Platelet-Active Drugs

The Relationships Among Dose, Effectiveness, and Side Effects

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Abbreviations: ACE trial = Acetylsalicylic Acid and Carotid Endarterectomy; ADP = adenosine diphosphate; AMP = adenosine monophosphate; CAPRIE study = Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events; CI = confidence interval; COX = cyclooxygenase; DVT = deep venous thrombosis; EPISTENT trial = Evaluation of Platelet IIIb/IIIa Inhibitors for Stenting; ESPS = European Stroke Prevention Study; EXCITE trial = Evaluation of Xemilofiban in Controlling Thrombotic Events; FDA = Food and Drug Administration; GP = glycoprotein; HOT study = Hypertension Optimal Treatment; INR = international normalized ratio; LMWH = low-molecular-weight heparin; MI = myocardial infarction; NSAID = nonsteroidal anti-inflammatory drug; OPUS trial = Orbofiban in Patients with Unstable Coronary Syndromes; PCI = percutaneous coronary intervention; PE = pulmonary embolism; PEP trial = Pulmonary Embolism Prevention Trial; PG = prostaglandin; PTCA = percutaneous transluminal coronary angioplasty; RGD = Arg-Gly-Asp sequence; RR = relative risk; TIA = transient ischemic attack; TPT = Thrombosis Prevention Trial; TTP = thrombocytopenic purpura; TX = thromboxane; VTE = venous thromboembolism.

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Since our last report on antithrombotic therapy in 1998,1 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) a large randomized study, the Acetylsalicylic Acid and Carotid Endarterectomy (ACE) trial,2 has directly compared low-dose and high-dose aspirin for the prevention of ischemic stroke in patients undergoing carotid endarterectomy; (2) the role of aspirin in prophylaxis of venous thromboembolism (VTE) has to be reassessed in the light of the Pulmonary Embolism Prevention (PEP) trial;3 (3) three nonrandomized studies with historical control subjects4-6 and one randomized trial7 have compared the safety of clopidogrel plus aspirin vs ticlopidine plus aspirin in patients undergoing intracoronary stent implantation; (4) the results of clinical and angiographic follow-up of the patients in the Evaluation of Platelet IIIb/IIIa Inhibitors for Stenting (EPISTENT) trial at 6 months8 and 1 year9 provide evidence that stent implantation and platelet glycoprotein (GP) IIIb/IIIa blockade by abciximab improve the efficacy and safety of percutaneous coronary revascularization; and (5) preliminary reports from three large trials of long-term GPIIb/IIIa blockade (Orbofiban in Patients with Unstable Coronary Syndromes [OPUS]; Evaluation of Xemilofiban in Controlling Thrombotic Events [EXCITE]10; and sibrafiban vs aspirin to yield maximum protection from ischemic heart events post-acute coronary syndromes [SYMPhONY] (sibrafiban)11) in approximately 27,000 patients taking oral drugs for 3 months to 1 year, are largely disappointing in terms of efficacy and/or safety.12

ASPIRIN AND OTHER CYCLOOXYGENASE INHIBITORS

Aspirin has been thoroughly evaluated as an antiplatelet drug and has been found to prevent vascular death by approximately 15% and nonfatal vascular events by about 30% in a meta-analysis of > 50 secondary prevention trials in various groups of patients.13

Mechanism of Action of Aspirin

The best characterized mechanism of action of the drug is related to its capacity to inactivate permanently the cyclooxygenase (COX) activity of prostaglandin (PG)H synthase-1 and PGH synthase-2 (also referred to as COX-1 and COX-2).14-15 These isozymes catalyze the first committed step in prostanoid 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 a approximately 72-kDa 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.16 Within the enzymatic domain, there is the peroxidase catalytic site and a separate, but adjacent, site for COX activity at the apex of a long, 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 the 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) that prevents access of the substrate to the catalytic site of the enzyme.19 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-2,20 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

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maintain virtually complete inhibition of platelet TXA₂
production. In contrast, the inhibition of COX-2-depen-
dent pathophysiologic processes (eg, hyperalgesia and
inflammation) requires larger doses of aspirin (because of
the 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 daily doses of aspirin when it is used
as an anti-inflammatory 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 TXA₂ and prostacyclin (PGI₂), respec-
tively. TXA₂ induces platelet aggregation and vasocon-
striction, while PGI₂ inhibits platelet aggregation and
induces vasodilatation. Aspirin is antithrombotic in a wide
range of doses, inhibiting TXA₂ and PGI₂. While
TXA₂ is largely a COX-1-derived product (mostly from
platelets) and, thus, highly sensitive to aspirin inhibition,
vascular PGI₂ can derive from both COX-1 (short-term
changes in response to agonist stimulation, eg, bradyki-
inin-sensitive to transient aspirin inhibition) and COX-2
long-term changes in response to laminar shear stress
largely insensitive to aspirin inhibition at conventional
antiplatelet doses). This may account for the substantial
residual COX-2-dependent PGI₂ biosynthesis in vivo at
daily doses of aspirin in the range of 30 to 100 mg, despite
transient suppression of COX-1-dependent PGI₂
release. It has not been established that more profound
suppression of PGI₂ formation by higher doses of aspirin
is sufficient to initiate or to predispose to thrombosis.
However, studies with mice that were deficient in the
gene encoding the PGI₂ receptor support the importance
of this prostanoid in the prevention of arterial thrombo-
sis. The results of the ACE trial, demonstrating a
significantly lower rate of vascular events in patients
receiving 650 or 1,300 mg daily, are also consistent with
an important role for PGI₂ in preventing thrombosis.

Pharmacokinetics

Aspirin is rapidly absorbed in the stomach and upper
intestine. Peak plasma levels occur 30 to 40 min after
aspirin ingestion, and inhibition of platelet function is
evident by 1 h. In contrast, it can take up to 3 to 4 h to
reach peak plasma levels after the administration of
enteric-coated aspirin. If only enteric-coated tablets are
available, and if 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. A considerably lower bioavailability has
been reported for enteric-coated tablets and sustained-
release, microencapsulated preparations. Because platelet
COX-1 is acetylated in the presystemic circulation, the
antiplatelet effect of aspirin is largely independent of
systemic bioavailability. Both a controlled-release formul-
ation and a transdermal patch with negligible systemic
bioavailability have been developed in an attempt to
achieve selective inhibition of platelet TXA₂ production
without suppressing systemic PGI₂ synthesis. However,
the clinical relevance of preparations that are relatively
selective for the presystemic circulation remains to be
established (see below).

The plasma concentration of aspirin decays with a
half-life of 15 to 20 min. Despite the rapid clearance of
aspirin from the circulation, the platelet-inhibitory effect
lasts for the life span of the platelet because aspirin
irreversibly inactivates platelet COX-1. Aspirin also
acetylates the enzyme in megakaryocytes before new
platelets are released into the circulation. The mean
life span of human platelets is approximately 10 days.
Therefore, about 10% of circulating platelets are replaced
every 24 h, and 5 to 6 days following aspirin ingestion,
approximately 50% of the platelets function normally.

Table 1—Structure, Distribution, and Regulation of COX-1 and COX-2

<table>
<thead>
<tr>
<th>Characteristics</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>mRNA</td>
<td>2.8 kB</td>
<td>4.8 kB</td>
</tr>
<tr>
<td>Protein</td>
<td>72 kDa: 599 amino acids</td>
<td>72 kDa: 604 amino acids</td>
</tr>
<tr>
<td>Homology</td>
<td>Amino acids 90% homologous between species; similar Vₘₐₓ and Kₘₐₓ values for arachidonic acid</td>
<td>Glucocorticoids inhibit expression; active site of COX-2 is larger than that for COX-1</td>
</tr>
<tr>
<td>Differences</td>
<td>Glucocorticoids do not inhibit expression</td>
<td>Predominantly inducible (10- to 20-fold)</td>
</tr>
<tr>
<td>Regulation</td>
<td>Predominantly constitutive; increased 2- to 4-fold 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, and fibroblasts; induced by hormones in the ovaries and fetal membranes; constitutive in the CNS, kidney, testes, tracheal epithelial cells</td>
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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 minimum effective dose of aspirin required for antithrombotic efficacy; (2) the relative importance of the effects of aspirin on TXA₂ and PGI₂ synthesis as determinants of clinical efficacy; (3) the suggestion that part of the antithrombotic effect of aspirin is unrelated to inhibition of platelet TXA₂; and (4) the possibility that some patients may develop aspirin resistance over time.

The Minimum Effective 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 is 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 angina³⁸ and chronic stable angina³⁹ as well as in reducing stroke or death in patients with transient cerebral ischemia⁴⁰ and the number of postoperative strokes after carotid endarterectomy.⁴¹ In the European Stroke Prevention Study (ESPS)-2, aspirin, 25 mg bid, was effective in reducing the risks of stroke or death in patients with prior stroke or transient ischemic attack (TIA).⁴² Finally, in a study of 3,131 patients after they had experienced a TIA or ischemic stroke, aspirin in a dose of 30 mg/d was compared with a dose of 283 mg/d, and no statistically significant difference was found in the incidence of the combined outcome of vascular death, stroke, or MI between the two aspirin regimens.⁴³ 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.²⁴⁻⁴⁷ In the United Kingdom-TIA study,⁴⁷ no difference in efficacy was found between regimens of 300 and 1,200 mg/d of aspirin (see below). The Dutch TIA study failed to show a difference between regimens of 30 and 283 mg/d of aspirin.⁴³ The ACE trial has recently reported that the risk of stroke, MI, or death within 3 months of carotid endarterectomy is significantly lower for patients taking 81 or 325 mg aspirin daily than for those taking 650 or 1,300 mg (6.2% vs 8.4%; p = 0.03).⁴ Thus, there is no convincing evidence from randomized studies that have compared different doses of aspirin for a dose dependence of the antithrombotic effect.

