple pathways by which platelets may be activated, it is perhaps more surprising that a clinical benefit is detectable in randomized trials of cardiovascular disease than that treatment failures complicate aspirin therapy."

At least three potential mechanisms may underlie the occurrence of aspirin-resistant TXA_2 biosynthesis. The transient expression of COX-2 in newly formed platelets in clinical settings of enhanced platelet turnover[4] is a potentially important mechanism that deserves further investigation. Extraplatelet sources of TXA_2 (eg, monocyte/macrophage COX-2) may contribute to aspirin-insensitive TXA_2 biosynthesis in acute coronary syndromes.[109] Furthermore, Catella-Lawson et al[110] reported that concomitant administration of a traditional NSAID (eg, ibuprofen) may interfere with the irreversible inactivation of platelet COX-1 by aspirin. This is due to competition for a common docking site within the COX channel (arginine-120), which aspirin binds to with weak affinity before irreversible acetylation of Serine-529.[13] This pharmacodynamic interaction also has been described between naproxen and aspirin[111] but does not occur with rofecoxib,[110] celecoxib,[112] or diclofenac,[110] drugs endowed with variable COX-2 selectivity.[83] Thus, concomitant treatment with readily available over-the-counter NSAIDs may limit the cardioprotective effects of aspirin and contribute to aspirin resistance. Based on current analysis of available data,[113–115] the US Food and Drug Administration (FDA) has issued a statement informing

patients and health-care professionals that ibuprofen can interfere with the antiplatelet effect of low-dose aspirin (81 mg/d), potentially rendering aspirin less effective when used for cardioprotection and stroke prevention (http://www.fda.gov/cder/drug/infopage/ibuprofen/default.htm).

The clinical relevance of aspirin-resistant TXA_2 biosynthesis has been explored by Eikelboom et al,[116] who performed a nested case-control study of baseline urinary TX metabolite excretion in relation to the occurrence of major vascular events in aspirin-treated high-risk patients enrolled in the Heart Outcomes Prevention Evaluation trial. After adjustment for baseline differences, the odds for the composite outcome of MI, stroke, or cardiovascular death increased with each increasing quartile of 11-dehydro-TXB_2 excretion, with patients in the upper quartile having a 1.8-times higher risk than those in the lower quartile. One limitation in this study, however, was the inability to differentiate between variable compliance in taking aspirin as prescribed (or avoiding NSAIDs) and variable occurrence of aspirin-resistant sources of TXA_2 biosynthesis.

Thus, in summary, both the mechanism(s) and clinical relevance of aspirin resistance, as defined by platelet aggregation measurements, remain to be established.[117] Until its true nature and prevalence *vis-à-vis* other antiplatelet drugs are better defined, no test of platelet function is recommended to assess the antiplatelet effect of aspirin in the individual patient.[118,119] On the other hand, additional studies on the mechanisms and clinical relevance of aspirin-resistant TXA_2 biosynthesis are clearly warranted.

2.4 The Antithrombotic Effect of Aspirin

2.4.1 Prevention of Atherothrombosis in Different Clinical Settings: The efficacy and safety of aspirin are documented from analysis of approximately 70 randomized clinical trials that included > 115,000 patients at variable risk of thrombotic complications of atherosclerosis. A detailed analysis of individual trials is beyond the scope of this article. It is more appropriately dealt within specific clinical sections of this volume.

Aspirin has been tested in patients demonstrating the whole spectrum of atherosclerosis, from apparently healthy low-risk individuals to patients presenting with an acute MI or an acute ischemic stroke; similarly, trials have extended for as short as a few weeks' duration or as long as 10 years.[6,7] Although aspirin has been shown consistently to be effective in preventing fatal and/or nonfatal vascular events in these trials, both the size of the proportional effects and the absolute benefits of antiplatelet therapy are somewhat heterogeneous in different clinical settings.

In the Second International Study of Infarct Survival,[55] a single tablet of aspirin (162.5 mg) started within 24 h of the onset of symptoms of a suspected MI and continued daily for 5 weeks produced highly significant reductions in the risk of vascular mortality (by 23%), nonfatal reinfarction (by 49%), and nonfatal stroke (by 46%). There was no increase in hemorrhagic stroke or GI bleeding in the aspirin-treated patients and only a small increase in minor bleeding.[55] Treatment of 1,000 patients with suspected acute MI with aspirin for 5 weeks will result in approximately 40 patients in whom a vascular event is prevented,[7] with a proportional odds reduction of 30% (see the "Acute ST-Segment Elevation Myocardial Infarction" chapter).

Two separate trials with a similar protocol, the International Stroke Trial[59] and the Chinese Acute Stroke Trial,[60] tested the efficacy and safety of early aspirin use in acute ischemic stroke. Approximately 40,000 patients were randomized within 48 h of the onset of symptoms to 2 to 4 weeks of daily aspirin therapy (300 mg and 160 mg, respectively) or placebo. An overview of the results of both trials suggests an absolute benefit of 9 fewer deaths or nonfatal strokes per 1,000 patients in the first month of aspirin therapy.[7] The proportional odds reduction in fatal or nonfatal vascular events is only 10% in this setting. Although the background risk of hemorrhagic stroke was threefold higher in the Chinese Acute Stroke Trial than in the International Stroke Trial, the absolute increase in this risk associated with early use of aspirin was similar in the two studies (excess 2 per 1,000 patients).[59,60] The broad clinical implications of these findings are discussed in the "Antithrombotic and Thrombolytic Therapy for Ischemic Stroke" chapter. In terms of their research implications, these results are consistent with biochemical evidence of episodic platelet activation during the first 48 h after the onset of symptoms of an acute ischemic stroke and with suppression of *in vivo* TXA_2 biosynthesis in patients receiving low-dose aspirin in this setting.[120]

Long-term aspirin therapy confers conclusive net benefit on risk of subsequent MI, stroke, or vascular death among subjects with high risk of vascular complications. These include patients with chronic stable angina,[33] patients with prior MI,[7] patients with unstable angina,[32,44–46] and patients with TIA or minor stroke[34,36,41,56–58] as well as other high-risk categories.[7] The proportional effects of long-term aspirin therapy on vascular events in these different clinical settings are rather homogeneous, ranging between 20% and 25% odds reduction based on an overview of all randomized trials.[7] However, individual trial data show substantial heterogeneity, ranging

from no statistically significant benefits in patients with peripheral vascular disease to approximately 50% risk reduction in patients with unstable angina.[7] Although other factors may play a role, we interpret these findings as reflecting the variable importance of TXA_2 as a mechanism amplifying the hemostatic response to plaque destabilization in different clinical settings. In terms of absolute benefit, these protective effects of aspirin translate into avoidance of a major vascular event in 50 per 1,000 patients with unstable angina treated for 6 months and in 36 per 1,000 patients with prior MI, stroke, or TIA treated for approximately 30 months.[7]

For patients with different manifestations of ischemic heart or brain disease, a widespread consensus exists in defining a rather narrow range of recommended daily doses (ie, 75 to 160 mg) for the prevention of MI, stroke, or vascular death. This is supported by separate trial data in patients randomized to treatment with low-dose aspirin or placebo as well as by an overview of all antiplatelet trials showing no obvious dose dependence, from indirect comparisons, for the protective effects of aspirin[7] (Table 3). There is no convincing evidence that the dose requirement for the antithrombotic effect of aspirin varies in different clinical settings.

Among most high-risk patient groups, the expected number avoiding a serious vascular event by using aspirin substantially exceeds the number experiencing a major bleed. However, it is unclear whether aspirin might benefit people who, although apparently healthy, are at intermediate risk of serious vascular events. The question of whether aspirin is effective for the primary prevention of vascular events has been addressed in a metaanalysis of randomized trials.[332]

Six primary prevention trials[81,121–125] including 92,873 participants were studied (Table 4). Mean follow-up was approximately 6 years. There was a 15% reduction in the odds of cardiovascular events (OR, 0.85; 95% CI, 0.79 to 0.92; $p < 0.001$) and highly significant reductions of 23% in total coronary heart disease (CHD) [OR, 0.77; 95% CI, 0.70 to 0.86; $p < 0.001$] and 24% in nonfatal MI (OR, 0.76; 95% CI, 0.67 to 0.85; $p < 0.001$).

There was no overall effect on stroke (OR, 0.95; 95% CI, 0.84 to 1.06; $p = 0.3$), but data were not available separately for hemorrhagic and nonhemorrhagic stroke,[126–128] so the effects on these two stroke subtypes could not be examined in detail. Aspirin had no significant effect on the aggregate of all vascular causes of death (OR, 0.89; 95% CI, 0.72 to 1.10; $p = 0.3$), or on overall mortality (OR, 0.94; 95% CI, 0.87 to 1.00; $p = 0.07$). In summary, therefore, in primary prevention, aspirin chiefly prevents nonfatal MI, and appears to have little effect on fatal vascular events.

2.5 Balance of Benefit and Harm

Previous metaanalyses of the effects of antiplatelet therapy among people at high risk of occlusive vascular disease[7] have shown that the benefits of aspirin far exceed the bleeding risks among such

Table 4—Primary Prevention Trials (Section 2.4.1)

Trial	Dates of Recruitment	Year of Publication	Mean Duration of Follow-up,* yr	Target Population	Eligible Age Range, yr	Intervention	Randomized Factorial Comparison	Placebo Control
British Doctors Study	11/1/1978 to 11/1/1979	1988	5.6	Male physicians	19–90	500 mg/d	None	No
US physicians	8/24/1981 to 4/2/1984	1988	5.0	Male physicians	45–73	325 mg alternate days	Beta-carotene (alternate days) vs placebo	Yes
Thrombosis Prevention Trial	2/6/1989 to 5/18/1994	1998	6.7	Men with risk factors for CHD	45–69	75 mg/d	Warfarin vs placebo	Yes
Hypertension Optimal Treatment	10/12/1992 to 5/7/1994	1998	3.8	Men and women with diastolic BP 100–115 mm Hg	31–75	75 mg/d	Three target diastolic BPs (< 80 mm Hg, < 85 mm Hg, < 90 mm Hg)	Yes
Primary Prevention Project	6/8/1993 to 4/21/1998	2001	3.7	Men and women with one or more risk factors for CHD	45–94	100 mg/d	Vitamin E vs open control	No
Women's Health Study	9/1992 to 5/1995	2005	10.1	Female health professionals	≥ 45	100 mg alternate days	Vitamin E vs placebo	Yes

*Mean duration of follow-up among surviving participants within each trial.

