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ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

# **Antiplatelet Drugs**

## Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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The article describes the mechanisms of action, pharmacokinetics, and pharmacodynamics of aspirin, dipyridamole, cilostazol, the thienopyridines, and the glycoprotein IIb/IIIa antagonists. The relationships among dose, efficacy, and safety are discussed along with a mechanistic overview of results of randomized clinical trials. The article does not provide specific management recommendations but highlights important practical aspects of antiplatelet therapy, including optimal dosing, the variable balance between benefits and risks when antiplatelet therapies are used alone or in combination with other antiplatelet drugs in different clinical settings, and the implications of persistently high platelet reactivity despite such treatment.

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**Abbreviations:** ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; ACTIVE = Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events; ADP = adenosine diphosphate; AMP = adenosine monophosphate; CAPRIE = Clopidogrel vs Aspirin in Patients at Risk for Ischemic Events; COMMIT = Clopidogrel and Metoprolol Myocardial Infarction Trial; COX = cyclooxygenase; CURE = Clopidogrel in Unstable Angina to Prevent Recurrent Events; CURRENT-OASIS 7 = Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/ Organization to Assess Strategies for Ischemic Syndromes; CYP450 = cytochrome P450; EPIC = Evaluation of 7E3 for the Prevention of Ischaemic Complications; ESPRIT = Aspirin Plus Dipyridamole Versus Aspirin Alone After Cerebral Ischaemia of Arterial Origin; ESPS = European Stroke Prevention Study; FDA = US Food and Drug Administration; GPIIb-IIIa = glycoprotein IIb/IIIa; HR = hazard ratio; IMPACT-II = Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis-II; MI = myocardial infarction; NSAID = nonsteroidal antiinflammatory drug; PCI = percutaneous coronary intervention; PGH<sub>2</sub> = prostaglandin H<sub>2</sub>; PGI<sub>2</sub> = prostacyclin; PLATO = Study of Platelet Inhibition and Patient Outcomes; PTCA = percutaneous transluminal coronary angioplasty; RR = rate ratio; TIA = transient ischemic attack; TTP = thrombotic thrombocytopenic purpura; TXA<sub>2</sub> = thromboxane A<sub>2</sub>

**P**latelets are vital components of normal hemostasis and key participants in atherothrombosis by virtue of their capacity to adhere to the injured blood vessel wall; recruit additional platelets to the site of injury; release vasoactive and prothrombotic mediators that trigger vasoconstriction and promote coagulation, respectively; and form aggregates that affect primary hemostasis.<sup>1</sup> Although platelet adhesion, activation, and aggregation can be viewed as a physiologic repair response to the sudden fissuring or rupture of an atherosclerotic plaque, uncontrolled progression of such a process through a series of self-sustaining amplification loops can lead to intraluminal thrombus formation, vascular occlusion, and subsequent ischemia or infarction. Currently available antiplatelet drugs

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interfere with one or more steps in the process of platelet release and aggregation<sup>2</sup> and produce a measurable reduction in the risk of thrombosis that cannot be dissociated from an increased risk of bleeding.<sup>3</sup>

When considering antiplatelet drugs, it is important to appreciate that  $\sim 10^{11}$  platelets are produced each day under physiologic circumstances, a level of production that can increase up to 10-fold at times of increased need.<sup>4</sup> Platelets are anucleated blood cells that form by fragmentation of bone marrow megakaryocyte cytoplasm and have a maximum circulating life span of  $\sim 10$  days. Regulation of platelet production is mediated by thrombopoietin, which is produced primarily in the liver as well as in the bone marrow and the kidney and cleared by binding to high-affinity receptors on platelets and megakaryocytes.<sup>5</sup> In the presence of a high-platelet mass, thrombopoietin levels are reduced, and platelet production falls, whereas in the presence of a low-platelet mass, thrombopoietin levels rise, thereby stimulating thrombopoiesis. Platelets provide a circulating source of chemokines, cytokines, and growth factors, which are preformed and packaged in storage granules. Activated platelets can synthesize prostanoids, primarily thromboxane  $A_2$  (TXA<sub>2</sub>), from arachidonic acid released from membrane phospholipids through rapid coordinated activation of phospholipases, cyclooxygenase (COX)-1, and TX synthase (Fig 1). The inducible form of COX (COX-2) not only is found primarily in the vascular endothelium and in monocytes but is also expressed in newly formed platelets, particularly in the setting of accelerated platelet production.<sup>6</sup> Although activated platelets are incapable of de novo protein synthesis, they can translate constitutive mRNA into protein over the course of several hours.7 Thus, platelets may play a part in inflammation, angiogenesis, and wound healing, and antiplatelet therapies may have an impact on these processes by blocking platelet-derived protein signals for inflammatory or proliferative responses.

Negative modulation of platelet adhesion and aggregation is exerted by a variety of physiologic mechanisms, including endothelium-derived prostacyclin (PGI<sub>2</sub>), nitric oxide, CD39/ecto-ADPase, and platelet endothelial cell adhesion molecule-1. Some drugs may interfere with these regulatory pathways, as exemplified by the dose-dependent inhibition of PGI<sub>2</sub> production by aspirin and other COX-1 and COX-2 inhibitors.<sup>3</sup>

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The article on antiplatelet therapy in the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition) reviewed the antiplatelet effects of traditional nonsteroidal antiinflammatory drugs (NSAIDs) and the cardiovascular effects of COX-2-selective NSAIDs. This topic will not be covered here, and interested readers are referred to the previous article.<sup>8</sup>

#### 1.0 Aspirin

Aspirin is the most widely studied antiplatelet drug. On the basis of >100 randomized trials in high-risk patients, aspirin reduces vascular death by  $\sim 15\%$  and nonfatal vascular events by  $\sim 30\%$ .<sup>9,10</sup>

## 1.1 Mechanism of Action

The best-characterized mechanism of action of aspirin is related to its capacity to permanently inhibit the COX activity of prostaglandin H-synthase-1 and prostaglandin H-synthase-2 (also referred to as COX-1 and COX-2, respectively).<sup>11-15</sup> COX isozymes catalyze the first committed step in prostanoid biosynthesis, the conversion of arachidonic acid to prostaglandin  $H_2$  (PGH<sub>2</sub>) (Fig 1). PGH<sub>2</sub> is the immediate precursor of TXA<sub>2</sub> and PGI<sub>2</sub>.

The molecular mechanism of permanent inhibition of COX activity by aspirin is related to blockade of the COX channel as a consequence of acetylation of a strategically located serine residue (Ser529 in COX-1, Ser516 in COX-2), thereby preventing substrate access to the catalytic site of the enzyme.<sup>16</sup> Complete or near-complete inhibition of platelet COX-1 can be achieved with low doses of aspirin (75-150 mg) given once daily. In contrast, inhibition of COX-2-dependent pathophysiologic processes (eg, hyperalgesia, inflammation) requires larger doses of aspirin and a much shorter dosing interval because nucleated cells rapidly resynthesize the enzyme. Thus, 10- to 100-fold higher daily doses of aspirin are required when the drug is used as an antiinflammatory agent rather than as an antiplatelet agent. The benefit/risk profile of aspirin depends on dose because its GI toxicity is dose dependent (discussed in section 1.3 "The Optimal Dose of Aspirin").

Human platelets and vascular endothelial cells process PGH<sub>2</sub> to produce primarily TXA<sub>2</sub> and PGI<sub>2</sub>, respectively.<sup>12</sup> TXA<sub>2</sub> induces platelet aggregation and vasoconstriction, whereas PGI<sub>2</sub> inhibits platelet aggregation and induces vasodilation.<sup>12</sup> Because TXA<sub>2</sub> is largely derived from COX-1 (mostly from platelets), it is highly sensitive to aspirin inhibition. In contrast, although vascular PGI<sub>2</sub> can be derived from COX-1, its major source is COX-2, even under physiologic conditions.<sup>17</sup> COX-1-dependent PGI<sub>2</sub> production

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FIGURE 1. Arachidonic acid metabolism and mechanism of action of aspirin. Arachidonic acid, a 20-carbon fatty acid containing four double bonds, is liberated from the sn2 position in membrane phospholipids by several forms of phospholipase, which are activated by diverse stimuli. Arachidonic acid is converted by cytosolic prostaglandin H synthases, which have both COX and HOX activity, to the unstable intermediate prostaglandin H<sub>2</sub>. The synthases are colloquially termed "cyclooxygenases" and exist in two forms, COX-1 and COX-2. Low-dose aspirin selectively inhibits COX-1, and high-dose aspirin inhibits both COX-1 and COX-2. Prostaglandin H<sub>2</sub> is converted by tissue-specific isomerases to multiple prostanoids. These bioactive lipids activate specific cell membrane receptors of the superfamily of G-protein-coupled receptors. COX = cyclooxygenase; DP = prostaglandin D<sub>2</sub> receptor; EP = prostaglandin F<sub>2</sub> areceptor; HOX = hydroperoxidase; IP = prostacyclin receptor.

occurs transiently in response to agonist stimulation (eg, bradykinin)<sup>18</sup> and is sensitive to aspirin inhibition. COX-2-mediated PGI<sub>2</sub> production occurs long term in response to laminar shear stress<sup>19</sup> and is relatively insensitive to low-dose aspirin, which may explain the substantial residual COX-2-dependent PGI<sub>2</sub> biosynthesis that occurs with daily doses of aspirin in the range of 30 to 100 mg,<sup>20</sup> despite transient suppression of COX-1-dependent PGI<sub>2</sub> release.<sup>18</sup> It is not established that the greater suppression of PGI<sub>2</sub> formation produced by higher doses of aspirin is sufficient to initiate or predispose to thrombosis. However, two lines of evidence suggest that PGI<sub>2</sub> is thromboprotective. First, mice lacking the PGI<sub>2</sub> receptor exhibit increased susceptibility to injury-induced thrombosis.<sup>21</sup> Second, the cardiovascular toxicity associated with COX-2 inhibitors<sup>22</sup> also supports the concept that PGI<sub>2</sub> is important for thromboresistance in the setting of inadequate inhibition of platelet TXA<sub>2</sub> biosynthesis.<sup>23</sup>

#### 1.2 Aspirin Pharmacokinetics

Aspirin is rapidly absorbed in the stomach and upper intestine. Plasma levels peak 30 to 40 min after aspirin ingestion, and inhibition of platelet function is

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evident within 1 h. In contrast, it can take 3 to 4 h to reach peak plasma levels after administration of enteric-coated aspirin. Therefore, if a rapid effect is required and only enteric-coated tablets are available, the tablets should be chewed instead of swallowed intact. The oral bioavailability of regular aspirin tablets is  $\sim 40\%$  to 50% over a wide range of doses.<sup>24</sup> A considerably lower bioavailability has been reported for enteric-coated tablets and for sustained-release, microencapsulated preparations.<sup>24</sup> The lower bioavailability of some enteric-coated preparations and their poor absorption from the higher pH environment of the small intestine may result in inadequate platelet inhibition when these preparations are used at low doses, particularly in heavier subjects.25 Both a controlled-release formulation<sup>18</sup> and a transdermal patch<sup>26</sup> with negligible systemic bioavailability have been developed in an attempt to achieve selective inhibition of platelet TXA<sub>2</sub> production without suppressing systemic PGI<sub>2</sub> synthesis. The former was used successfully in the Thrombosis Prevention Trial,<sup>27</sup> but it remains unknown whether the controlled-release formulation has any advantages over plain aspirin.