The antithrombotic effects of a range of doses of aspirin have also been compared with the effects on an untreated control group in a number of thrombotic vascular disorders. The doses have varied between 50 and 1,500 mg/d. Aspirin has been shown to be effective in 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,³⁸ 325 mg,⁴⁸ 650 mg,⁴⁹ and 1,300 mg⁵⁰; stable angina in which a dose of 75 mg daily reduced the incidence of acute MI or sudden death⁵⁰; aortocoronary bypass surgery in which the incidence of early occlusion was similarly reduced with daily doses of 100 mg,⁵¹ 325 mg,⁵² 975 mg,⁵² and 1,200 mg⁵³; 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,⁵⁴ 500 mg,⁵⁵ and 1,500 mg⁵⁶,⁵⁷; thromboprophylaxis of patients with arterial venous shunts who were undergoing long-term hemodialysis in whom a dose of 160 mg/d was shown to be effective⁵⁸; acute MI in which a dose of 162.5 mg/d reduced early mortality (35 days) as well as nonfatal reinfarction and stroke⁵⁹; transient cerebral ischemia in which doses between 50 and 1,200 mg/d were effective;⁴⁰,⁴²,⁴⁷,⁶⁰–⁶² and acute ischemic stroke in which doses of 160 to 300 mg/d were effective in reducing early mortality and stroke recurrence,⁶³,⁶⁴ although the proportional effects of aspirin therapy on vascular events in these patients were small when compared with the effects in other high-risk settings.

Thus, aspirin is an effective antithrombotic agent in doses between 50 and 1,500 mg/d. It is also possible from the results of the Dutch TIA study that a dose of 30 mg/d is effective. There is no evidence that low doses (ie, 50 to 100 mg/d) are less effective than high doses (ie, 650 to 1,500 mg/d), and, in fact, the opposite may be true. The data from the Antiplatelet Trialists’ Collaboration overview are consistent with this conclusion (Table 3).

There is evidence, however, that doses of approximately 300 mg/d produce fewer GI side effects than doses of approximately 1,200 mg/d.⁴⁷ There is also some evidence that a dose of 30 mg/d produces fewer side effects than 300 mg/d.⁴¹ In summary, the results of biochemical studies on its mechanism of action, the lack of dose-response

| Table 2—Vascular Disorders for Which Aspirin Has Been Shown To Be Effective and Minimum Effective Dose |
| --- | --- |
| Disorder | Minimum Effective Daily Dose, mg |
| Men at high cardiovascular risk | 75 |
| Hypertension | 75 |
| Stable angina* | 75 |
| Unstable angina* | 75 |
| Acute MI | 160 |
| TIA and ischemic stroke* | 150 |
| Severe carotid artery stenosis* | 75 |
| Acute ischemic stroke* | 160 |

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

| Table 3—Indirect Comparison of Aspirin Doses Reducing Vascular Events in High-Risk Patients* |
| --- | --- |
| Aspirin Dose, mg/d | Trials, No. | Patients, No. | Odds Reduction, % |
| 500–1,500 | 30 | 18,471 | 21 ± 4 |
| 160–325 | 12 | 23,670 | 28 ± 3 |
| 75 | 4 | 5,012 | 29 ± 7 |

*Data from Antiplatelet Trialists’ Collaboration.¹³
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.²⁰,⁶⁵

The Relative Importance of TXA₂ vs PGI₂ Synthesis: Although there is some evidence from in vitro experiments and in vivo studies that aspirin may inhibit platelet function by a mechanism that is unrelated to the inhibition of TXA₂ synthesis,⁶⁶–⁶⁹ the results of clinical trials, in which different doses of aspirin ranging from 30 to 1,500 mg/d have been used, are consistent with the hypothesis that the antithrombotic effect of aspirin is caused by the inhibition of platelet TXA₂ synthesis. Thus, both the reduction in risk of MI or death in patients with unstable angina, and stroke or death in patients with transient cerebral ischemia, have been reported with daily doses of aspirin as low as 50 to 75 mg, and no further protection was afforded by 20-fold to 30-fold higher doses. There are both theoretical and practical reasons to choose the lowest effective dose of aspirin (Table 2). The GI side effects of aspirin appear to be dose-dependent (see below), and, for many clinical situations, treatment with aspirin is indicated for an indefinite period. There are theoretical reasons to select a dose of aspirin that inhibits TXA₂ synthesis without inhibiting PGI₂ synthesis. Thus, a low dose might be more antithrombotic because it inhibits PGI₂ less than a high dose. Although attempts to identify a dosage (or frequency of usage) of aspirin that blocks TXA₂ production without inhibiting PGI₂ synthesis have yielded conflicting results,²¹–²⁴ use of the lowest effective dose (ie, 50 to 100 mg daily for long-term treatment) is probably the most sensible strategy to maximize efficacy and minimize toxicity.

The recently reported Thrombosis Prevention Trial (TPT)⁷⁰ employed a novel formulation of controlled-release aspirin (75 mg) designed to minimize the inhibition of vascular PGI₂ synthesis by virtue of presystemic acetylation of platelet COX-1.²⁷ However, because the design of the trial did not include a regular aspirin arm, it is not possible to assess the clinical relevance of absolute vs relative biochemical selectivity in the setting of primary prevention.

Effects of Aspirin Not Related to TXA₂: Aspirin has been reported to have effects on hemostasis that are unrelated to its ability to inactivate platelet COX-1. These include dose-dependent inhibition of platelet function,⁶⁶–⁶⁹,⁷¹ enhancement of fibrinolysis,⁷²–⁷⁴ and suppression of plasma coagulation.⁷⁵–⁷⁸ In contrast to the saturable and well-characterized (ie, nanomolar aspirin concentration, rapid time course, physiologic conditions, and single serine modification) inhibition of COX-1 by aspirin,⁷⁹,⁸⁰ the putative mechanisms underpinning the nonprostaglandin 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 vitro with high doses of aspirin (650 mg twice daily)⁷² and proceeds more rapidly in vitro under nonphysiologic alkaline conditions.⁸¹ Aspirin suppresses plasma coagulation through several mechanisms. The first, initially described by Link and associates in 1943 and confirmed by others,⁷⁷,⁷⁸ 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.⁷⁷,⁷⁸ A single dose of 500 mg depresses the rate of thrombin generation, while repeated daily dosing with 300 mg aspirin reduces the total amount of thrombin formed.⁸² An interaction with platelet phospholipids, which is blunted in hypercholesterolemia, has been proposed to explain the effects of aspirin on thrombin generation.⁸² It is possible (but unproven) that this effect occurs as a consequence of impaired platelet coagulant activity secondary to the inhibition of TXA₂-dependent platelet aggregation. It is unknown whether lower doses of aspirin are able to produce this effect. Furthermore, high-dose aspirin therapy can cause abnormal coagulation 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 in both animal models and human subjects have detected antithrombotic effects of aspirin that may occur, at least in part, through mechanisms unrelated to inactivation of platelet COX-1. For example, Buchanan et al⁸³ and Hanson et al,⁶⁶ using different animal models, reported that optimal antithrombotic activity of aspirin required doses in excess of those required to inhibit TXA₂. Moreover, the results of a subgroup analysis of the North American Symptomatic Carotid Endarterectomy Trial study⁸⁶ suggested that aspirin in doses of ≥ 650 mg/d might be more effective than ≤ 325 mg/d for the prevention of perioperative stroke in patients having carotid artery surgery.⁸⁴ Based on these findings, the ACE trial 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.² Thus, approximately 3,000 patients scheduled for carotid endarterectomy were randomly assigned 81, 325, 650, or 1,300 mg aspirin daily, started before surgery, and continued for 3 months. The combined dose of stroke, MI, or death at 3 months was significantly (p = 0.03) lower in the low-dose groups (6.2%) than in the high-dose groups (8.4%) (primary analysis). There were no significant differences between the 81-mg and 325-mg groups, or between the 650-mg and 1,300-mg groups, in any of the secondary analyses of the data.² These results underscore the potentially misleading nature of subgroup analyses⁸⁵ as well as the weakness of the underlying mechanistic hypothesis being tested, which formed the basis for the design of the ACE trial.

A subgroup analysis of the Physicians’ Health Study,⁵⁶ based on post hoc measurements of baseline plasma C-reactive protein (CRP: the prototypic acute-phase protein, whose serum levels can increase in response to tissue damage, infection, or inflammation) performed in 543
constitute 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.

Table 4—Dose-Dependence and Time-Dependence of the Effects of Aspirin on Platelets and Inflammatory Cells

<table>
<thead>
<tr>
<th>Cellular Target</th>
<th>Enzyme</th>
<th>Single Dose, mg*</th>
<th>Duration of Prostanoid Suppression, h</th>
<th>Cumulative Effects on Repeated Dosing</th>
<th>Daily Dose, mg/d†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets</td>
<td>COX-1</td>
<td>100</td>
<td>24–48</td>
<td>Yes</td>
<td>50–81</td>
</tr>
<tr>
<td>Inflammatory cells</td>
<td>COX-2</td>
<td>≥ 650</td>
<td>3–4</td>
<td>No</td>
<td>3,000–5,000</td>
</tr>
</tbody>
</table>

* Dose causing full suppression of prostanoid formation and/or clinically detectable functional effect after single dosing.
† Range of doses shown clinically effective in long-term trials of cardiovascular protection or rheumatoid arthritis.
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 approximately 50 randomized clinical trials of aspirin prophylaxis in high-risk patients can be reconciled by acknowledging the limitations of platelet function studies. Thus, platelet aggregation, as measured by conventional methods *ex vivo*, has less than ideal intrasubject and intersubject variability and displays limited sensitivity to the effect of aspirin, which often is considered 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 *in vivo* is largely unknown. Similarly, bleeding time has serious problems of methodologic standardization and is of limited value in predicting hemostatic competence.

In a recent study, Weber et al reported that circulating platelets from healthy subjects express COX-2 protein and messenger RNA, and they suggested that this may represent a factor in aspirin resistance. This finding has been disputed by Patrignani et al. However, incomplete suppression of 11-dehydro-TXB excretion, a noninvasive index of *in vivo* TXA2 biosynthesis, has been observed episodically in some patients with unstable angina treated with IV low-dose aspirin, despite > 95% suppression of platelet COX-1 activity. COX-2 induction in plaque monocytes/macrophages or activated endothelial cells may contribute to aspirin-insensitive TXA2 biosynthesis in patients with unstable angina by generating PGH2 as a substrate for the TX-synthase of the same cell (*constitutive* biosynthesis) or by providing PGH2 to the TX-synthase of aspirinated platelets (*transcellular* metabolism). The clinical importance of this phenomenon remains to be established.