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patients. By contrast, the majority of participants (92%) in the primary prevention trials were at low absolute risk of coronary disease; on average, the annual risk of a vascular event in the primary prevention trials was only about one tenth of that occurring in the high-risk trials. Hence, although the proportional benefits of aspirin appeared broadly similar in primary and secondary prevention, the absolute benefits and risks of aspirin in the primary prevention trials were very small. Each year, fewer than 1 person in every 1,000 could expect to avoid an occlusive vascular event by taking aspirin, whereas a comparably small number could expect to experience a major extracranial bleed. The relative size of these opposing effects is too imprecisely known in low-risk people to predict the net public health consequences of widespread aspirin use in healthy people. The ATT Collaboration is currently analyzing individual participant data from the six primary prevention trials, and these new analyses will help to clarify the benefits and risks of aspirin in particular groups of individuals. Until the benefits of aspirin can be defined more precisely, however, the possibility of a benefit does not seem to justify the probability of a hazard. This emphasizes the need for trials of aspirin for primary prevention among specific groups at increased risk of vascular disease, such as people > 70 years of age and people with diabetes but no vascular disease.

2.5.1 *Atrial Fibrillation:* Moderate-dose warfarin alone (international normalized ratio [INR], 2.0 to 3.0) is very effective in reducing the risk of stroke in patients with nonvalvular atrial fibrillation.[129–131] The effectiveness of aspirin in doses between 75 and 325 mg has been compared with warfarin and placebo in three randomized trials of patients with nonvalvular atrial fibrillation.[130,132,133] In one study,[130] aspirin was significantly more effective than placebo, whereas in the other two[132,133] there was a nonsignificant trend in favor of aspirin. Pooled analysis of the three studies shows a relative risk reduction in favor of aspirin over placebo of about 25% (range, 14 to 44%). Aspirin was significantly less effective than warfarin in two studies on an intention-to-treat analysis,[132,133] and in the third study on an efficacy analysis.[130] On pooled analysis, warfarin was significantly more effective than aspirin, with a 47% relative risk reduction (range, 28 to 61%; p < 0.01).[134] Moreover, adjusted-dose warfarin therapy (INR, 2.0 to 3.0) was more effective than fixed low-dose warfarin therapy (INR, 1.2 to 1.5) and aspirin, 325 mg/d, in high-risk patients with atrial fibrillation.[135] Thus, aspirin appears to be effective in preventing stroke in patients with atrial fibrillation but is substantially less effective than warfarin.[136,137]

2.5.2 *Deep Vein Thrombosis:* The Pulmonary Embolism Prevention Trial[138] has established that aspirin is effective in preventing venous thromboembolism after surgery for hip fracture. This was a double-blind multicenter study of 13,356 patients undergoing surgery for hip fracture and of an additional 4,088 patients undergoing elective hip or knee arthroplasty. Patients were assigned 160 mg of aspirin or placebo qd for 5 weeks, with the first dose starting before surgery. Other forms of prophylaxis were allowed, and either heparin or low-molecular-weight heparin was used in about 40% of the patients. Among the 13,356 patients with hip fracture, aspirin produced a 36% reduction in symptomatic deep vein thrombosis or pulmonary embolism (PE) [absolute risk reduction 0.9%; p = 0.0003]. A similar relative risk reduction in patients who were assigned aspirin was observed in patients who also received heparin.

This important study,[138] therefore, clearly shows that aspirin reduces the incidence of fatal PE and symptomatic nonfatal deep vein thrombosis or PE in patients with hip fracture. The results of the Pulmonary Embolism Prevention trial are consistent with the meta-analysis performed by the Antiplatelet Trialists' Collaboration,[139] and supersede the findings in most of the previous trials.[140–142] However, in three randomized studies in major orthopedic surgery comparing aspirin with either warfarin[143] or a low-molecular-weight heparin,[144,145] the incidence of venous thrombosis was significantly higher in the aspirin group in all three.

2.5.3 *Placental Insufficiency:* The pathogenesis of preeclampsia and fetal growth retardation is related to reduced placental blood flow, which is believed to be caused by constriction and/or thrombosis of small placental arteries.[146] The initial reports that low-dose aspirin therapy reduces the risk of severe low birth weight among newborns,[147] and the risk of cesarean section in mothers with pregnancy-induced hypertension,[146] led to the widespread use of prophylactic aspirin to prevent preeclampsia. Subsequently, several larger trials reported no beneficial effects of aspirin.[148–154]

A systematic review[155] of data from 39 trials in > 30,000 women showed that antiplatelet therapy (mostly aspirin, 60 mg/d) is associated with a 15% decrease in the risk of preeclampsia. This effect was consistent, regardless of risk status (moderate or high), dose of aspirin, or gestation at trial entry. There was some evidence that there may be greater benefits for women given > 75 mg of aspirin, although the numbers of women in the subgroup were small and so a potential for random error. There was also an 8% reduction in the risk of preterm birth and

a 14% reduction in the risk of fetal or neonatal death for women allocated antiplatelet therapy.[155] Remaining questions are whether particular subgroups of high-risk women might have greater benefit and whether earlier treatment (*ie*, before 12 weeks) or aspirin doses of > 75 mg would have additional benefits without an increase in adverse effects.[155] The potential involvement of extra platelet sources of vasoactive eicosanoids expressing COX-2 in response to a local growth-promoting milieu might contribute, at least in part, to the limited efficacy of low-dose aspirin therapy in this setting.

2.6 Adverse Effects of Aspirin

Aspirin does not cause a generalized bleeding abnormality unless it is given to patients with an underlying hemostatic defect, such as hemophilia, uremia, or that induced by anticoagulant therapy. Aspirin-induced impairment of primary hemostasis cannot be separated from its antithrombotic effect and is similar at all doses ≥ 75 mg/d.[6]

The balance between preventing vascular occlusion and causing excess bleeding with aspirin depends critically on the absolute thrombotic vs hemorrhagic risk of the patient. Thus, in individuals at low risk for vascular occlusion (*eg*, $\leq 1\%$/yr), a very small absolute benefit is offset by exposure of a large number of healthy subjects to undue bleeding complications. In contrast, in patients at high risk of cardiovascular or cerebrovascular complications (*eg*, > 3%/yr), the substantial absolute benefit of aspirin prophylaxis clearly outweighs the harm (Table 5). For example, the absolute excess of major bleeds (*ie*, those requiring transfusion) in acute MI is approxi-

mately 1/100th the absolute number of major vascular events avoided by aspirin therapy.[7]

The overall risk of major extracranial and intracranial hemorrhage associated with antiplatelet drugs is difficult to assess in individual trials because their incidence is low (*ie*, < 1%/yr), making detection of even a 50 to 60% relative increase in risk unrealistic in most trials of a few thousand patients.

Aspirin-induced GI toxicity, as detected in randomized clinical trials, appears to be dose related in the range of 30 to 1,300 mg/d.[156] This, along with studies of the relationship of efficacy to dose, is based largely on indirect comparisons of different trials and on a limited number of randomized, direct comparisons of different aspirin doses, as reviewed above. Such a dose-response relationship is thought to reflect at least two COX-1-dependent components, dose-dependent inhibition of COX-1 in the GI mucosa and dose-independent (within the range of examined doses) inhibition of COX-1 in platelets.[6] Thus, it is not surprising that the antithrombotic effect of aspirin can be dissociated, at least in part, from its most common side effect. However, even when administered at low doses, aspirin can cause serious GI bleeding, as reported in studies using 30 to 50 mg/d.[36,42] Because of the underlying prevalence of gastric mucosal erosions related to concurrent use of other NSAIDs and/or *Helicobacter pylori* infection in the general population, it should be expected that any antiplatelet dose of aspirin will cause more bleeding from preexisting lesions than a placebo. Consistent with this mechanistic interpretation, the relative risk of hospitalization due to upper-GI bleeding and/or perforation associated with low-dose aspirin therapy (mostly, 100 to 300 mg/d) is comparable to that of other antiplatelet agents and anticoagulants (*ie*, 2.3 [95% CI, 1.7 to 3.2], 2.0 [95% CI, 1.4 to 2.7], and 2.2 [95% CI, 1.4 to 3.4], respectively) in a large population-based observational study.[157]

In the overview of the ATT Collaboration,[7] information was available on 787 major extracranial hemorrhages in 60 trials recording at least one such hemorrhage. These were generally defined as hemorrhages that were fatal or required transfusion; among them, 159 (20%) caused death. Overall, the proportional increase in risk of a major extracranial bleed with antiplatelet therapy was about one half (odds ratio [OR], 1.6; 95% CI, 1.4 to 1.8), with no significant difference between the proportional increases observed in each of the five high-risk categories of patients. After allowing for noncompliance in the trials, they are compatible with the 2- to 2.5-fold excess observed in case-control studies.

A case-control study with hospital and community controls has examined the risks of hospitalization for

Table 5—*Benefit and Harm of Antiplatelet Prophylaxis With Aspirin in Different Settings (Section 2.6)*

Clinical Setting	Benefits*	Harm†
Men at low to high cardiovascular risk	1–2	1–2
Essential hypertension	1–2	1–2
Chronic stable angina	10	1–2
Prior MI	20	1–2
Unstable angina	50	1–2

*No. of patients in whom a major vascular event is avoided per 1,000/yr. Benefits are calculated from randomized trial data reviewed in this article and depicted in Figure 3.

†No. of patients in whom a major GI bleeding event is caused per 1,000/yr. Excess of upper-GI bleedings is estimated from a background rate of 1 event per 1,000/yr in the general population of nonusers[157] and an RR of 2.0 to 3.0 associated with aspirin prophylaxis.[157–159] Such an estimate assumes comparability of other risk factors for upper-GI bleeding, such as age and concomitant use of NSAIDs, and may actually underestimate the absolute risk in an elderly population exposed to "primary" prevention.

bleeding peptic ulcer associated with three different regimens of aspirin prophylaxis.[158] ORs were raised for all doses of aspirin taken: 75 mg, OR 2.3 (95% CI, 1.2 to 4.4); 150 mg, OR 3.2 (95% CI, 1.7 to 6.5); and 300 mg, OR 3.9 (95% CI, 2.5 to 6.3). Additional epidemiologic studies have found a dose-response relationship between aspirin prescription and upper-GI complications, as reviewed by García Rodríguez et al.[159] It has been calculated that approximately 900 of the 10,000 episodes of ulcer bleeding occurring in people > 60 years of age each year in England and Wales could be associated with, and ascribed to, prophylactic aspirin use.[158] A general change to lower doses of aspirin (75 mg) would not eliminate risks but would reduce risk by about 40% compared with 300-mg doses and by 30% compared with 150-mg doses if the assumptions from indirect comparisons are correct.[158] Given that the mortality rate among patients who are hospitalized for NSAID-induced upper-GI bleeding is about 5 to 10%,[160,161] such a strategy could save a significant number of lives.

