Platelet-Active Drugs: The Relationships Among Dose, Effectiveness, and Side Effects

The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy

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This article discusses platelet active drugs as part of the Seventh American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines. New data on antiplatelet agents include the following: (1) the role of aspirin in primary prevention has been the subject of recommendations based on the assessment of cardiovascular risk; (2) an increasing number of reports suggest a substantial interindividual variability in the response to antiplatelet agents, and various phenomena of “resistance” to the antiplatelet effects of aspirin and clopidogrel; (3) the benefit/risk profile of currently available glycoprotein IIb/IIIa antagonists is substantially uncertain for patients with acute coronary syndromes who are not routinely scheduled for early revascularization; (4) there is an expanding role for the combination of aspirin and clopidogrel in the long-term management of high-risk patients; and (5) the cardiovascular effects of selective and noneffective cyclooxygenase-2 inhibitors have been the subject of increasing attention.

(CHEST 2004; 126:234S–264S)

Key words: aspirin; clopidogrel; efficacy; platelet-active drugs; side effects

Abbreviations: ACE = angiotensin-converting enzyme; ADP = adenosine diphosphate; AMP = adenosine monophosphate; CAPRIE = Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events; CI = confidence interval; COX = cyclooxygenase; CURE = Clopidogrel in Unstable Angina to Prevent Recurrent Events; EPIC = Evaluation of 7E3 for the Prevention of Ischemic Complications; ESPRIT = Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy; ESPFS = European Stroke Prevention Study; FDI = Food and Drug Administration; Gp = glycoprotein; HOT = Hypertension Optimal Treatment; IMPACT = Integrin to Manage Platelet Aggregation to Prevent Coronary Thrombosis; INR = international normalized ratio; MI = myocardial infarction; NSAID = nonsteroidal antiinflammatory drug; OR = odds ratio; PCI = percutaneous coronary intervention; PE = pulmonary embolism; PG = prostaglandin; PTCa = percutaneous transthoracic angioplasty; RESTORE = Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis; RGD = Arg-Gly-Asp sequence; RR = relative risk; TIA = transient ischemic attack; TTP = thrombotic thrombocytopenic purpura; TX = thromboxane

Since our last report on antithrombotic therapy in 2001,1 new information has been published on the role of aspirin and other platelet-active drugs in the treatment and prevention of atherothrombosis. These new data can be summarized as follows: (1) the role of aspirin in primary prevention has been the subject of a number of recommendations2–4 based on the assessment of cardiovascular risk; (2) an increasing number of reports suggest a substantial interindividual variability in the response to antiplatelet agents,5–6a and various phenomena of “resistance” to the antiplatelet effects of aspirin7–9 and clopidogrel10–10b; (3) the benefit/risk profile of currently available GPIIb/IIIa antagonists is substantially uncertain for patients with acute coronary syndromes who are not routinely scheduled for early revascularization11–13; (4) there is an expanding role for the combination of aspirin and clopidogrel in the long-term management of high-risk patients14,15; and (5) the cardiovascular effects of selective and noneffective cyclooxygenase (COX)-2 inhibitors have been the subject of increasing attention.16–18

1.0 Aspirin and Other COX Inhibitors

Aspirin has been thoroughly evaluated as an antiplatelet drug, and it has been found to prevent vascular death by approximately 15% and to prevent nonfatal vascular events by about 30% in a meta-analysis19 of > 100 randomized trials in high-risk patients.

1.1 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 (PG) H-synthese-1 and PGH-synthese-2 (also referred to as COX-1 and COX-2).20–24 These isozymes catalyze the first committed step in prostanoïd biosynthesis (ie, the conversion of arachidonic acid to PGH2). PGH2 is the immediate precursor of PGD2, PGE2, PGF2α, PGI2 and thromboxane (TX)-A2. COX-1 and COX-2 are homodimers of an approximately 72-kd monomeric unit. Each dimer has the following three independent folding units: an epidermal growth factor-like domain; a membrane-binding domain; and an enzymatic domain.24 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. There are a number of important differences between COX-1 and COX-2 (Table 1), some of which may contribute to variable inhibitor selectivity.

The molecular mechanism of permanent inactivation of COX activity by aspirin is related to blockade of the COX channel as a consequence of the acetylation of a strategically located serine residue (ie, Ser529 in the human COX-1 and Ser516 in the human COX-2), which prevents access of the substrate to the catalytic site of the enzyme.25 Because aspirin has a short half-life (15 to 20 min) in the human circulation and is approximately 50-fold to 100-fold more potent in inhibiting platelet COX-1 than monocyte
COX-2,26 it is ideally suited to act on anucleate platelets, inducing a permanent defect in TXA2-dependent platelet function. Moreover, since aspirin probably also inactivates COX-1 in relatively mature megakaryocytes, and since only 10% of the platelet pool is replenished each day, once-a-day dosing of aspirin is able to maintain virtually complete inhibition of platelet TXA2 production. In contrast, the inhibition of COX-2-dependent pathophysiologic processes (eg, hyperalgesia and inflammation) requires larger doses of aspirin (because of decreased sensitivity of COX-2 to aspirin) and a much shorter dosing interval (because nucleated cells rapidly resynthesize the enzyme). Thus, there is an approximately 100-fold variation in the daily doses of aspirin when used as an antiinflammatory rather than as an antiplatelet agent. Furthermore, the benefit/risk profiles of the drug depend on the dose and indication since its GI toxicity is dose-dependent (see below).

Human platelets and vascular endothelial cells process PGH2 to produce primarily TXA2 and prostacyclin (ie, PGI2), respectively.23 TXA2 induces platelet aggregation and vasoconstriction, while PGI2 inhibits platelet aggregation and induces vasodilation.23 Aspirin is antithrombotic in a wide range of doses.26–32 While TXA2 is largely a COX-1-derived product (mostly from platelets) and thus is highly sensitive to aspirin inhibition under physiologic conditions, vascular PGI2 can derive from both COX-1 (short-term changes in response to agonist stimulation [eg, bradykinin31], which is sensitive to transient aspirin inhibition) and to a greater extent, even under physiologic conditions, from COX-2 (long-term changes in response to laminar shear stress,35 which is largely insensitive to aspirin inhibition at conventional antiplatelet doses). This may account for the substantial residual COX-2-dependent PGI2 biosynthesis in vitro at daily doses of aspirin in the range of 30 to 100 mg, despite transient suppression of COX-1-dependent PGI2 release.33 It has not been established that more profound suppression of PGI2 formation by higher doses of aspirin is sufficient to initiate or predispose to thrombosis. However, mice lacking the PGI2 receptor had increased susceptibility to experimental thrombosis, thus supporting the importance of this prostanoid in thromboresistance.36

1.2 Pharmacokinetics

Aspirin is rapidly absorbed in the stomach and upper intestine. Peak plasma levels occur 30 to 40 min after aspirin ingestion, and the 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 the 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.37 A considerably lower bioavailability has been reported37 for enteric-coated tablets and sustained-release, microencapsulated preparations. Because platelet COX-1 is acetylated in the presystemic circulation,37 the antiplatelet effect of aspirin is largely independent of systemic bioavailability. Both a controlled-release formulation33 and a transdermal patch39 with negligible systemic bioavailability have been developed in an attempt to achieve selective inhibition of platelet TXA2 production without suppressing systemic PGI2 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.

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 lifespan of the platelet because aspirin irreversibly inactivates platelet COX-1.20,21 Aspirin also acetylates the enzyme in megakaryocytes before new platelets are released into the circulation.22,39 The mean lifespan of human platelets is approximately 10 days. Therefore, about 10% of circulating platelets are replaced every 24 h,42,43 and 5 to 6 days following aspirin ingestion approximately 50% of the platelets function normally.

<table>
<thead>
<tr>
<th>Variables</th>
<th>COX-1</th>
<th>COX-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA</td>
<td>Chromosome 9 (22 kB)</td>
<td>Chromosome 1 (8.3 kB)</td>
</tr>
<tr>
<td>Messenger RNA</td>
<td>2.8 kB</td>
<td>4.8 kB</td>
</tr>
<tr>
<td>Protein</td>
<td>72 kd (599 amino acids)</td>
<td>72 kda (604 amino acids)</td>
</tr>
<tr>
<td>Homology</td>
<td>Amino acids 90% homologous between species for both isoforms; similar Vmax and Km values for arachidonic acid</td>
<td>Predominantly inducible (10-fold–20-fold)</td>
</tr>
<tr>
<td>Regulation</td>
<td>Predominantly constitutive. Increased twofold to fourfold by inflammatory stimuli</td>
<td>Constitutive in certain organs</td>
</tr>
<tr>
<td>Tissue expression</td>
<td>Most tissues, but particularly platelets, stomach, and kidney</td>
<td>Induced by inflammatory and mitogenic stimuli in monocytes/macrophages, synoviocytes, chondrocytes, fibroblasts; induced by laminar shear stress and platelet microparticles in vascular endothelial cells; induced by hormones in the ovaries and fetal membranes; constitutive in the CNS, kidney, testes, and tracheal epithelial cells</td>
</tr>
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[Table 1—Structure, Distribution, and Regulation of COX-1 and COX-2]
1.3 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 needed to maximize efficacy and minimize toxicity; (2) the suggestion that part of the antithrombotic effect of aspirin is unrelated to the inhibition of platelet TXA2; and (3) the possibility that some patients may be “aspirin-resistant.”

The optimal dose of aspirin

Well-designed randomized trials have shown that aspirin is an effective antithrombotic agent when used in doses ranging between 50 and 100 mg/d, and there has been a suggestion that it is effective in doses as low as 30 mg/d. Aspirin in a dose of 75 mg/d was shown to be effective in reducing the risk of acute myocardial infarction (MI) or death in patients with unstable angina44 and chronic stable angina,45 as well as in reducing the incidence of stroke or death in patients with transient cerebral ischemia46 and in reducing the number of postoperative strokes after carotid endarterectomy.47 In the European Stroke Prevention Study (ESPS)-2 trial,48 aspirin (25 mg twice daily) was effective in reducing the risks of stroke and of stroke or death in patients who had experienced prior stroke or transient ischemic attack (TIA). The lowest effective dose of aspirin for these various indications is shown in Table 2.

The clinical effectiveness of different doses of aspirin has been compared directly in a small number of randomized trials.49–54 In the United Kingdom-TIA study,52 no difference in efficacy was found between doses of 300 and 1,200 mg/d aspirin (see below). In a study53 of 3,131 patients after they had experienced 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 hazard ratio for the group receiving the lower dose was 0.91 (95% confidence interval [CI], 0.76 to 1.09). The Acetylsalicylic Acid and Carotid Endarterectomy trial54 reported that the risk of stroke, MI, or death within 3 months of undergoing a carotid endarterectomy is significantly lower for patients who had experienced prior stroke or transient ischemic attack (TIA). The lowest effective dose of aspirin from the results of the Dutch TIA study53 that 30 mg/d is effective.