The coadministration of aspirin and other NSAIDs can lead to pharmacodynamic interactions between the two, which leads to attenuation of the antiplatelet effect of aspirin. Because the ability of aspirin to acetylate a critical serine residue at the apex of the COX channel is dependent on its initial binding to arginine-120, a common docking site for all NSAIDs, the stronger binding affinity of nonaspirin NSAIDs may preclude aspirin from permanently modifying platelet COX-1. Highly selective COX-2 inhibitors (coxibs) are less likely to interfere with the antiplatelet effect of aspirin than conventional NSAIDs because of their limited interaction with platelet COX-1. Finally, it is theoretically possible that polymorphisms and/or mutations in the COX-1 gene affecting Ser529 may represent the structural basis for aspirin resistance in some patients, although this hypothesis remains to be tested.

Thus, in summary, both the mechanism(s) and clinical relevance of aspirin resistance remain to be established. Until its true nature and prevalence are better defined, no test of platelet function is recommended to assess the antiplatelet effect of aspirin in the individual patient.

### The Antithrombotic Effect of Aspirin

**Prevention of Atherosclerosis in Different Clinical Settings.** The efficacy and safety of aspirin are documented from an analysis of > 50 randomized clinical trials that included approximately 100,000 patients at variable risk of thrombotic complications of atherosclerosis. Although a detailed analysis of individual trials is beyond the scope of this article and is more appropriately dealt with in specific clinical sections of this volume, 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 as short as a few weeks’ duration 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, a dose of a single tablet of aspirin, 162.5 mg, started within 24 h of the onset of symptoms of a suspected MI and continued daily for 5 weeks produced highly significant reductions in the risk of vascular mortality (reduction, 23%), nonfatal reinfarction (reduction, 49%), and nonfatal stroke (reduction, 46%). There was no increase in hemorrhagic stroke or GI bleeding in the aspirin-treated patients and only a small increase in minor bleeding. Thus, aspirin confers conclusive net benefits in the acute phase of evolving MI and should be administered routinely to virtually all patients with suspected acute MI. The treatment of 1,000 such patients with aspirin for 5 weeks will result in approximately 40 patients in whom a vascular event is prevented, with a proportional odds reduction of 30%.

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. As in the Second International Study of Infarct Survival, the fundamental criterion for entry was that the responsible physician was uncertain whether aspirin treatment was indicated for a particular patient. 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 with 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 early use of aspirin was similar in the two studies (excess of 2 per 1,000 patients). The broad clinical implications of these findings are discussed in the article by Albers et al, in this supplement. In terms
of the research implications, these results are consistent with biochemical evidence of episodic platelet activation during the first 48 h after the onset of symptoms of an acute ischemic stroke and with suppression of in vitro TXA2 biosynthesis in patients receiving low-dose aspirin in this setting.110–112 However, when contrasting the effects of aspirin in acute MI with those in acute stroke, it seems reasonable to assume that TXA2-driven amplification of the platelet response to acute vascular injury plays a more important role in the coronary 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 intermediate-to-high risk of vascular complications. These include patients with chronic stable angina,39 patients with prior MI,85 patients with unstable angina,39,48–50 and patients with TIA or minor stroke,40,42,47,60–62 as well as other high-risk categories.85 The proportional effects of aspirin therapy on vascular events in these different clinical settings are rather homogenous, ranging between a 20% and 25% odds reduction based on an overview of all randomized trials.85 However, individual trial data show substantial heterogeneity, ranging from no statistically significant benefits in patients with peripheral vascular disease13 to ≥ 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 the avoidance of a major vascular event in 50 patients per 1,000 patients with unstable angina who have been treated for 6 months and in approximately 35 patients per 1,000 patients with prior MI, stroke, or TIA who have been treated for 30 months.85

For patients with different manifestations of ischemic heart disease, a widespread consensus exists in defining a rather narrow range of recommended daily doses (ie, 75 to 160 mg) for the prevention of MI, stroke, or vascular death.1,26,65,109 This is supported by separate trial data in > 20,000 patients randomized to treatment with low-dose aspirin or placebo as well as by an overview of all antithrombotic trials showing no obvious dose dependence for the protective effects of aspirin85 (Table 3).

In contrast, for patients with cerebrovascular disease, a much larger degree of uncertainty still exists about the optimal aspirin dose, with recommendations ranging from 30 to 1,300 mg/d. In particular, a strong case has been put forward by some members of the North-American neurologic community for higher daily doses of aspirin (650 to 1,300 mg) being more effective than lower doses for stroke prevention.84,113 The evidence supporting this contention is largely based on indirect and selective comparisons of different trial data, mini-meta-analyses, or subgroup analyses of individual trials. In the absence of definitive evidence from direct randomized comparisons of low-dose vs high-dose aspirin therapy in trials of adequate size to detect a moderate difference (one way or the other) between the two, it is reasonable to use the lowest dose of aspirin shown to be effective in patients with transient cerebral ischemia because of safety considerations.114

Aspirin has been evaluated in five primary prevention trials19,70,86,115,116 in approximately 53,000 persons at variable cardiovascular risk (Table 5). In the US Physicians’ Health Study,86 among 22,071 healthy physicians, an alternate-day regimen of 325 mg aspirin conferred a statistically significant 44% reduction in risk of first MI. Neither the overall cardiovascular mortality, which was the primary end point of the study, nor the total number of strokes was reduced by long-term aspirin prophylaxis, but there was evidence of a possible increase in the number of hemorrhagic strokes.86 The British doctors’ trial115 found no statistically significant effects of aspirin, 500 mg daily, but it had a much smaller sample size (5,139) than the US trial. An overview of both trials167 suggested a highly significant 32% reduction in the risk of first MI, but the data for stroke and cardiovascular mortality were inconclusive. In terms of absolute benefit, the protective effect of aspirin translated into a major vascular event being avoided in 4 healthy physicians per 1,000 treated for 5 years (Fig 1). It should be emphasized that this self-selected group of health-conscious male physicians had an absolute risk of developing a major vascular event, if untreated, of < 1.0% per year, which is much lower than the expected rate in the general population. In the reported TPT,70 5,499 men aged between 45 and 69 years were recruited from > 100 general practices in the United Kingdom because they were considered to be at high risk for ischemic heart disease (ie, in the top 20 to 25% of the risk score distribution). Low-dose aspirin therapy, 75 mg/d, in the controlled-release formulation discussed above, produced a statistically significant 20% relative reduction in the risk of the primary end point of all ischemic heart disease (ie, coronary death and fatal or nonfatal MI), which was almost entirely due to a 32% reduction in nonfatal events. As in the two previous

<table>
<thead>
<tr>
<th>Trial</th>
<th>Subjects (No.)</th>
<th>Follow-up, yr</th>
<th>Placebo Event Rate, %/yr</th>
<th>Aspirin RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK Doctors115</td>
<td>Healthy men (5,139)</td>
<td>5.8</td>
<td>1.4</td>
<td>1.03</td>
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<td>US Physicians’ Health Study86</td>
<td>Healthy men (22,071)</td>
<td>5.0</td>
<td>0.7</td>
<td>0.82</td>
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<tr>
<td>TPT70</td>
<td>High-risk men (5,085)</td>
<td>6.3</td>
<td>1.6</td>
<td>0.83</td>
</tr>
<tr>
<td>HOT116</td>
<td>Hypertensive patients (18,790)</td>
<td>3.8</td>
<td>1.1</td>
<td>0.85</td>
</tr>
<tr>
<td>SAPAT39</td>
<td>Stable angina patients (2,035)</td>
<td>4.2</td>
<td>3.7</td>
<td>0.71</td>
</tr>
</tbody>
</table>

RR = relative risk of nonfatal MI, nonfatal stroke or vascular death

Table 5—Primary Prevention Trials of Aspirin vs Placebo

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primary prevention trials, neither the total number of strokes nor the overall cardiovascular mortality was modified by aspirin prophylaxis in TPT. Although the men recruited in TPT were selected for being at high risk for ischemic heart disease, their actual risk of developing a major vascular complication, as assessed in the control group, was considerably lower than expected and was only a little more than the rate found in the British doctors’ trial (ie, approximately 1.5% per year). In this setting, an ischemic cardiac event would be avoided in two high-risk subjects by treating 1,000 such men with aspirin for a year (Fig 1).

Quite similar results were obtained in the Hypertension Optimal Treatment (HOT) study, in which 18,790 male and female patients with intensively treated hypertension were randomly allocated to therapy with aspirin, 75 mg daily, or placebo. Aspirin reduced the incidence of major vascular events by 15% (p = 0.03), and all MI by 36% (p = 0.002), with no effects on stroke or cardiovascular mortality. Because of the low vascular risk of these well-treated hypertensive patients (only about 1.0% per year), a major cardiovascular event would be avoided in one to two patients by treating 1,000 hypertensive men and women with low-dose aspirin therapy for a year (Fig 1). If one compares these absolute benefits of aspirin prophylaxis with those achieved in the primary prevention of MI in patients with stable chronic angina, it becomes apparent that the level of cardiovascular risk in the control population (ie, those receiving placebo) represents a major determinant of the absolute benefit of antiplatelet therapy (Fig 1). These results do not support the widespread use of aspirin for primary cardiovascular prophylaxis, because they 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 (see below).

Additional data assessing the benefit-to-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 mg when primary prevention with aspirin is considered in the setting of individual clinical judgment by health-care providers.