The widely held belief that enteric-coated and buffered varieties of aspirin are less likely to occasion major upper-GI bleeding than plain tablets was tested in data from a multicenter case-control study.[162] The relative risks of upper-GI bleeding for plain, enteric-coated, and buffered aspirin at average daily doses of ≤ 325 mg were 2.6, 2.7, and 3.1, respectively. At doses > 325 mg, the relative risks were 5.8 for plain and 7.0 for buffered aspirin; there were insufficient data to evaluate enteric-coated aspirin at this dose level.[162] Similar conclusions were reached by a case-control study using data from the UK General Practice Research Database.[163] Thus, physicians who recommend aspirin in an enteric-coated or buffered form should not assume that these formulations are less likely to cause GI tract bleeding than plain aspirin.

Suppressing acid secretion is thought to reduce the risk of ulcers associated with regular use of NSAIDs. In patients who required continuous treatment with NSAIDs and who had ulcers or > 10 erosions in either the stomach or duodenum, omeprazole healed and prevented ulcers more effectively than did ranitidine.[164] In these patients, maintenance therapy with omeprazole was associated with a lower rate of relapse and was better tolerated than misoprostol.[165] In high-risk patients (history of previous ulcer bleeding) taking low-dose aspirin for 6 months, omeprazole and *H pylori* eradication were associated with similar rates of recurrent bleeding (0.9% vs 1.9%),[166] although clinically important differences between the two preventive strategies could not be excluded owing to the small sample size (n = 250).

Two relatively small studies[167,168] have challenged current guidelines that recommend clopidogrel for patients who have major GI contraindications to aspirin, principally recent significant bleeding from a peptic ulcer or gastritis.[169,170] Both studies enrolled patients with ulcer bleeding after the use of low-dose aspirin. In the study of Chan et al,[167] after healing of ulcers and eradication of *H pylori*, if present, 320 patients were randomly assigned to receive either clopidogrel, 75 mg/d, or aspirin, 80 mg/d, plus 20 mg bid of esomeprazole for 12 months. The cumulative incidence of recurrent bleeding was 8.6% (95% CI, 4.1 to 13.1%) among patients who received clopidogrel and 0.7% (95% CI, 0 to 2.0%) among those who received aspirin plus esomeprazole (p = 0.001).[167] In the study of Lai et al,[168] 170 patients with prior ulcer bleeding were randomly assigned to treatment with clopidogrel, 75 mg/d, or aspirin, 100 mg/d, and esomeprazole, 20 mg/d, for 1 year. The cumulative incidence of recurrent ulcer complications was 13.6% and 0%, respectively (95% CI for the difference, 6.3 to 20.9%; p = 0.0019).[168] The consistent findings of two independent studies suggest that the combination of esomeprazole and low-dose aspirin is superior to clopidogrel in preventing recurrent ulcer bleeding in patients with a history of aspirin-related ulcer bleeding.

Substantially less information is available about the risk of intracranial hemorrhage associated with aspirin use. In the Nurses' Health Study[171] cohort of approximately 79,000 women 34 to 59 years of age, infrequent use of aspirin (1 to 6 tablets per week) was associated with reduced risk of ischemic stroke, whereas high frequency of use (≥ 15 aspirin tablets per week) was associated with increased risk of subarachnoid hemorrhage, particularly among older or hypertensive women. In the overview of the ATT Collaboration,[7] the overall absolute excess of intracranial hemorrhage due to aspirin therapy was < 1 per 1,000 patients per year in high-risk trials, with somewhat higher risks in patients with cerebrovascular disease.

Low-dose aspirin therapy has not been reported to affect renal function or BP control,[172] consistent with its lack of effect on renal prostaglandins[173] that derive primarily from constitutively expressed COX-2 in the human kidney.[83] Moreover, aspirin, 75 mg/d, did not affect BP or the need for antihypertensive therapy in intensively treated hypertensive patients.[122] The suggestion that the use of aspirin and other antiplatelet agents is associated with reduced benefit from enalapril in patients with left ventricular systolic dysfunction[174] is not supported by the results of a large metaanalysis of MI trials.[175] Similarly, no negative interaction occurs between angiotensin-converting enzyme (ACE) inhibition and the cardiovascular benefits of low-dose aspirin in intensively treated hypertensive patients.[176] The ACE Inhibitors Col-

laborative Group[177] has performed a systematic overview of data for 22,060 patients from six long-term randomized trials of ACE inhibitors to assess whether aspirin altered the effects of ACE inhibitor therapy on major clinical outcomes. Even though results from these analyses cannot rule out the possibility of some sort of interaction, they show unequivocally that even if aspirin is given, the addition of ACE inhibitor therapy produced substantial additional benefit in all major vascular outcomes. Therefore, in the absence of clear contraindications, concomitant use of aspirin and ACE inhibitors should be considered in all patients at high risk of major vascular events.[177]

Thus, in summary, inhibition of TXA_2-dependent platelet function by aspirin is effective for the prevention of thrombosis, but is also associated with excess bleeding. Assessing the net effect requires an estimation of the absolute thrombotic vs hemorrhagic risk of the individual patient. In individuals at very low risk for vascular occlusion, a very small absolute benefit may be offset by exposure of very large numbers of healthy subjects to undue bleeding complications. As the risk of experiencing a major vascular event increases, so does the absolute benefit of antiplatelet prophylaxis with aspirin, as shown in Figure 3, for a number of clinical settings in which the efficacy of the drug has been tested in randomized clinical trials. Based on the results of such trials,

the antithrombotic effect of aspirin does not appear to be dose related over a wide range of daily doses (30 to 1,300 mg), an observation consistent with saturability of platelet COX inhibition at very low doses. In contrast, GI toxicity of the drug does appear to be dose related, consistent with dose- and dosing interval-dependent inhibition of COX activity in the nucleated lining cells of the GI mucosa. Thus, aspirin once daily should be considered in all clinical conditions in which antiplatelet prophylaxis has a favorable benefit/risk profile. Because of GI toxicity and its potential impact on compliance, physicians are encouraged to use the lowest dose of aspirin shown effective in each clinical setting (Table 1).

2.7 Reversible COX Inhibitors

In the absence of definitive randomized studies, traditional NSAIDs have long been thought to pose no cardiovascular hazard or to be somewhat cardioprotective. Because of their reversible mechanism of action in inhibiting platelet COX-1 and of their short half-lives, most traditional NSAIDs inhibit TXA_2-dependent platelet activation only transiently and incompletely in the vast majority of users.[178] A notable exception is provided by naproxen, which when administered regularly at 500 mg bid, has been shown to inhibit TXA_2 biosynthesis *in vivo* to the same extent as low-dose aspirin,[179] consistent with its
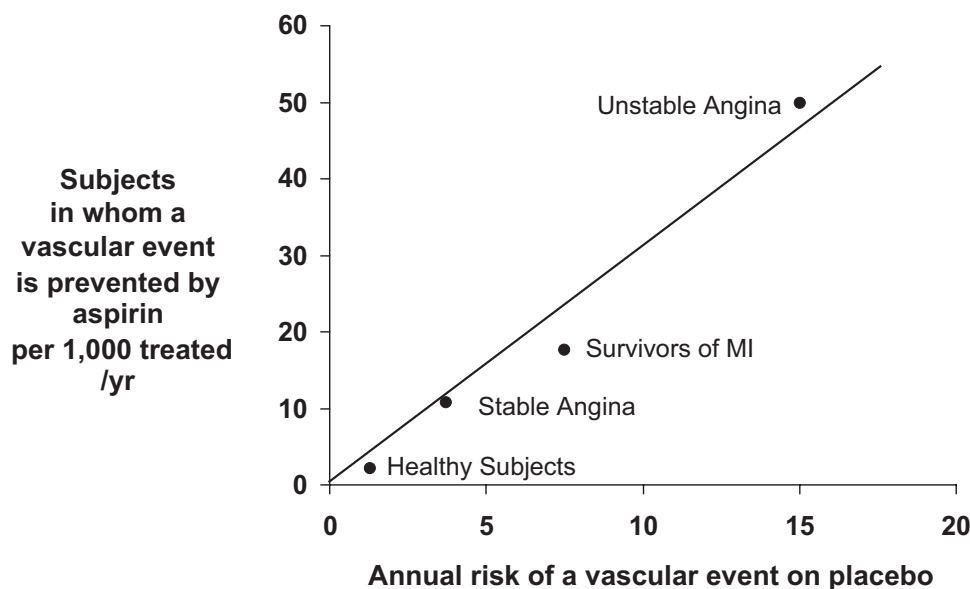
FIGURE 3. The absolute risk of vascular complications is the major determinant of the absolute benefit of antiplatelet prophylaxis. Data are plotted from placebo-controlled aspirin trials in different clinical settings. For each category of patients, the abscissa denotes the absolute risk of experiencing a major vascular event as recorded in the placebo arm of the trial(s). The absolute benefit of antiplatelet treatment is reported on the ordinate as the number of subjects in whom an important vascular event (nonfatal MI, nonfatal stroke, or vascular death) is actually prevented by treating 1,000 subjects with aspirin for 1 year.

relative COX-1 selectivity and longer half-life than other commonly used NSAIDs.

The only reversible COX inhibitors that have been tested in randomized clinical trials for their antithrombotic efficacy are sulfinpyrazone, indobufen, flurbiprofen, and triflusal. Sulfinpyrazone is a uricosuric agent structurally related to the antiinflammatory agent phenylbutazone. When used at the highest approved dosage of 200 mg qid, the drug inhibits platelet COX activity by approximately 60%, after conversion from an inactive sulfoxide to an active sulfide metabolite.[180] The conflicting or negative results obtained in randomized clinical trials of sulfinpyrazone in patients with MI or unstable angina[7] (reviewed in the "Valvular and Structural Heart Disease" chapter) are not surprising in light of the drug being a weak COX inhibitor with no other established antiplatelet mechanism of action.

In contrast, indobufen is a very potent inhibitor of platelet COX-1 activity and has comparable biochemical, functional, and clinical effects to those of a standard dose of aspirin. Thus, at therapeutic plasma levels achieved after oral dosing of 200 mg bid, indobufen inhibits serum TXB_2 by $> 95\%$ throughout the dosing interval[181] and reduces urinary TX metabolite excretion to an extent quite comparable to aspirin.[182] The finding that indobufen is as effective as aspirin in preventing coronary graft occlusion in two randomized trials[183,184] is mechanistically consistent with the concept of platelet COX-1 inhibition largely accounting for the antithrombotic effect of aspirin, as discussed above. Indobufen also has been investigated in a small placebo-controlled study of patients with heart disease at increased embolic risk[185] and compared with warfarin[186] and ticlopidine[187] in patients with nonrheumatic atrial fibrillation and patients with recent reversible cerebral ischemia, respectively. However, none of these studies in $> 4,000$ patients clearly established an advantage of indobufen vs standard treatments, although the 95% CIs for these comparisons are wide. Indobufen has been reported to suppress in vivo TXA_2 biosynthesis more effectively than low-dose aspirin in patients with unstable angina, an effect possibly related to inhibition of monocyte COX-2 by therapeutic plasma levels of indobufen.[14] The clinical relevance of these findings remains to be established.