The plasma concentration of aspirin decays with a half-life of 15 to 20 min. Despite the rapid clearance

of aspirin from the circulation, the platelet-inhibitory effects last the life span of the platelet<sup>28</sup> because aspirin irreversibly inactivates platelet COX-1.<sup>13,14</sup> Aspirin also acetylates megakaryocyte COX-1, thereby inhibiting thromboxane production in newly released platelets as well as those already in the circulation.<sup>11,29-31</sup> The mean life span of human platelets is  $\sim 10$  days, which means that  $\sim 10\%$  to 12% of circulating platelets are replaced every day.<sup>32,33</sup> The recovery of thromboxane production and thromboxane-dependent platelet aggregation after prolonged aspirin treatment is stopped is faster than what would be predicted based on the rate of platelet turnover<sup>20</sup> possibly because of the nonlinear relationship between inhibition of platelet COX-1 activity and TXA<sub>2</sub> biosynthesis<sup>34,35</sup> (Fig 2) and the capacity of small amounts of thromboxane produced by nonaspirinated platelets to sustain thromboxane-dependent platelet aggregation.

## 1.3 The Optimal Dose of Aspirin

Effectiveness of Low-Dose Aspirin: Placebocontrolled randomized trials have shown that aspirin is an effective antithrombotic agent when used long term in doses ranging between 50 and 100 mg/d, and there are data to suggest that it is effective in doses as low as 30 mg/d.<sup>9,10</sup> At a dose of 75 mg/d, aspirin was shown to (1) reduce the risk of acute myocardial infarction (MI) or death in patients with unstable angina<sup>36</sup> or chronic stable angina,<sup>37</sup> (2) reduce the risk of stroke or death in patients with transient cerebral ischemia,<sup>38</sup> and (3) reduce the risk of stroke after carotid endarterectomy.<sup>39</sup> In the European Stroke Prevention Study (ESPS)-2, aspirin 25 mg bid reduced the risk of stroke and the composite outcome of stroke or death in patients with prior stroke or transient ischemic attack (TIA).<sup>40</sup> In the European Collaboration on Low-dose Aspirin in Polycythemia vera trial,<sup>41</sup> aspirin (100 mg/d) was effective in preventing thrombotic complications in patients with polycythemia vera, even in the face of higher-than-normal platelet counts. The lowest doses of aspirin demonstrated to be effective for these various indications are shown in Table 1.

Aspirin Dose Comparisons: The clinical effects of different doses of aspirin have been directly compared in randomized controlled trials.<sup>42-48</sup> In the United Kingdom-Transient Ischaemic Attack (UK-TIA) study that randomized 2,435 patients after a TIA or minor ischemic stroke to receive one of two doses of aspirin or placebo, aspirin doses of 300 and 1,200 mg/d were associated with a similar rate of MI, major stroke, or vascular death (20% and 20%, respectively; OR, 1.03; 95% CI, 0.83-1.29).<sup>42</sup> In the Dutch TIA trial, which randomized 3,131 patients after a TIA or minor ischemic stroke, aspirin doses of 30 and 283 mg/d



FIGURE 2. Maximal capacity of human platelets to synthesize  $TXB_2$ , rate of  $TXB_2$  production in healthy subjects, and relationship between the inhibition of platelet cyclooxygenase activity and  $TXB_2$  biosynthesis in vivo. Left, The level of  $TXB_2$  production stimulated by endogenous thrombin during whole-blood clotting at 37°C.<sup>34, 35</sup> Center, The metabolic fate of  $TXA_2$  in vivo and the calculated rate of its production in healthy subjects on the basis of  $TXB_2$  infusions and measurement of its major urinary metabolite. Right, The nonlinear relationship between inhibition of serum  $TXB_2$  measured ex vivo and the reduction in the excretion of thromboxane metabolite measured in vivo.<sup>31</sup>  $TXA_2$  = thromboxane  $A_3$ ;  $TXB_2$  = thromboxane  $B_3$ .

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Table 1—Vascular Disorders for Which Aspirin Has Been Shown to Be Effective and Lowest Effective Dose

Disorder	Lowest Effective Daily Dose, mg
Transient ischemic attack and ischemic stroke <sup>a</sup>	50
Men at high cardiovascular risk	75
Hypertension	75
Stable angina	75
Unstable angina <sup>a</sup>	75
Severe carotid artery stenosis <sup>a</sup>	75
Polycythemia vera	100
Acute myocardial infarction <sup>a</sup>	160
Acute ischemic stroke <sup>a</sup>	160

<sup>a</sup>Higher doses have been tested in other trials and not found to confer any greater risk reduction.

were associated with a similar rate of MI, stroke, or cardiovascular death (14.7% and 15.2%, respectively; hazard ratio [HR], 0.91; 95% CI, 0.76-1.09).47 The ASA and Carotid Endarterectomy (ACE) trial reported that the risk of stroke, MI, or death within 3 months of carotid endarterectomy was significantly lower for patients taking aspirin 81 or 325 mg/d than for those taking 650 or 1,300 mg/d (6.2% vs 8.4%, P = .03).<sup>46</sup> The Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Organization to Assess Strategies for Ischemic Syndromes (CURRRENT-OASIS 7) trial, which included 25,086 patients with acute coronary syndromes (ACSs), found that 30 days of treatment with aspirin 300 to 325 mg/d was no more effective than aspirin 75 to 100 mg/d for the prevention of stroke, MI, or cardiovascular death (4.2% and 4.4%, respectively; HR, 0.97; 95% CI, 0.86-1.09).<sup>48</sup> Thus, on the basis of results from randomized studies comparing different doses of aspirin, there is no convincing evidence that higher doses are any more effective at reducing the risk of serious vascular events than lower doses. In fact, the indirect comparisons reported in the overview of the Antithrombotic Trialists' Collaboration (Table 2) and the results of several direct randomized comparisons are compatible with the reverse; that is, there is blunting of the antithrombotic effect with higher doses of aspirin, a finding consistent with dose-dependent inhibition of PGI<sub>2</sub>.

The Range of Effective Aspirin Doses: The antithrombotic effects of a range of doses of aspirin have

 Table 2—Indirect Comparison of Aspirin Doses

 Reducing Vascular Events in High-Risk Patients

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

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been compared with an untreated control group in a number of thrombotic vascular disorders. The aspirin doses have ranged from 50 to 1,500 mg/d. Aspirin has been shown to be effective in the following conditions: unstable angina where the incidence of acute MI or death was significantly reduced in four separate studies using daily doses of 75,36 325,49 650,50 or 1,300 mg<sup>51</sup>; stable angina where a dose of 75 mg/d reduced the incidence of acute MI or sudden death<sup>37</sup>; aortocoronary bypass surgery where the incidence of early graft occlusion was similarly reduced with daily doses of 100,<sup>52</sup> 325,<sup>53</sup> 975,<sup>54</sup> or 1,200 mg<sup>54</sup>; thromboprophylaxis in patients with prosthetic heart valves who also received warfarin where the incidence of systemic embolism was reduced with daily doses of 100,<sup>55</sup> 500,<sup>56</sup> or 1,500 mg<sup>57,58</sup>; thromboprophylaxis in long-term hemodialysis patients with arterial venous shunts where a dose of 160 mg/d was shown to be effective<sup>59</sup>; acute MI in which a dose of 162.5 mg/d reduced 35-day mortality as well as nonfatal reinfarction and stroke<sup>60</sup>; transient cerebral ischemia in which doses between 50 and 1,200 mg/d were effective<sup>38,40,42,61-63</sup>; acute ischemic stroke where doses of 160 to 300 mg/d were effective in reducing early mortality and stroke recurrence<sup>64,65</sup>; and polycythemia vera in which 100 mg/d,<sup>41</sup> but not 900 mg/d,<sup>66</sup> was effective in reducing fatal and nonfatal vascular events. Thus, aspirin is an effective antithrombotic agent at doses between 50 and 1,500 mg/d. Based on the results of the Dutch TIA study, it is also possible that 30 mg/d is effective.47