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 in doses between 75 and 325 mg has been compared with that of warfarin and placebo in three randomized trials of patients with nonvalvular atrial fibrillation. In one study, aspirin was significantly more effective than placebo, whereas in the other two, there was a nonsignificant trend in favor of aspirin. Pooled analysis of the three studies shows a relative risk (RR) reduction in favor of aspirin over placebo of about 25% (range, 14 to 44%). Aspirin was significantly less effective than warfarin in two studies as determined by an intention-to-treat analysis, and in the third study by an
and aspirin (325 mg/d) in high-risk patients with atrial fibrillation. The adjusted-dose warfarin therapy (INR, 2.0 to 3.0) was more effective than fixed-dose warfarin therapy (INR, 1.2 to 1.5) and aspirin (325 mg/d) in high-risk patients with atrial fibrillation.124 Thus, aspirin appears to be effective in preventing stroke in patients with atrial fibrillation but is substantially less effective than warfarin. However, aspirin is less expensive, safer, and more convenient than warfarin and may be considered for patients unable to receive anticoagulation therapy or for those with lone atrial fibrillation who have a low risk of stroke.125,126

Deep Venous Thrombosis: The PEP trial3 has now established that aspirin is effective in preventing VTE after surgery for hip fracture. This was a double-blind multicenter study of 13,356 patients undergoing surgery for hip fracture and an additional 4,088 patients undergoing elective hip or knee arthroplasty. Patients were assigned to a regimen of 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 (LMWH) was used in about 40% of the patients. Among the 13,356 patients with hip fractures, aspirin produced a 36% reduction in symptomatic deep venous thrombosis (DVT) or pulmonary embolism (PE) (absolute risk reduction, 0.9%; p = 0.0003). A similar RR reduction in patients who were assigned to aspirin therapy was observed in patients who also received heparin. Similar benefits from aspirin were observed at weeks 1, 2, and 3 to 5, with a nonsignificant trend for the risk reduction to be greater after week 1. Surprisingly, PE was a cause of death in < 10% of patients, and aspirin had no effect on total mortality or on other vascular deaths. However, there was an important reduction in fatal PE in patients assigned to aspirin therapy; fatal PE was reduced by 58% (95% CI, 27 to 76%; p = 0.002), from 43 (0.6%) in patients assigned to placebo therapy to 18 (0.3%) in those assigned to aspirin therapy.

Aspirin treatment was associated with a small increase in blood transfusion requirements but not in serious or fatal bleeding. The effect of aspirin on blood transfusion requirements appeared to be greater in those patients also receiving heparin. The beneficial effect of aspirin outweighed its effect on bleeding.

Among the 4,088 elective arthroplasty patients randomly assigned to aspirin or placebo therapy, there was a small and nonsignificant reduction in the incidence of symptomatic DVT or PE observed with aspirin therapy (1.1% vs 1.4%).3

This important study, therefore, clearly shows that aspirin reduces the incidence of fatal PE and symptomatic nonfatal DVT or PE in patients with hip fractures. The results of the PEP trial are consistent with the meta-analysis performed by the Antiplatelet Trialists’ Collaboration127 and supersede the findings in most of the previous trials. However, much smaller studies using mandatory venography at or close to hospital discharge indicate that aspirin 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,128–130 and in indirect comparisons of studies in elective hip surgery, Mohr and associates128 reported that aspirin use was associated with a pooled incidence of 47% for DVT. Similar conclusions were reached in the analysis by Gallus and associates.129 The weakness of these two analyses is that they included only a relatively small number of patients 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 aspirin with either warfarin131 or a LMWH.132,133 In all three, the incidence of DVT was significantly higher in the aspirin group.

As pointed out by the authors of the PEP trial, the benefit of aspirin is less than with anticoagulants. What then is the role of aspirin in the prevention of VTE?134 It cannot be recommended for use in combination with LMWH or low-dose heparin until randomized trials show that the possible benefits of such a combination are not outweighed by their risks. It cannot be recommended as a replacement for LMWH or warfarin, because it is less effective than these anticoagulants, although it is likely to be safer and is less expensive. Finally, although the benefits of aspirin continued to be observed after the first week, a definitive recommendation to use aspirin for VTE prophylaxis after hospital discharge cannot be made until such an approach is evaluated in a randomized trial.

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.135 The initial reports that low-dose aspirin therapy reduces the risk of severe low birth weight among newborns,136 and the risk of cesarean section in mothers with pregnancy-induced hypertension,137 led to the widespread use of prophylactic aspirin to prevent preeclampsia. Subsequently, several larger trials reported no beneficial effects of aspirin.137–142 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 at high risk for the disease.143 Twenty percent of the placebo-treated women did develop preeclampsia during the study. However, aspirin therapy did not reduce the incidence of this maternal complication or improve perinatal outcomes. On a positive note, several months of low-dose aspirin treatment was not associated with adverse consequences for either the mothers or the neonates, there being no increase in abruptio placentae, postpartum hemorrhage, or neonatal intraventricular hemorrhage.143

Thus, although aspirin may reduce the risk of preeclampsia by 10 to 15%, this is not reflected in a substantive clinical benefit, such as reduction in perinatal death or intrauterine growth restriction.144 Whether aspirin given early in the first trimester is more effective in preventing
preeclampsia remains unanswered. Also, 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 lack of response to low-dose aspirin therapy in this setting.

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 similarly independent of the dose.

The balance between preventing vascular occlusion and causing excess bleeding with aspirin depends critically on the absolute thrombotic vs hemorrhagic risk of the patient. Thus, in individuals at very low risk for vascular occlusion (eg, 1% per year), a very small absolute benefit is offset by the exposure of a large number of healthy subjects to undue bleeding complications. In contrast, in patients at high risk for cardiovascular or cerebrovascular complications (eg, >5% 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 acute MI is approximately 1/100th the absolute number of major vascular events avoided by aspirin therapy.

Hypertension often has been considered a contraindication to aspirin therapy because of the concern that possible 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 study are reassuring in this regard, since hypertensive patients whose BP was well-controlled were protected from MI by aspirin without an increase in cerebral bleeding or strokes.

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

Aspirin-induced GI toxicity, as detected in randomized clinical trials, appears to be dose related in the range of 30 to 1,300 mg daily. This is based largely on indirect comparisons of different trials and on a limited number of randomized, direct comparisons of different aspirin doses, as reviewed above. Such a dose-response relationship is thought to reflect at least two COX-1-dependent components, ie, dose-dependent inhibition of COX-1 in the GI mucosa and dose-independent (within the range of examined doses) inhibition of COX-1 in platelets. Thus, it is not surprising that the antithrombotic effect of aspirin can be dissociated, at least in part, from its most common side effect. However, even when administered at low doses, aspirin can cause serious GI bleeding, as reported in studies using 30 to 50 mg daily. Because of the underlying prevalence of gastric mucosal erosions related to concurrent use of other NSAIDs and/or Helicobacter pylori infection in the general population, it should be expected that any antiplatelet dose of aspirin will cause more bleeding from preexisting lesions than a placebo. Consistent with this mechanistic interpretation, the 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 that of other antiplatelet agents (RR, 2.0; 95% CI, 1.4 to 2.7) and anticoagulants (RR, 2.2; 95% CI, 1.4 to 3.4) in a large population-based observational study. 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. Odds ratios were raised for all doses of aspirin taken as follows: 75 mg, 2.3 (95% CI, 1.2 to 4.4); 150 mg, 3.2 (95% CI, 1.7 to 6.5); 300 mg, 3.9 (95% CI, 2.5 to 6.3). It has been calculated that approximately 900 of the 10,000 episodes of ulcer bleeding occurring in people >60 years of age each year in England and Wales could be associated with, and ascribed to, prophylactic aspirin use. A general change to lower doses (75 mg) of aspirin would not eliminate risks but, if these figures are soundly based, would reduce risk by about 40% compared with 300 mg, and by 30% compared with 150-mg doses. Given that the mortality rate among patients who are hospitalized for NSAID-induced upper GI bleeding is about 5 to 10%, 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. The RR 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

<table>
<thead>
<tr>
<th>Clinical Setting</th>
<th>Benefit*</th>
<th>Risk†</th>
</tr>
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<tbody>
<tr>
<td>Men at low to high cardiovascular risk</td>
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<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>

*Benefits are calculated from randomized trial data reviewed in this article and depicted in Figures 1 and 2. Values are given as the No. of patients in whom a major vascular event is avoided per 1,000 patients per year.
†Risks of upper GI bleeding are estimated from a background rate of 1 event per 1,000 per year in the general population of nonusers and an RR of 2.0 to 3.0 associated with aspirin prophylaxis. 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. Values are given as the No. of patients in whom a major GI bleeding event is caused per 1,000 patients per year.
plain aspirin and 7.0 for buffered aspirin; there were insufficient data to evaluate enteric-coated aspirin at this dose level.\textsuperscript{149} Thus, physicians who recommend aspirin in an enteric-coated or buffered form should not assume that these formulations are less likely to cause GI tract bleeding than plain aspirin.

Suppressing acid secretion is thought to reduce the risk of ulcers associated with regular use of NSAIDs. In patients who required continuous treatment with NSAIDs and who had ulcers or > 10 erosions in either the stomach or duodenum, omeprazole healed and prevented ulcers more effectively than did ranitidine.\textsuperscript{150} In these patients, maintenance therapy with omeprazole was associated with a lower rate of relapse and was better tolerated than misoprostol.\textsuperscript{151} However, whether suppressing acid secretion might reduce GI toxicity associated with low-dose aspirin remains to be established.

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 (ie, \(\geq 15\) aspirin per week) was associated with increased risk of subarachnoid hemorrhage, particularly among older or hypertensive women.\textsuperscript{152} In the overview of the Antithrombotic Trialists’ Collaboration,\textsuperscript{85} the absolute excess of intracranial hemorrhage due to aspirin therapy is < 1 per 1,000 patients per year in high-risk trials, with somewhat higher risks in patients with cerebrovascular disease.

Low-dose aspirin therapy has not been reported to affect renal function or BP control,\textsuperscript{153} consistent with its lack of effect on renal PG synthesis.\textsuperscript{154} Moreover, aspirin therapy, 75 mg daily, did not affect BP or the need for antihypertensive therapy in intensively treated hypertensive patients.\textsuperscript{116} The suggestion that the use of aspirin and other antiplatelet agents is associated with reduced benefit from enalapril in patients with left ventricular systolic dysfunction\textsuperscript{155} is not supported by the results of a large meta-analysis of MI trials.\textsuperscript{156}

Thus, in summary, the inhibition of TXA\(_2\)-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 vs hemorrhagic risk of the individual patient. In individuals at very low risk for vascular occlusion, a very small absolute benefit may be offset by exposure of very large numbers of healthy subjects to undue bleeding complications. As the risk of experiencing a major vascular event increases, so does the absolute benefit of antiplatelet prophylaxis with aspirin, as shown in Figure 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 > 50 such trials that are discussed elsewhere in this volume, 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, 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, aspirin once daily is recommended in all clinical conditions in which antiplatelet prophylaxis has a favorable benefit/risk profile. Because of GI toxicity and its potential impact on compliance,

![Figure 2](https://example.com/figure2.png)

**Figure 2.** The absolute risk of vascular complications is the major determinant of the absolute benefit of antiplatelet prophylaxis. Data are plotted from placebo-controlled aspirin trials in different clinical settings. For each category of patients, the abscissa denotes the absolute risk of experiencing a major vascular event as recorded in the placebo arms of the trials. The absolute benefit of antiplatelet treatment is reported on the ordinate axis as the number of subjects in whom an important vascular event (ie, nonfatal MI, nonfatal stroke, or vascular death) is actually prevented by treating 1,000 subjects with aspirin for 1 year.
physicians are encouraged to use the lowest dose of aspirin that was shown to be effective in each clinical setting.