Flurbiprofen has been evaluated in a single placebo-controlled, randomized trial of 461 patients with acute MI.[188] The 6-month reinfarction rate was significantly lower in the flurbiprofen group (3%) than in the placebo group (10.5%), with an extremely low mortality rate (1.1%) in both groups. The small sample size of the study limits interpretation of these findings.

Triflusal, a salicylic acid derivative, reversibly inhibits platelet COX activity after conversion to a long-lived metabolite, 2-hydroxy-4-trifluoromethyl-benzoic acid.[189] Although the half-life of the parent compound is only about 30 min, that of the deacetylated metabolite approximates 2 days. Although triflusal is claimed to have negligible effects on vascular PGI_2 production, this is likely to reflect the experimental conditions used for the assessment of PGI_2 production ex vivo. The limited sample size of head-to-head comparisons of triflusal vs aspirin in patients randomized within 24 h of acute MI[190] and in patients with cerebrovascular disease[191] precludes unequivocal interpretation of the similar rates of major vascular events in the two treatment groups. None of these reversible COX inhibitors are approved as an antiplatelet drug in the United States, and it is unclear under which circumstances they are prescribed instead of aspirin in other countries.

2.8 Coxibs and Cardiovascular Disease

Coxibs were developed in an attempt to prevent the adverse GI effects of nonselective NSAIDs (by avoiding inhibition of COX-1) while maintaining equivalent antiinflammatory efficacy (by inhibiting COX-2).[83] Several large randomized trials[192–194] have demonstrated that coxibs are associated with lower risk of serious GI events than nonselective NSAIDs, but the Vioxx GI Outcomes Research Study[193] among approximately 8,000 patients with rheumatoid arthritis showed that those allocated to rofecoxib, 50 mg/d, experienced a higher risk of vascular events than those allocated to naproxen 500 mg bid. This excess was almost entirely accounted for by a difference in the incidence of MI (20 in 2,699 person-years of follow-up among rofecoxib-allocated patients, vs 4 in 2,699 person-years among naproxen-allocated patients). There were no significant differences in stroke (11 rofecoxib vs 9 naproxen) or vascular deaths (7 rofecoxib vs 7 naproxen).[193] Three placebo-controlled trials have now revealed a twofold- to threefold-increased risk of vascular events in approximately 6,000 patients treated short term (10 days) with valdecoxib[195] or long term (up to 3 years) with celecoxib[196] or rofecoxib[197] both with and without concomitant aspirin treatment. These recent findings are consistent with a mechanism-based cardiovascular hazard for the class[198] and have led to the withdrawal of rofecoxib and valdecoxib from the market.

A metaanalysis of tabular data from 138 randomized trials of five different coxibs in approximately 145,000 patients has revealed that in placebo comparisons, allocation to a coxib was associated with a

42% increased incidence of vascular events with no statistically significant heterogeneity among the different coxibs.[20] This excess risk of vascular events was derived primarily from a twofold-increased risk of MI. Overall, there was no significant difference in the incidence of vascular events between a coxib and any traditional NSAID, but there was evidence of a significant difference between naproxen and the other traditional NSAIDs.[20] Given the nonlinear relationship between inhibition of platelet COX-1 activity and inhibition of platelet activation *in vivo* (Fig 2),[31] it is perhaps not surprising that the cardiovascular safety profile of coxibs and some non-naproxen NSAIDs (primarily diclofenac and ibuprofen) appears similar because these drugs fail to inhibit platelet activation adequately irrespective of their COX-2 selectivity. The results of the Multinational Etoricoxib and Diclofenac Arthritis Long-Term study,[199] comparing long-term treatment with etoricoxib and diclofenac in approximately 35,000 arthritis patients, are consistent with this conclusion. Whether the variable level and duration of COX-1 inhibition by different NSAIDs modulate the cardiovascular consequences of COX-2 inhibition presently is unknown, given the limited utilization of NSAIDs other than ibuprofen, diclofenac, and naproxen in coxib trials. Thus, coxibs and some traditional NSAIDs moderately increase the risk of vascular events, particularly MI, but there remains considerable uncertainty about the magnitude of this hazard for particular drug regimens and patients subgroups. A metaanalysis of individual participant data from randomized coxib trials is currently being conducted by the Coxib Trialists' Collaboration in order to address some of the open questions related to the influence of dose, duration, and baseline characteristics, including the concomitant use of low-dose aspirin, on this cardiotoxicity.

3.0 Dipyridamole

Dipyridamole is a pyrimidopyrimidine derivative with vasodilator and antiplatelet properties. The mechanism of action of dipyridamole as an antiplatelet agent has been a subject of controversy.[200] Both inhibition of cyclic nucleotide phosphodiesterase (the enzyme that degrades cyclic adenosine monophosphate [AMP] to 5(1)-AMP, resulting in the intraplatelet accumulation of cyclic AMP, a platelet inhibitor) and blockade of the uptake of adenosine (which acts at A_2 receptors for adenosine to stimulate platelet adenylyl cyclase and thus increase cyclic AMP) have been suggested. Moreover, direct stimulation of PGI_2 synthesis and protection against its degradation have been reported, although the dipy-

ridamole concentrations required to produce these effects far exceed the low micromolar plasma levels achieved after oral administration of conventional doses (100 to 400 mg/d).[200] Dipyridamole also differentially inhibits the expression of critical inflammatory genes in platelet-leukocyte aggregates.[201]

The absorption of dipyridamole from conventional formulations is quite variable and may result in low systemic bioavailability of the drug. A modified-release formulation of dipyridamole with improved bioavailability has been developed in association with low-dose aspirin.[202] Dipyridamole is eliminated primarily by biliary excretion as a glucuronide conjugate and is subject to enterohepatic recirculation. A terminal half-life of 10 h has been reported. This is consistent with the twice-daily regimen used in recent clinical studies.

Although the clinical efficacy of dipyridamole, alone or in combination with aspirin, has been questioned on the basis of earlier randomized trials,[2,203] the whole issue has been reopened by the reformulation of the drug to improve bioavailability and the results of the ESPS-2 and European Stroke Prevention Reversible Ischemia Trial (ESPRIT) studies.[36,204] In ESPS-2, the new preparation of dipyridamole was evaluated in 6,602 patients with prior stroke or TIA.[36] This study showed that the addition of modified-release dipyridamole 200 mg bid to aspirin 25 mg bid was associated with a 22% relative risk reduction of major vascular events compared with aspirin alone. Headache was the most common adverse effect of dipyridamole. Bleeding at any site was almost doubled in the two aspirin arms but was surprisingly indistinguishable from placebo in the dipyridamole-treated patients.[36] In a *post hoc* analysis of cardiac events in patients with CHD or MI at entry, dipyridamole did not result in a higher number of fatal and nonfatal cardiac events.[204]

More recently, the ESPRIT Study Group[205] has performed a randomized trial in which they assigned 2,739 patients within 6 months of a TIA or minor stroke of presumed arterial origin to aspirin (30 to 325 mg/d) with or without dipyridamole (200 mg bid). The primary outcome (a composite of major vascular events or major bleeding complications) was significantly reduced by the combined treatment vs aspirin alone by 20%. Patients receiving aspirin and dipyridamole discontinued trial medication almost three times more often than those receiving aspirin alone, mainly because of headache.[205] Addition of the ESPRIT data to the metaanalysis of previous trials resulted in an overall risk ratio of 0.82 (95% CI, 0.74 to 0.91) for the composite of vascular death, stroke, or MI. However, based on the most recent Cochrane review,[203] the additional benefit of the combination over aspirin alone is not detectable in

patients with other types of vascular disease. Whether this apparent discrepancy reflects a different prevalence of dipyridamole-sensitive mechanisms of disease or, perhaps more likely, the different types of formulation and daily dosage of the drug remains to be established. The fixed combination of modified-release dipyridamole and low-dose aspirin has been approved for stroke prevention by the FDA and other regulatory authorities.

4.0 THIENOPYRIDINES

Ticlopidine and clopidogrel are structurally related thienopyridines with platelet-inhibitory properties. Both drugs selectively inhibit ADP-induced platelet aggregation with no direct effects on arachidonic acid metabolism.[206] Although ticlopidine and clopidogrel also can inhibit platelet aggregation induced by collagen and thrombin, these inhibitory effects are abolished by increasing the agonist concentration and, therefore, are likely to reflect blockade of ADP-mediated amplification of the platelet response to other agonists.

Neither ticlopidine nor clopidogrel affect ADP-induced platelet aggregation when added *in vitro*, up to 500 μmol/L, thus suggesting that *in vivo* hepatic transformation to an active metabolite(s) is necessary for their antiplatelet effects. In the liver, clopidogrel is metabolized into 2-oxo-clopidogrel through a cytochrome P450-dependent pathway. This intermediate metabolite is then hydrolyzed and generates the highly labile active metabolite,[207] which reacts as a thiol reagent with the ADP receptors on platelets when they pass through the liver.[208] The active metabolite belongs to a family of eight stereoisomers, only one of which (bearing 7S, 3Z, and 4S or 4R configuration) retains biological activity.[208]

Experimental evidence suggests that clopidogrel and, probably, ticlopidine induce irreversible alterations of the platelet receptor P2Y12 mediating inhibition of stimulated adenylyl cyclase activity by ADP.[209,210] The active metabolite of clopidogrel couples through a disulfide bridge to the P2Y12 receptor, presumably to the cysteine residue in the first extracellular loop; this results in oligomers dissociating into dimeric receptors that are partitioned out of lipid rafts, thereby losing the ability to bind their endogenous ligand.[211] Interestingly, mutations in the P2Y12 gene are associated with a congenital bleeding disorder and abnormality in the platelet response to ADP, resembling that induced by thienopyridines.[212] Permanent modification of a platelet ADP receptor by thienopyridines is consistent with time-dependent cumulative inhibition of ADP-induced platelet aggregation on repeated daily dosing with ticlopidine or clopidogrel and with slow recovery of platelet function after drug withdrawal.[206]

4.1 Ticlopidine

Up to 90% of a single oral dose of ticlopidine is rapidly absorbed in humans.[206] Peak plasma concentrations occur 1 to 3 h after a single oral dose of 250 mg. Plasma levels of ticlopidine increase by approximately threefold on repeated twice-daily dosing over 2 to 3 weeks because of drug accumulation. Greater than 98% of ticlopidine is reversibly bound to plasma proteins, primarily albumin. Ticlopidine is metabolized rapidly and extensively. A total of 13 metabolites have been identified in humans. Of these, only the 2-keto derivative of ticlopidine is more potent than the parent compound in inhibiting ADP-induced platelet aggregation.[206]

The apparent elimination half-life of ticlopidine is 24 to 36 h after a single oral dose and up to 96 h after 14 days of repeated dosing.[206] The standard regimen of ticlopidine is 250 mg bid, although it is unclear how a twice-daily regimen is related to the pharmacokinetic and pharmacodynamic features noted above. A delayed antithrombotic effect was noted in at least one clinical trial of ticlopidine in patients with unstable angina with no apparent protection during the first 2 weeks of drug administration.[213] Therefore, ticlopidine is not useful when a rapid antiplatelet effect is required.