Effect of Aspirin Dose on GI Side Effects and Bleeding: There is evidence that the GI side effects of aspirin are dose dependent. Thus, aspirin doses of  $\sim$ 300 mg/d are associated with fewer GI side effects than doses of  $\sim$ 1,200 mg/d.<sup>42</sup> There is also evidence that aspirin doses  $\leq 100 \text{ mg/d}$  are associated with fewer side effects than 300 mg/d.47 In an observational analysis in patients with ACS, the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) investigators demonstrated that aspi $rin \leq 100 \text{ mg/d}$  alone or in combination with clopidogrel was associated with lower rates of major or life-threatening bleeding complications than aspirin alone at a dose of  $\geq 200 \text{ mg/d}$ .<sup>67</sup> In the randomized CURRENT-OASIS 7 trial, aspirin given at a dose of 75 to 100 mg/d produced less GI bleeding than a dose of 300 to 325 mg/d. The incidence of other types of major bleeding was not different between the two groups.<sup>48</sup> In summary, the lack of a doseresponse relationship for the efficacy of aspirin in clinical studies and the dose dependence of GI bleeding support the use of lowest proven effective doses of aspirin as the most appropriate strategy to maximize efficacy and minimize toxicity (Table 1).<sup>9</sup>

## 1.4 High On-Treatment Platelet Reactivity (Aspirin Resistance)

High platelet reactivity in patients prescribed aspirin has been associated with an increased risk of thrombotic events. Therefore, this phenomenon has been used as one definition of aspirin resistance. Observational studies demonstrate that about one-third of patients treated with aspirin demonstrate less-thanexpected inhibition of agonist-induced platelet aggregation and increased levels of urinary thromboxane.<sup>8-10</sup> Estimates of the prevalence of high on-treatment platelet reactivity are affected by differences among the studies in patient characteristics (eg, age, female sex, diabetes), concomitant therapies (particularly NSAIDs, eg, ibuprofen), the laboratory test used to measure the antiplatelet effects of aspirin (light transmission or whole-blood aggregometry, shear stressinduced platelet activation, expression of activation markers on the platelet surface as measured by flow cytometry, inhibition of thromboxane production), the cutoff used to define high on-treatment reactivity, and patient compliance with aspirin therapy.<sup>25</sup> Despite these differences, high platelet reactivity in patients prescribed aspirin has been consistently associated with a twofold to fourfold higher risk of MI, stroke, or death.9,10,26,27

If thrombotic events in aspirin-treated patients with high on-treatment platelet reactivity were solely attributable to reduced responsiveness to aspirin, strategies aimed at improving the response would be expected to reduce this risk. Observational studies suggest that aspirin inhibits platelet function68-72 and coagulation<sup>73-79</sup> in a dose-dependent manner; a finding confirmed in a randomized dose comparison.<sup>80</sup> Thus, in a randomized, double-blind, crossover trial that included 125 patients with stable coronary artery disease, Gurbel and colleagues<sup>80</sup> demonstrated that at doses of 81, 162, or 325 mg/d, aspirin inhibited adenosine diphosphate (ADP) and collagen-induced platelet aggregation, blocked sheardependent platelet aggregation measured by the PFA-100 device, and reduced urinary thromboxane concentrations in a dose-dependent manner. Most of the patients included in this study demonstrated near-complete inhibition of arachidonic acid-induced platelet aggregation with the 81-mg/d dose of aspirin, but higher aspirin doses reduced the proportion of patients in whom arachidonic acid-induced aggregation exceeded a cutoff value of 20%.<sup>80</sup> However, the dose-dependent inhibition of platelet function and thromboxane production by aspirin observed in this study does not fit with the results of the CURRENT-OASIS 7 trial, which failed to demonstrate a reduction in the risk of thrombotic events with higher doses of aspirin (See section 1.3 "The

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Optimal Dose of Aspirin"). How do we explain this apparent paradox?

The most likely explanation is that the relationship between platelet reactivity and thrombotic risk is confounded by comorbidities, such as smoking or diabetes, that affect both platelet function and cardiovascular risk. It is also possible that the laboratory tests used to measure platelet reactivity fail to monitor the mechanism by which aspirin reduces the risk of thrombotic events. Many of these tests use nonphysiologic stimuli to induce platelet aggregation, and none assess platelet interaction with the vessel wall or the effect of aspirin on COX-2-dependent PGI<sub>2</sub> production. Thromboxane production appears to be the most specific measure of the inhibitory effects of aspirin because thromboxane is the major biochemical end product of the platelet COX-1 biosynthetic pathway that is targeted by aspirin. However, serum thromboxane levels reflect the maximum capacity of platelets to produce thromboxane; urinary thromboxane is also produced from nonplatelet sources, and measures of thromboxane concentration do not capture the effect of aspirin on PGI<sub>2</sub> production.

Given the multifactorial triggers of atherothrombosis and the likelihood that platelet activation and subsequent aggregation are not the sole mediators of vascular events, it is not surprising that only a fraction (usually one-fourth to one-third) of all vascular complications can be prevented by aspirin alone. There is no evidence that patients who experience a thrombotic event despite aspirin therapy benefit from treatment with higher-dose aspirin. Concomitant administration of nonselective NSAIDs, such as ibuprofen, should be avoided because, as outlined previously, these drugs can interfere with the antiplatelet effect of aspirin.<sup>16</sup> A pharmacodynamic interaction between naproxen and aspirin has also been described,<sup>81</sup> but this does not appear to occur with rofecoxib,<sup>82</sup> celecoxib,<sup>83</sup> or diclofenac,<sup>82</sup> drugs endowed with variable COX-2 selectivity.<sup>84</sup> The US Food and Drug Administration (FDA) has issued a statement informing patients and health-care professionals that ibuprofen can interfere with the antiplatelet effect of low-dose aspirin (81 mg/d), potentially rendering aspirin less effective when used for cardioprotection or stroke prevention.85

## 1.5 Efficacy and Safety

(a) Prevention of Atherothrombosis: The efficacy and safety of aspirin are documented from analyses of >100 randomized controlled trials that have included thousands of patients representing the entire spectrum of atherosclerosis, ranging from apparently healthy low-risk individuals to patients presenting with an acute MI or acute ischemic stroke. Trials have evaluated aspirin therapy of only a few weeks duration or as long as 10 years.<sup>9,10</sup> Although aspirin has consistently been shown to be effective in preventing fatal and nonfatal vascular events in these trials, the absolute benefits depend on the clinical setting.

In Second International Study of Infarct Survival (ISIS-2),<sup>59</sup> a single 162.5-mg tablet of aspirin started within 24 h of the onset of symptoms of a suspected MI and continued at the same dose daily for 5 weeks produced highly significant reductions in vascular mortality, nonfatal reinfarction, and nonfatal stroke (23%, 49%, and 46%, respectively). There was no associated increase in hemorrhagic stroke or GI bleeding with aspirin, although there was a small increase in minor bleeding.<sup>59</sup> Based on the results of this study, a 5-week course of aspirin treatment in 1,000 patients with suspected acute MI will prevent ~40 vascular events,<sup>10</sup> a proportional odds reduction of 30%.

Two separate trials with a similar protocol tested the efficacy and safety of early aspirin use in acute ischemic stroke. The Chinese Acute Stroke Trial<sup>64</sup> and the International Stroke Trial<sup>65</sup> collectively randomized  $\sim$ 40,000 patients within 48 h of the onset of stroke symptoms to 2 to 4 weeks of daily aspirin therapy (at doses of 160 and 300 mg/d, respectively) or to placebo. An overview analysis of the results of both trials indicated an absolute benefit of nine fewer deaths or nonfatal strokes per 1,000 patients in the first month of aspirin therapy.<sup>10</sup> The proportional odds reduction in the risk of fatal or nonfatal vascular events was only 10% in this setting. Although the background risk of hemorrhagic stroke was threefold higher in the Chinese Acute Stroke Trial than in the International Stroke Trial, the absolute increase in this risk was similar in the two studies (an excess of 2/1,000 aspirin-treated patients).<sup>64,65</sup>

Long-term aspirin therapy confers a conclusive net benefit on the risk of subsequent MI, stroke, or vascular death among subjects with a high risk of vascular complications. These include patients with chronic stable angina,<sup>37</sup> prior MI,<sup>10</sup> unstable angina,<sup>36,49-51</sup> history of TIA or minor stroke, 37,40,42,62,63,86 and other high-risk categories.<sup>10</sup> The proportional reduction in vascular events with long-term aspirin therapy in these various clinical settings ranges from 20% to 25% based on an overview of all of the randomized trials.<sup>10</sup> Estimates of relative benefits based on the results of individual trials vary from no statistically significant benefit in patients with peripheral arterial disease to an  $\sim 50\%$  risk reduction in patients with unstable angina.<sup>10</sup> In terms of absolute benefit, the protective effects of aspirin translate into avoidance of a major vascular event in 50 of 1,000 patients with unstable angina treated with aspirin for 6 months to 36 of 1,000 patients with prior MI, stroke, or TIA treated with aspirin for  $\sim 30$  months.<sup>10</sup>

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For patients with various manifestations of ischemic cardiac or neurologic disease, there is consensus that the optimal dose of aspirin for prevention of MI, stroke, or vascular death lies within the narrow range of 75 to 160 mg/d. This concept is supported by an overview of all antiplatelet trials that showed no obvious aspirin dose dependence for the protective effects of aspirin based on direct and indirect comparisons<sup>10</sup> as well as by the results of individual trials that randomized patients to treatment with low-dose aspirin or placebo or to two different doses of aspirin (Table 3). As discussed earlier, there is no convincing evidence that the dose requirement for the antithrombotic effect of aspirin varies in different clinical settings.

(b) Primary Prevention: Among most high-risk patient groups, the expected number of individuals avoiding a serious vascular event by using aspirin substantially exceeds the number experiencing a major bleed. It is less certain, however, whether aspirin is of benefit in apparently healthy people who are at intermediate risk for serious vascular events because they have well-established cardiovascular risk factors. The Antithrombotic Trialists' Collaboration addressed this issue in an individual participant data meta-analysis of the results of large randomized trials of aspirin for primary prevention of vascular events.<sup>87</sup> The analysis was based on the results of six primary prevention trials that included 95,456 subjects<sup>27,88-92</sup> with a mean follow-up of 6.9 years and a median follow-up among survivors of 5.5 years, reflecting the fact that the Women's Health Study,<sup>91</sup> which accounted for almost one-half of the participants, had a mean follow-up of  $\sim 10$  years (Table 4). The effects of aspirin for primary prevention were compared with its effects in high-risk settings using the results of six trials among patients with a history of MI, nine trials among patients with a history of TIA or stroke, and one trial in patients with moderately severe diabetic retinopathy.<sup>10</sup>

The results of the Antithrombotic Trialists' Collaboration individual patient meta-analysis indicated a 12% proportional reduction in the incidence of serious vascular events (rate ratio [RR], 0.88; 95% CI, 0.82-0.94; P = .0001) and an 18% proportional reduction in the incidence of major coronary events (RR, 0.82; 95% CI, 0.75-0.90; P < .0001). Most of the benefit of aspirin was due to a 23% reduction in nonfatal MI (RR, 0.77; 95% CI, 0.67-0.89; P < .0001); there was no apparent reduction in cardiovascular death (RR, 0.95; 95% CI, 0.78-1.15; P = .50). Aspirin was associated with a nonsignificant 10% reduction in nonhemorrhagic stroke (RR, 0.90; 95% CI, 0.80-1.01; P = .08).