**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 conventional analgesic dosages, 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. In fact, in a prospective population-based cohort study of approximately 165,000 postmenopausal women, the long-term use of nonaspirin NSAIDs was not associated with a protective effect against the risk of a first MI (RR, 1.32; 95% CI, 0.97 to 1.81).

The only reversible COX inhibitors that have been tested in randomized clinical trials for their antithrombotic efficacy are sulfinpyrazone, indobufen, flurbiprofen, and triflusal. Sulfinpyrazone is a uricosuric agent structurally related to the anti-inflammatory agent phenylbutazone. When used at the highest approved dosage of 200 mg bid, the drug inhibits platelet COX activity by approximately 60%, after conversion from an inactive sulfone 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 article by Cairns et al, in this volume) 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 activity and has comparable biochemical, functional, and clinical effects to those of a standard dose of aspirin. Thus, at therapeutic plasma levels achieved after oral dosing of 200 mg bid, indobufen inhibits serum TXB₂ by > 95% throughout the dosing interval and reduces urinary TXA₂ metabolite excretion to an extent quite comparable to aspirin. The finding that indobufen is as effective as aspirin in preventing coronary graft occlusion in two randomized trials is mechanistically consistent with the concept of platelet COX inhibition, which largely accounts for the antithrombotic effect of aspirin, as discussed above. Indobufen also has been investigated in a small placebo-controlled study of patients with heart disease at increased embolic risk and compared with warfarin and ticlopidine in patients with nonrheumatic atrial fibrillation and in patients with recent reversible cerebral ischemia, respectively. However, none of these studies, which comprised > 4,000 patients, clearly established an advantage of indobufen vs standard treatments, although the CIs for these comparisons are wide. Indobufen has been reported to suppress in vitro TXA₂ biosynthesis more effectively than low-dose aspirin therapy in patients with unstable angina, an effect possibly related to the inhibition of monocyte COX-2 by therapeutic plasma levels of indobufen. The clinical relevance of these findings remains to be established.

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

Triflusal, a salicylic acid derivative, reversibly inhibits platelet COX activity after conversion to a long-lived metabolite, 2-hydroxy-4-trifluoromethyl-benzoic acid. While the half-life of the parent compound is only about 30 min, that of the deacetylated metabolite approximates 2 days. Although triflusal is claimed to have negligible effects on vascular PGI₂ production, this is likely to reflect the experimental conditions used for the assessment of PGI₂ production ex vivo. Several clinical trials comparing triflusal and aspirin are currently ongoing.

None of these reversible COX inhibitors is approved as an antiplatelet drug in the United States, and it is unclear under what circumstances they are prescribed instead of aspirin in other countries. Because nonaspirin NSAIDs have been investigated inadequately in terms of their potential cardiovascular effects, physicians prescribing these drugs to arthritic patients with prior vascular complications should not discontinue treatment with low-dose aspirin, even though concomitant administration of the two may amplify the risk of upper GI bleeding. The cardiovascular safety of selective COX-2 inhibitors (coxibs) in arthritic patients at low cardiovascular risk is currently being debated, based on the recently reported results of two relatively large GI safety studies (VIGOR, 170a and CLASS, 170b) with short follow-up and inadequate statistical power to detect a realistic difference, one way or the other, in vascular end points between coxibs and conventional NSAIDs.

**Dipyridamole**

Dipyridamole is a pyrimidopyrimidine derivative with vasodilator and antiplatelet properties. The mechanism of action of dipyridamole as an antiplatelet agent has been a subject of controversy. 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 the blockade of the uptake of adenosine (which acts at A₂ receptors for adenosine to stimulate platelet adenylyl cyclase and, thus, increases the level of cyclic AMP) have been suggested. Moreover, 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-nanomolar plasma levels achieved after the oral administration of conventional doses (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-daily regimen used in recent clinical studies.

Although the clinical efficacy of dipyridamole, alone or in combination with aspirin, has been questioned on the basis of earlier randomized trials, the whole issue has been reopened by the results of ESPS-2. In that study of 6,602 patients who had experienced prior strokes or TIAAs, stroke risk in comparison to placebo was reduced by 15% with low-dose aspirin therapy (25 mg bid) (p = 0.013), 16% with dipyridamole alone (200 mg bid) (p = 0.039), and 37% with aspirin plus dipyridamole (p < 0.001). The corresponding RR reductions for the outcome of stroke or death were 15% (p = 0.016), 15% (p = 0.015), and 24% (p < 0.001), respectively. Headache was the most common adverse effect of dipyridamole. Bleeding at any site was almost doubled in the two aspirin arms but was surprisingly indistinguishable from placebo in the dipyridamole-treated patients.

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 therapy compared with conventional formulations, or whether they reflect the substantially larger sample size and statistical power of the study compared with previous trials, remains to be established. The combination of modified-release dipyridamole and low-dose aspirin therapy has been recently approved by the US Food and Drug Administration (FDA).

**THIENOPYRIDINES**

Ticlopidine and clopidogrel are structurally related thienopyridines with platelet inhibitory properties. Both drugs selectively inhibit adenosine diphosphate (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 blockade of ADP-mediated amplification of the platelet response to other agonists.

Neither ticlopidine nor clopidogrel affects 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. Platelets contain two well-characterized receptors for ADP, a ligand gated ion channel (P2X₁) and a G-protein-linked receptor that affects platelet shape change and contributes to platelet aggregation (P2Y₁). Several lines of evidence suggest that clopidogrel, and most likely also ticlopidine, induce irreversible alterations of a presumed third ADP receptor that is postulated to mediate the inhibition of stimulated adenyl cyclase activity (P2Tₐc). 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. An active metabolite of clopidogrel has recently been described. 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 that of a cysteine residue of the platelet (P2Tₐc) ADP receptor. The hypothesis of permanent modification of a putative ADP receptor by thienopyridines is consistent with time-dependent cumulative inhibition of ADP-induced platelet aggregation on repeated daily dosing with ticlopidine or clopidogrel and with slow recovery of platelet function after drug withdrawal.

Up to 90% of a single oral dose of ticlopidine is rapidly absorbed in humans. Peak plasma concentrations occur 1 to 3 h after a single oral dose of 250 mg. Plasma levels of ticlopidine increase by approximately threefold on repeated twice-daily dosing over a period of 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.

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. 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 antithrombotic effect was noted in at least one clinical trial of ticlopidine, in patients with unstable angina, with no apparent protection during the first 2 weeks of drug administration. Therefore, ticlopidine is not useful when a rapid antiplatelet effect is required.

Ticlopidine as a single agent has been evaluated in patients who experienced stroke, transient cerebral ischemia, unstable angina, and intermittent claudication, and in patients undergoing aortocoronary bypass surgery. Ticlopidine was significantly more effective than aspirin in reducing the incidence of stroke in patients who have experienced transient focal ischemia or minor stroke, although there was a statistically significant difference in the combined outcome of stroke, MI, or death, was more effective than placebo in reducing the risk of the combined outcome of stroke, MI, or vascular death in patients who experienced thromboembolic stroke, was more effective than conventional antiplatelet therapy in reducing vascular death or MI in patients with unstable angina, was more effective than placebo in reducing acute occlusion of coronary bypass grafts, and was more effective than control in improving walking distance and reducing vascular complications in patients with peripheral vascular disease. The association of ticlopidine therapy with hypercholesterolemia and neutropenia (for which the reported rate of occurrence is 2.4% for neutrophil counts < 1.2 x 10⁹/L and 0.5% for neutrophil counts < 0.45 x 10⁹/L) and its comparative expense has reduced enthusiasm for this therapy as an alternative to aspirin in most situations. Ticlopidine has also been associated with thrombocytopenia, aplastic anemia, and thrombotic thrombocytopenic purpura.
ticlopidine has been approved for clinical use in patients with cerebral ischemia when aspirin has failed, cannot be tolerated, or is contraindicated, although this limitation does not apply to all countries where the drug is registered.

The additive effects of ticlopidine and aspirin have been described in rats, in inhibition of ADP-induced platelet aggregation ex vivo, tail bleeding time prolongation, and protection from thrombosis in experimental models of platelet-dependent vascular occlusion.\(^ {183} \) Additive antiplatelet effects of aspirin, 40 mg, and ticlopidine, 250 mg, have been reported in healthy volunteers.\(^ {186} \) Several studies have demonstrated the superiority of ticlopidine with aspirin compared to aspirin alone, or aspirin plus warfarin, in preventing thrombotic complications after coronary artery stent placement.\(^ {187,188} \) Ticlopidine has been used routinely in combination with aspirin in patients receiving coronary artery stents, but the better safety profile of clopidogrel has resulted in the substitution of clopidogrel for ticlopidine in many centers (see below). The risk of TTP associated with ticlopidine use has been estimated as 0.02% in patients receiving the drug after stent placement.\(^ {189} \) This compares with an incidence of 0.0004% in the general population. The mortality rate for this rare complication exceeds 20%.\(^ {190} \)

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.\(^ {190} \) 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 vs Aspirin in Patients at Risk of Ischemic Events [CAPRIE] study)\(^ {191} \) 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.\(^ {190} \) The plasma elimination half-life of SR 26334 is approximately 8 h. As noted above, clopidogrel, inactive in vitro, is metabolically transformed by the liver into a short-lived active platelet inhibitor, the structure of which recently was elucidated.\(^ {174} \)

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.\(^ {190} \) On repeated daily dosing of 50 to 100 mg clopidogrel to healthy volunteers, ADP-induced platelet aggregation was inhibited from the second day of treatment (25 to 30% inhibition) and reached a steady-state (ie, 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 than clopidogrel. No appreciable differences in the maximum inhibitory effects of 50, 75, and 100 mg clopidogrel were noted in this study, suggesting that 50 mg daily may be at or close to the top of the dose-response curve. It is interesting to note that 50 mg is only about 12% of the dose of clopidogrel necessary to achieve the maximal inhibition of ADP-induced platelet aggregation after single dosing. 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.\(^ {192} \) This approach currently is being used in the ongoing CURE trial of clopidogrel plus aspirin vs aspirin alone in patients with unstable coronary syndromes.