Ticlopidine as a single agent has been evaluated in patients with stroke,[214] transient cerebral ischemia,[215] unstable angina,[213] MI,[216] intermittent claudication,[217–219] and aortocoronary bypass surgery.[220] Ticlopidine was significantly (but marginally in absolute terms) more effective than aspirin in reducing stroke in patients with transient cerebral ischemia or minor stroke[215] (although there was no statistically significant difference in the combined outcome of stroke, MI, or death)[7]; was as effective as aspirin in the treatment of patients with a recent MI[216]; was more effective than placebo in reducing the risk of the combined outcome of stroke, MI, or vascular death in patients with thromboembolic stroke[214]; was more effective than conventional antianginal therapy in reducing vascular death or MI in patients with unstable angina[213]; was more effective than placebo in reducing acute occlusion of coronary bypass grafts[220]; and was more effective than controls in improving walking distance[218] and reducing vascular complications in patients with peripheral vascular disease.[217–219] The association of ticlopidine therapy with hypercholesterolemia and neutropenia (for which the reported rate of occurrence is 2.4% for neutrophils $< 1.2 \times 10^9$/L and 0.8% for neutrophils

$< 0.45 \times 10^9$/L) and its comparative expense have reduced enthusiasm for this therapy as an alternative to aspirin in most situations.[221] Ticlopidine also has been associated with thrombocytopenia,[221] aplastic anemia,[222] and thrombotic thrombocytopenic purpura (TTP).[223] Ticlopidine has been approved for clinical use in patients with cerebral ischemia when aspirin has failed, cannot be tolerated, or is contraindicated, although this limitation does not apply to all countries where the drug is registered.

Additive effects of ticlopidine and aspirin have been described in rats, in inhibition of ADP-induced platelet aggregation *ex vivo*, tail bleeding time prolongation, and protection from thrombosis in experimental models of platelet-dependent vascular occlusion.[224] Additive antiplatelet effects of aspirin (40 mg) and ticlopidine (250 mg) have been reported in healthy volunteers.[225] Two studies[226,227] have demonstrated the superiority of ticlopidine with aspirin compared to aspirin alone or aspirin plus warfarin in preventing thrombotic complications after coronary artery stent placement. Ticlopidine has been routinely used in combination with aspirin in patients receiving coronary artery stents, but the better safety profile of clopidogrel has resulted in the replacement of clopidogrel for ticlopidine as the standard antiplatelet regimen after stent deployment.[228] The risk of TTP associated with ticlopidine use has been estimated as 0.02% in patients receiving the drug after stent placement.[229] This risk compares with an incidence of 0.0004% in the general population. The mortality rate for this rare complication exceeds 20%.[229] The place of ticlopidine in the current therapeutic armamentarium is uncertain: (1) the drug is not uniformly cheaper than clopidogrel in different countries; (2) in contrast to clopidogrel, ticlopidine has no approved indication for the long-term management of post-MI patients; (3) ticlopidine has a higher bone-marrow toxicity than clopidogrel; and (4) because of safety concerns, an adequate loading dose of ticlopidine, as required in the acute setting, is unlikely to be used.

4.2 Clopidogrel

The pharmacokinetics of clopidogrel are somewhat different from those of ticlopidine. Thus, after administration of single oral doses (up to 200 mg) or repeated doses (up to 100 mg/d), unchanged clopidogrel was not detectable in peripheral venous plasma.[230] Concentrations of 1 to 2 ng/mL were measured in the plasma of patients who received 150 mg/d of clopidogrel (twice as much as the dose used in the Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events [CAPRIE] study[231] and approved for clinical use) for 16 days. The main systemic metabolite of clopidogrel is the carboxylic acid derivative, SR 26334. Based on measurements of circulating levels of SR 26334, it has been inferred that clopidogrel is rapidly absorbed and extensively metabolized.[230] The plasma elimination half-life of SR 26334 is approximately 8 h. As noted above, clopidogrel, inactive *in vitro*, is metabolically transformed by the liver into a short-lived active platelet inhibitor. However, the interindividual variability in this metabolic activation is still being assessed, and to our knowledge, there are no published data on whether liver impairment decreases the ability of clopidogrel to inhibit platelet function. A pharmacokinetic/pharmacodynamic study[232] of a 600-mg loading dose of clopidogrel in healthy subjects revealed linear correlations between the maximal antiplatelet effect and peak plasma concentrations of unchanged clopidogrel, of the carboxyl metabolite, and of the thiol metabolite as well as linear correlations between peak plasma concentration values of clopidogrel and its metabolites. These results have been interpreted to suggest that the pharmacodynamic response variability is predominantly caused by individual differences in clopidogrel absorption.[232] Because the cytochrome P450 isozymes CYP3A4 and 3A5 metabolize clopidogrel faster than other human P450 isozymes and are the most abundant P450s in human liver, they are predicted to be predominantly responsible for the activation of clopidogrel *in vivo*.[233] When clopidogrel and atorvastatin, a CYP3A4 substrate, are present at equimolar concentrations *in vitro*, clopidogrel metabolism is inhibited by $> 90\%$.[233] Variable metabolic activity of CYP3A4 may contribute to the interindividual variability in the platelet inhibitory effect of clopidogrel.[234] Thus, Angiolillo et al[235] recently characterized the influence of CYP3A4 genotype on interpatient variability in clopidogrel responsiveness. An intronic single nucleotide polymorphism in the CYP3A4 gene, IVS10 + 12G > A (also called CYP3A4*1G) modified platelet reactivity *ex vivo* as measured by GP-IIb/IIIa receptor activation in response to clopidogrel in a group of patients with stable CHD receiving long-term antiplatelet therapy. The findings were replicated in a group of clopidogrel-naïve patients undergoing elective percutaneous coronary intervention (PCI) treated with a 300-mg loading dose of the drug.[235]

Clopidogrel inhibited ADP-induced platelet aggregation in a dose-dependent fashion with an apparent ceiling effect (40% inhibition) at 400 mg after single oral doses in healthy volunteers. Inhibition of platelet aggregation was detectable 2 h after oral dosing of 400 mg and remained relatively stable up to 48 h.[230] On repeated daily dosing of 50 to 100 mg of clopidogrel to healthy volunteers, ADP-induced platelet aggregation was inhibited from the second day of treatment (25 to 30% inhibition) and reached

a steady state (50 to 60% inhibition) after 4 to 7 days. Such level of maximal inhibition was comparable to that achieved with ticlopidine, 500 mg/d, although the latter showed a slower onset of the antiplatelet effect than the clopidogrel. No appreciable differences in the maximum inhibitory effects of 50, 75, and 100 mg of clopidogrel were noted in this study.[230] As would be expected from these pharmacokinetic and pharmacodynamic features, a loading dose (*eg*, 300 mg) of clopidogrel results in a much more rapid onset of platelet inhibition than is achieved with the 75-mg dose.[236]

Several recent studies have examined the adequacy of a 300-mg loading dose of clopidogrel in patients scheduled for cardiac catheterization as potential candidates for PCI.[237–240] After loading with 600 mg of clopidogrel, the full antiplatelet effect of the drug was achieved after 2 h.[237] Moreover, a loading dose of 600 mg resulted in higher plasma concentrations of the active metabolite, clopidogrel, and the carboxyl metabolite than did a loading dose of 300 mg.[238] ADP-induced platelet aggregation also was significantly lower in patients receiving 600 mg than in those receiving 300 mg.[238–240] The incremental antiplatelet effect of 900 mg over 600 mg of clopidogrel appears marginal,[238,239] possibly because of limited drug absorption.[238]

Clopidogrel treatment exhibited marked interindividual variability in inhibiting platelet function in three different studies[241–243] of patients undergoing elective PCI and stenting. A variable proportion of these patients were considered to be clopidogrel nonresponders or to have clopidogrel resistance based on ADP-induced platelet aggregation. Three separate studies[241,244,245] suggested that concurrent treatment with lipophilic statins that are substrates of CYP3A4 (*eg*, atorvastatin and simvastatin) may interfere with the inhibitory effects of clopidogrel on platelet function. In the study of Lau et al,[244] atorvastatin, but not pravastatin, attenuated the antiplatelet effect of clopidogrel in a dose-dependent manner. Because many drugs are metabolized by CYP3A4,[246] it is likely that other drugs may modify the systemic bioavailability of the active metabolite of clopidogrel and affect its clinical efficacy. Moreover, variable metabolic activity of CYP3A4 may contribute to the interindividual variability in the platelet inhibitory effects of clopidogrel, as noted above. Although *ex vivo* measurements of ADP-induced platelet aggregation have suggested a pharmacokinetic interaction between a CYP3A4-metabolized statin and clopidogrel, *post hoc* analyses of placebo-controlled studies [247,248] of clopidogrel, a single center cohort study,[249] and data from a large multinational registry[250] have failed to detect a statistically significant clinical interaction between the two. However, it should be emphasized that retrospective *post hoc* analyses have limitations that preclude definitive conclusions. Moreover, the lack of information on statin daily doses used in trials notably restricts our ability to assess the dose dependence of potential drug interactions.