Aspirin has 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 treatment for patients with the following conditions: unstable angina in which the incidence of acute MI or death was significantly reduced to a similar degree in four separate studies using daily doses of 75 mg,44 325 mg,55 650 mg,56 and 1,300 mg;57 stable angina in which a dose of 75 mg daily reduced the incidence of acute MI or sudden death;45 aorticcoronary bypass surgery in which the incidence of early occlusion was similarly reduced with daily doses of 100 mg,58 325 mg,59 975 mg,56 and 1,200 mg;60 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,61 500 mg,62 and 1,500 mg;63,64 thromboprophylaxis of patients with arterial venous shunts undergoing long-term hemodialysis in whom a dose of 160 mg/d was shown to be effective;65 acute MI in which a dose of 162.5 mg/d reduced early mortality (ie, 35 day) as well as nonfatal infarction and stroke;66 transient cerebral ischemia in which doses between 50 and 1,200 mg/d were effective;67,68 the incidence of systemic embolism was reduced with daily doses of 100 mg,58 325 mg,59 975 mg,56 and 1,200 mg;60 and acute ischemic stroke in which doses of 160 to 300 mg/d were effective in reducing early mortality and stroke recurrence.69,70

Thus, aspirin is an effective antithrombotic agent in doses between 50 and 1,500 mg/d.71,72 It is also possible from the results of the Dutch TIA study53 that 30 mg/d is effective. 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. The data from the Antithrombotic Trialists Collaboration overview19 are consistent with this conclusion (Table 3).

There is evidence, however, that doses of approximately 300 mg/d produce fewer GI side effects than those of approximately 1,200 mg/d.52 There is also some evidence that a dose of 30 mg/d produces fewer side effects than a dose of 283 mg/d.53 The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) investigators73 have retrospectively investigated the relationship between the aspirin dose (CURE protocol recommendation, 75 to 325 mg daily) and the risk of major bleeding. This study was a randomized comparison of clopidogrel with placebo in a “background” of aspirin therapy. Patients with acute coronary syndromes receiving dose of aspirin of ≤100 mg daily had the lowest rate of major or life-threatening bleeds.
bleeding complications both in the placebo (1.9%) and clopidogrel (3%) arms of the trial. Bleeding risks increased with increasing aspirin dose, with or without clopidogrel, without any increase in efficacy.\textsuperscript{73}

In summary, the results of biochemical studies on its mechanism of action, 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\textsuperscript{32,72} (Table 2). Use of the lowest effective dose of aspirin (ie, 50 to 100 mg daily for long-term treatment) is probably the most rational strategy to maximize its efficacy and to minimize its toxicity.

**Effects of aspirin not related to TXA\textsubscript{2}**

Aspirin has been reported to have effects on hemostasis that are unrelated to its ability to inactivate platelet COX-1. These effects include the dose-dependent inhibition of platelet function,\textsuperscript{74–78} the enhancement of fibrinolysis,\textsuperscript{79–81} and the suppression of plasma coagulation.\textsuperscript{82–85}

In contrast to the saturable and well-characterized (nanomolar aspirin concentration, rapid time course, physiologic conditions, and single serine modification) inhibition of COX-1 by aspirin,\textsuperscript{86,87} the putative mechanisms underpinning the non-PG effects of aspirin on hemostasis are dose-dependent and less clearly defined. For example, the 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 twice daily)\textsuperscript{79} and proceeds more rapidly *in vitro* under nonphysiologic alkaline conditions.\textsuperscript{88} Aspirin suppresses plasma coagulation through several mechanisms. The first, initially described by Link and associates in 1943 and confirmed by others,\textsuperscript{82,83} is caused by an anti-vitamin 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 mechanism is platelet-dependent and is characterized by the inhibition of thrombin generation in a whole-blood system.\textsuperscript{84,85} A single 500-mg dose of aspirin depresses the rate of thrombin generation, while repeated daily dosing with 300 mg reduces the total amount of thrombin formed.\textsuperscript{89} An interaction with platelet phospholipids, which is blunted in patients with hypercholesterolemia, has been proposed to explain the effects of aspirin on thrombin generation.\textsuperscript{89} It is possible (but unproven) that this effect occurs as a consequence of impaired platelet coagulant activity secondary to the 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 experimental studies both in animal models and human subjects have detected antithrombotic effects of aspirin that may occur, at least in part, through mechanisms that are unrelated to the inactivation of platelet COX-1. For example, Buchanan et al\textsuperscript{76} and Hanson et al,\textsuperscript{74} using different animal models, reported that the optimal antithrombotic activity of aspirin required doses in excess of those required to inhibit TXA\textsubscript{2}. Moreover, the results of a subgroup analysis of the North American Symptomatic Carotid Endarterectomy Trial study\textsuperscript{80} suggested that aspirin in doses of 650 mg/d might be more effective than doses of ≤ 325 mg/d for the prevention of perioperative stroke in patients undergoing carotid artery surgery.\textsuperscript{91} Based on these findings, the Acetylsalicylic Acid and Carotid Endarterectomy trial\textsuperscript{82} 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. Thus, approximately 3,000 patients scheduled to undergo carotid endarterectomy were randomly assigned to receive doses of 81, 325, 650, or 1,300 mg aspirin daily, starting before surgery and continuing 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 groups receiving 81 and 325 mg/d, or between the groups receiving 650 and 1,300 mg/d, in any of the secondary analyses of the data.\textsuperscript{54}

A subgroup analysis of the Physicians’ Health Study,\textsuperscript{92} based on *post hoc* measurements of baseline plasma level of C-reactive protein (the prototypic acute-phase protein, the serum levels of which can increase in response to tissue damage, infection, or inflammation) that was performed in 543 apparently healthy men who subsequently developed 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) appeared to be directly related to the level of C-reactive protein, raising the possibility of antiinflammatory effects as well as antiplatelet effects of the drug when used for cardiovascular prophylaxis.\textsuperscript{93} 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 that is induced in response to inflammatory cytokines,\textsuperscript{24} as these clinical effects can be fully reproduced by highly selective COX-2 inhibitors (coxibs) in patients with rheumatoid arthritis.\textsuperscript{16} As shown in Table 4, the dose dependence and time dependence of the effects of aspirin on nucleated inflammatory cells expressing COX-2 vs unucleated platelets expressing COX-1 are markedly different, thus making a clinically relevant antiinflammatory effect of the drug administered at a dose of 325 mg every other day pharmacologically implausible. Finally, aspirin has been reported to modify the way in which neutrophils and platelets\textsuperscript{94} or erythrocytes and platelets\textsuperscript{65,95} interact, to protect endothelial cells from oxidative stress,\textsuperscript{97} and to improve endothelial dysfunction in atherosclerotic patients.\textsuperscript{98} However, neither the molecular mechanism nor the dose dependence of these effects has been clearly established. Although improved endothelial dysfunction
could reflect an antiinflammatory effect of aspirin that is 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 the presence of dose-dependent effects for aspirin is indirect, and is inconsistent with the failure to show a dose effect in randomized clinical trials and in the Antithrombotic Trialists overview analysis.19 This failure to show a dose effect is the critical point of this discussion, because it correlates with the saturability of the aspirin effect on platelet COX-1. For example, in studies72 with purified enzymes and isolated platelets, nanomolar concentrations of aspirin will completely block PG synthesis within 20 min after exposure. Higher concentrations and longer exposures will not alter the inhibitory effect of aspirin on PG synthesis because of this quality of saturability. Exactly the same features (ie, maximal effect at low doses and absence of dose effect) are seen in clinical trials using 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, the maximal inhibition of platelet TX synthesis. Thus, the consistency of dose requirements and the saturability of the effects of aspirin in acetylating the platelet enzyme,22 inhibiting TXA2 production,31 and preventing atherothrombotic complications32,72 constitutes the best evidence that aspirin prevents thrombosis through the inhibition of TXA2 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.

Aspirin resistance

The term aspirin resistance has been used to describe a number of different phenomena, including the inability of aspirin to accomplish the following: (1) to protect individuals from thrombotic complications; (2) to cause a prolongation of the bleeding time; (3) to reduce TXA2 production; or (4) to produce an anticipated effect on one or more in vitro tests of platelet function.98a From the therapeutic standpoint, it is important to establish whether aspirin resistance can be overcome by increasing the dose of aspirin, but unfortunately there are very few data that 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 quarter to one third) of all vascular complications can be prevented by any single preventive strategy.

A variable proportion of patients (up to one quarter) with cerebrovascular disease achieve only 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.99–101 The results of these long-term studies carried out by Helgason and coworkers99–101 are at variance with those of a short-term study by Weksler et al,102 showing that 40 mg aspirin daily inhibited platelet aggregation and TXA2 formation as effectively as higher doses of aspirin in patients who had recently experienced cerebral ischemia. Variable platelet responses to aspirin also have been described in patients with peripheral arterial disease103 and ischemic heart disease.7,9,104 In the study by Buchanan and Brister,104 aspirin “nonresponders” were identified on the basis of the time 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 was associated with increased platelet adhesion and 12-hydroxy eicosatetraenoic acid synthesis.104 In contrast, repeated measurements of platelet aggregation carried out during >24 months of placebo-controlled treatment by Berglund and Wallentin105 demonstrated that 100 patients with unstable coronary artery disease who were randomized to receive 75 mg aspirin daily in the RISC study104 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%, respectively, of patients with stable cardiovascular disease who were receiving aspirin (325 mg/d for ≥7 days) were defined as being “resistant” and “seniresponders.”7 Using a variety of techniques, including conventional aggregometry, shear stress-induced activation, and the expression of platelet surface receptors, Sane et al9 have reported that 57% of a group of 98 patients with documented heart failure who had been treated with aspirin, 325 mg/d for ≥1 month, showed “aspirin nonresponsiveness.” However, the lack of appropriate controls in these studies7,8 (eg, patients treated with another antiplatelet agent) precludes the unequivocal interpretation of these findings.

Several relatively small studies of stroke patients (range,
39 to 180 patients\textsuperscript{106--108} have suggested that aspirin resistance may contribute to treatment failure (i.e., recurrent ischemic events while receiving antiplatelet therapy) and that doses of >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\textsuperscript{109} failed to substantiate a dose-dependent effect of aspirin in stroke prevention, an effect that one would theoretically expect if aspirin resistance could be overcome, at least in part, by increasing the daily dose of the drug. The apparent discrepancy between the theoretical predictions originating from studies of aspirin resistance and the actual findings of randomized clinical trials of aspirin prophylaxis in high-risk patients\textsuperscript{109} can be reconciled by acknowledging the limitations of platelet function studies. Thus, platelet aggregation, as measured by conventional methods \textit{ex vivo}, has less than ideal intra- and intersubject variability, and displays limited sensitivity to the effect of aspirin, which is often considered to be a weak antiplatelet agent based on such measurements. Moreover, the relevance of changes in this index of capacity to the actual occurrence of platelet activation and inhibition \textit{in vivo} is largely unknown. Similarly, the bleeding time has serious problems of methodological standardization and is of limited value in predicting hemostatic competence.\textsuperscript{108a}

At least three potential mechanisms may underlie the occurrence of aspirin-resistant TXA\textsubscript{2} biosynthesis. The transient expression of COX-2 in newly formed platelets in clinical settings of enhanced platelet turnover\textsuperscript{109} is a potentially important mechanism that deserves further investigation. Extraplatelet sources of TXA\textsubscript{2} (e.g., monocyte/macrophage COX-2) may contribute to aspirin-insensitive TXA\textsubscript{2} biosynthesis in patients with acute coronary syndromes.\textsuperscript{110} Furthermore, Catella-Lawson et al\textsuperscript{111} have reported that the concomitant administration of a traditional NSAID (e.g., 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 (i.e., arginine-120), which aspirin binds to with weak affinity prior to the irreversible acetylation of serine-529.\textsuperscript{25} This pharmacodynamic interaction does not occur with rofecoxib or diclofenac, which are drugs that are endowed with variable COX-2 selectivity.\textsuperscript{111} Thus, concomitant treatment with readily available over-the-counter NSAIDs may limit the cardioprotective effects of aspirin and contribute to aspirin resistance. A recent observational study\textsuperscript{111a} in patients with established cardiovascular disease and a post hoc analysis of the Physicians’ Health Study\textsuperscript{111b} lend support to the hypothesis about the occurrence of a clinically relevant interaction of ibuprofen and aspirin that results in an increased risk of fatal and nonfatal vascular complications.