The most likely interpretation of the above findings is that the active metabolite of clopidogrel has a pharmacodynamic pattern quite similar to that of aspirin, in causing the cumulative inhibition of platelet function on repeated daily administration of low doses.\(^ {197} \) As in the case of aspirin, platelet function returned to normal 7 days after the last dose of clopidogrel. Both the cumulative nature of the inhibitory effects and the slow rate of recovery of platelet function are consistent with the active moiety of aspirin (acetylsalicylic acid) and clopidogrel (active metabolite), causing a permanent defect in a platelet protein that cannot be repaired during the 24-h dosing interval and can only be replaced as a function of platelet turnover. This also justifies the once-daily regimen of both drugs, despite their short half-life in the human circulation.

Bleeding time measurements performed in the same multiple-dose study described above showed a comparable prolongation (by 1.5-fold to 2.0-fold over control measurements) with clopidogrel, 50 to 100 mg daily, or ticlopidine, 500 mg daily.\(^ {199} \)

Clopidogrel has undergone a quite unusual clinical development, with very limited phase II studies and a single, very large phase III trial (ie, CAPRIE) to test its efficacy and safety at a dosage of 75 mg daily vs aspirin, 325 mg daily.\(^ {191} \) CAPRIE is unique among the studies that have directly compared antiplatelet agents to aspirin in that it incorporated the following three groups of patients, all of whom are recognized to be at an increased risk for recurrent ischemic events: patients who have experienced a recent stroke; patients who have experienced a recent MI; and patients presenting with symptomatic peripheral arterial disease.

Overall, CAPRIE showed a modest difference in effectiveness between aspirin and clopidogrel; the annual event rate calculated for aspirin was 5.83% compared with 5.32% for clopidogrel, a RR reduction of 8.7% (95% CI, 0.3 to 16.5%; p = 0.043).\(^ {191} \) What is particularly interesting, however, are the results obtained 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 antiplatelet agent in that particular clinical setting, although the statistical power of such comparison is inadequate to detect a modest difference between the two. This analysis shows that the majority of the difference in effectiveness occurred in the patients who entered the trial because of symptomatic peripheral arterial disease. A 23.8% reduction in RR (95% CI, 8.9 to 36.2%; p = 0.0028) over aspirin was seen in the clopidogrel-treated patients who had peripheral arterial dis-
ease, while a nonsignificant 7.3% reduction in RR (95% CI, −5.7 to 18.7%; p = 0.26) and a nonsignificant 3.7% increase in risk (95% CI, −22.1 to 12.0%; p = 0.66) were obtained in the clopidogrel-treated groups of stroke and MI patients, respectively. A formal test of heterogeneity of these three treatment effects was statistically significant (p = 0.042), suggesting that the true benefit of clopidogrel may not be identical across the three clinical settings. Although it is possible that such a differential 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 destabilization when this occurs in the absence of peripheral arterial disease, while ADP may be the key player in platelet activation when it 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 and medium-dose aspirin therapy were well-tolerated in the CAPRIE study. The frequency of severe rash and severe diarrhea was higher with clopidogrel than with aspirin, while GI discomfort and hemorrhage were more frequent with aspirin than with clopidogrel. No excess neutropenia was found in the clopidogrel group. Based on these findings, clopidogrel has been approved for the reduction of atherosclerotic events in patients who experienced recent strokes or recent MIs, or who have established peripheral arterial disease. TTP can occur after the initiation of clopidogrel therapy. When it occurs, it is often within the first 2 weeks of treatment.

The complementary mechanism of action and safety of clopidogrel and low-dose aspirin therapy suggest that their combination may produce additive antithrombotic effects in a high-risk setting with an acceptable safety margin. Studies are ongoing to test this hypothesis (eg, CURE). Proof of concept is provided by relatively small, short-term studies of aspirin and clopidogrel after coronary stenting. A new class of direct P2Y₁₁ receptor antagonists (eg, AR-C69931MX) currently is being developed that appears to block this ADP receptor more effectively than clopidogrel.

**INTEGRIN αIIbβ₃ (GPIIb/IIIa) RECEPTOR ANTAGONISTS**

Given the redundancy of discrete pathways leading to platelet aggregation, it is not surprising that the clinical efficacy of aspirin, ticlopidine, and clopidogrel is only partial. These drugs, while inhibiting TXA₂-mediated or ADP-mediated platelet aggregation, leave the activity of other platelet agonists such as thrombin largely unaffected. Following recognition that the expression of functionally active integrin αIIbβ₃ (GPIIb/IIIa) on the platelet surface is the final common pathway of platelet aggregation, regardless of the initiating stimulus, this glycoprotein has become the target of novel antiplatelet drugs. The inhibitors of GPIIb/IIIa include a monoclonal antibody against the receptor, the naturally occurring Arg-Gly-Asp sequence (RGD) containing peptides isolated from snake venoms, synthetic RGD, or Lys-Gly-Asp sequence containing peptides, as well as peptidomimetic and non-peptide RGD mimetics that compete with fibrinogen, von Willebrand factor, and/or perhaps other ligands for occupancy of the platelet receptor. Recent reviews of the subject are available.

Blockade of GPIIb/IIIa receptors by a murine monoclonal antibody such as 7E3 essentially induces a functional thrombusthenic phenotype. 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. 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. Because of concerns about immunogenicity of the original 7E3 antibody, a mouse/human chimeric 7E3 Fab (abciximab) was created for clinical development.

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

The receptor blockade, inhibition of platelet aggregation, and prolongation of bleeding time produced by administering a 0.25 mg/kg-bolus dose of abciximab could be maintained for 12 h by administering a 10-μg/min infusion during that time period. This regimen was chosen for a phase III trial (EPIC) 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 in the article by Popma et al). Although the 6-month follow-up of patients in the EPIC study suggested a potential effect of abciximab on clinical restenosis, the results of several subsequent studies did not support this finding.
Major bleeding was significantly increased in abciximab-treated patients in EPIC. Subsequently, however, it was found that a reduction in the dosage of concomitant heparin and more rapid sheath removal can greatly reduce the bleeding complications attendant to abciximab administration. Besides hemorrhage, thrombocytopenia represents an important side effect of abciximab treatment. Approximately 1 to 2% of patients treated with abciximab develop platelet counts < 50,000/μL, of which approximately 0.5 to 1% reflect very rapid decreases (beginning within 2 h of administration) due to abciximab. 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. Thus far, all reports indicate that the thrombocytopenia can be treated effectively by stopping the drug therapy, and is reversible, with recovery occurring over several days. In the EPIC trial, approximately 6% of patients treated with abciximab developed antibodies to the variable region(s) of abciximab (human antichimeric antibody). Few data are currently available to assess the potential risks of reinjecting abciximab, which theoretically include anaphylaxis, neutralization of injected abciximab, and thrombocytopenia. Although the antiplatelet effect of abciximab in preventing vascular occlusion by suppressing platelet aggregation is likely to be the major mechanism for its beneficial effects, it is quite possible that the potent inhibition of thrombus formation by this antibody may result in decreased thrombin formation. In fact, abciximab produced dose-dependent inhibition of tissue factor-induced thrombin generation, reaching a plateau of 45 to 50% inhibition at concentrations ≥ 15 μg/mL. Whether the inhibition of thrombin generation by abciximab contributes to its immediate antithrombotic effect remains to be established. Abciximab is unique among the GPIIb/IIIa antagonists in also blocking the αβ3 receptor and binding to an activated form of the leukocyte αMβ2 receptor. It is unclear whether any of the effects of abciximab are due to the inhibition of these receptors.

Eptifibatide (Integrilin) is a synthetic disulfide-linked cyclic heptapeptide. It is patterned after the Lys-Gly-Asp derivative of tyrosine that selectively inhibits the GPIIb/IIIa receptor. It inhibits platelet aggregation of gel-filtered platelets induced by 10 μM ADP with an inhibitory concentration (IC50) of 9 nM, but the IC50 for the inhibition of human umbilical vein adhesion to vitronectin, which depends on αβ3 vitronectin receptors, is 62 μM. When administered to humans at a concentration of 0.15 μg/kg/min for 4 h, tirofiban produced a 2.5-fold increase in bleeding time and a 97% inhibition of ADP-induced platelet aggregation. The mean plasma clearance was 329 mL/min, and the half-life in plasma was 1.6 h. After stopping tirofiban therapy, bleeding times returned to normal within 4 h and inhibition of platelet aggregation declined to approximately 20%. When tirofiban was administered with aspirin, the bleeding time increased 4.1 ± 1.5-fold, even though tirofiban plasma levels were unaffected. The plasma concentration of tirofiban needed to inhibit platelet aggregation by 50% decreased, however, from approximately 12 ng/mL to approximately 9 ng/mL when aspirin was coadministered. Peak plasma concentrations were approximately 40 ng/mL, and the plasma levels decreased to < 3 ng/mL within 6 h after therapy was discontinued.

In a pilot study, 73 patients undergoing PTCA were treated with aspirin, heparin, and bolus doses of tirofiban of 5, 10, or 15 μg/kg followed by tirofiban infusions of 0.05, 0.10, and 0.15 μg/kg/min, respectively. The onset of platelet inhibition was rapid, with platelet aggregation in response to 5 μM ADP inhibited by 93% and 96%, respectively, within 5 min of administering the two higher-dose regimens. Bleeding times for the three regimens at 2 h after starting the infusion were 19.5, > 30, and > 30 min, respectively. At the end of the infusion (16 to 24 h), platelet aggregation was inhibited by 57%, 87%, and 95%, respectively, in response to the escalating tirofiban regimens. Platelet aggregation began to return toward normal within 1.5 h after discontinuing the infusion in all groups; 4 h after discontinuing therapy, platelet aggregation inhibition decreased to < 50%, even in the group receiving the highest dose.

Severe but reversible thrombocytopenia has been reported in a small percentage of patients treated with tirofiban, for which 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. No data are available on the safety of reinjecting tirofiban.