As with aspirin, both the mechanism(s) and the clinical relevance of clopidogrel resistance or nonresponsiveness[251] remain to be established. Thus, no test of platelet function can currently be recommended to assess the effects of clopidogrel in the individual patient, as there is no uniformly established method for quantification of *ex vivo* platelet reactivity after clopidogrel treatment and to what extent platelet activity is inhibited by the drug.[251]

Thus, the active metabolite of clopidogrel has a pharmacodynamic pattern quite similar to that of aspirin in causing cumulative inhibition of platelet function on repeated daily administration of low doses. As in the case of aspirin, platelet function returns to normal 7 days after the last dose of clopidogrel. Both the cumulative nature of the inhibitory effects and the slow rate of recovery of platelet function are consistent with the active moieties of aspirin (acetylsalicylic acid) and clopidogrel (active metabolite), causing a permanent defect in a platelet protein that cannot be repaired during the 24-h dosing interval and can only be replaced as a function of platelet turnover. This consideration also justifies the once-daily regimen of both drugs, despite their short half-life in the human circulation. It should be noted, however, that although aspirin currently is used at doses that represent a 2.5- to 10-fold excess over the dose of 30 mg necessary and sufficient to fully inactivate platelet COX-1 activity on repeated daily dosing,[25,62] clopidogrel is used at doses causing only partial inactivation of P2Y12. Thus, the main determinants of the interindividual variability in the antiplatelet effects of the two drugs are substantially different (Table 6).

Bleeding time measurements performed in the same multiple dose study[230] described above showed a comparable prolongation (by 1.5- to 2.0-fold over control) at 50 to 100 mg/d of clopidogrel or 500 mg/d ticlopidine.

Clopidogrel has undergone a quite unusual clinical development, with very limited phase II studies and a single, very large phase III trial (*ie*, CAPRIE, to test its efficacy and safety at 75 mg/d vs aspirin at 325 mg/d).[231] CAPRIE is unique among the studies that have directly compared antiplatelet agents against aspirin in that it incorporated three groups of patients, all of whom are recognized to be at an increased risk of recurrent ischemic events: those who have experienced a recent stroke or recent MI

Table 6—*Main Determinants of the Interindividual Variability in the Antiplatelet Effects of Aspirin and Clopidogrel (Section 4.2)*

Determinant	Aspirin	Clopidogrel
Dependence on systemic bioavailability	No	Yes
Dependence on liver metabolism to active moiety	No	Yes
Recommended dose: minimum effective dose for full pharmacodynamic effect	2–3	1
Relevance of pharmacodynamic interactions at the target site	Yes	?
Relevance of extraplatelet sources of the platelet agonist	Yes	No

and those presenting with symptomatic peripheral arterial disease. Overall, CAPRIE showed a modest difference in effectiveness between aspirin and clopidogrel that did not result in regulatory approval of a superiority claim. What is particularly interesting, however, are the results obtained when the effects of aspirin and clopidogrel in the three groups are compared. Each comparison between clopidogrel and aspirin involved approximately 6,400 patients and, therefore, represents the largest head-to-head comparison between aspirin and another antiplatelet agent in that particular clinical setting, although the statistical power of such comparison is inadequate to detect a modest difference between the two. This analysis shows that the majority of the difference in effectiveness occurred in the patients who entered the trial because of symptomatic peripheral arterial disease. A formal test of heterogeneity of these three treatment effects was statistically significant ($p = 0.042$), suggesting that the true benefit of clopidogrel may not be identical across the three clinical settings.

Both clopidogrel and medium-dose aspirin therapy were well tolerated in the CAPRIE study.[231] The incidence of early permanent discontinuation of the study drug due to adverse events was practically identical in the two treatment groups (12%). Similarly, the overall incidence of hemorrhagic events was identical in the aspirin and clopidogrel groups (9.3%). The frequency of severe rash and severe diarrhea was higher with clopidogrel than with aspirin, whereas GI discomfort and hemorrhage were more frequent with aspirin than with clopidogrel. No excess neutropenia was found in the clopidogrel group, and thrombocytopenia was identical in the clopidogrel and aspirin groups. Based on these findings, clopidogrel has been approved for the reduction of atherosclerotic events in patients with recent stroke, recent MI, or established peripheral arterial disease. TTP can occur within the first 2 weeks after the initiation of clopidogrel therapy.[252]

The complementary mechanisms of action of clopidogrel and low-dose aspirin has led to testing the efficacy and safety of their combination in high-risk clinical settings.[253] The CURE trial[253] randomly assigned 12,562 patients with acute coronary syndromes without ST-segment elevation who presented within 24 h after the onset of symptoms to receive clopidogrel (300-mg loading dose followed by 75 mg qd) or placebo in addition to aspirin (75 to 325 mg/d) for 3 to 12 months. After a mean duration of treatment of 9 months, the primary outcome (a composite of cardiovascular death, nonfatal MI, or stroke) occurred in 9.3% of the patients in the clopidogrel group and 11.4% of the patients in the placebo group (RR, 0.80; 95% CI, 0.72 to 0.90; $p < 0.001$). The benefit of clopidogrel was apparent within the first 30 days after randomization and remained constant during the 12 months of the study. There were significantly more patients with major bleeding in the clopidogrel group than in the placebo group (3.7% vs 2.7%; $p = 0.001$).

The clinical benefit of dual antiplatelet therapy vs aspirin alone has been confirmed in patients undergoing PCI,[254] and in those presenting with an acute MI with ST-segment elevation within 12 h[256] to 24 h[257] after the onset of symptoms. In the Clopidogrel and Metoprolol Myocardial Infarction Trial[257] (COMMIT), addition of 75 mg/d of clopidogrel to 162 mg/d of aspirin reduced mortality and major vascular events in the hospital by 9% (95% CI, 3 to 14%), corresponding to nine fewer events per 1,000 MI patients treated for about 2 weeks. Overall, when all transfused, fatal, or cerebral bleeds were considered together, there was no significant excess risk associated with the use of clopidogrel during the scheduled treatment period (0.58% clopidogrel plus aspirin vs 0.55% aspirin alone; $p = 0.59$), nor was there any excess of major bleeds in patients > 70 years of age or in those given fibrinolytic therapy before randomization.[257] Clopidogrel was, however, associated with a small, but significant, excess of 4.7 (95% CI, 1.4 to 8.0) reported minor bleeds per 1,000 patients treated. Taking major and minor bleeds together, there was no apparent trend with respect to age in the excess risk.[257] Factors that may have contributed to the remarkable safety of dual antiplatelet therapy in the COMMIT trial include the lack of a loading dose of clopidogrel, the uniform use of 162 mg of aspirin, and the short duration of treatment.

In contrast to the consistent finding of a favorable benefit/risk profile of dual antiplatelet therapy in patients with acute coronary syndromes,[253,256,257] the same strategy was not proven successful when compared to clopidogrel alone in patients after a recent ischemic stroke or TIA,[255] when compared to aspirin

alone in patients at high risk for atherothrombotic events,[258] or when compared to oral anticoagulation in patients with atrial fibrillation.[259] Although there might be mechanistic reasons underlying this apparent heterogeneity in treatment effects, it is important to emphasize that the size of the additional benefit associated with dual antiplatelet therapy vs aspirin alone in patients with acute coronary syndromes is only a fraction (about one third) of the benefit associated with aspirin vs no antiplatelet therapy. Perhaps more importantly, both CURE[253] and COMMIT[257] investigators tested realistic hypotheses of relative risk reduction (17% and 10%, respectively) and actually observed reductions (20% and 9%, respectively) that were consistent with these conservative expectations. In contrast, both the Management of Atherothrombosis with Clopidogrel in High-Risk Patients (MATCH)[255] and the Clopidogrel and High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA)[258] investigators tested overoptimistic hypotheses of risk reduction and actually observed only a fraction (approximately one half to one third) of the expected benefit. As expected, major bleeding was increased by dual antiplatelet therapy in both MATCH[255] and CHARISMA.[258]

5.0 Integrin αIIbβ3 (GP-IIb/IIIa) Receptor Antagonists

Given the redundancy of discrete pathways leading to platelet aggregation, it is not surprising that the clinical efficacy of aspirin, ticlopidine, and clopidogrel is only partial. These drugs, while inhibiting TXA_2- or ADP-mediated platelet aggregation, leave the activity of other platelet agonists, such as thrombin, largely unaffected. Following recognition that the expression of functionally active integrin αIIbβ3 (GP-IIb/IIIa) on the platelet surface is the final common pathway of platelet aggregation, regardless of the initiating stimulus, this GP became the target of novel antiplatelet drugs.[260–263] The inhibitors of GP-IIb/IIIa include monoclonal antibodies against the receptor, naturally occurring Arg-Gly-Asp sequence (RGD) containing peptides isolated from snake venoms, synthetic RGD- or Lys-Gly-Asp sequence (KGD) containing peptides, and peptidomimetic and nonpeptide RGD mimetics that compete with fibrinogen, von Willebrand factor, and/or perhaps other ligands for occupancy of the platelet receptor.[264–266]

5.1 Abciximab

Blockade of GP-IIb/IIIa receptors by murine monoclonal antibodies such as 7E3 essentially induces a functional thrombasthenic phenotype.[267] Approximately 40,000 antibody molecules bind to the surface of platelets, but because they probably bind bivalently there are probably 80,000 GP-IIb/IIIa receptors per platelet.[260] Platelet aggregation is significantly inhibited at antibody doses that decrease the number of available receptors to < 50% of normal. Platelet aggregation is nearly completely abolished at approximately 80% receptor blockade, but the bleeding time is only mildly affected at this level of receptor blockade. It is only with > 90% receptor blockade that the bleeding time becomes extremely prolonged.[260] Because of concerns about immunogenicity of the original 7E3 antibody, a mouse/human chimeric 7E3 Fab (abciximab) was created for clinical development.

Pharmacokinetic data on abciximab indicate that following IV bolus administration, free plasma concentrations decrease rapidly (initial half-life of about 30 min) as a result of rapid binding to platelet GP-IIb/IIIa receptors, with approximately 65% of the injected antibody becoming attached to platelets in the circulation and spleen.[268] After bolus injection of abciximab, a dose-dependent inhibition of ADP-induced platelet aggregation was recorded in patients judged to be at moderate to high risk of percutaneous transluminal coronary angioplasty (PTCA)-associated ischemic complications.[268] A bolus dose of 0.25 mg/kg was found to result in blockade of > 80% of platelet receptors and reduce platelet aggregation in response to 20 μmol/L ADP to < 20% of baseline. A steep dose-response curve was apparent in this study.[268] Peak effects on receptor blockade, platelet aggregation, and bleeding time were observed at the first sampling time of 2 h after bolus administration of 0.25 mg/kg. Gradual recovery of platelet function then occurred over time, with bleeding times returning to near normal values by 12 h.[268] Platelet aggregation in response to 20 μmol/L ADP returns to ≥ 50% of baseline within 24 h in most patients, and within 48 h in nearly all patients. Small amounts of abciximab can be detected on circulating platelets as late as 14 days after administration, presumably as a result of antibody redistribution from platelet to platelet.[269]

The receptor blockade, inhibition of platelet aggregation, and prolongation of bleeding time produced by administering a 0.25 mg/kg bolus dose of abciximab could be maintained for 12 h by administering a 10 μg/min infusion during that time period.[268] This regimen was chosen for the phase III trial (Evaluation of 7E3 for the Prevention of Ischemic Complications [EPIC])[270] that demonstrated the clinical efficacy of abciximab, added to conventional antithrombotic therapy, in reducing the incidence of ischemic events in patients undergoing

PTCA (discussed in the "Antithrombotic Therapy for Non-ST-Segment Elevation Acute Coronary Syndromes" chapter). Subsequently, the 10-μg/min infusion was modified to 0.125 μg/kg/min (to a maximum of 10 μg/min) to adjust for differences in body weight.