The clinical relevance of aspirin-resistant TXA\textsubscript{2} biosynthesis has been explored by Eikelboom et al,\textsuperscript{5} 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 who were 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\textsubscript{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 the use of NSAIDs) and the variable occurrence of aspirin-resistant sources of TXA\textsubscript{2} biosynthesis. Moreover, the reported association does not implicate cause and effect. These interesting findings, however, provide a rationale for studying the efficacy and safety of additional treatments (e.g., highly selective COX-2 inhibitors or TP-antagonists) that may more effectively block \textit{in vivo} TXA\textsubscript{2} biosynthesis or action in a subset of high-risk patients displaying aspirin-resistant TXA\textsubscript{2} biosynthesis.

Gum et al\textsuperscript{111c} 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.

Thus, in summary, both the mechanisms and the clinical relevance of aspirin resistance, as defined by platelet aggregation measurements, remain to be established. Until its true nature and prevalence vis-à-vis other antiplatelet drugs are better defined, no test of platelet function can be recommended to assess the antiplatelet effect of aspirin in the individual patient. On the other hand, additional studies on the mechanisms and clinical relevance of aspirin-resistant TXA\textsubscript{2} biosynthesis are clearly warranted.

1.4 The antithrombotic effect of aspirin

\textbf{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 who were at variable risk of thrombotic complications from atherosclerosis. A detailed analysis of individual trials is beyond the scope of this article. It is more appropriately dealt with in specific clinical sections of this supplement. Nevertheless, common features of these trials form a basis for general treatment recommendations.

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 been extended for a duration as short as a few weeks or as long as many years. 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,\textsuperscript{66} a single tablet of aspirin, 162.5 mg, administered 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 the risk of hemorrhagic stroke or GI bleeding in the aspirin-treated patients, and only a small increase in minor bleeding. The 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, with a proportional odds reduction in fatal or nonfatal vascular events of 40%. Two separate trials with a similar protocol, the International Stroke Trial and the Chinese Acute Stroke Trial, tested the efficacy and safety of early aspirin use in patients with 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 and 160 mg, respectively) or placebo. An overview of the results of both trials suggests an absolute benefit of about 10 fewer deaths or nonfatal strokes per 1,000 patients in the first month of aspirin therapy plus an extra 10 patients per 1,000 who experienced a complete recovery. 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 small absolute increase in this risk associated with the early use of aspirin was similar in the two studies (an excess of 2 strokes per 1,000 patients).

The broad clinical implications of these findings are discussed elsewhere in this supplement. In terms of their research implications, these results are consistent with biochmical 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 TXA2 biosynthesis in patients receiving low-dose aspirin in this setting. However, when contrasting the effects of aspirin in patients who have experienced an acute MI with those in patients who have experienced an acute stroke, it seems reasonable to assume that TX-mediated amplification of the platelet response to acute vascular injury plays a more important role in the coronary territory than in the cerebrovascular territory.

Long-term aspirin therapy confers a conclusive net benefit on the risk of subsequent MI, stroke, or vascular death among subjects with an intermediate-to-high risk of vascular complications. These include patients with chronic stable angina, patients with prior MI, patients with unstable angina, and patients with TIA or minor stroke, as well as other high-risk categories. The proportional effects of long-term aspirin therapy on vascular events in these different clinical settings are rather homogenous, ranging between a 20% and a 25% odds reduction based on an overview of all randomized trials. However, individual trial data show substantial heterogeneity, ranging from no statistically significant benefit in patients with peripheral vascular disease to approximately 50% risk reduction in patients with unstable angina. We interpret these findings as reflecting the variable importance of TXA2 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 patients per 1,000 patients with unstable angina who had been treated for 6 months and in 36 patients per 1,000 patients with prior MI, stroke, or TIA who had been treated for approximately 30 months.

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 (i.e., 75 to 160 mg) for the prevention of MI, stroke, or vascular death. This is supported by separate trial data in patients who were 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 (Table 3). While this provides a rational basis for therapy at present, it is worth remembering that such indirect comparisons may fail to detect an important divergence in clinical effect. There is no convincing evidence that the dose requirement for the antithrombotic effect of aspirin may vary in different clinical settings.

Aspirin has been evaluated in six “primary” prevention trials in approximately 58,000 persons who were at variable cardiovascular risk (Table 5). If one compares the absolute benefits of aspirin prophylaxis in these trials with those achieved in the “primary” prevention of MI in patients with chronic stable angina, it becomes apparent that the level of cardiovascular risk in the control population (i.e., those receiving placebo) is a major determinant of the absolute benefit of antiplatelet therapy (Fig 1). As a

**Table 5—Primary Prevention Trials of Aspirin vs Placebo**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Subjects†</th>
<th>Aspirin, mg</th>
<th>Follow-up, yr</th>
<th>Placebo Event Rate, %/yr</th>
<th>Aspirin RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Physicians</td>
<td>Healthy men (22,071)</td>
<td>325 every other day</td>
<td>5.0</td>
<td>0.7</td>
<td>0.82</td>
</tr>
<tr>
<td>PFP110</td>
<td>High-risk men and women (4,495)</td>
<td>100 daily</td>
<td>3.6</td>
<td>0.8</td>
<td>0.71</td>
</tr>
<tr>
<td>HOT114</td>
<td>Hypertensive patients (18,790)</td>
<td>75 daily</td>
<td>3.8</td>
<td>1.1</td>
<td>0.85</td>
</tr>
<tr>
<td>UK Doctors113</td>
<td>Healthy men (5,139)</td>
<td>500 daily</td>
<td>5.8</td>
<td>1.4</td>
<td>1.03</td>
</tr>
<tr>
<td>TPT116</td>
<td>High-risk men (5,085)</td>
<td>75 daily</td>
<td>6.3</td>
<td>1.6</td>
<td>0.83</td>
</tr>
<tr>
<td>SAPAT45</td>
<td>Stable angina patients (2,035)</td>
<td>75 daily</td>
<td>4.2</td>
<td>3.7</td>
<td>0.71</td>
</tr>
</tbody>
</table>

*PPP = Primary Prevention Project; HOT = Hypertension Optimal Treatment; TPT = Thrombosis Prevention Trial; SAPAT = Swedish Angina Pectoris Aspirin Trial.
†Values in parentheses are No.
result, the first step in deciding whether to consider aspirin for primary prophylaxis is an assessment of the 5-year to 10-year risk for that individual of developing a cardiovascular event. From that information and from the known risk reduction expected from aspirin therapy, one can estimate the number of vascular events that would be avoided. Individuals then can assess whether they believe that this likely benefit outweighs the expected toxicity related to GI bleeding and hemorrhagic stroke. The results obtained in aspirin trials that have recruited high-risk men and women (ie, the Thrombosis Prevention Trial, Hypertension Optimal Treatment [HOT] trial, and the Primary Prevention Project) [Fig 1] clearly demonstrate that proper management of modifiable risk factors by current multifactorial strategies can reduce the actual risk of experiencing a major vascular event to a level at which the additional benefit of aspirin does not clearly outweigh the risk of major bleeding complications (Fig 1). Additional data assessing the benefit/risk ratio of long-term aspirin prophylaxis in apparently healthy persons are currently being collected by the Women’s Health Study, an ongoing trial of low-dose aspirin therapy (100 mg every other day) among 40,000 US female health-care professionals.

While the clinical issues related to policy recommendations concerning aspirin in the primary prevention of cardiovascular disease are discussed in detail elsewhere in this supplement, the results of the studies reviewed above do not justify the use of a daily dose of aspirin of > 75 to 100 mg when primary prevention with aspirin is considered in the setting of varying individual patient values and preferences.

### 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. The effectiveness of aspirin therapy in doses between 75 and 325 mg has been compared with therapy with warfarin and placebo in three randomized trials of patients with nonvalvular atrial fibrillation. In one study, therapy with aspirin was significantly more effective than that with placebo, whereas in the other two studies there was a nonsignificant trend in favor of aspirin therapy. A pooled analysis of the three studies shows a reduction in relative risk (RR) of about 25% (range, 14 to 44%), which is in favor of therapy with aspirin over that with placebo. Aspirin therapy was significantly less effective than that with warfarin, with a 47% RR reduction (range, 28 to 61%; p < 0.01). 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 therapy (325 mg/d) in high-risk patients with atrial fibrillation. Thus, therapy with aspirin appears to be effective in preventing stroke in patients with atrial fibrillation but is substantially less effective than therapy with warfarin. However, aspirin is less expensive, safer, and more convenient than warfarin, and may be considered for patients who are unable to receive anticoagulation therapy or those with lone atrial fibrillation who have a low risk of stroke.
Deep venous thrombosis

The Pulmonary Embolism Prevention trial\textsuperscript{126} 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 to receive aspirin, 160 mg, or placebo, once daily 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 venous thrombosis or pulmonary embolism (PE) \[ absolute risk reduction, 0.9\%; p = 0.0003\]. A similar RR reduction in patients who were assigned to received aspirin was observed in patients who also received heparin.

This important study, therefore, clearly shows that therapy with aspirin reduces the incidence of fatal PE and symptomatic nonfatal deep venous 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\textsuperscript{127} and supersede the findings in most of the previous trials. However, smaller studies using mandatory venography at or close to hospital discharge indicate that aspirin therapy is not as effective as other forms of prophylaxis. Thus, the overall event rate was high with aspirin in the studies that used mandatory venography,\textsuperscript{128–130} and in indirect comparisons of studies in elective hip surgery. Mohr and associates\textsuperscript{131} reported that aspirin use was associated with a pooled incidence of 47\% for venous thrombosis. Similar conclusions were reached in the analysis by Gallus and associates.\textsuperscript{132} The weakness of these two analyses is that they included only a relatively small number of patients who were treated with aspirin, and the comparisons with other forms of prophylaxis were indirect. However, the indirect comparisons are supported by the results of three randomized studies in patients undergoing major orthopedic surgery comparing therapy with aspirin with either warfarin\textsuperscript{133} or a low-molecular-weight heparin.\textsuperscript{132,133} In all three studies, the incidence of venous thrombosis was significantly higher in the aspirin group.\textsuperscript{134}

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.\textsuperscript{135} The initial reports that low-dose aspirin therapy reduces the risk of severe low birth weight among newborns\textsuperscript{136} and the risk of cesarean section in mothers with pregnancy-induced hypertension\textsuperscript{135} led to the widespread use of prophylactic aspirin therapy to prevent preeclampsia. Subsequently, several larger trials\textsuperscript{137–142} reported no beneficial effects of aspirin. Although the women in these studies were thought to be at increased risk for preeclampsia, this complication developed in only 2.5 to 7.6\% of the women taking placebo. The National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units completed a large trial in \( > 2,500 \) pregnant women to test the hypothesis that aspirin, 60 mg/d, reduces the incidence of preeclampsia in women who are at high risk for the disease.\textsuperscript{143} Twenty percent of the placebo-treated women developed preeclampsia during the study. However, aspirin therapy failed to reduce the incidence of this maternal complication or to improve perinatal outcomes. On a positive note, several months of low-dose aspirin treatment was not associated with adverse consequences to either the mothers or the neonates, there being no increase in abruptio placentae, postpartum hemorrhage, or neonatal intraventricular hemorrhage.\textsuperscript{143}

A systematic review\textsuperscript{144} of data from 39 trials in \( > 30,000 \) women showed that antiplatelet therapy (mostly aspirin, 60 mg daily) is associated with a 15\% decrease in the risk of preeclampsia. This effect was consistent, regardless of risk status (ie, moderate or high risk), dose of aspirin, or gestation at trial entry. There was some evidence that there may be greater benefits for women who are given \( > 75 \) mg aspirin, although the numbers of women in the subgroup were small, and so there is 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 who were assigned to antiplatelet therapy.\textsuperscript{144} 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.\textsuperscript{144} The potential involvement of extraplatelet 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.