Aspirin had no significant effect on the aggregate of all vascular causes of death (RR, 0.98; 95% CI,

Table 3—[Section 2.4] Dose and Time Dependence of the Effects of Aspirin on Platelets and Inflammatory Cells

Cellular Target	Enzyme	Single Dose, mg <sup>a</sup>	Duration of Prostanoid Suppression, h	Cumulative Effects Upon Repeated Dosing	Daily Dose, mg <sup>b</sup>
Platelets	COX-1	100	24-48	Yes	50-81
Inflammatory cells	COX-2	$\geq\!650$	3-4	No	3,000-5,000

COX = cyclooxygenase.

<sup>a</sup>Dose causing complete or near-complete suppression of prostanoid formation and clinically detectable functional effect after single dosing. <sup>b</sup>Range of doses shown clinically effective in long-term trials of cardiovascular protection or rheumatoid arthritis.

0.87-1.10; *P* not significant), and there was no evidence of a protective effect on the two-thirds of vascular deaths due to coronary heart disease (RR, 0.95; 95% CI, 0.78-1.15; *P* = .5), the one-sixth due to stroke (RR, 1.21; 95% CI, 0.84-1.74; *P* = .2), or the remaining vascular causes of death (RR, 0.90; 95% CI, 0.65-1.26; *P* = .4). Aspirin had no significant effect on nonvascular mortality (RR, 0.93; 95% CI, 0.85-1.02; *P* = .1) or unknown causes of death (RR, 0.95; 95% CI, 0.75-1.21; *P* not significant) but increased the risk of major extracranial bleeds (RR, 1.55; 95% CI, 1.31-1.83; *P* < .0001).

The absolute benefits of aspirin were summarized under the term "occlusive vascular events," that is, vascular events other than hemorrhagic stroke or fatal extracranial bleeds. Among low-risk individuals (annual risk of coronary heart disease  $\leq 1\%$ ), allocation to aspirin resulted in the avoidance of four (95% CI, 2-6) occlusive vascular events per 1,000 after 5 years, which was chiefly attributable to three (95% CI, 1-5) fewer major coronary events. This benefit was offset by two (95% CI, 1-3) additional major extracranial bleeds per 1,000 over the same 5-year period, but there was no significant excess risk of hemorrhagic stroke (0.1 [95% CI, -0.5 to 0.7] excess;*P* not significant). Among the much smaller number of moderate-risk participants (yearly coronary heart disease risk >1%), the net effect of aspirin over 5 years on occlusive vascular events was statistically uncertain (13 [95% CI, -3-29] fewer; P = .1) because despite a definite reduction in major coronary events (18 [95% CI, 5-30] fewer per 1,000), there was no significant reduction in presumed ischemic stroke (one fewer per 1,000 [95% CI, nine more to 11 fewer]), and there was an excess of both hemorrhagic stroke (five [95% CI, 1-9] more per 1,000) and major bleeds (4 more per 1,000 [95% CI, one fewer to 10 more]). About one-half of the hemorrhagic strokes were fatal (and the remainder would be expected to result in moderate or severe disability), so this hazard substantially offsets any cardiac benefits in moderate-risk individuals.

The results of three subsequently completed primary prevention trials involving 7,165 patients with diabetes, peripheral arterial disease, or both (Table 4<sup>27,88-95</sup>) are consistent with those of the individual patient meta-analysis performed by the Antithrombotic Trialists' Collaboration.<sup>93-95</sup> A meta-analysis of all nine primary prevention trials demonstrated a borderline significant reduction in all-cause mortality with aspirin but no reduction in cardiovascular mortality,<sup>96</sup> a finding that raises the possibility that aspirin also prevents nonvascular (cancer) mortality (Discussed in "Cancer Incidence and Mortality").

Previous meta-analyses of the effects of antiplatelet therapy in persons at high risk of occlusive vascular disease<sup>7</sup> have shown that the benefits of aspirin far exceed the bleeding risks. By contrast, the majority (92%) of participants in the primary prevention trials was at low absolute risk of coronary disease; on average, the annual risk of a vascular event in the primary prevention trials was only about one-tenth of that in the high-risk trials. Although the proportional benefits of aspirin appeared broadly similar when used for primary or secondary prevention, the absolute benefits of aspirin in the primary prevention trials were very small. When used for primary prevention, fewer than one person of every 1,000 treated with aspirin would avoid an occlusive vascular event, whereas a comparably small number would experience a major extracranial bleed. Until the benefits of aspirin can be defined more precisely, therefore, the possibility of a benefit for vascular prevention does not seem to justify the potential for harms. However, these estimates do not take into account the benefits of aspirin for the prevention of cancer and cancerrelated mortality, which might tip the balance in favor of aspirin use for primary prevention. Additional trials evaluating the utility of aspirin for primary prevention of cardiovascular disease in elderly patients<sup>97,98</sup> and in patients with diabetes<sup>99</sup> are ongoing. Readers are referred to the prevention of cardiovascular disease article in this supplement by Vandvik et al.<sup>100</sup>

(c) Atrial Fibrillation: Anticoagulant therapy with dose-adjusted warfarin (international normalized ratio, 2.0-3.0),<sup>101</sup> the direct thrombin inhibitor dabigatran etexilate,<sup>102</sup> or the direct factor Xa inhibitors rivaroxaban and apixaban<sup>103</sup> is very effective in reducing the risk of stroke in patients with nonvalvular atrial fibrillation. The efficacy of aspirin (in doses ranging from 75-1,200 mg/d) has been compared with that of

	Dates of	Year of	Mean Duration		Eligible		Randomized Factorial	Placebo
Trial	Recruitment	Publication	of Follow-up, y	Target Population	Age Range, y	Intervention	Comparison	Control
British Doctors Study <sup>90</sup>	November 1, 1978, to November 1, 1979	1988	5.6	Male physicians	19-90	500  mg/d	None	No
US Physicians <sup>92</sup>	August 24, 1981, to April 2, 1984	1988	5.0	Male physicians	45-73 (men)	325 mg alternate d	β-carotene (alternate days) vs placebo	Yes
Thrombosis Prevention Trial <sup>27</sup>	February 6, 1989, to May 18, 1994	1998	6.7	Men with risk factors for CHD	45-69	75 mg/d	Warfarin vs placebo	Yes
Hypertension Optimal Treatment <sup>59</sup>	October 12, 1992, to May 7, 1994	1998	3.8	Men and women with DBP 100-115 mm Hg	31-75	75 mg/d	3 target DBPs $(< 80, < 85, < 90)$	Yes
Primary Prevention Project <sup>ss</sup>	June 8, 1993, to April 21, 1998	2001	3.7	Men and women with $\geq 1$ risk factor for CHD	45-94	100  mg/d	Vitamin E vs open control	No
Women's Health Study <sup>81</sup>	September 1992 to May 1995	2005	10.1	Female health professionals	>45	100 mg alternate d	Vitamin E vs placebo	Yes
Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes <sup>83</sup>	December 2002 to May 2005	2008	4.4	Type 2 diabetes without history of atherosclerotic disease	30-85	81 or 100 mg/d	None	No
Prevention of Progression of Arterial Disease and Diabetes <sup>94</sup>	November 1997 to July 2001	2008	6.7	Diabetes and ABI≤0.99, no symptomatic cardiovascular disease	≥40	100 mg/d	Antioxidant vs placebo	Yes
Aspirin for Asymptomatic Atherosclerosis study <sup>65</sup>	April 1998 to October 2008	2010	8.2	ABI ≤ 0.95, free of clinical cardiovascular disease	50-75	100 mg/d	None	Yes
The first six trials listed in the table w BP.	vere included in the Antith	rrombotic Trial	ists' Collaboration	individual patient meta-analysi	s. ABI = ankle-b	orachial index; CHD =	coronary heart disease; DBP =	diastolic

 Table 4—Primary Prevention Trials

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placebo or no antiplatelet treatment in seven randomized trials that included 3,990 patients with nonvalvular atrial fibrillation.<sup>101</sup> A pooled analysis revealed a relative risk reduction of  $\sim 19\%$  with aspirin compared with placebo or no treatment (95% CI, -1%-35%), which is consistent with the 22% (95% CI, 6%-35%) relative risk reduction obtained when comparing any antiplatelet therapy with placebo or no antiplatelet therapy for stroke prevention in patients with nonvalvular atrial fibrillation.<sup>101</sup> Pooled analysis of 10 trials involving 4,620 patients with nonvalvular atrial fibrillation revealed that dose-adjusted vitamin K antagonist therapy was significantly more effective than aspirin, with a 39% relative risk reduction (95% CI, 19%-53%).<sup>104</sup> Warfarin is also more effective than the combination of aspirin and clopidogrel.<sup>105</sup>

The efficacy of antiplatelet therapy for stroke prevention in atrial fibrillation has been confirmed by the results of the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE) A trial, which compared the combination of aspirin plus clopidogrel with aspirin alone in 7,554 patients deemed ineligible for warfarin.<sup>106</sup> Aspirin plus clopidogrel reduced the risk of major vascular events, comprising the composite of stroke, MI, non-CNS embolism, or death from vascular causes, by 11% compared with aspirin (95% CI, 2%-19%) primarily because of a 28% reduction in stroke (95% CI, 17%-38%). However, the combination of clopidogrel plus aspirin is less effective than warfarin and is associated with a similar risk of bleeding.<sup>105</sup> Readers are referred to You et al<sup>107</sup> in this guideline for further discussion of the use of antiplatelet therapy for stroke prevention in patients with atrial fibrillation.