Reteplase and/or ticlopidine do not affect the pharmacodynamics of abciximab.[271] Pretreating platelets with tirofiban or eptifibatide does not alter the subsequent binding of abciximab to platelets.[272] It is unclear, however, whether abciximab can bind simultaneously with either tirofiban or eptifibatide to a single GP-IIb/IIIa receptor, and indirect studies using monoclonal antibodies[273] raise the possibility that abciximab binding may decrease the binding of the other drugs.[274]

Major bleeding was significantly increased in abciximab-treated patients in EPIC.[270] Subsequently, however, it was found that a reduction in the dosage of concomitant heparin and more rapid sheath removal could greatly reduce the bleeding complications attendant to abciximab administration.[275] Besides hemorrhage, thrombocytopenia represents an important side effect of abciximab treatment. Approximately 1 to 2% of patients treated with abciximab have platelet counts < 50,000/μL, of which approximately 0.5 to 1% reflect very rapid (beginning within 2 h of administration) and severe (< 20,000/μL) decreases. The abciximab package insert specifies that a platelet count should be obtained 2 to 4 h after initiating therapy, thus permitting the rapid identification of patients with thrombocytopenia developing. In almost all cases, the thrombocytopenia can be treated effectively by stopping the drug and, if necessary, administering platelet transfusions, with recovery occurring over several days.[270,275,278] Binding of patient antibody to abciximab-treated platelets has been reported in patients with abciximab-associated thrombocytopenia, but the nature of the binding is unclear.[279] Delayed thrombocytopenia has been ascribed to abciximab therapy, but its prevalence is unknown. In the EPIC trial,[270] approximately 6% of patients treated with abciximab developed antibodies to the variable region(s) of abciximab (human antichimeric antibody). Few data are currently available to assess the potential risks of reinjecting abciximab,[280–282] which theoretically include anaphylaxis, neutralization of injected abciximab, and thrombocytopenia. It appears, however, that the risk of thrombocytopenia is greater with abciximab readministration,[282,283] especially if the drug is readministered relatively soon after the initial administration, and that the mechanism involves antibody binding to abciximab-coated platelets.[279] In patients with chronic renal insufficiency, abciximab produced only a modest increase in the OR for major bleeding (1.18; p = 0.06) and essentially no increase in the OR for minor bleeding (1.01; p = 0.94).[284]

Although the antiplatelet effect of abciximab in preventing vascular occlusion by suppressing platelet aggregation is likely to be the major mechanism for its beneficial effects, it is quite possible that the potent inhibition of thrombus formation by this antibody may result in decreased thrombin formation.[285] In fact, abciximab produced dose-dependent inhibition of tissue factor-induced thrombin generation, reaching a plateau of 45 to 50% inhibition at concentrations ≥ 15 μg/mL.[285] Whether the inhibition of thrombin generation by abciximab contributes to its immediate antithrombotic effect remains to be established. Abciximab is unique among the GP-IIb/IIIa antagonists in also blocking the $\alpha_v\beta_3$ receptor at therapeutic doses[260] and binding to an activated form of the leukocyte $\alpha_M\beta_2$ receptor[261,262]; it is unclear whether any of the effects of abciximab are due to inhibition of these receptors.

5.2 Tirofiban

Tirofiban (MK-383; Aggrastat) is a nonpeptide derivative of tyrosine that selectively inhibits the GP-IIb/IIIa receptor, with minimal effects on the $\alpha_v\beta_3$ vitronectin receptor.[286,287] It inhibits platelet aggregation of gel-filtered platelets induced by 10 μmol/L ADP with an inhibitory concentration (IC_{50}) of 9 nM, but the IC_{50} for inhibition of human umbilical vein adhesion to vitronectin, which depends on $\alpha_v\beta_3$ vitronectin receptors, is 62 μmol/L.[260] Both renal and biliary excretion contribute to tirofiban clearance, with unchanged tirofiban found in urine and feces.[288]

When administered to humans at 0.15 μg/kg/min for 4 h, tirofiban produced a 2.5-fold increase in bleeding time and 97% inhibition of ADP-induced platelet aggregation.[289,290] The mean plasma clearance was 329 mL/min, and the half-life in plasma was 1.6 h. After stopping tirofiban therapy, bleeding times returned to normal within 4 h, and inhibition of platelet aggregation declined to approximately 20%. When administered with aspirin, the bleeding time increased 4.1 ± 1.5-fold, even though tirofiban plasma levels were unaffected. The plasma concentration of tirofiban needed to inhibit platelet aggregation by 50% decreased, however, from approximately 12 ng/mL to approximately 9 ng/mL when aspirin was coadministered. Peak plasma concentrations were approximately 40 ng/mL, and the plasma levels decreased to < 3 ng/mL within 6 h after therapy was discontinued.

In a pilot study, 73 patients undergoing PTCA were treated with aspirin, heparin, and bolus doses

of tirofiban of 5, 10, or 15 μg/kg followed by tirofiban infusions of 0.05, 0.10, and 0.15 μg/kg/min, respectively.[291] The onset of platelet inhibition was rapid, with platelet aggregation in response to 5 μmol/L ADP inhibited by 93% and 96%, respectively, within 5 min of administering the two higher-dose regimens. Bleeding times at 2 h after starting the infusion were 19.5 min, > 30 min, and > 30 min, respectively. At the end of the infusion (16 to 24 h), platelet aggregation was inhibited by 57%, 87%, and 95%, respectively, in response to the escalating tirofiban regimens. Platelet aggregation began to return toward normal within 1.5 h after discontinuing the infusion in all groups; 4 h after discontinuing therapy, platelet aggregation inhibition decreased to < 50%, even in the group receiving the highest dose.

In patients with renal insufficiency (creatinine clearance < 30 mL/min), plasma clearance of tirofiban was reduced, and plasma half-life increased by more than threefold.[292] The manufacturer recommends reducing both the bolus and infusion doses by 50%, but the pharmacokinetic basis for this recommendation has been challenged.[292] In the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms trial,[293] the 40 patients with creatinine clearance < 30 mL/min were found to have increased risk of bleeding, and tirofiban treatment further increased the risk.

Severe, but reversible thrombocytopenia has been reported[278,294] in a small percentage of patients treated with tirofiban; an immunologic mechanism has been proposed, mediated by preformed antibodies to a conformation of the GP-IIb/IIIa receptor induced by the binding of tirofiban to the receptor. To our knowledge, no data are available on the safety of reinfusing tirofiban, but high-titer antibodies have been identified in patients with thrombocytopenia after repeat administration.[295]

5.3 Eptifibatide

Eptifibatide (Integrilin; Millenium Pharmaceuticals, Schering Corporation; Kenilworth, NJ) is a synthetic disulfide-linked cyclic heptapeptide. It is patterned after the KGD sequence found in the snake venom disintegrin obtained from *Sistrurus miliarius barbouri* (barbourin) and has high, but not absolute, specificity for inhibition of GP-IIb/IIIa compared with inhibition of the $\alpha_v\beta_3$ vitronectin receptor.[296,297] Preliminary reports suggested that eptifibatide produced less prolongation of the bleeding time than other GP-IIb/IIIa inhibitors at doses producing comparable inhibition of platelet aggregation. Later studies found that the citrate anticoagulation used for platelet aggregation studies resulted

in an overestimation of inhibition of platelet aggregation by eptifibatide[298]; thus, it is unclear whether there is a differential effect of eptifibatide on the bleeding time.

A study[299] of ^{14}C-eptifibatide administered as a single 135 μg/kg IV bolus revealed peak plasma concentrations of 879 ± 251 ng/mL (mean ± SD) at 5 min, a distribution half-life of 5 ± 2.5 min, and a terminal elimination half-life of 1.1 ± 0.17 h. Of the approximately 73% of administered radioactivity recovered in 72 h, renal clearance accounted for 98% of total recovered radioactivity and approximately 40% of total body clearance. Unmodified eptifibatide, deamidated eptifibatide, and more polar metabolites were all found in the urine, but only trace amounts of radioactivity were found in the breath and feces.

Because renal clearance is an important component of eptifibatide catabolism, patients with renal impairment can have prolonged inhibition of platelet function after receiving eptifibatide. This is of particular theoretical concern because patients with end-stage renal failure have platelet dysfunction. The proper dose of eptifibatide in patients with modest-to-moderate renal insufficiency (creatinine, 2 to 4 mg/dL) is uncertain.[292] In the ESPRIT,[300] patients with creatinine clearances ≤ 60 mL/min had increased major and minor bleeding rates compared to those with creatinine clearances > 60 mL/min, and eptifibatide treatment increased both major and minor bleeding in both groups of patients.