1.5 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 \( \geq 75 \) mg/d.\textsuperscript{132} The balance between preventing vascular occlusion and causing excess bleeding with aspirin depends critically on the absolute thrombotic risk vs hemorrhagic risk of the patient. Thus, in individuals who are at low risk for vascular occlusion (ie, \( \leq 1\% \) per year), a very small absolute benefit is offset by exposure of a large number of healthy subjects to undue bleeding complications. In contrast, in patients who are at high risk of cardiovascular or cerebrovascular complications (ie, \( > 3\% \) per year), the substantial absolute benefit of aspirin prophylaxis clearly outweighs the risk (Table 6). For example, the absolute excess of major bleeds (ie, those requiring transfusion) in patients who have experienced acute MI is approximately one hundredth the absolute number of major vascular events avoided by aspirin therapy.\textsuperscript{19}

Hypertension often has been considered a contraindication to aspirin because of the concern that possible
NSAIDs and/or mucosal erosions related to the concurrent use of other GI bleeding and/or perforation associated with low-dose aspirin therapy (mostly, 100 to 300 mg daily) [RR, 2.3; 95% confidence interval [CI], 1.7 to 3.2] is comparable to those associated with other antiplatelet agents (RR, 2.0; 95% CI, 1.4 to 2.7) and anticoaguants (RR, 2.2; 95% CI, 1.4 to 3.4) in a large population-based observational study.146

In the overview of the Antithrombotic Trialists’ Collaboration,19 information was available on 787 major extracranial hemorrhages in 60 trials that recorded at least one such hemorrhage. These were generally defined as hemorrhages that were fatal or required transfusion. Among them, 159 hemorrhages (20%) caused death. Overall, the proportional increase in the 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.

A case-control study with hospital and community control subjects has examined the risks of hospitalization for bleeding peptic ulcer associated with three different regimens of aspirin prophylaxis.147 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; 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.148 Similarly, the incidence of major bleeding was 1.9%, 2.8%, and 3.7%, respectively, in patients with acute coronary syndromes who were prescribed doses of aspirin of ≤ 100 mg, 101 to 199 mg, and 200 to 325 mg in the CURE Trial.73 It has been calculated that each year in England and Wales approximately 900 of the 10,000 episodes of ulcer bleeding occurring in people aged > 60 years could be associated with, and ascribed to, prophylactic aspirin use.147 A general change to lower doses of aspirin (ie, 75 mg) would not eliminate risks but would reduce risk by about 40% compared with doses of 300 mg and by 30% compared with doses of 150 mg, if the assumptions from indirect comparisons are correct.147 Given that the mortality rate among patients who are hospitalized for NSAID-induced upper GI bleeding is about 5 to 10%,149 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.150 The RRs 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 of > 325 mg, the RR was 5.8 for plain aspirin and 7.0 for buffered aspirin. There were insufficient data to evaluate enteric-coated aspirin at this dose level.150 Similar conclusions were reached by a case-control study using data from the UK General Practice Research Database.151 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 the regular use of NSAIDs. In patients who required continuous treatment with NSAIDs benefits in the prevention of cardiovascular events may be counterbalanced by an increased risk of cerebral bleeding. The results of the aspirin component of the HOT study114 are reassuring in this regard, since hypertensive patients whose BP was well-controlled were protected from MI by aspirin therapy without an increase in the number of hospitalizations due to upper GI bleeding than plain aspirin. Consistent with this mechanistic interpretation, the RR of hospitalization due to upper GI bleeding and/or perforation associated with low-dose aspirin therapy (mostly, 100 to 300 mg daily) [RR, 2.3; 95% confidence interval [CI], 1.7 to 3.2] is comparable to those associated with other antiplatelet agents (RR, 2.0; 95% CI, 1.4 to 2.7) and anticoaguants (RR, 2.2; 95% CI, 1.4 to 3.4) in a large population-based observational study.146

<table>
<thead>
<tr>
<th>Clinical Setting</th>
<th>Benefit*</th>
<th>Risk†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men at low to high cardiovascular risk</td>
<td>1–2</td>
<td>1–2</td>
</tr>
<tr>
<td>Essential hypertension</td>
<td>1–2</td>
<td>1–2</td>
</tr>
<tr>
<td>Chronic stable angina</td>
<td>10</td>
<td>1–2</td>
</tr>
<tr>
<td>Prior MI</td>
<td>20</td>
<td>1–2</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>50</td>
<td>1–2</td>
</tr>
</tbody>
</table>

*Values given as 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 chapter and depicted in Figures 1 and 2.
†Values given as No. of patients in whom a major GI bleeding event is caused per 1,000/yr. Risks of upper GI bleeding are estimated from a background rate of 1 event per 1,000 per year in the general population of nonusers146 and a relative risk of 2.0 to 3.0 associated with aspirin prophylaxis.146,148 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. The absolute excess of major bleeding complications in the “primary” prevention trials reviewed in Table 5 ranged between 0.3 and 1.7 per 1,000 patient-years.
and who had ulcers or > 10 erosions in either the stomach or duodenum, omeprazole healed and prevented ulcers more effectively than did ranitidine. In these patients, maintenance therapy with omeprazole was associated with a lower rate of relapse and was better tolerated than misoprostol. In high-risk patients (i.e., those with a history of previous ulcer bleeding) receiving low-dose aspirin therapy for 6 months, omeprazole and \textit{H pylori} eradication were associated with similar rates of recurrent bleeding (0.9% vs 1.9%), although the small sample size of the study (250 patients) does not allow the exclusion of clinically important differences between the two preventive strategies.

Substantially less information is available concerning the risk of intracranial hemorrhage associated with aspirin use. In the Nurses’ Health Study cohort of approximately 79,000 women aged 34 to 59 years, the infrequent use of aspirin (1 to 6 tablets per week) was associated with a reduced risk of ischemic stroke, while high frequency of use (i.e., ≥15 aspirin per week) was associated with increased risk of subarachnoid hemorrhage, particularly among older or hypertensive women. In the overview of the Antithrombotic Trialists’ Collaboration, the absolute excess of intracranial hemorrhage due to aspirin therapy is less than one hemorrhage 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, which is consistent with its lack of effect on renal PGs that derive primarily from constitutively expressed COX-2 in the human kidney. Moreover, aspirin therapy, 75 mg daily, did not affect BP or the need for antihypertensive therapy in intensively treated hypertensive patients. The suggestion that the use of aspirin and other antiplatelet agents is associated with reduced benefit from therapy with enalapril in patients with left ventricular systolic dysfunction was not supported by the results of a large meta-analysis of MI trials. Similarly, no negative interaction occurs between angiotensin-converting enzyme (ACE) inhibition and the cardiovascular benefits of low-dose aspirin in intensively treated hypertensive patients. The ACE Inhibitors Collaborative Group has carried out 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 administered, the addition of ACE inhibitor therapy produced substantial additional benefit in all major vascular outcomes. Therefore, in the absence of clear contraindications, the concomitant use of aspirin and ACE inhibitors should be considered in all patients who are at high risk for major vascular events.

Thus, in summary, the inhibition of TXA2-dependent platelet function by aspirin may lead to the prevention of thrombosis as well as to excess bleeding. Assessing the net effect requires an estimation of the absolute thrombotic risk vs the hemorrhagic risk of the individual patient. In individuals who are at very low risk for vascular occlusion, a very small absolute benefit may be offset by the 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 (Fig 2) 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 that is consistent with the saturability of platelet COX inhibition at very low doses. In contrast, the GI toxicity of the drug does appear to be dose-related, which is consistent with dose-dependent and dosing interval-dependent inhibition of COX activity in the nucleated lining cells of the GI mucosa. Thus, the administration of aspirin once daily is recommended for patients with 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 that has been shown to be effective in each clinical setting (Table 2).

**2.0 Reversible COX Inhibitors**

A variety of NSAIDs can inhibit TXA2-dependent platelet function through competitive, reversible inhibition of platelet COX-1. In general, these drugs, when used at a conventional analgesic dosage, inhibit reversibly platelet COX activity by 70 to 90%. This level of inhibition may be insufficient to block adequately platelet aggregation in vivo, because of the very substantial biosynthetic capacity of human platelets to produce TXA2. Population-based observational studies have failed to detect an association between nonaspirin NSAID use and the risk of MI, although it has been debated whether individual pharmacokinetic/pharmacodynamic features may explain conflicting results with the use of naproxen. Unfortunately, such case-control studies involve inherent biases that may be difficult or impossible to identify and adjust for, so they cannot reliably detect moderate treatment effects.

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 that is 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. The conflicting or negative results obtained in randomized clinical trials of sulfinpyrazone in patients with MI or unstable angina (reviewed in this supplement) 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 biochemical, functional, and clinical effects that are comparable to those of a standard dose of aspirin. Thus, at the therapeutic plasma levels achieved after oral dosing of 200 mg bid, indobufen inhibits serum TXB2 by > 95% throughout the dosing
interval\textsuperscript{168} and reduces urinary TX metabolite excretion to an extent that is quite comparable to that of aspirin.\textsuperscript{169} The finding that indobufen is as effective as aspirin in preventing coronary graft occlusion in two randomized trials\textsuperscript{170,171} is mechanistically consistent with the concept of platelet COX-1 inhibition, largely accounting for the antithrombotic effect of aspirin, as discussed above. Indobufen therapy also has been investigated in a small placebo-controlled study of patients with heart disease who are at increased embolic risk\textsuperscript{172} and compared with warfarin therapy\textsuperscript{173} and ticlopidine therapy\textsuperscript{174} in patients with nonrheumatic atrial fibrillation and with recent reversible cerebral ischemia, respectively. However, none of these studies in $>4,000$ patients clearly established an advantage for treatment with indobufen vs standard treatments, although the 95% CIs for these comparisons are wide. Indobufen therapy has been reported to suppress \textit{in vivo} TXA\textsubscript{2} biosynthesis more effectively than low-dose aspirin therapy in patients with unstable angina, an effect that is possibly related to the inhibition of monocyte COX-2 by therapeutic plasma levels of indobufen.\textsuperscript{20} The clinical relevance of these findings remains to be established.