(d) VTE: The Pulmonary Embolism Prevention (PEP) trial results demonstrated that aspirin is effective in preventing VTE after major orthopedic surgery.<sup>108</sup> This double-blind, multicenter study included 13,356 patients undergoing surgery for hip fracture and an additional 4,088 patients undergoing elective hip or knee arthroplasty. Patients were randomized to receive aspirin (160 mg/d) or placebo for 5 weeks, with the first dose administered prior to surgery. Other forms of prophylaxis were allowed, and either heparin or low-molecular-weight heparin was used in  $\sim 40\%$  of the patients. Among the 13,356 patients undergoing surgery for hip fracture, aspirin produced a 36% reduction in symptomatic DVT or pulmonary embolism (absolute risk reduction, 0.9%; P = .0003). A similar relative risk reduction was observed in aspirin-treated patients who did or did not receive concomitant heparin or low-molecular-weight heparin. These results are consistent with those of meta-analyses performed

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by the Antiplatelet Trialists' Collaboration<sup>109</sup> and by Sandercock and colleagues<sup>110</sup> of antiplatelet trials in patients with stroke.

When compared with warfarin, heparin, lowmolecular-weight heparin, or danaparoid, aspirin was associated with similar or higher rates of DVT detected by screening ultrasound or venography; however, the frequency of symptomatic events was low.<sup>111</sup> A large randomized controlled trial is required to compare the effectiveness of aspirin with that of anticoagulants for the prevention of fatal or symptomatic VTE events. Readers are referred to Falck-Ytter et al<sup>112</sup> in this guideline for further discussion of the use of antiplatelet therapy for prevention of VTE.

(e) Placental Insufficiency: Preeclampsia and fetal growth restriction are believed to be related to reduced placental blood flow, which is believed to be caused by constriction, thrombosis, or both of small placental arteries.<sup>113</sup> The initial reports that low-dose aspirin therapy reduces the risk of severe low birth weight among newborns<sup>114</sup> and lowers the need for cesarean section in mothers with pregnancy-induced hypertension<sup>114</sup> led to the widespread use of prophylactic aspirin for prevention of preeclampsia. Subsequently, several larger trials reported no beneficial effects of aspirin.<sup>115-121</sup> However, a systematic review of data from 59 trials in 37,560 women confirmed that antiplatelet therapy (mostly aspirin 60 mg/d) is beneficial. Aspirin was associated with a 17% decrease in the risk of preeclampsia, an 8% reduction in the risk of preterm birth, a 14% reduction in the risk of fetal or neonatal death, and a 10% reduction in smallfor-gestational age babies.<sup>122</sup> An individual patient meta-analysis of 31 trials involving 32,217 patients who received antiplatelet therapy for primary prevention of preeclampsia revealed a consistent benefit of aspirin for the prevention of eclampsia (overall 10% relative risk reduction) in all of the subgroups studied (first pregnancy with or without any high risk factor; second pregnancy with or without high risk factors or history of hypertensive disorder of pregnancy; preexisting renal disease, diabetes, hypertension, or previous infant small for gestational age; maternal age; singleton or multiple pregnancy; and timing of starting of treatment or intended aspirin dose  $\leq 75 \text{ mg/d}$  or  $\geq 75 \text{ mg/d}$ .<sup>123</sup> Aspirin given in doses ranging from 50 to 150 mg/d accounted for 98% of women included in this data set. Readers are referred to Bates et al<sup>124</sup> in this guideline for further discussion of the use of antithrombotic therapy during pregnancy.

(f) Cancer Incidence and Mortality: There is compelling evidence from randomized controlled trials that aspirin reduces the incidence of colorectal cancer

and cancer mortality.<sup>125,126</sup> An individual patient metaanalysis of eight randomized controlled trials that included 25,570 subjects demonstrated that compared with no aspirin, daily aspirin for a scheduled mean treatment duration of at least 4 years reduced the odds of cancer deaths by 21% (95% CI, 8%-32%). The mortality benefit appeared to be unrelated to aspirin dose, only became apparent after 5 years of follow-up, and the absolute benefit increased over time. The greatest mortality benefit was seen with adenocarcinoma. Among patients aged  $\geq 65$  years at the start of the trials, the absolute reduction in cancer deaths over 20 years was 7.1% (95% CI, 2.4%-11.7%).<sup>126</sup> Separate analyses based on individual patient data from four trials of 14,033 patients followed for a median of 18.3 years demonstrated that aspirin (at doses of 75-300 mg/d) also reduced the incidence of colorectal cancer. Furthermore, an analysis from the Dutch TIA trial suggested that the risk of fatal colorectal cancer was higher with aspirin doses of 30 mg/d than it was with a dose of 283 mg/d.126

(g) Adverse Effects of Aspirin: Aspirin-induced impairment of primary hemostasis cannot be separated from its antithrombotic effect and appears to be similar with all doses  $\geq 75 \text{ mg/d.}^9$  The balance between preventing thrombotic events and causing bleeding with aspirin critically depends on the absolute thrombotic vs hemorrhagic risk of the patient. Thus, in individuals at low risk for vascular occlusion (eg,  $\leq 1\%$  per year), the very small reduction of vascular events is probably offset by bleeding complications. In contrast, in patients at high risk of cardiovascular or cerebrovascular complications (eg, > 3% per year), the substantial absolute benefit of aspirin prophylaxis clearly outweighs the harm (Table 5). For example, the absolute excess of major bleeds (ie, those requiring transfusion) in patients with acute MI is  $\sim 1/100$ th the absolute number of major vascular events avoided by aspirin therapy.<sup>10</sup>

The overall risk of major extracranial and intracranial hemorrhage associated with antiplatelet drugs is difficult to assess in individual trials because their incidence is < 1% per year. This makes 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, with doses in the range of 30 to 1,300 mg/d.<sup>127</sup> This conclusion is based on both indirect comparisons of different trials and direct randomized comparisons of different aspirin doses, as reviewed previously in this article. The dose-response relationship for GI toxicity is believed to reflect at least two COX-1-dependent components: dose-dependent inhibition of COX-1 in the GI mucosa and dose-independent (within the range of examined

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#### Table 5—Benefit and Harm of Antiplatelet Prophylaxis With Aspirin in Different Settings

Clinical Setting	Benefits, No. of Patients in Whom a Major Vascular Event Is Avoided per 1,000/y <sup>a</sup>	Harm, No. of Patients in Whom a Major GI Bleeding Event Is Caused per 1,000/y <sup>b</sup>
Patients at low to high cardiovascular risk	1-2	1-2
Essential hypertension	1-2	1-2
Chronic stable angina	10	1-2
Prior myocardial infarction	20	1-2
Unstable angina	50	1-2

<sup>a</sup>Benefits are calculated from randomized trial data reviewed in this article and depicted in Figure 3.

<sup>b</sup>Excess of upper-GI bleedings are estimated from a background rate of one event per 1,000/y in the general population of nonusers and a relative risk 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 nonsteroidal antiinflammatory drugs and may actually underestimate the absolute risk in an elderly population exposed to primary prevention.

doses) inhibition of COX-1 in platelets.<sup>6</sup> Thus, it is not surprising that the antithrombotic effect of aspirin can be dissociated, at least in part, from GI bleeding. Even at low doses, aspirin causes serious GI bleeding.40,47 Because of the underlying prevalence of gastric mucosal erosions related to concurrent use of other NSAIDs and *Helicobacter pylori* infection in the general population, it should be expected that any dose of aspirin will cause more GI bleeding from preexisting lesions than placebo. Consistent with this mechanistic interpretation, the relative risk of hospitalization due to upper-GI bleeding and perforation associated with low-dose aspirin therapy (mostly 100-300 mg/d) is comparable to that with other antiplatelet drugs and anticoagulants (ie, 2.3 [95% CI, 1.7-3.2], 2.0 [95% CI, 1.4-2.7], and 2.2 [95% CI, 1.4-3.4], respectively, in a large population-based observational study<sup>128</sup>).

In the 2002 overview of randomized trials of aspirin for secondary vascular prevention performed by the Antithrombotic Trialists' Collaboration,<sup>10</sup> information was available on 787 major extracranial hemorrhages in 60 trials recording at least one such hemorrhage. These were generally defined as hemorrhages that were fatal or required transfusion; among them, 159 (20%) caused death. Overall, the proportional increase in risk of a major extracranial bleed with antiplatelet therapy was about one-half (OR, 1.6; 95% CI, 1.4-1.8), with no significant difference between the proportional increases observed in each of the five high-risk categories of patients. A similar proportional increase in extracranial bleeding was obtained in the 2009 individual patient metaanalysis by the Antithrombotic Trialists' Collaboration of six trials of aspirin for primary prevention that

![](_page_11_Figure_0.jpeg)

FIGURE 3. The absolute risk of vascular complications is the major determinant of the absolute benefit of antiplatelet prophylaxis. Data are plotted from placebo-controlled aspirin trials in different clinical settings. For each category of patients, the abscissa denotes the absolute risk of experiencing a major vascular event as recorded in the placebo arm of the trials. The absolute benefit of antiplatelet treatment is reported on the ordinate as the number of subjects in whom an important vascular event (nonfatal MI, nonfatal stroke, or vascular death) is actually prevented by treating 1,000 subjects with aspirin for 1 year. MI = myocardial infarction.