Because the steady-state level of eptifibatide is approximately 1,900 ng/mL when using an infusion rate of 2 μg/kg/min,[301] the ratio of eptifibatide molecules to GP-IIb/IIIa molecules is > 50:1[302]; thus, platelet transfusions may not be able to reverse the effects of the drug, although *in vitro* data raise some hope in this regard.[303] Treatment with eptifibatide prolongs the activated clotting time of heparinized patients, suggesting an inhibitory effect on thrombin generation.[304,305]

In 21 patients undergoing elective PTCA or directional coronary atherectomy who were treated with aspirin, heparin (10,000 U bolus + additional doses to maintain an activated clotting time at 300 to 350 s), and a bolus dose of 90 μg/kg of eptifibatide followed by a 1-μg/kg/min infusion for 4 or 12 h, platelet aggregation was measured before, 1 h after the bolus, at the end of the infusion, and 4 h after the end of the infusion.[304] The extent of platelet aggregation in response to 20 μmol/L ADP decreased from approximately 80% before eptifibatide to approximately 15% both at 1 h after the bolus dose and at the end of the infusion. There was, however, significant interindividual variation in the inhibitory responses (95% CI, 0% to approximately 30%, and

0% to approximately 40%, respectively) at the two time points tested. Four hours after stopping the infusion, the average aggregation response was approximately 55%, but there was marked individual variation (95% CI, approximately 10% to 90%). Median bleeding times were prolonged with eptifibatide therapy, going from approximately 6 min before treatment to approximately 26 min both at 1 h after beginning the infusion and at the end of the infusion. The bleeding times returned to normal (median, 15 min) within 15 min after stopping eptifibatide therapy and declined to approximately 12 min after stopping the drug therapy for 1 h. At each time point, however, there were considerable interindividual differences.[304]

In a later study,[306] four eptifibatide regimens were tested in 54 patients undergoing coronary interventions who also were treated with aspirin and heparin: (1) 180 μg/kg bolus + 1 μg/kg/min infusion for 18 to 24 h (n = 4); (2) 135 μg/kg bolus + 0.5 μg/kg/min infusion for 18 to 24 h (n = 16); (3) 90 μg/kg bolus + 0.75 μg/kg/min infusion for 18 to 24 h (n = 6); and (4) 135 μg/kg bolus + 0.75 μg/kg/min for 18 to 24 h (n = 28). Fifteen minutes after the 180 μg/kg bolus dose, platelet aggregation was inhibited by > 95% in response to 20 μmol/L ADP, with virtually no interindividual variation, whereas the 135-μg/kg bolus dose resulted in 80 to 90% inhibition in 75% of the patients, and the 90 μg/kg bolus produced only slightly less inhibition than the 135 μg/kg dose. The inhibition of platelet aggregation achieved with the 180 μg/kg bolus dose was sustained throughout the infusion by the 1 μg/kg/min dose, but there was a tendency for the platelet aggregation response to return toward normal during the infusion in some patients given the 0.75 μg/kg/min dose, and the return of the platelet aggregation response toward normal was more marked in those given the 0.5 μg/kg/min infusion dose. Two hours after discontinuing the eptifibatide infusion, there was substantial return of platelet function in all groups and return of more than half of the baseline aggregation response in all groups after 4 h. Median bleeding times were prolonged in all groups at the time the infusion was terminated (22, 12, 12, and 17 min, respectively, compared with control values of 7 to 8 min), and they returned toward normal after 1 h (9, 10, 9, and 11 min, respectively). As in the previous study, activated clotting times were longer in patients treated with eptifibatide plus heparin than in those treated with placebo plus heparin. After the effect of citrate was discovered, the dose of eptifibatide was increased, and platelet studies were conducted on blood anticoagulated with the direct thrombin inhibitor D-Phe-Pro-Arg chloromethyl ketone, which does not chelate calcium.[301] Combina-

tions of different single bolus doses (μg/kg) followed by different infusion doses (μg/kg/min) [135/0.75, 180/2.0, 250/3.0] were evaluated in patients with acute coronary syndromes[307] and during PCI.[301,304,306] High-level inhibition of ADP-induced aggregation could be achieved soon after the bolus dose, but there was an early loss of inhibition of platelet aggregation before steady-state was achieved. Regimens using a second bolus dose 30 min after the first were then studied (180/2.0 plus second bolus of 90; 250/2.0 plus second bolus of 125)[301] From these studies, the dose used in the ESPRIT[300] (bolus dose of 180 μg/kg/min, second bolus dose of 180 μg/kg at 10 min followed by 2 μg/kg/min infusion) was selected.[301]

A modest increase in hemorrhagic complications has been reported in patients treated with eptifibatide in the PURSUIT trial[308] and the ESPRIT.[300,309,310] Eptifibatide treatment has been associated with a small increase in profound thrombocytopenia.[308,311] An immunologic mechanism has been identified in some patients.[295] Thus, patients receiving eptifibatide should be monitored soon after initiation of therapy for development of thrombocytopenia. An algorithm for the detection and management of thrombocytopenia after GP-IIb/IIIa blockade has been proposed.[278] To our knowledge, no data are available about the safety of reinfusing eptifibatide, but high levels of antibody that bind to platelets in the presence of eptifibatide have been found in patients who have thrombocytopenia after reexposure to eptifibatide.[295]

5.4 Efficacy and Safety of IV GP-IIb/IIIa Antagonists

The efficacy and safety of GP-IIb/IIIa antagonists have been evaluated initially in patients undergoing PCI. More than 20,000 patients have been enrolled in nine studies of abciximab, eptifibatide, and tirofiban. The first of these phase III trials, the EPIC trial,[270] resulted in approval in many countries of abciximab (ReoPro; Eli Lilly Company and Centocor; Indianapolis, IN) in 1994 for PCI patients at high risk for ischemic complication. Eptifibatide has been studied in the IMPACT-II[305] and ESPRIT trials,[309,310] and tirofiban has been studied in the RESTORE trial.[312] Although neither the IMPACT-II nor the RESTORE trials achieved their predefined efficacy end points, there was a positive trend in each case. Eptifibatide received approval from the FDA for PCI in 1998 based on data from the IMPACT-II and PURSUIT trials, and the dosing was modified based on the efficacy demonstrated in the ESPRIT.[309,310] The CAPTURE trial[313] demonstrated the efficacy of an 18- to 24-h abciximab treatment before PCI in

patients with unstable angina refractory to conventional antithrombotic and antianginal therapy. The EPILOG trial[275] demonstrated the efficacy of abciximab in a broad patient population undergoing PCI, not just high-risk patients as enrolled in the EPIC and CAPTURE trials. The EPISTENT trial demonstrated that abciximab decreases the frequency of ischemic complications of PCI associated with stent insertion during the first 30 days, and that there are fewer ischemic complications during this period in patients treated with PCI and abciximab alone without stent insertion vs those treated with stent alone.[314] Furthermore, the 1-year mortality difference was statistically significant between stent alone (2.4%) and stent plus abciximab (1%), and this mortality difference was sustained for longer periods.[315] Both abciximab and stenting were studied in the CADILLAC trial[316] of patients with MI. In this group of patients, who appeared to be at relative low risk, abciximab had a beneficial effect in the PTCA group but did not affect death or reinfarction in the stent group.[316]

During the past 4 years, a series of randomized clinical trials conducted by the Intracoronary Stenting and Antithrombotic Regimen Group[317–320] have reexamined the efficacy and safety of GP-IIb/IIIa blockade in a broad range of patients undergoing PCI on dual oral antiplatelet therapy. Using a 600-mg clopidogrel loading dose given at least 2 h before PCI in all patients, the investigators evaluated the effects of adjunctive abciximab in low- to intermediate-risk patients,[317] in patients undergoing revascularization of small-diameter vessels,[318] in patients with diabetes mellitus,[319] and in patients with non–ST-segment elevation acute coronary syndromes.[320] In stable patients undergoing elective PCI, pretreatment with 600 mg of clopidogrel provides platelet inhibition sufficient to enable a safe procedure without the need of GP-IIb/IIIa blockade.[317–319] However, the same abciximab regimen was associated with a statistically significant 25% relative risk reduction in the 30-day combined end point of death, MI, or urgent target vessel revascularization in patients with acute coronary syndromes.[320] Although the additional benefit of GP-IIb/IIIa blockade appeared to be confined to patients with an elevated troponin level (> 0.03 μg/L), the p value for the interaction was not statistically significant.

Abciximab was compared to tirofiban as treatment for PCI in the TARGET study.[321,322] Abciximab treatment was found to be associated with a statistically significant lower rate of ischemic complications after 30 days; at 6 months, the differences were less apparent.

Five completed trials[308,323–326] have examined the efficacy and safety of tirofiban, lamifiban (a nonpeptide GP-IIb/IIIa blocker whose development has been discontinued), eptifibatide, and abciximab in approximately 25,000 patients with acute coronary syndromes without persistent ST-segment elevation randomized to receive a GP-IIb/IIIa antagonist or placebo in addition to conventional antithrombotic therapy. These studies demonstrated a 0 to 27% relative risk reduction in MI or death at 30 days. Both eptifibatide and tirofiban have received approval from the FDA for the treatment of acute coronary syndromes, including patients who are to be managed medically and those undergoing PCI. However, in the GUSTO IV-ACS trial,[326] abciximab for 24 h (0.25 mg/kg bolus followed by a 0.125 μg/kg/min infusion) or 48 h was not beneficial as first-line medical treatment in patients with acute coronary syndromes. A metaanalysis of all major randomized clinical trials of GP-IIb/IIIa antagonists in patients with acute coronary syndromes who were not routinely scheduled to undergo early coronary revascularization suggests a 9% reduction in the odds of death or MI at 30 days.[327] However, the true size of the additional benefit resulting from short-term, high-grade blockade of GP-IIb/IIIa combined with standard antithrombotic therapy is somewhat uncertain because the 95% CI ranged from 2 to 16%. Moreover, the 1% absolute difference in death or MI was balanced by an absolute excess of 1% in major bleeding complications associated with GP-IIb/IIIa antagonists vs control.[327]

Thus, the benefit/risk profile of currently available GP-IIb/IIIa antagonists is substantially uncertain for patients with acute coronary syndromes who are not routinely scheduled for early revascularization. In contrast, for high-risk patients undergoing PCI, intensification of antiplatelet therapy by adding an IV GP-IIb/IIIa blocker is an appropriate strategy to reduce the risk of procedure-related thrombotic complications.

Phase II trials in acute MI with abciximab, eptifibatide, and lamifiban have suggested potential benefits of GP-IIb/IIIa blockade as an adjunct to thrombolysis. The Thrombolysis in Myocardial Infarction 14A trial[328] demonstrated that combining abciximab with aspirin and reduced-dose tissue plasminogen activator in the treatment of acute MI resulted in improved TIMI 3 flow rates at 60 min and 90 min after starting therapy compared to the best full-dose tissue plasminogen activator regimen. The bleeding risk was not substantially increased.[328] The GUSTO V trial[329] compared the efficacy and safety of half-dose reteplase and full-dose abciximab vs standard-dose reteplase in 16,588 patients in the first 6 h of evolving ST-segment elevation MI. The primary end point of 30-day mortality was similar in the two

treatment groups (5.6% vs 5.9%). Combination therapy led to a consistent reduction in secondary complications of MI, including reinfarction, which was partly counterbalanced by increased extracranial bleeding.[329] There was no mortality benefit of combined therapy after 1 year, and thus there appears to be little or no net benefit in combined therapy.[330] Despite reassuring data from a phase II trial of abciximab in patients with acute ischemic stroke,[331] a phase III trial has been stopped because of safety concerns.

Conflict of Interest Disclosures

Dr. Patrono discloses that he has received grant monies from the University of Rome 'La Sapienza,' Catholic University School of Medicine, the Italian Ministry of Research and University, the European Commission, Bayer Italy, and MSD Italy. Dr. Patrono has received consultant fees from Servier and NicOx. He has served on the speakers bureau of AstraZeneca, Bayer AG, Eli Lilly, Sanofi-Aventis, and Schering-Plough.

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Antiplatelet Drugs[*]

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