Eptifibatide (Integrilin) is a synthetic disulfide-linked cyclic heptapeptide. It is patterned after the Lys-Gly-Asp sequence found in the snake venom disintegrin obtained from Sistrurus m barbouri (barbourin) and has high specificity for the inhibition of GPIIb/IIIa compared with inhibition of the αβ3 vitronectin receptor. Preliminary reports 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 found that the citrate anticoagulation used for platelet aggregation studies resulted in an overestimation of the inhibition of platelet aggregation by eptifibatide. Thus, it is unclear whether there is a differential effect of eptifibatide on the bleeding time. The elimination of eptifibatide depends principally on plasma clearance. Patients treated with heparin plus eptifibatide had longer activated clotting times than patients treated with heparin alone, indicating that eptifibatide, like abciximab, can inhibit thrombin generation in vitro.

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 μg/kg eptifibatide followed by a 1-μg/kg/min infusion for 4 or 12 h, platelet aggregation was measured before the bolus administration, 1 h after the bolus, at the end of the infusion, and 4 h after the end of the infusion. The extent of platelet aggregation in response to 20 μM ADP decreased from approximately 90% before eptifibatide administration to approximately 15% at both 1 h after 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, going 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 infusion. The bleeding times returned toward normal approximately 6 min before treatment to approximately 26 min at the end of the therapy, and they 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, the following four eptifibatide regimens were tested in 54 patients undergoing coronary interventions who also were treated with aspirin and heparin: (1) 180 μg/kg bolus plus 1 μg/kg/min infusion for 18 to 24 h (n = 4); (2) 135 μg/kg bolus plus 0.5 μg/kg/min infusion for 18 to 24 h (n = 16); (3) 90 μg/kg bolus plus 0.75 μg/kg/min infusion for 18 to 24 h (n = 6); and (4) 135 μg/kg bolus plus 0.75 μg/kg/min for 18 to 24 h (n = 28). Fifteen minutes after the 150-μg/kg bolus dose, platelet aggregation was inhibited by > 95% in response to 20 μM ADP, with virtually no interindividual variation, whereas the 135-μg/kg bolus dose resulted in 80 to 90% inhibition in 75% of the patients, and the 90-μg/kg bolus produced only slightly less inhibition than the 135-μg/kg dose. The inhibition of platelet aggregation achieved with the 180-μg/kg bolus dose was sustained throughout the infusion by the 1-μg/kg/min dose, but there was a tendency for the platelet aggregation response to return toward normal during infusion in some patients who were given the 0.75-μg/kg/min dose, and the return of the platelet aggregation response toward normal was more marked in those who were given the 0.5-μg/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 that the infusion was terminated (22, 12, 12, and 17 min, respectively, for the four regimens 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. A modest increase in hemorrhagic complications has been reported in patients treated with eptifibatide in the PURSUIT trial. Eptifibatide treatment has not been associated with an increased frequency of cases of overall thrombocytopenia, but it may be associated with a small increase in cases of profound thrombocytopenia. All patients receiving parenteral GPIIb/IIIa blockers should be monitored within 24 h of the initiation of therapy for development of thrombocytopenia. An algorithm for the detection and management of thrombocytopenia after GPIIb/IIIa blockade has been proposed. To our knowledge, no data are available concerning the safety of reinfusing eptifibatide.

The efficacy and safety of GPIIb/IIIa antagonists were evaluated initially in patients undergoing percutaneous coronary intervention (PCI). More than 13,000 patients have been enrolled in six studies of abciximab, eptifibatide, and tirofiban (Table 7). The first of these phase III trials, the EPIC trial, resulted in the approval of abciximab (ReoPro; Eli Lilly; Indianapolis, IN) in many countries in 1994 for PCI patients at high risk of developing ischemic complication. Eptifibatide and tirofiban have been studied in the IMPACT-II and RESTORE trials, respectively. Although neither of these trials achieved their predefined efficacy end points, there was a positive trend in each case (Table 7). Eptifibatide received approval from the US FDA for PCI in 1998 based on data from the IMPACT-II and PURSUIT trials. The CAPTURE trial demonstrated the efficacy of an 18- to 24-h abciximab treatment prior to PCI in patients with unstable angina refractory to conventional antithrombotic and antianginal therapy. The EPILOG trial demonstrated the efficacy of abciximab in a broad patient population undergoing PCI, not just in high-risk patients such as those enrolled in the EPIC and CAPTURE trials. The EPISTENT trial demonstrated that abciximab decreases the frequency of ischemic complications of PCI associated with stent insertion during the first 30 days and that there are fewer ischemic complications during this time period in patients treated with PCI and abciximab alone without stent insertion than in those treated with stents alone. Furthermore, the 1-year mortality rate difference is statistically significant between patients receiving stents alone (2.4%) and those receiving stents plus

Table 7—GPIIb/IIIa Antagonists in PCI

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Compound</th>
<th>Placebo, %</th>
<th>GPIIb/IIIa Antagonist, %</th>
<th>RRR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPIC</td>
<td>2,099</td>
<td>Abciximab</td>
<td>10.3</td>
<td>6.9</td>
<td>30.0</td>
</tr>
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<td>EPILOG</td>
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<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>56.7</td>
</tr>
<tr>
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<td>Abciximab</td>
<td>10.2</td>
<td>4.8†</td>
<td>52.9</td>
</tr>
<tr>
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<td>Eptifibatide</td>
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<td>17.9</td>
</tr>
<tr>
<td>RESTORE</td>
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<td>Tirofiban</td>
<td>6.4</td>
<td>5.0</td>
<td>21.9</td>
</tr>
</tbody>
</table>

* Rates of death or MI at 30 days are shown for each trial. RRR = RR reduction; EPIC = Evaluation of Platelet IIb/IIIa Inhibition of Prevention of Ischemic Complication.
† Abciximab + low-dose heparin.
‡ Abciximab + stenting vs placebo + stenting.
abciximab therapy (1%). Thus, there continues to be support for the hypothesis that periprocedural myocardial damage, as judged by increases in creatine kinase, confers increased long-term mortality risk.

Although it is possible that all GPIIb/IIIa antagonists will be equally effective with optimal dosing, differences in the pharmacokinetics/pharmacodynamics of these agents may explain the apparent differences in effectiveness observed to date in PCI trials.

Four completed trials have examined the efficacy and safety of tirofiban, lamifiban (a nonpeptide GPIIb/IIIa blocker, the development of which has been discontinued), and eptifibatide in approximately 18,000 patients who had had unstable angina or non-Q-wave MI and were randomized to receive a GPIIb/IIIa antagonist or placebo, in addition to conventional antithrombotic therapy (Table 8).223,228–230 These studies demonstrated a 10 to 27% RR reduction in MI or death at 30 days. Both eptifibatide and tirofiban have received approval from the US FDA for the treatment of acute coronary syndromes, including patients who are to be managed medically and those who are undergoing PCI. Abciximab previously received approval for the treatment of patients with refractory unstable angina who are expected to undergo PCI within 18 to 24 h of beginning abciximab treatment.

The results of phase II trials for abciximab, eptifibatide, and lamifiban, with patients who have had acute MI, have suggested potential benefits of GPIIb/IIIa blockade as an adjunct to thrombolysis. The Thrombolysis in Myocardial Infarction 14A trial demonstrated that combining abciximab with aspirin and reduced-dose tissue-type plasminogen activator in the treatment of acute MI resulted in improved Thrombolysis in Myocardial Infarction grade 3 flow rates at 60 and 90 min after starting therapy when compared to the best full-dose tissue-type plasminogen activator regimen.231 The bleeding risk was not substantially increased.231

Orally active nonpeptide GPIIIa inhibitors have been developed, and they have the potential to be given long term.222,233 However, a number of issues remain unsolved.208–200,234 These include the following: (1) uncertainty as to the optimal degree of GPIIb/IIIa receptor blockade to maximize safety and efficacy; (2) the difficulty of performing assays to monitor therapy such as ADP-induced platelet aggregation or skin bleeding time; and (3) a steep relationship of dose with a surrogate of safety (ie, bleeding time). Assays to monitor the effects of these drugs have been developed, but the benefits of drug monitoring and dose adjustment remain to be established.

In the largest completed trial of an oral GPIIb/IIIa blocker, SYMPHONY,11 9,233 patients whose conditions had stabilized after an acute coronary syndrome were randomized to treatment with aspirin (80 mg bid), low-dose sibrafiban, or high-dose sibrafiban, given within 7 days of and sustained for 90 days after the qualifying event. Sibrafiban doses were based on a model accounting for weight and serum creatinine value and were designed to achieve 25% (low-dose) and 50% (high-dose) steady-state inhibition of ADP-induced platelet aggregation. The incidence of the primary end point, a composite of death, nonfatal (re)infarction, or severe recurrent ischemia at 90 days, did not differ significantly between groups (aspirin, 9.82%; low-dose sibrafiban, 10.06%; and high-dose sibrafiban, 10.05%).11 Similar results were obtained for death or (re)infarction (aspirin, 7.0%; low-dose sibrafiban, 7.4%; and high-dose sibrafiban, 7.9%). Major bleeding was significantly more common with both high-dose (5.7%) and low-dose (5.2%) sibrafiban therapy than with aspirin (3.9%).11 The same was true for minor bleeding (high-dose sibrafiban, 24.6%; low-dose sibrafiban, 17.7%; and aspirin, 12.6%). There were no significant differences for the occurrence of thromboctopenia. Two other large trials have tested oral GPIIb/IIIa antagonists in combination with aspirin as a background therapy, OPUS

### Table 8—GPIIb/IIIa Antagonists in Unstable Angina and Non-Q-Wave MI*

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</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</td>
<td>2,292</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>Eptifibatide</td>
<td>15.7</td>
<td>14.2</td>
<td>9.6</td>
</tr>
</tbody>
</table>

*Rates of death or MI at 30 days are shown for each trial. See Table 7 for abbreviations not used in text.