included 554 extracranial hemorrhages (OR, 1.5; 95% CI, 1.3-1.8).<sup>87</sup>

A case-control study with hospital and community controls examined the risks of hospitalization for bleeding peptic ulcer associated with three different regimens of aspirin prophylaxis.<sup>129</sup> ORs were calculated for different doses of aspirin: 75 mg (2.3; 95% CI, 1.2-4.4), 150 mg (3.2; 95% CI, 1.7-6.5), and 300 mg (3.9; 95% CI, 2.5-6.3). Additional epidemiologic studies have found a dose-response relationship between aspirin prescription and upper-GI complications, as reviewed by García Rodríguez et al.<sup>130</sup> It has been calculated that  $\sim 900$  of the 10,000 episodes of ulcer bleeding occurring in persons aged >60 years each year in England and Wales could be associated with and ascribed to prophylactic aspirin use.<sup>129</sup> If the assumptions from indirect comparisons are correct, a general change to lower doses (75 mg/d) of aspirin would not eliminate the risk but would reduce it by  $\sim 40\%$  compared with a 300-mg dose and by 30% compared with a 150-mg dose.<sup>129</sup> The mortality rate among patients who are hospitalized for NSAID-induced upper-GI bleeding is 5% to 10%.131,132

The widely held belief that enteric-coated and buffered aspirin preparations are less likely to cause major upper-GI bleeding than plain tablets was evaluated in a multicenter case-control study.<sup>133</sup> The relative risks of upper-GI bleeding for plain, entericcoated, and buffered aspirin at average daily doses of  $\leq 325$  mg were 2.6, 2.7, and 3.1, respectively. At doses > 325 mg, the relative risk was 5.8 for plain and 7.0 for buffered aspirin; there were insufficient data to evaluate enteric-coated aspirin at this dose level.<sup>133</sup>

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Similar conclusions were reached by a case-control study using data from the UK General Practice Research Database. $^{134}$ 

Suppressing acid secretion is believed to reduce the risk of ulcers associated with the regular use of NSAIDs. In patients who required continuous treatment with NSAIDs and who had ulcers or > 10 erosions in their stomach or duodenum, omeprazole healed and prevented ulcers more effectively than did ranitidine.<sup>135</sup> In these patients, maintenance therapy with omeprazole was associated with a lower rate of relapse and was better tolerated than misoprostol.<sup>136</sup> In patients with a history of previous ulcer bleeding who took low-dose aspirin for 6 months, omeprazole and *H pylori* eradication were associated with similar rates of recurrent bleeding (0.9% and 1.9%, respectively),<sup>137</sup> although clinically important differences between the two preventive strategies could not be excluded owing to the small sample size (n = 250).

Two relatively small studies<sup>138,139</sup> have challenged earlier guidelines that recommended the use of clopidogrel for patients who have major GI contraindications to aspirin, principally recent significant bleeding from a peptic ulcer or gastritis. Both studies enrolled patients who developed ulcer bleeding after the use of low-dose aspirin. In a study by Chan et al,<sup>138</sup> after healing of ulcers and eradication of *H pylori*, if present, 320 patients were randomly assigned to receive either clopidogrel 75 mg/d or aspirin 80 mg/d plus esomeprazole 20 mg bid for 12 months. The cumulative incidence of recurrent bleeding was 8.6% (95% CI, 4.1%-13.1%) among patients who received clopidogrel and 0.7% (95% CI, 0%-2.0%) among those who received aspirin plus esomeprazole (P = .001).<sup>138</sup> In a study by Lai et al,<sup>139</sup> 170 patients with prior ulcer bleeding were randomly assigned to treatment with clopidogrel 75 mg/d or aspirin 100 mg/d and esomeprazole 20 mg/d for 1 year. The cumulative incidence of recurrent ulcer complications was 13.6% and 0%, respectively (95% CI for the difference, 6.3%-20.9%; P = .0019).<sup>139</sup> The combination of esomeprazole and low-dose aspirin is superior to clopidogrel for the prevention of recurrent GI bleeding as is now recommended by the 2008 guidelines of the American College of Cardiology/American College of Gastroenterology/American Heart Association.<sup>140</sup>

Substantially less information is available about the risk of intracranial hemorrhage associated with aspirin use. In the Nurses' Health Study cohort of ~79,000 women aged 34 to 59 years, infrequent use of aspirin (1-6 tablets per week) was associated with a reduced risk of ischemic stroke, whereas high frequency use ( $\geq$  15 tablets per week) was associated with an increased risk of subarachnoid hemorrhage, particularly among older or hypertensive women.<sup>141</sup> In the 2002 overview of the Antithrombotic Trialists' Collaboration,<sup>10</sup> the overall absolute excess of intracranial hemorrhage due to aspirin therapy was less than one per 1,000 patients per year in trials that involved patients at high risk for cardiovascular events, with a somewhat higher risk in patients with cerebrovascular disease. The 2009 individual patient meta-analysis of primary prevention trials indicated that aspirin was associated with five additional hemorrhagic strokes per 1,000 among moderate-risk participants (risk of coronary event, > 1% per year) over 5 years (ie, ~1/1,000 per year) but substantially fewer events in low-risk participants.<sup>87</sup>

Low-dose aspirin therapy has not been reported to affect renal function or BP control,142 consistent with its lack of effect on renal prostaglandins<sup>143</sup> primarily derived from constitutively expressed COX-2 in the kidney.84 Moreover, aspirin 75 mg/d did not affect BP or the need for antihypertensive therapy in intensively treated patients with hypertension.<sup>89</sup> The suggestion that the use of aspirin and other antiplatelet agents is associated with reduced benefit in enalapriltreated patients with left ventricular systolic dysfunction<sup>144</sup> is not supported by the results of a large meta-analysis of MI trials.<sup>145</sup> Similarly, no negative interaction occurred between angiotensin-converting enzyme (ACE) inhibition and the cardiovascular benefits of low-dose aspirin in intensively treated patients with hypertension.<sup>146</sup> The ACE Inhibitors Collaborative Group performed a systematic overview of data from 22,060 patients included in six long-term randomized trials of ACE inhibitors to assess whether aspirin altered the effects of ACE inhibitor therapy on major clinical outcomes.<sup>147</sup> Even though the results from these analyses cannot rule out the possibility of an interaction, they show unequivocally that even if aspirin is given, the addition of ACE inhibitor therapy produces substantial additional benefit in all major vascular outcomes. Therefore, in the absence of clear contraindications, concomitant use of aspirin and ACE inhibitors should be considered in all patients who are at high risk of major vascular events.147

## 2.0 Dipyridamole

#### 2.1 Mechanism of Action

Dipyridamole is a pyrimidopyrimidine derivative with vasodilator and antiplatelet properties. The mechanism of action of dipyridamole as an antiplatelet agent is controversial.<sup>148</sup> Both inhibition of cyclic nucleotide phosphodiesterase (the enzyme that degrades cyclic adenosine monophosphate [AMP] to 5'-AMP, resulting in the intraplatelet accumulation of cyclic AMP, an inhibitor of platelet aggrega-

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tion) and blockade of the uptake of adenosine (which binds to  $A_2$  receptors, stimulates platelet adenyl cyclase, and increases cyclic AMP) have been suggested. Moreover, direct stimulation of PGI<sub>2</sub> synthesis and protection against its degradation have been reported, although the dipyridamole concentrations required to produce these effects far exceed the low-micromolar plasma levels achieved after oral administration of conventional doses (100-400 mg/d).<sup>148</sup> Dipyridamole also differentially inhibits the expression of critical inflammatory genes by plateletleukocyte aggregates.<sup>149</sup>

#### 2.2 Pharmacokinetics

The absorption of dipyridamole from conventional formulations is quite variable and may result in low systemic bioavailability of the drug. A modifiedrelease formulation of dipyridamole with improved bioavailability has been developed in a combination pill with low-dose aspirin.<sup>150</sup> Dipyridamole is highly protein bound to albumin, 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 bid regimen used in recent clinical studies.

## 2.3 Efficacy and Safety

The clinical efficacy of immediate-release dipyridamole, alone or in combination with aspirin, was questioned on the basis of earlier randomized trials.<sup>3,151</sup> As a result, the reformulated extended-release preparation was evaluated in the more recent ESPS-2, Aspirin Plus Dipyridamole Versus Aspirin Alone After Cerebral Ischaemia of Arterial Origin (ESPRIT), and Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) randomized trials. In ESPS-2, the new preparation of dipyridamole was evaluated in 6,602 patients with prior stroke or TIA.<sup>40</sup> This study showed that the addition of modifiedrelease dipyridamole (200 mg bid) to aspirin (25 mg bid) was associated with a 22% relative risk reduction in major vascular events compared with aspirin alone. Headache was the most common adverse effect of dipyridamole.

In the ESPRIT trial,<sup>152</sup> 2,739 patients within 6 months of a TIA or minor stroke of presumed arterial origin were randomized to receive aspirin (30-325 mg/d) with or without dipyridamole (200 mg bid). Compared with aspirin alone, the primary outcome (a composite of major vascular events or major bleeding complications) was reduced by 20% with the combined treatment. Patients on aspirin plus dipyridamole discontinued trial medication almost three times more often than those on a spirin alone mainly because of headache.  $^{\rm 152}$ 

In the PRoFESS trial,<sup>153</sup> 20,332 patients with recent ischemic stroke were randomized to receive the combination of aspirin (25 mg bid) plus extended-release dipyridamole (200 mg bid) or clopidogrel (75 mg once daily) for a mean of 2.5 years. The HR for the primary efficacy outcome (1.01; 95% CI, 0.92-1.11) failed to reach the prespecified noninferiority margin. Major hemorrhages occurred more frequently in those given aspirin plus extended-release dipyridamole than in patients treated with clopidogrel (HR, 1.15; 95% CI, 1.00-1.32), and the combination was associated with an excess of intracranial hemorrhage (HR, 1.42; 95% CI, 1.11-1.83).