Flurbiprofen has been evaluated in a single placebo-controlled, randomized trial\textsuperscript{175} of 461 patients with acute MI. 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%) present in both groups. The small sample size of the study limits the 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.\textsuperscript{176} While the half-life of the parent compound is only about 30 min, that of the deacetylated metabolite is approximately 2 days. Although it is claimed that triflusal has negligible effects on vascular PGI\textsubscript{2} production, this is likely to reflect the experimental conditions used for the assessment of PGI\textsubscript{2} production \textit{ex vivo}. The limited sample sizes of head-to-head comparisons of triflusal with aspirin in patients who were randomized to therapy within 24 h of experiencing an acute MI\textsuperscript{177} and in patients with cerebrovascular disease\textsuperscript{177a} precludes unequivocal interpretation of the similar rates of major vascular events in the two treatment groups.

None of these reversible COX inhibitors has been 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.

2.1 Coxibs and cardiovascular disease

Coxibs were developed in an attempt to prevent the adverse GI effects of nonselective NSAIDs (by avoiding the inhibition of COX-1), while maintaining equivalent antiinflammatory efficacy (by the inhibition of COX-2).\textsuperscript{16} Several large randomized trials\textsuperscript{178,179} have demonstrated that coxibs are associated with a lower risk of serious GI events than are nonselective NSAIDs. But, the Vioxx GI Outcomes Research study,\textsuperscript{179} with a population size of around 8,000 patients with rheumatoid arthritis, showed that those patients allocated to receive rofecoxib, 50 mg daily, experienced a higher risk of vascular events than did those allocated to receive naproxen, 500 mg twice daily. This excess was almost entirely accounted for by a differ-
ence in the incidence of MI (20 MIs in 2,699 person-years of follow-up among rofecoxib-allocated patients vs 4 MIs in 2,699 person-years among naproxen-allocated patients [RR, 0.20; 95% CI, 0.07 to 0.58]). There were no significant differences in stroke (rofecoxib group, 11 patients; naproxen group, 9 patients) or vascular deaths (rofecoxib group, 7 patients; naproxen group, 7 patients). While the cause of the apparent excess risk of MI in the Vioxx GI Outcomes Research trial cannot be conclusively established, a combination of some cardioprotective effect of naproxen and the play of chance does seem to offer a plausible explanation for these unexpected findings. While other mechanisms cannot be discounted, there is currently little evidence in humans to support a prothrombotic effect for coxibs.

Any residual concern about the cardiovascular safety of coxibs compared with NSAIDs is unlikely to be addressed by randomized clinical trials with vascular end points, because of the large sample size, and the extended duration required to test a statistically and biologically plausible hypothesis in a low cardiovascular risk setting. However, further insight might be possible if data from all coxib trials (including those investigating valdecoxib, etoricoxib, and lumiracoxib) were to be made available for a meta-analysis of individual patient data. Such an analysis might provide more statistically robust information on issues such as the influence of daily dose and patient substrate than that provided by published analyses of rofecoxib and celecoxib.

3.0 Dipyridamole

Dipyridamole is a pyrimidopirimidine derivative with vasodilator and antiplatelet properties. The mechanism of action of dipyridamole as an antiplatelet agent has been a subject of controversy. Both the inhibition of cyclic nucleotide phosphodiesterase (the enzyme that degrades cyclic adenosine monophosphate [AMP] to 5′-AMP, resulting in the intraplatelet accumulation of cyclic AMP, a platelet inhibitor) and blockade of the uptake of adenosine (which acts at A2 receptors for adenosine to stimulate platelet adenylyl cyclase and thus increase cyclic AMP) have been suggested. Moreover, the direct stimulation of PGI2 synthesis and protection against its degradation have been reported, although the dipyridamole concentrations required to produce these effects far exceed the low micromolar plasma levels achieved after the oral administration of conventional doses (ie, 100 to 400 mg daily).

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. 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-a-day 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 the results of earlier randomized trials, the whole issue has been reopened by the reformulation of the drug to improve bioavailability and the results of the ESPS-2 study of the new preparation in 6,602 patients with prior stroke or TIA (see elsewhere in this Supplement). Headache was the most common adverse effect of dipyridamole therapy. Bleeding at any site was almost doubled in the two aspirin arms of the study but was surprisingly indistinguishable from the results of treatment with placebo in the dipyridamole-treated patients. In a post hoc analysis of cardiac events in patients with coronary heart disease or MI at study entry, therapy with dipyridamole did not result in a higher number of fatal and nonfatal cardiac events.

The ESPS-2 study has been criticized for the continued inclusion of a placebo arm after the place of aspirin in the secondary prevention of stroke had been established to the satisfaction of most authorities. Whether the favorable results obtained in ESPS-2 reflect the higher dose (400 vs 225 mg daily) and improved systemic bioavailability of modified-release dipyridamole compared with conventional formulations, or the substantially larger sample size and statistical power of the study as compared with previous trials, remains to be established. The combination of modified-release dipyridamole and low-dose aspirin has been approved by the US Food and Drug Administration (FDA).

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. 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 the 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 μM, thus suggesting that in vivo hepatic transformation to an active metabolite is necessary for their antiplatelet effects. A short-lived metabolite of clopidogrel has been characterized. Some evidence suggests that clopidogrel and, probably, ticlopidine induce irreversible alterations of the platelet receptor P2Y12 that mediates the inhibition of stimulated adenylyl cyclase activity by ADP. Interestingly, mutations in the P2Y12 gene are associated with a congenital bleeding disorder and an abnormality in the platelet response to ADP resembling that induced by thienopyridines. The inhibition of platelet function by clopidogrel is associated with a selective reduction in the number of ADP-binding sites, with no consistent change in the binding affinity. The irreversible modification of this ADP receptor site could be explained by the formation of a disulfide bridge between the reactive thiol group of the active metabolite of clopidogrel and one or more cysteine residues of the platelet P2Y12 receptor. The permanent modification of a platelet ADP receptor by thienopyridines is consistent with the time-dependent, cumulative
inhibition of ADP-induced platelet aggregation on repeated daily dosing with ticlopidine or clopidogrel and with the slow recovery of platelet function after drug withdrawal.\textsuperscript{185}

4.1 Ticlopidine

Up to 90\% of a single oral dose of ticlopidine is rapidly absorbed in humans.\textsuperscript{185} Peak plasma concentrations occur 1 to 3 h after a single oral dose of 250 mg is administered. 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.\textsuperscript{185}

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.\textsuperscript{185} The recommended 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 anti-thrombotic effect was noted in at least one clinical trial of ticlopidine,\textsuperscript{189} in patients with unstable angina, with no apparent protection during the first 2 weeks of drug administration. Therefore, ticlopidine therapy is not useful when a rapid antiplatelet effect is required.

Ticlopidine as a single agent has been evaluated in patients with stroke,\textsuperscript{190} transient cerebral ischemia,\textsuperscript{190} unstable angina,\textsuperscript{188} MI,\textsuperscript{191} intermittent claudication,\textsuperscript{192–194} and in patients undergoing aortocoronary bypass surgery.\textsuperscript{195} Therapy with ticlopidine was significantly (but marginally, in absolute terms) more effective than aspirin in reducing the number of strokes in patients with transient cerebral ischemia or minor stroke,\textsuperscript{190} although there was no statistically significant difference in the combined outcome of stroke, MI, or death,\textsuperscript{191} it was as effective as aspirin in the treatment of patients with a recent MI,\textsuperscript{191} or death,\textsuperscript{191} it was more effective than placebo in reducing the risk of the combined outcome of stroke, MI, or vascular death in patients with thromboembolic stroke,\textsuperscript{189} it was more effective than conventional antiplatelet therapy in reducing vascular death or MI in patients with unstable angina,\textsuperscript{188} it was more effective than placebo in reducing acute occlusion of coronary bypass grafts,\textsuperscript{195} and it was more effective than controls in improving walking distance\textsuperscript{193} and reducing vascular complications in patients with peripheral vascular disease.\textsuperscript{192–194} The association of ticlopidine therapy with hypercholesterolemia and neutropenia (occurrence rates: \(< \text{1.2} \times 10^9\) neutrophils/L, 2.4\%; \(< \text{0.45} \times 10^9\) neutrophils/L, 0.8\%), and its comparative expense has reduced enthusiasm for this therapy as an alternative to aspirin in most situations.\textsuperscript{186} Ticlopidine therapy also has been associated with thrombocytopenia,\textsuperscript{196} aplastic anemia,\textsuperscript{197} and thrombotic thrombocytopenic purpura (TTP).\textsuperscript{198} Ticlopidine has been approved for clinical use in patients with cerebral ischemia when the patient has not responded to therapy with aspirin, when aspirin cannot be tolerated, or when aspirin therapy is contraindicated, although these limitations do not apply to all countries where the drug is registered.

The additive effects of ticlopidine and aspirin have been described in rats, in the inhibition of ADP-induced platelet aggregation \textit{ex vivo}, in tail-bleeding time prolongation, and in protection from thrombosis in experimental models of platelet-dependent vascular occlusion.\textsuperscript{199} The additive antiplatelet effects of aspirin, 40 mg, and ticlopidine, 250 mg, have been reported in healthy volunteers.\textsuperscript{200} Several studies\textsuperscript{201,202} have demonstrated the superiority of therapy with ticlopidine and aspirin compared to that with 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 ticlopidine as the standard anti-platelet regimen after stent deployment.\textsuperscript{203} The risk of TTP that is associated with ticlopidine use has been estimated as 0.02\% in patients receiving the drug after stent placement.\textsuperscript{204} This compares with an incidence of 0.0004\% in the general population. The mortality rate for this rare complication exceeds 20\%.\textsuperscript{204}

The place of ticlopidine in the current therapeutic armamentarium is uncertain, because of the following considerations: (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 the administration of single oral doses (up to 200 mg) or repeated doses (up to 100 mg daily), unchanged clopidogrel was not detectable in peripheral venous plasma.\textsuperscript{205} Concentrations of 1 to 2 ng/mL were measured in the plasma of patients who received 150 mg/d clopidogrel (twice as much as the dose used in the Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events [CAPRIE] study\textsuperscript{206} 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.\textsuperscript{205} The plasma elimination half-life of SR 26334 is approximately 8 h. As noted above, clopidogrel, inactive \textit{in vitro}, is metabolically transformed by the liver into a short-lived active platelet inhibitor.\textsuperscript{196,207} However, the interindividual variability in this metabolic activation is still being assessed, and there are no published data on whether liver impairment decreases the ability of clopidogrel to inhibit platelet function. Since the cytochrome P450 isozymes CYP3A4 and 3A5 metabolize clopidogrel faster than other human P450 isozymes and are the most abundant P450s in the human liver, they are
predicted to be predominantly responsible for the activation of clopidogrel in vitro.\textsuperscript{207a} When clopidogrel and atorvastatin, a CYP3A4 substrate, are present at equimolar concentrations in vitro, clopidogrel metabolism is inhibited by > 90%.\textsuperscript{207a}

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. The inhibition of platelet aggregation was detectable 2 h after oral dosing of 400 mg and remained relatively stable up to 48 h.\textsuperscript{205} On repeated daily dosing of 50 to 100 mg clopidogrel in 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 a level of maximal inhibition was comparable to that achieved with ticlopidine (500 mg daily), although the latter showed a slower onset of the antiplatelet effect compared with that of clopidogrel. No appreciable differences in the maximum inhibitory effects of therapy with 50, 75, and 100 mg clopidogrel were noted in this study, suggesting that a dose of 50 mg daily may be at or close to the top of the dose-response curve. It is interesting to note that a dose of 50 mg is only about 12% of the dose of clopidogrel that is necessary to achieve the maximal inhibition of ADP-induced platelet aggregation after single dosing, a fraction roughly equivalent to the fractional daily platelet turnover. 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.\textsuperscript{208}

However, both the optimal timing and size of the loading dose for achieving a prompt antiplatelet effect in the acute setting is substantially uncertain, and doses up to 600 mg are currently being used as a loading dose of clopidogrel before a patient undergoes percutaneous coronary intervention (PCI).