### Table 9—Main Features of Aspirin, Clopidogrel, and Oral GPIIb/IIIa Antagonists for Long-term Therapy

<table>
<thead>
<tr>
<th>Feature</th>
<th>Aspirin</th>
<th>Clopidogrel</th>
<th>GPIIb/IIIa Antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Targeted platelet protein</td>
<td>COX-1</td>
<td>P2Y_12</td>
<td>GPIIb/IIIa</td>
</tr>
<tr>
<td>Reversibility of the effect</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Desirability of saturation of the target</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Half-life of the drug or active metabolite</td>
<td>Minutes</td>
<td>Minutes</td>
<td>Hours</td>
</tr>
<tr>
<td>Need for monitoring</td>
<td>No</td>
<td>No</td>
<td>Unknown</td>
</tr>
<tr>
<td>Need for dose titration</td>
<td>No</td>
<td>No</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Sixth ACCP Consensus Conference on Antithrombotic Therapy
OPUS was stopped prematurely because of excess mortality in one of the orbofibran groups. An initial review of cause of death suggests that the excess mortality may have been attributable to coronary thrombosis. This finding raises concerns about a paradoxical prothrombotic effect. In fact, induction of fibrinogen binding and platelet aggregation has been described as a potential intrinsic property of various GPIIb/IIa antagonists. Patients receiving orbofibran in the OPUS trial had a paradoxical increase in platelet reactivity with respect to both fibrinogen binding and alpha-granule degranulation. Moreover, in each of the three trials of oral GPIIb/IIa antagonists, the odds ratio for mortality favored aspirin therapy, although it was statistically significant only in OPUS. In all three trials, there were excess bleeding complications in the groups assigned oral GPIIb/IIa antagonists.

In trying to interpret these largely disappointing results, it should be emphasized that GPIIb/IIa antagonists have less than ideal features for long-term antiplatelet prophylaxis, particularly when compared to aspirin and clopidogrel (Table 9). The accumulation of evidence that aspirin, clopidogrel, and dipyridamole are all effective at well-tolerated doses in patients with clinical syndromes of platelet-dependent vascular occlusion is likely to antecede evidence supportive of their combination, as heralded by the roughly additive efficacy of aspirin and dipyridamole in ESPS-2. This is welcome news but increases the challenge for novel antithrombotic agents. Particularly in the setting of long-term oral dosing, tolerability may prove to be an even more important consideration than the magnitude of the increment in efficacy. Thus, issues such as predictable pharmacokinetics and shallow dose-response relationships are likely to be fundamental to the success of future oral therapies.

Whether the different binding features of some of the newer oral agents, such as roxifiban, that have much slower rates of dissociation from platelet GPIIb/IIa than others, or whether new methods of monitoring GPIIb/IIa antagonist therapy, will make a difference for the future development of this interesting class of drugs is currently being debated.

REFERENCES

40 The SALT Collaborative Group Swedish Aspirin Low-Dose Trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischemic events. Lancet 1991; 338:1345–1491


114 Patrono C, Roth GJ. Aspirin in ischemic cerebrovascular disease: how strong is the case for a different dosing regimen? Stroke 1996; 27:756–760


García Rodríguez LA, Phillips-Cay M, et al. Barba-
dos Low dose Aspirin Study in Pregnancy (BLASAP): a
randomised trial for the prevention of pre-eclampsia and its

142 Golding J. A randomised trial of low dose aspirin for
primiparae in pregnancy: The Jamaica Low Dose Aspirin

143 Caritis S, Ribai B, Hauth J, et al. Low-dose aspirin to prevent
338:701–705

144 Dudley L. Aspirin for preventing and treating pre-eclampsia.
BMJ 1999; 318:751–752

145 Roderick PJ, Wilkes HC, Meade TW. The gastrointestinal
toxicity of aspirin: an overview of randomised controlled

146 García Rodríguez LA, Cattaruzzi C, Troncon MG, et al. Risk
of hospitalization for upper gastrointestinal tract bleeding
associated with ketorolac, other nonsteroidal anti-inflamma-
tory drugs, calcium antagonists, and other antihypertensive

aspirin and risk of peptic ulcer bleeding. BMJ 1995; 310:
827–830

148 Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal
toxicity of nonsteroidal anti-inflammatory drugs. N Engl

149 Kelly JP, Kaufman DW, Jurgelson JM, et al. Risk of aspirin-
associated major upper-gastrointestinal bleeding with enteric-
coated or buffered product. Lancet 1996; 348:1413–1416

150 Yeomans ND, Tulassay Z, Juha´sz L, et al. A comparison of
omeprazole with ranitidine for ulcers associated with non-
388:719–726

compared with misoprostol for ulcers associated with non-
steroidal anti-inflammatory drugs. Omeprazole versus Misoprostol
for NSAID-induced Ulcer Management (OMNIUM) Study

152 Iso H, Hennekens CH, Stampfer MJ, et al. Prospective
study of aspirin use and risk of stroke in women. Stroke
1999; 30:1764–1771

153 Mené P, Pugliese F, Patrono C. The effects of nonsteroidal
anti-inflammatory drugs on human hypertensive vascular

154 Pierucci A, Simonetti BM, Pecchi G, et al. Improvement of
renal function with selective thromboxane antagonist in

agents and survival: a cohort analysis from the studies of left

early ACE inhibitor treatment for acute myocardial infar-
cation are similar in the presence and absence of aspirin:
meta-analysis of individual data from nearly 96,000 random-

157 FitzGerald GA, Patrono C. Antiplatelet drugs. In: Verstraete
M, Fuster V, Topol E, eds. Cardiovascular thrombosis-
thromboangiopathy, thromboneurology. Philadelphia, PA:
Lippincott-Raven, 1998; 121–139

158 Patrono C, Cibattoni G, Pugliese F, et al. Estimated rate of
thromboxane secretion into the circulation of normal hu-

159 Reilly IAG, FitzGerald GA. Inhibition of thromboxane
formation in vivo and ex vivo: implications for therapy with

160 García Rodríguez LA, Varas C, Patrono C. Differential
effects of aspirin and non-aspirin nonsteroidal anti-inflam-
matory drugs in the primary prevention of myocardial
infarction in postmenopausal women. Epidemiology 2000;
11:382–387

161 Pedersen AK, FitzGerald GA. Cyclooxygenase inhibition,
platelet function and drug metabolite formation during
chronic administration of sulfipyrazone in man. Clin Pharmaco-
ther 1985; 37:36–42

162 Rebuzzi AG, Natale A, Bianchi C, et al. Effects of indobufen
on platelet thromboxane B2 production in patients with

163 Davi G, Patrono C, Catalano I, et al. Inhibition of throm-
boxane biosynthesis and platelet function by indobufen in
type II diabetes mellitus. Arterioscler Thromb 1993; 13:
1346–1349

therapy with indobufen or aspirin-dipridamole on graft
penancy 1 year after coronary artery bypass grafting. J Thorac
Cardiovasc Surg 1994; 107:1146–1153

165 The SINBA Group. Indobufen versus aspirin plus diprid-
amole after coronary artery surgery. Coron Artery Dis 1991;
2:897–906

166 Fornaro G, Rossi P, Mantica P, et al. Indobufen in the
prevention of thrombo-embolic complications in patients
with heart disease. Circulation 1993; 87:162–164

versus warfarin in the secondary prevention of major vascu-
lar events in nonrheumatic atrial fibrillation. Stroke 1997;
28:1015–1021

testing ticlopidine hydrochloride with indobufen for the
prevention of stroke in high-risk patients (TISS Study):
Ticlopidine Indobufen Stroke Study. Funct Neurol 1997;
12:33–43

169 Brochier ML. Evaluation of flurbiprofen for prevention of
reinfarction and reocclusion after successful thrombolysis or
angioplasty in acute myocardial infarction: the Flurbiprofen
French Trial. Eur Heart J 1993; 14:951–957

170 Ramis J, Torrent J, Mis R, et al. Pharmacokinetics of triflusal
after single and repeated doses in man. Int J Clin Pharmacol
Ther Toxicol 1990; 28:344–349

comparison of rofecoxib and naproxen on the incidence of
clinically important upper gastrointestinal events: The

171b Silverstein FE, Faich G, Goldstein JL, et al. Gastrointesti-
nal toxicity with celecoxib vs nonsteroidal anti-inflammatory
drugs for osteoarthritis and rheumatoid arthritis. The
CLASS Study: a randomized controlled trial. JAMA 2000;
284:1247–1255

172 FitzGerald GA Dipyridamole. N Engl J Med 1987; 316:
1247–1257

alone or combined with low-dose acetylsalicylic acid inhibits
platelet aggregation in human whole blood ex vivo. Br J Clin
Pharmacol 1990; 30:179–186

174 Quinn MJ, FitzGerald DJ. Ticlopidine and clopidogrel.
Circulation 1999; 100:1667–1672

175 Savi P, Pereillo JM, Uzabiaga J, et al. Identification and
biological activity of the active metabolite of clopidogrel.
Circulation 1999; 100:1667–1672

176 Gent M, Blakely JA, Easton JD, et al. The Canadian
American Ticlopidine Study (CATS) in thromboembolic


190 Coller BS, Peerschke EL, Scudder LE, et al. A murine monoclonal antibody that completely blocks the binding of fibrinogen to platelets produces a thrombocytopenic-like state in normal platelets and binds to glycoproteins IIb and/or IIIa. J Clin Invest 1983; 72:325–328


194 Topol EJ, Byzova TV, Flow EJ. Platelet GPIIb/IIIa blockers Lancet 1993; 335:227–231


197 Scarborough RM, Kleinman NS, Phillips DR. Platelet glycoprotein IIb/IIIa antagonists: what are the relevant issues concerning their pharmacology and clinical use? Circulation 1999; 100:437–444


213 Egbertson MS, Chang CT, Duggan ME, et al. Non-peptide

221 Bednar B, Cunningham ME, McQueney PA, et al. Monitoring platelet glycoprotein-IIb/IIIa antagonist therapy. The PURSUIT Trial Investigators. Immediate and reversible platelet inhibition after intravenous administration of a peptide glycoprotein IIb/IIIa inhibitor during percutaneous intervention. Am J Cardiol 1995; 76:1222–1227


224 The RESTORE Investigators. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. Circulation 1997; 96:1445–1453


229 The PARAGON Investigators. A randomized trial of potent platelet IIb/IIIa antagonism, heparin, or both in patients with unstable angina: the PARAGON study [abstract]. Circulation 1996; 94:1–553


235 Collier BS. Monitoring platelet GP IIb/IIIa antagonist therapy. Circulation 1998; 97:5–9