A meta-analysis of six randomized trials involving 7,648 patients with a history of TIA or stroke in which stroke was reported as an outcome demonstrated that compared with aspirin alone (dose range, 50-1,300 mg/d), the combination of aspirin (dose range, 50-1,300 mg/d) plus dipyridamole reduced stroke by 23% (RR, 0.77; 95% CI, 0.67-0.89), with no statistical evidence of heterogeneity.<sup>154</sup> Consistent estimates were obtained from trials that used the immediaterelease preparation of dipyridamole (four trials) and those that used the extended-release preparation. A Cochrane review of 29 randomized trials involving 23,019 patients confirmed the superiority of the combination of aspirin plus dipyridamole over aspirin alone for prevention of vascular events in patients with a history of TIA or stroke but found no evidence of a benefit of the combination in studies involving patients with a history of coronary or peripheral arterial disease or in other high-risk patients.<sup>155</sup>

## 3.0 Cilostazol

## 3.1 Mechanism of Action

Cilostazol is a 2-oxoquinolone derivative that is reported to have vasodilatory and antiplatelet properties as well as antiproliferative effects, reducing smooth muscle cell proliferation and neointimal hyperplasia after endothelial injury. Cilostazol is a common cause of GI side effects, and headache occurs in up to one-fourth of patients within the first 2 weeks of starting treatment. Cilostazol is contraindicated in patients with heart failure because of the potential to trigger ventricular tachycardia, an effect that has been attributed to the increase in intracellular cyclic AMP, a mechanism that likely also accounts for the vasodilatory effects of cilostazol.

## 3.2 Pharmacokinetics

There is substantial variability in the absorption of orally administered cilostazol. Coadministration of

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food increases the rate and extent of drug absorption. Cilostazol is highly albumin bound and is extensively metabolized by cytochrome P450 (CYP450) enzymes, with excretion of metabolites in the urine. It has a half-life of 11 h, and the half-life is prolonged in patients with severe renal impairment.

## 3.3 Efficacy and Safety

Meta-analyses of mainly small, open-label, placeboand active-controlled trials have demonstrated that cilostazol (50 mg bid or 100 mg once daily) increases maximal and pain-free walking distance in patients with intermittent claudication,<sup>156</sup> prevents thrombotic events in patients with peripheral arterial disease,<sup>157</sup> and prevents restenosis and target vessel revascularization in patients undergoing stenting of coronary or peripheral arteries.<sup>158</sup>

The Cilostazol for Prevention of Secondary Stroke (CSPS-2) study evaluated the efficacy and safety of cilostazol (100 mg bid) compared with aspirin (81 mg/d) in 2,757 Japanese patients with recent stroke, using a noninferiority study design.<sup>159</sup> The mean duration of follow-up was 29 months. In an on-treatment analysis, the annual rate of recurrent stroke was 2.8% in patients randomized to receive cilostazol and 3.7% in those randomized to receive aspirin (HR, 0.74; 95% CI, 0.56-0.98), which met the prespecified criterion for noninferiority. Consistent with the results of the placebo-controlled comparisons, which demonstrated no increase in bleeding with cilostazol, the annual rate of bleeding with cilostazol was lower than that with aspirin (0.77 and 1.78%, respectively;HR, 0.46; 95% CI, 0.30-0.71), although bleeding rates were unexpectedly low in both groups. Headache, diarrhea, palpitation, dizziness, and tachycardia were more frequent with cilostazol than with aspirin and led to an almost twofold higher rate of discontinuation of cilostazol (20% vs 12%).

## 4.0 Thienopyridines

Ticlopidine, clopidogrel, and prasugrel represent three generations of oral thienopyridines that selectively inhibit ADP-induced platelet aggregation. The firstgeneration agent ticlopidine was limited by bone marrow toxicity and has largely been replaced by clopidogrel, which has become established as standard therapy across the spectrum of patients with ACS and in those undergoing percutaneous coronary intervention (PCI). However, clopidogrel also has limitations, including variable absorption; variable antiplatelet effects related, at least in part, to common polymorphisms in the genes that regulate the metabolic activation of clopidogrel; and a delayed onset and offset of action. Prasugrel, the third-generation thienopyridine, has a more rapid onset of action, is more potent than clopidogrel, and produces more consistent platelet inhibition. All three thienopyridines are prodrugs that must undergo metabolic activation through the hepatic CYP450 system to generate the active metabolites that inhibit the platelet P2Y12 receptor. Permanent inhibition of the platelet P2Y12 receptor by thienopyridines is consistent with the time-dependent, cumulative inhibition of ADP-induced platelet aggregation that occurs with repeated daily dosing of the slower-acting thienopyridines ticlopidine and clopidogrel and with the slow recovery of platelet function after drug withdrawal.<sup>160</sup> Although thienopyridines can also suppress platelet aggregation induced by arachidonic acid, collagen, and thrombin,<sup>161,162</sup> these inhibitory effects are attenuated or abolished by increasing the agonist concentration and are probably explained by blockade of ADP-mediated amplification of the platelet response to other agonists.

## 4.1 Ticlopidine

4.1.1 Pharmacokinetics: Up to 90% of a single oral dose of ticlopidine is rapidly absorbed.<sup>160</sup> Plasma concentrations peak 1 to 3 h after a single oral dose of 250 mg. More than 98% of absorbed 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 at inhibiting ADP-induced platelet aggregation.<sup>160</sup> 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.<sup>160</sup> The standard dosing regimen of ticlopidine is 250 mg bid.

4.1.2 Efficacy and Safety: As a single agent, ticlopidine has been evaluated in patients with stroke,<sup>163</sup> transient cerebral ischemia,<sup>164</sup> unstable angina,<sup>165</sup> MI,166 and intermittent claudication167-169 and in those undergoing aortocoronary bypass surgery.<sup>170</sup> Ticlopidine was more effective than aspirin in reducing stroke in patients with transient cerebral ischemia or minor stroke<sup>164</sup> (although there was no statistically significant difference in the combined outcome of stroke, MI, or death<sup>10</sup>); was as effective as aspirin in the treatment of patients with a recent MI166; was more effective than placebo in reducing the risk of the combined outcome of stroke, MI, or vascular death in patients with thromboembolic stroke<sup>163</sup>; was more effective than conventional antianginal therapy in reducing vascular death or MI in patients with unstable angina<sup>165</sup>; was more effective than placebo in reducing acute occlusion of coronary bypass grafts<sup>170</sup>; and was more effective than controls in improving walking distance<sup>168</sup> and reducing vascular complica-

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tions in patients with peripheral arterial disease.<sup>167-169</sup> The association of ticlopidine therapy with hypercholesterolemia and neutropenia (for which the reported rate of occurrence is 2.4% for a neutrophil count of  $< 1.2 \times 10^{9}$ /L and 0.8% for a count of  $< 0.45 \times 10^{9}$ /L), and its comparative expense has reduced enthusiasm for this therapy as an alternative to aspirin in most situations.<sup>171</sup> Ticlopidine has also been associated with thrombocytopenia,<sup>171</sup> aplastic anemia,<sup>172</sup> and thrombotic thrombocytopenic purpura (TTP).<sup>173</sup> 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 in all countries where the drug is registered.

Several studies have demonstrated the superiority of the combination of ticlopidine plus aspirin compared with aspirin alone or aspirin plus warfarin in preventing thrombotic complications after coronary artery stent placement.<sup>174,175</sup> Ticlopidine was routinely used in combination with aspirin in patients receiving coronary artery stents, but the superior safety profile of clopidogrel has resulted in the replacement of ticlopidine by clopidogrel as the standard of care after stent deployment.<sup>176</sup> The risk of TTP associated with ticlopidine is estimated to be 0.02% in patients receiving the drug after stent placement.<sup>177</sup> This compares with an incidence of 0.0004% in the general population. The mortality rate for this complication exceeds 20%.<sup>177</sup>

The role of ticlopidine in the current therapeutic armamentarium is uncertain because of the toxicities presented. In most jurisdictions, it has been largely replaced by clopidogrel.

## 4.2 Clopidogrel

4.2.1 Pharmacokinetics: Clopidogrel is rapidly absorbed and metabolized through a two-step process to generate a highly labile active metabolite<sup>178</sup> that irreversibly binds to the platelet P2Y12 receptor when platelets pass through the liver.<sup>179</sup> The main systemic metabolite of clopidogrel is the inactive carboxylic acid derivative SR 26334, which has a halflife of  $\sim 8$  h. On repeated daily dosing of 50 to 100 mg of clopidogrel in healthy volunteers, ADP-induced platelet aggregation was inhibited from the second day of treatment (25%-30% inhibition) and reached a steady state (50%-60% inhibition) after 4 to 7 days. Such a level of maximal inhibition was comparable to that achieved with ticlopidine (500 mg/d), although the antiplatelet effects of the latter was more delayed than that of clopidogrel. No appreciable differences in the maximum inhibitory effects produced by 50, 75, or 100 mg of clopidogrel were noted in this study.<sup>180</sup> As would be expected from these

pharmacokinetic and pharmacodynamic features, a loading dose (eg, 300 mg) of clopidogrel results in more-rapid platelet inhibition than is achieved with the 75-mg dose.<sup>181</sup> After loading with 600 mg of clopidogrel, the full antiplatelet effect of the drug was achieved after 2 to 4 h.182 Moreover, a loading dose of 600 mg resulted in higher plasma concentrations of the active metabolite and the inactive carboxyl metabolite compared with a loading dose of 300 mg.<sup>183</sup> Inhibition of ADP-induced platelet aggregation was also significantly greater with a 600-mg loading dose of clopidogrel compared with a 300-mg loading dose.183-185 The incremental antiplatelet effect of 900 mg over 600 mg of clopidogrel appears marginal<sup>183,185</sup> possibly because of limited drug absorption.183

The active metabolite of clopidogrel has a pharmacodynamic pattern similar to that of aspirin; there is cumulative inhibition of platelet function with repeated daily administration of low doses. Platelet function does not return to normal until 7 to 10 days after the last dose of clopidogrel. Both the cumulative nature of the inhibitory effects and the slow rate of recovery of platelet thromboxane production (aspirin) or ADP-induced platelet aggregation (clopidogrel) are consistent with permanent inhibition of COX-1 and the P2Y12 receptor, respectively, by the active moieties of aspirin and clopidogrel (active metabolite). This also justifies a once-daily regimen for aspirin and clopidogrel in patients with normal rates of platelet turnover, despite the short half-life of both drugs in the circulation. It should be noted, however, that although aspirin currently is used at doses that represent a 2.5- to 10-fold excess over the 30-mg dose necessary to fully inactivate platelet COX-1 activity on repeated daily dosing,28,35 clopidogrel is used at doses that produce only partial inhibition of the P2Y12 receptor. Thus, the main determinants of the interindividual variability in the antiplatelet effects of the two drugs are also likely to be substantially different (Table 6).