Moreover, clopidogrel treatment exhibited marked interindividual variability in inhibiting platelet function in three different studies\textsuperscript{6,6a,10} of patients undergoing elective PCI and stenting. A variable proportion of these patients was considered to comprise clopidogrel “nonresponders” or to have clopidogrel “resistance,” based on ADP-induced platelet aggregation. Three separate studies\textsuperscript{6,10a,10b} have 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 by Lau et al.\textsuperscript{10a} atorvastatin, but not pravastatin, attenuated the antiplatelet effect of clopidogrel in a dose-dependent manner. Because many drugs are metabolized by CYP3A4, 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 reported by several recent studies. Although ex vivo measurements of ADP-induced platelet aggregation have suggested a pharmacokinetic interaction between a CYP3A4-metabolized statin and clopidogrel, post hoc analyses\textsuperscript{208a,209} of placebo-controlled studies of clopidogrel 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 these trials notably restricts our ability to assess the dose dependence of potential drug interactions.\textsuperscript{209}

As with aspirin, since both the mechanism and clinical relevance of clopidogrel resistance remain to be established, no test of platelet function can currently be recommended to assess the effects of clopidogrel in the individual patient. Additional studies are, however, clearly warranted.

The most likely interpretation of the above findings is that the active metabolite of clopidogrel has a pharmacodynamic pattern that is quite similar to that of aspirin, in causing the cumulative inhibition of platelet function on repeated daily administration of low doses.\textsuperscript{159} As in the case of aspirin, platelet function returned to normal 7 days after the last dose of clopidogrel was administered. 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, which cannot be repaired during the 24-h dosing interval and can only be replaced as a function of platelet turnover. This also justifies the once-daily regimen of both drugs, despite their short half-life in the human circulation. It should be noted, however, that while aspirin is currently used at doses that represent a 2.5-fold to 10-fold excess over the dose of 30 mg that is necessary and sufficient to fully inactivate platelet COX-1 activity on repeated daily dosing,\textsuperscript{28} clopidogrel is used routinely at only 1 times the dose that appears to be necessary and sufficient to fully inactivate platelet P2Y12 on repeated daily dosing. Thus, the main determinants of the interindividual variability in the antiplatelet effects of the two drugs are substantially different (Table 7).

Bleeding time measurements performed in the same multiple-dose study\textsuperscript{205} described above showed similar

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| Table 7—Main Determinants of the Interindividual Variability in the Antiplatelet Effects of Aspirin and Clopidogrel\textsuperscript{a} |
|---|---|---|
| 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 |

\textsuperscript{a}?= unknown.
peripheral arterial disease. TTP can occur after the initi-
in patients with recent stroke, recent MI, or established
aspirin groups. Based on these findings, clopidogrel has
found in the clopidogrel group, and the incidence of
hemorrhage were more frequent with aspirin therapy than
therapy than with aspirin therapy, while GI discomfort and
incidence of early permanent discontinuation of the study
were well-tolerated in the CAPRIE study. The
overall, the CAPRIE study206 showed a modest differ-
ence in effectiveness between aspirin and clopidogrel that
did not result in the approval of a superiority claim. What
is particularly interesting, however, are the results ob-
tained when the effects of aspirin and clopidogrel in the
three separate groups of patients that were recruited into
the study are compared. Each of these comparisons
between clopidogrel and aspirin involved approximately
6,400 patients, and therefore represents the largest head-
to-head comparison between aspirin and another anti-
platelet agent in that particular clinical setting, although
the statistical power of such a comparison is inadequate to
detect a modest difference between the two. This analysis
showed 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 statisti-
cally significant (p = 0.042), suggesting that the true
benefit of clopidogrel may not be identical across the three
clinical settings. Although it is possible that such a differ-
tential effect may reflect the play of chance, the possibility
also exists that TXA₂ and ADP may be equally important
in amplifying the platelet response to plaque destabiliza-
tion, when this occurs in the absence of peripheral arterial
disease, while ADP may be the key player in platelet
activation when this occurs in the presence of peripheral
arterial disease. This working hypothesis is consistent with
the results of direct and indirect comparisons of aspirin
and ticlopidine in similar clinical settings.

Both clopidogrel therapy and medium-dose aspirin
therapy were well-tolerated in the CAPRIE study.206 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 inci-
dence of hemorrhagic events was identical in the aspirin
and clopidogrel groups (9.3%). The frequencies of severe
rash and severe diarrhea were higher with clopidogrel
therapy than with aspirin therapy, while GI discomfort and
hemorrhage were more frequent with aspirin therapy than
with clopidogrel therapy. No excess neutropenia was
found in the clopidogrel group, and the incidence of
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 after the initi-
ation of clopidogrel therapy, and when it does occur it is
often within the first 2 weeks of treatment.210

The complementary mechanisms of action of clopi-
dogrel and low-dose aspirin have led to testing the efficacy
and safety of their combination in high-risk clinical settings.14,15 The CURE trial14 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 a dose of 75 mg once daily) or placebo in
addition to aspirin (75 to 325 mg daily) 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 in 11.4% of the patients in the
placebo group (RR, 0.50; 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%, respectively; p = 0.001). Interestingly, a subgroup analysis of the
CURE trial13 based on the daily dose of prescribed aspirin
revealed a clear dose-related effect on major bleeding, in
both treatment groups. Those patients receiving the low-
est dose of aspirin (ie, ≤ 100 mg) combined with clopi-
dogrel had virtually the same rate of major bleeding
complications (3.0%) as those receiving higher doses of
aspirin and placebo. The safety advantage of lower doses
of aspirin was not associated with any loss of efficacy. In
fact, the rate of major vascular events was also lowest in
those patients receiving ≤ 100 mg aspirin daily.74

While the combination of aspirin and clopidogrel has
become the standard treatment for 1 month after coronary
stent implantation,211 the Clopidogrel for the Reduction of
Events During Observation trial20 demonstrated that long-
term (ie, 1-year) clopidogrel therapy can significantly
reduce the risk of major vascular events following PCI. At
least eight randomized clinical trials in a variety of high-
risk clinical settings are currently ongoing to further
evaluate the efficacy and safety of therapy with clopidogrel
and aspirin.

5.0 Integrin αIIbβ3 (GPIIb/IIIa) Receptor
Antagonists

Given the redundance 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 TXA₂-mediated or
ADP-mediated platelet aggregation, leave the activity of
other platelet agonists such as thrombin largely unaf-
fected. Following recognition that the expression of func-
tionally active integrin αIIbβ3 (GPIIb/IIIa) on the platelet
surface is the final common pathway of platelet aggrega-
tion, regardless of the initiating stimulus, this GP became
the target of novel antiplatelet drugs.212–214 The inhibitors
of GPIIb/IIIa include monoclonal antibodies against the
receptor, the naturally occurring Arg-Gly-Asp sequence
(RGD)-containing peptides isolated from snake venoms,
the synthetic RGD or Lys-Gly-Asp sequence-containing
peptides, as well as peptidomimetic and nonpeptide RGD mimetics that compete with fibrinogen, von Willebrand factor, and/or perhaps other ligands, for occupancy of the platelet receptor.\textsuperscript{215–217}

### 5.1 Abciximab

The blockade of GPIIb/IIIa receptors by murine monoclonal antibodies such as 7E3 essentially induces a functional thrombasthenic phenotype.\textsuperscript{218} Approximately 40,000 antibody molecules bind to the surface of platelets, but since they probably bind bivalently, there are probably 80,000 GPIIb/IIIa receptors per platelet.\textsuperscript{212} 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.\textsuperscript{219} Because of concerns about the immunogenicity of the original 7E3 antibody, a mouse/human chimeric 7E3 Fab antibody (i.e., abciximab) was created for clinical development.

Pharmacokinetic data on abciximab indicate that following IV bolus administration, free plasma concentrations decrease rapidly (initial half-life, about 30 min) as a result of rapid binding to platelet GPIIb/IIIa receptors, with approximately 65% of the injected antibody becoming attached to platelets in the circulation and spleen.\textsuperscript{219} After a bolus injection of abciximab, a dose-dependent inhibition of ADP-induced platelet aggregation was recorded in patients who were judged to be at a moderate to high risk of percutaneous transluminal coronary angioplasty (PTCA)-associated ischemic complications.\textsuperscript{219} 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 the baseline value. A steep dose-response curve was apparent in this study.\textsuperscript{219} Peak effects on receptor blockade, platelet aggregation, and bleeding time were observed at the first sampling time, 2 h after a 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.\textsuperscript{219} Platelet aggregation in response to 20 μmol/L ADP returns to ≥ 50% of baseline values 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.\textsuperscript{220}

The receptor blockade, the inhibition of platelet aggregation, and the prolongation of bleeding time produced by administering a 0.25 mg/kg bolus dose of abciximab could be maintained for 12 h by administering abciximab by infusion at 10 μg/min during that time period.\textsuperscript{219} This regimen was chosen for a phase III trial (the Evaluation of 7E3 for the Prevention of Ischemic Complications [EPIC] trial)\textsuperscript{221} that demonstrated the clinical efficacy of abciximab, when added to conventional antithrombotic therapy, in reducing the incidence of ischemic events in patients undergoing PTCA (discussed elsewhere in this Supplement). Subsequently, the infusion rate of 10 μg/min was modified to 0.125 μg/kg/min (to a maximum of 10 μg/min) to adjust for differences in body weight. Although the 6-month follow-up of patients in the EPIC study suggested a potential effect of abciximab on "clinical restenosis,"\textsuperscript{222} several subsequent studies\textsuperscript{222} did not support this finding, except perhaps in diabetic patients undergoing stent placement.\textsuperscript{224}

Repetispir and/or ticlopidine do not affect the pharmacodynamics of abciximab.\textsuperscript{225} Pretreating platelets with tirofiban or eptifibatide does not alter the subsequent binding of abciximab to platelets.\textsuperscript{226} It is unclear, however, whether abciximab can bind simultaneously with either tirofiban or eptifibatide to a single GPIIb/IIIa receptor, and indirect studies using monoclonal antibodies\textsuperscript{227} have raised the possibility that abciximab binding may decrease the binding of the other drugs.\textsuperscript{225}

*In vitro* studies using a rapid platelet function assay\textsuperscript{229} to monitor GPIIb/IIIa-dependent platelet aggregation have demonstrated that most patients achieve ≥ 80% inhibition of platelet function with the standard bolus dose of abciximab, but there is considerable interindividual variability, and that variability increases during the infusion period.\textsuperscript{5,230–232} Patients undergoing PCI who had the lowest levels of platelet inhibition at 5 min and 8 h after the bolus dose of abciximab had significantly higher rates of major adverse cardiac events.\textsuperscript{5} Since platelet inhibition thresholds were established post hoc, however, the results should be interpreted with caution. Moreover, it remains to be tested whether adjusting the dose in the patients obtaining lesser degrees of platelet function inhibition will result in improved outcomes. Other platelet function tests have been used to assess the effect of abciximab, but the data have not been correlated with clinical outcomes.\textsuperscript{233}

Major bleeding was significantly increased in abciximab-treated patients in the EPIC trial.\textsuperscript{221} 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.\textsuperscript{223} Besides hemorrhage, thrombocytopenia represents an important side effect of abciximab treatment. Approximately 1 to 2% of patients treated with abciximab develop platelet counts of < 50,000 cells/μL, of whom approximately 0.5% to 1% reflect very rapid decreases (ie, beginning within 2 h of administration) and severe decreases (ie, < 20,000 cells/μL). 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 who are developing thrombocytopenia. In almost all cases, the thrombocytopenia can be treated effectively by stopping administration of the drug and, if necessary, by administering platelet transfusions, with recovery occurring over several days.\textsuperscript{223,234–236} The 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.\textsuperscript{237} Delayed thrombocytopenia has been ascribed to abciximab therapy, but its prevalence is unknown.\textsuperscript{238,238a} In the EPIC trial,\textsuperscript{221} approximately 6% of patients treated with abciximab developed
antibodies to the variable region of abciximab (ie, human antichimeric antibody). Few data are currently available to assess the potential risks of reinjecting abciximab, especially if the drug is readministered relatively soon after the initial administration.

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. The onset of platelet inhibition was rapid, with platelet aggregation in response to the administration of 5 μmol/L ADP inhibited by 93% and 96%, respectively, within 5 min of administering the two higher doses. Bleeding times at 2 h after starting the infusion were 19.5, >30, and >30 min. 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, and 4 h after discontinuing therapy platelet aggregation inhibition decreased to <50%, even in the group receiving the highest dose.

Studies using the rapid platelet function assay found that at doses of tirofiban of 0.4 μg/kg/min for 30 min, followed by doses of 0.1 μg/kg/min for 20 to 24 h, there was less inhibition of platelet function than with the administration of eptifibatide (ie, bolus dose of 180 μg/kg and 2.0 μg/kg/min infusion) or abciximab (ie, bolus dose of 0.25 μg/kg and 0.125 μg/kg/min infusion). When tirofiban was administered as a 10 μg/kg bolus followed by a 0.1 μg/kg infusion, the inhibition of platelet function measured by this assay was similar to that produced by abciximab and eptifibatide, but the inhibition of platelet function measured by light transmission aggregometry was significantly less. In the Au-Assessing Ultegra (Gold) study, as with abciximab, there was a trend toward an association between lower levels of platelet function inhibition and the risk of major adverse cardiac events, but only a small number of patients was studied. In the Comparison of Measurements of Platelet Aggregation With Aggrastat, Reopro, and Eptifibatide (COMPARE) study, the effects of two dose regimens of tirofiban (infusion of 0.4 μg/kg/min for 30 min and 0.1 μg/kg/min thereafter, or a bolus dose of 10 μg/kg followed by 0.15 μg/kg/min infusion) were evaluated from 15 min to 12 h after starting therapy by aggregometry. At the early time points, the administration of tirofiban achieved less inhibition than that with abciximab or a single bolus of eptifibatide. At late time points, however, tirofiban administration achieved levels of inhibition that were comparable to those for eptifibatide and were greater than those achieved with abciximab.
were found to have an increased risk of bleeding, and tirofiban treatment further increased the risk.

Severe but reversible thrombocytopenia has been reported in a small percentage of patients treated with tirofiban, and an immunologic mechanism has been proposed, mediated by preformed antibodies to a conformation of the GPIIb/IIIa receptor induced by the binding of tirofiban to the receptor.\textsuperscript{236,252} No data are available on the safety of reinfusing tirofiban, but high-titer antibodies have been identified in patients who developed thrombocytopenia after repeat administration.\textsuperscript{253}

### 5.3 Eptifibatide

Eptifibatide (Integrilin; Millennium Pharmaceuticals; Cambridge, MA) is a synthetic disulfide-linked cyclic heptapeptide. It is patterned after the Lys-Gly-Asp sequence found in the snake venom disintegrin, obtained from \textit{Sistrurus m. barbouri} (barbourin), and it has high specificity, but not absolute specificity, for inhibition of GPIIb/IIIa compared with inhibition of the aVb3 vitronectin receptor.\textsuperscript{254,255} Preliminary reports have suggested that eptifibatide produced less prolongation of the bleeding time than other GPIIb/IIIa inhibitors at doses producing comparable inhibition of platelet aggregation. Later studies\textsuperscript{256} found that the citrate anticoagulation used for platelet aggregation studies resulted in an overestimation of the inhibition by eptifibatide of platelet aggregation. Thus, it is unclear whether there is a differential effect of eptifibatide on the bleeding time.

Studies of \textsuperscript{14}C-eptifibatide administered as a single 135 \(\mu\)g/kg IV bolus revealed mean peak plasma concentrations of 879 \(\pm\) 251 ng/mL at 5 min, a mean distribution half-life of 5 \(\pm\) 2.5 min, and a mean terminal elimination half-life of 1.1 \(\pm\) 0.17 h.\textsuperscript{257} Of the approximately 73% of administered radioactivity recovered in 72 h, renal clearance accounted for 98% of the total recovered radioactivity, and for 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.

Since 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 level, 2 to 4 mg/dL) is uncertain.\textsuperscript{250} In the Enhanced Suppression of the Platelet Ib/IIa Receptor with Integrilin Therapy (ESPRIT) trial,\textsuperscript{256} patients with creatinine clearances of \(\leq 60\) mL/min had increased major and minor bleeding rates compared to those patients with creatinine clearances of \(> 60\) mL/min, and eptifibatide treatment increased both major and minor bleeding in both groups of patients.

Since the steady-state level of eptifibatide is approximately 1,900 ng/mL when using an infusion rate of 2 \(\mu\)g/kg/min,\textsuperscript{259} the ratio of eptifibatide molecules to GPIIb/IIIa molecules is \(> 50:1.\textsuperscript{260} Thus, platelet transfusions may not be able to reverse the effects of the drug, although \textit{in vitro} data raise some hope in this regard.\textsuperscript{251} Treatment with eptifibatide prolongs the activated clotting time of patients who have received heparin, suggesting an inhibitory effect on thrombin generation.\textsuperscript{262,263}

In 21 patients undergoing elective PTCA or directional coronary atherectomy who were treated with aspirin, heparin (10,000 U bolus plus additional doses to maintain an activated clotting time of 300 to 350 s), and a bolus dose of 90 \(\mu\)g/kg eptifibatide followed by infusion at a rate of 1 \(\mu\)g/kg/min for 4 or 12 h, platelet aggregation was measured before infusion, 1 h after the bolus administration, at the end of the infusion, and 4 h after the end of the infusion.\textsuperscript{262} The extent of platelet aggregation in response to 20 \(\mu\)mol/L ADP administration decreased from approximately 80% before eptifibatide administration to approximately 15% at both 1 h after the administration of the bolus dose and at the end of the infusion. There was, however, significant interindividual variation in the inhibitory responses at the two time points tested (95% CI, 0% to approximately 30% and 0% to approximately 40%, respectively). 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, ranging from approximately 6 min before treatment to approximately 26 min at both 1 h after beginning the infusion and at the end of the infusion. The bleeding times returned toward 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.

In a later study,\textsuperscript{264} the following four eptifibatide regimens were tested in 54 patients undergoing coronary interventions who were also being treated with aspirin and heparin: (1) 150 \(\mu\)g/kg bolus plus 1 \(\mu\)g/kg/min infusion for 18 to 24 h (4 patients); (2) 135 \(\mu\)g/kg bolus plus 0.5 \(\mu\)g/kg/min infusion for 18 to 24 h (16 patients); (3) 90 \(\mu\)g/kg bolus plus 0.75 \(\mu\)g/kg/min infusion for 18 to 24 h (6 patients); and (4) 135 \(\mu\)g/kg bolus plus 0.75 \(\mu\)g/kg/min for 18 to 24 h (28 patients). Fifteen minutes after the 150 \(\mu\)g/kg bolus dose, platelet aggregation was inhibited by > 95% in response to the administration of 20 \(\mu\)mol/L ADP, with virtually no interindividual variation, whereas the 135 \(\mu\)g/kg bolus dose resulted in 80 to 90% inhibition in 75% of the patients, and the 90 \(\mu\)g/kg bolus produced only slightly less inhibition than the 135 \(\mu\)g/kg dose. The inhibition of platelet aggregation achieved with the 180 \(\mu\)g/kg bolus dose was sustained throughout the infusion by the 1 \(\mu\)g/kg/min dose. However, there was a tendency for the platelet aggregation response to return toward normal during infusion in some patients who received the 0.75 \(\mu\)g/kg/min dose, and the return of the platelet aggregation response toward normal was more marked in those who received the 0.5 \(\mu\)g/kg/min infusion dose. Two hours after discontinuing the eptifibatide infusion, there was a substantial return of platelet function in all groups, and a 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 (ie, 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 that had undergone anticoagulation with the direct thrombin inhibitor D-Phe-Pro-Arg chloromethyl ketone, which does not chelate calcium.269 Combinations of different single-bolus doses followed by different infusion doses (ie, 135 μg/kg/0.75 μg/kg/min, 180 μg/kg/2.0 μg/kg/min, and 250 μg/kg/3.0 μg/kg/min) were evaluated in patients with acute coronary syndromes305 and during PCI.247,260,261 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 a steady state was achieved. Regimens employing a second bolus dose 30 min after the first were then studied (180 μg/kg/2.0 μg/kg/min plus a second bolus of 90 μg/kg/250 μg/kg/2.0 μg/kg/min plus a second bolus of 125 μg/kg).259 From these studies, the dose used in the ESPRIT trial259 (ie, bolus dose of 180 μg/kg, second bolus dose of 180 μg/kg at 10 min followed by 2 μg/kg/min infusion) was selected.259

Studies247 of patients with unstable angina undergoing PCI have demonstrated that a bolus dose of 180 μg/kg followed by an infusion of 2.0 μg/kg/min produced more complete and sustained inhibition of platelet function than did standard-dose therapy with abciximab (ie, 0.25 mg/kg bolus plus 0.125 μg/kg/min infusion). In another, similar study,248 however, platelet inhibition produced 5 min after the bolus dose of abciximab was administered was greater than that produced by eptifibatide. In the Au-Assessing Ultegra (GOLD) study,5 patients with lower levels of inhibition of platelet function had the greatest risk of developing major adverse cardiac events.

A modest increase in hemorrhagic complications has been reported in patients treated with eptifibatide in the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial266 and the ESPRIT trial.258,267,268 Eptifibatide treatment has been associated with a small increase in profound thrombocytopenia.266,269 An immunologic mechanism has been identified in some patients.253 Thus, patients receiving eptifibatide should be monitored soon after the initiation of therapy for the development of thrombocytopenia. An algorithm for the detection and management of thrombocytopenia after GPIIb/IIIa blockade has been proposed.236 No data are available concerning the safety of reinfusing eptifibatide, but high levels of antibodies that bind to platelets in the presence of eptifibatide have been found in patients who develop thrombocytopenia after reexposure to eptifibatide.253

5.4 Efficacy and safety of IV GPIIb/IIIa antagonists

The efficacy and safety of GPIIb/IIIa antagonists were evaluated initially in patients undergoing PCI. Over 20,000 patients have been enrolled in nine studies of abciximab, eptifibatide, and tirofiban (Table 8). The first of these phase III trials, the EPIC trial,221 resulted in approval in many countries for the use of abciximab (ReoPro; Lilly; Indianapolis, IN) in 1994 for PCI patients who are at high risk of developing ischemic complications. Eptifibatide has been studied in the IMPACT-II260 and ESPRIT trials267,268 and tirofiban has been studied in the RESTORE trial.270 Although neither the IMPACT-II nor RESTORE trials achieved their predefined efficacy end points, there was a positive trend in each case (Table 8). Eptifibatide received approval from the FDA for use in

Table 8—GPIIb/IIIa Antagonists in PCI*

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients, No.</th>
<th>Compound</th>
<th>Placebo, %</th>
<th>GPIIb/IIIa Antagonist, %</th>
<th>RRR, %</th>
</tr>
</thead>
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<tr>
<td>EPIC</td>
<td>2,090</td>
<td>Abciximab</td>
<td>10.3</td>
<td>6.9</td>
<td>30.0</td>
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<td>EPILOG</td>
<td>2,792</td>
<td>Abciximab</td>
<td>9.1</td>
<td>3.8†</td>
<td>58.2</td>
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<tr>
<td>CAPTURE</td>
<td>1,265</td>
<td>Abciximab</td>
<td>9.0</td>
<td>4.8</td>
<td>46.7</td>
</tr>
<tr>
<td>EPISTENT</td>
<td>1,603</td>
<td>Abciximab</td>
<td>10.2</td>
<td>4.8‡</td>
<td>52.9</td>
</tr>
<tr>
<td>IMPACT-II</td>
<td>4,010</td>
<td>Eptifibatide</td>
<td>8.4</td>
<td>6.9</td>
<td>17.9</td>
</tr>
<tr>
<td>RESTORE</td>
<td>2,139</td>
<td>Tirofiban</td>
<td>6.4</td>
<td>5.0</td>
<td>21.9</td>
</tr>
<tr>
<td>ESPRIT</td>
<td>1,023</td>
<td>Eptifibatide</td>
<td>9.2</td>
<td>5.5</td>
<td>40.0</td>
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<tr>
<td>TARGET</td>
<td>2,398</td>
<td>Tirofiban</td>
<td>7.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,411</td>
<td>Abciximab</td>
<td>5.7</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CADILLAC‡</td>
<td>1,046</td>
<td>Abciximab</td>
<td>3.3</td>
<td>1.9</td>
<td>42.4</td>
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<tr>
<td>Stent</td>
<td>1,036</td>
<td>Abciximab</td>
<td>3.2</td>
<td>3.5</td>
<td>-9.4</td>
</tr>
</tbody>
</table>

*Rates of death or myocardial infarction at 30 days are shown. RRR = RR reduction; EPILOG = Evaluation in PTCA to Improve Long-term Outcome With Abciximab GPIIb/IIIa Blockade; CAPTURE = c7E3 Antiplatelet Therapy in Unstable Refractory Angina; EPISTENT = Evaluation of Platelet IIb/IIIa Inhibitor for Stenting Trial; TARGET = Tirofiban (Aggrastat) and ReoPro Give Similar Efficacy Outcomes Trial; CADILLAC = Controlled Abciximab (ReoPro) and Device Investigation to Lower Late Angioplasty Complications.

†Abciximab plus low-dose heparin.
‡Abciximab plus stenting vs placebo plus stenting.
§Death and reinfarction were recorded separately, not as a composite.
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 trial. The EPILOG trial demonstrated the efficacy of treatment with abciximab for 18 to 24 h prior to PCI in patients with unstable angina who were refractory to conventional antithrombotic and antiangiial therapy. The Evaluation in PTCA to Improve Long-Term Outcome With Abciximab (EPIC) trial demonstrated the efficacy of abciximab therapy in a broad population of patients undergoing PCI, not just in high-risk patients, as in the EPIC and CAPTURE trials. The Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trial demonstrated that abciximab therapy decreased the frequency of ischemic complications of PCI associated with stent insertion during the first 30 days, and that there were fewer ischemic complications during this time period in patients who were treated with PCI and abciximab alone without stent insertion compared to those treated with stenting alone. Furthermore, the 1-year mortality rate difference was statistically significant between stenting alone (2.4%) and stenting plus abciximab therapy (1%), and this mortality rate difference was sustained for longer periods of time. Both abciximab therapy and stenting were studied in the Controlled Abciximab (ReoPro) and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial of patients with MI. In this group of patients, who appeared to be at a relatively low risk (Table 8), abciximab had a beneficial effect in the PTCA group but did not affect death or reinfarction in the stent group.

Abciximab was compared to tirofiban as treatment for PCI in the TARGET study (Table 8). Abciximab treatment was found to be associated with a statistically significant lower rate of ischemic complications after 30 days, but at 6 months the differences were less apparent. Five completed trials have examined the efficacy and safety of tirofiban, lamifiban (a nonpeptide GPIIb/IIIa blocker of which has been discontinued), and epifibatide in approximately 25,000 patients with acute coronary syndromes without persistent ST-segment elevation who were randomized to receive a GPIIb/IIIa antagonist or placebo, in addition to conventional antithrombotic therapy (Table 9). These studies demonstrated a 0 to 27% reduction in the RR of MI or death at 30 days. Both epifibatide 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, abciximab therapy (0.25 mg/kg bolus followed by a 0.125 mg/kg/min infusion) for 24 or 48 h was not beneficial as a first-line medical treatment in patients with acute coronary syndromes. A meta-analysis of all major randomized clinical trials of GPIIb/IIIa antagonists in patients with acute coronary syndromes who were not routinely scheduled to undergo early coronary revascularization suggested a 9% reduction in the odds of death or MI at 30 days. However, the true size of the additional benefit resulting from short-term, high-grade blockade of GPIIb/IIIa combined with standard antithrombotic therapy is somewhat uncertain, since 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 GPIIb/IIIa antagonists vs control. The Platelet IIb/IIIa Antagonist for the Reduction of Acute coronary syndrome events in a Global Organization Network (PARAGON)-B Investigators have reported that dose-titrated lamifiban had no significant effects on clinical outcomes in patients with non-ST-segment elevation acute coronary syndromes and yet caused excess bleeding, thus reinforcing the uncertainty noted above. Of note, a subgroup analysis of these studies identified a consistent and significant mortality advantage for patients with diabetes, even in the GUSTO IV-ACS study, raising the possibility that platelets may play a more important role in the pathogenesis of the ischemic damage in diabetic patients.

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

Phase II trials in patients with acute MI treated with abciximab, epifibatide, and lamifiban have suggested

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**Table 9—GPIIb/IIIa Antagonists in Acute Coronary Syndromes Without Persistent ST-Segment Elevation**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients, No.</th>
<th>Compound</th>
<th>Placebo, %</th>
<th>GPIIb/IIIa Antagonist, %</th>
<th>RRR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRISM</td>
<td>3,232</td>
<td>Tirofiban</td>
<td>7.1</td>
<td>5.8</td>
<td>18.3</td>
</tr>
<tr>
<td>PRISM-Plus</td>
<td>1,570</td>
<td>Tirofiban</td>
<td>11.9</td>
<td>8.7</td>
<td>26.9</td>
</tr>
<tr>
<td>PARAGON-B</td>
<td>2,282</td>
<td>Lamifiban</td>
<td>11.7</td>
<td>10.3</td>
<td>12.0</td>
</tr>
<tr>
<td>PURSUIT</td>
<td>10,948</td>
<td>Epifibatide</td>
<td>15.7</td>
<td>14.2</td>
<td>9.6</td>
</tr>
<tr>
<td>GUSTO IV-ACS</td>
<td>7,800</td>
<td>Abciximab 24 h</td>
<td>8.0</td>
<td>8.2</td>
<td>-3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abciximab 48 h</td>
<td>8.0</td>
<td>9.1</td>
<td>-14</td>
</tr>
</tbody>
</table>

*PRISM = Platelet Receptor Inhibition for Ischemic Syndrome Management; PRISM-PLUS = Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited to Very Unstable Signs and Symptoms; PARAGON = Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome events in the Global Organization Network; PURSUIT = Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy; GUSTO = Global Utilization of Streptokinase and tPA (Tissue Plasminogen Activator) for Occluded Arteries. See legend of Table 8 for abbreviation not used in the text.
potential benefits of GPIIb/IIIa blockade as an adjunct to thrombolysis. The Thrombolysis in Myocardial Infarction (TIMI) 14A trial demonstrated that therapy combining abciximab with aspirin and reduced dose tissue plasminogen activator in the treatment of acute MI resulted in improved TIMI grade 3 flow rates at 60 and 90 min after starting therapy when compared to the best full-dose tissue plasminogen activator regimen. The bleeding risk was not substantially increased. The GUSTO V trial compared the efficacy and safety of half-dose therapy with reteplase and full-dose therapy with abciximab vs standard-dose reteplase therapy in 16,588 patients in the first 6 h of evolving ST-segment elevation MI. The primary end point of 30-day mortality rate was similar in the two treatment groups (5.6% vs 5.9%, respectively). Combination therapy led to a consistent reduction in secondary complications of MI, including reinfarction, which was partly counterbalanced by increased extracranial bleeding. 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.

5.5 Oral GPIIb/IIIa antagonists

The success of short-term, high-grade blockade of platelet GPIIb/IIIa with IV agents has led to the development of an array of oral GPIIb/IIIa antagonists in the hope of extending this benefit to the long-term management of patients with acute coronary syndromes. To date, five large-scale clinical trials have been completed (ie, Evaluation of Oral Xemilofiban in Controlling Thrombotic Events trial, Orbofiban in Patients With Unstable Coronary Syndromes trial, Sibrafiban versus Aspirin to Yield Maximum Protection From Ischemic Heart Events Post-Acute Coronary Syndromes trial and Blockade of the GP IIb/IIIa Receptor to Avoid Vascular Occlusion trial) and a meta-analysis of four of these trials has been published. The consistent finding of these large-scale trials involving > 40,000 patients is that therapy with oral GPIIb/IIIa antagonists (ie, xemilofiban, orbofiban, sibrafiban, and lotrafiban) is not more effective than aspirin therapy or, when combined with aspirin, is not superior to placebo and may in fact increase mortality. Several mechanisms have been put forward to explain these results. One is that the poor oral bioavailability of these compounds and the target of approximately 50% inhibition of platelet aggregation resulted in poor antiplatelet activity in many patients. This would explain a lack of clinical response, but not an increase in mortality. Indeed, overall there was an increase in the frequency of bleeding and a reduced requirement of urgent revascularization, suggesting some degree of clinical efficacy.

An alternative explanation is that GPIIb/IIIa antagonists can activate platelets, at least in some individuals. GPIIb/IIIa is not a passive receptor, rather like all integrins it responds to ligand binding by activating the cell. Thus, fibrinogen binding leads to signals that further activate platelets and are essential for platelet aggregation. Several studies have suggested that ligands designed to bind to the receptor and prevent platelet aggregation may paradoxically activate the receptor so that it can bind ligand or perhaps directly trigger some activating signals. It is also important to emphasize that relatively limited phase II dose-finding studies were performed with these oral agents before beginning large phase III clinical trials, a fact that may have limited the capacity of establishing the most appropriate dosing regimens for long-term treatment. Issues such as predictable pharmacokinetics, shallow dose-response relationship, and, perhaps, new methods of monitoring GPIIb/IIIa blockade are likely to be fundamental to any reconsideration of the development of these agents.

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