Table 6— <i>Main D</i>	<b>Determinants</b>	of the In	nterindivid	lual
Variability in the	Antiplatelet	Effects	of Aspirin	and
•	Clopidog	rel	• •	

Determinant	Aspirin	Clopidogrel
Dependence on systemic bioavailability	No	Yes
Dependence on liver metabolism to active moiety	No	Yes
Ratio of recommended dose: minimum effective dose for full pharmacodynamic effect	2-3	1
Relevance of pharmacodynamic interactions at the target site	Yes	;
Relevance of genetic polymorphisms affecting drug absorption or metabolism	No	Yes

4.2.2 High On-Treatment Platelet Reactivity (Clopidogrel Resistance): Numerous studies have demonstrated variable levels of platelet P2Y12 receptor inhibition in patients treated with clopidogrel and an increased risk of thrombotic events in those with high on-treatment platelet reactivity.<sup>186</sup> High on-treatment platelet reactivity is reported to occur in about onethird of those prescribed clopidogrel and has been associated with a 1.5-fold to fivefold increased risk of thrombosis.

Estimates of the prevalence of high platelet reactivity in patients prescribed clopidogrel vary according to comorbidities (eg, diabetes, dyslipidemia), concomitant therapies (lipophilic statins, eg, simvastatin and atorvastatin; proton pump inhibitors, eg, omeprazole; and calcium channel blockers), and the test and cutoffs used to define high reactivity. Particular attention has focused on the mechanisms responsible for insufficient active metabolite generation as an explanation for high platelet reactivity in patients prescribed clopidogrel. Variable levels of active metabolite generation can be caused by smoking, drugs that stimulate or inhibit CYP450 isoenzymes (2C19, 1A2, 2B6, 2C9, 3A4) involved in the conversion of clopidogrel to its active metabolite and genetic polymorphisms involving CYP450 isoenzymes and ABCB1, the p-glycoprotein efflux transporter gene involved in GI absorption of clopidogrel.<sup>186</sup>

A reduced laboratory response to clopidogrel has been observed following coadministration of CYP3A4metabolized statins<sup>187</sup> and CYP2C19-metabolized proton pump inhibitors,188 but the clinical relevance of these pharmacodynamic interactions remains uncertain because observational studies and post hoc analyses of randomized trials have yielded conflicting results.<sup>189-194</sup> In the COGENT (Clopidogrel and the Optimization of Gastrointestinal Events) trial, 3,861 patients with an indication for dual antiplatelet therapy were randomly assigned to receive omeprazole or placebo.<sup>191</sup> Omeprazole reduced the rates of GI events, including GI bleeding, by > 60%, but the primary vascular outcome, a composite of MI, revascularization, stroke, or cardiovascular death, occurred in a similar proportion of patients in each treatment group (HR, 0.99; 95% CI, 0.68-1.44). These results provide no evidence for a clinically important interaction between omeprazole and clopidogrel.<sup>191</sup>

Multiple observational studies have demonstrated an association between loss-of-function polymorphisms involving CYP2C19 and the risk of thrombotic events. In an individual patient meta-analysis of nine such studies involving 9,685 patients with ACS or undergoing PCI, Mega and colleagues<sup>195</sup> demonstrated a significantly increased risk of MI, stroke, or cardiovascular death in carriers compared with noncarriers of one (HR, 1.55; 95% CI, 1.11-2.17) and two (HR, 1.76; 95% CI, 1.24-2.50) reduced-function CYP2C19 alleles. The greatest effect of carriage of the loss-of-function alleles was on the incidence of stent thrombosis. Overall, 71.5% of subjects included in the trials were noncarriers, 26.3% had one reduced-function CYP2C19 allele, and 2.2% had two reduced-function CYP2C19 alleles.

In contrast to the findings of observational studies,<sup>195</sup> genetic analyses of three randomized trials, Study of Platelet Inhibition and Patient Outcomes (PLATO) and CURE in patients with ACS and ACTIVE A in patients with atrial fibrillation, did not demonstrate an interaction between CYP2C19 loss-of-function carrier status and randomized clopidogrel treatment of any outcome, including stent thrombosis.<sup>196,197</sup> In the PLATO genetics study involving 10,285 patients with ACS randomized to receive ticagrelor or clopidogrel, estimates of relative risk for primary outcome of MI, stroke, or cardiovascular death were similar irrespective of CYP2C19 genotype (interaction P = .46), and likewise, no interaction was found for ABCB1 genotype or for the gain-of-function CYP2C19\*17 allele.<sup>196</sup> In the CURE genetics study involving 5,059 patients with ACS randomized to receive clopidogrel or placebo, the effect of clopidogrel in reducing the rate of the primary efficacy outcome of MI, stroke, or cardiovascular death was similar in patients who were heterozygous or homozygous for loss-of-function alleles and in those who were not carriers of these alleles.<sup>197</sup> In contrast, carriers of gain-offunction alleles derived more benefit from clopidogrel treatment compared with placebo than did noncarriers, although this finding was only nominally significant (interaction P = .02). Among 1,156 genotyped patients with atrial fibrillation in the ACTIVE A trial, there was no evidence of an interaction with respect to either efficacy or bleeding between CYP2C19 genotype and study treatment.<sup>197</sup>

One proposed explanation for the discrepant findings of observational and randomized clopidogrel genetic studies is that only 14.5% of patients in the CURE trial underwent PCI, and the ACTIVE A trial enrolled patients with AF at relatively low risk of thrombotic events.<sup>198</sup> However, this explanation cannot account for lack of a significant interaction between CYP2C19 loss-of-function polymorphisms and randomized clopidogrel treatment in the PLATO trial, which included high-risk patients with ACS of whom two-thirds underwent PCI.<sup>196</sup> An alternative potential explanation is that the association between carriage of a loss-of-function allele and outcome is confounded or that loss-of-function alleles have pleiotropic effects (ie, independent of their effects on the levels of the active metabolite of clopidogrel) on clinical outcome.

As is the case for high on-treatment platelet reactivity in patients prescribed aspirin, there currently is

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no evidence to support the use of platelet function or genetic testing to individualize antiplatelet therapy. The Gauging Responsiveness With a Verify Now Assay-Impact on Thrombosis and Safety (GRAVITAS) trial found no evidence of reduced cardiovascular outcomes or stent thrombosis when double-dose clopidogrel was given to patients with high residual platelet reactivity after implantation of a drug-eluting stent despite aspirin plus usual-dose clopidogrel.<sup>199</sup> Several trials currently under way are testing the hypothesis that adjusting therapy in response to the results of platelet function testing can improve clinical outcomes.<sup>200</sup> Ongoing trials are also evaluating the possible benefit of a genotype-guided strategy for the management of patients at risk for poor outcomes either because they have already had an adverse event (eg, stent thrombosis) or because of other highrisk characteristics, such as diabetes mellitus, chronic renal failure, or angiographic high-risk features.<sup>198</sup>

4.2.3 Efficacy and Safety: The clinical development of clopidogrel was unusual because the phase 2 studies were limited and its approval was based on a single, large phase 3 trial, which compared the efficacy and safety of clopidogrel (75 mg/d) with those of aspirin (325 mg/d).<sup>201</sup> The Clopidogrel vs Aspirin in Patients at risk for Ischemic Events (CAPRIE) trial included three groups of patients at increased risk of recurrent ischemic events, with each group involving  $\sim$ 6,400 patients: those who had experienced a recent stroke, those with a recent MI, and those with symptomatic peripheral arterial disease. Compared with aspirin in the overall CAPRIE study population of 19,185 high-risk patients, clopidogrel reduced the relative risk of MI, ischemic stroke, or vascular death by 8.7% (95% CI, 3%-65%) and the absolute risk by 0.51%.

Both clopidogrel and medium-dose aspirin therapy were well tolerated in the CAPRIE study.<sup>201</sup> The incidence of early permanent discontinuation of study drug due to adverse events was 12% in both groups. Similarly, the overall incidence of hemorrhagic events was 9.3% in both groups. No excess neutropenia was found in the clopidogrel group, and the incidence of thrombocytopenia was identical in the clopidogrel and aspirin groups. On the basis of these findings, clopidogrel has been approved for the reduction of atherosclerotic events in patients with recent stroke, recent MI, or established peripheral arterial disease. TTP is rare but can occur after the initiation of clopidogrel therapy; when TTP occurs, its onset is usually within 2 weeks of initiation of treatment.<sup>202</sup>

Because clopidogrel and aspirin act on distinct and complementary pathways of platelet activation, combination therapy has been evaluated in high-risk clinical settings.<sup>203-208</sup> The CURE trial<sup>208</sup> randomly assigned 12,562 patients with ACS without ST-segment elevation who presented within 24 h of symptom onset to receive clopidogrel (300-mg loading dose followed by 75 mg once daily) or placebo in addition to aspirin (75-325 mg/d) for 3 to 12 months. After a mean duration of treatment of 9 months, the primary outcome (a composite of cardiovascular death, nonfatal MI, or stroke) occurred in 9.3% of the patients in the clopidogrel group and 11.4% of those given placebo (RR, 0.80; 95% CI, 0.72-0.90; P < .001). The benefit of clopidogrel was apparent within the first 30 days after randomization and remained constant during the 12 months of the study. There were significantly more patients with major bleeding in the clopidogrel group than in the placebo group (3.7% vs 2.7%; P = .001).

The clinical benefit of dual antiplatelet therapy over aspirin alone has been confirmed in patients undergoing PCI (Clopidogrel for the Reduction of Events During Observation [CREDO])<sup>207</sup> and in those presenting with an acute ST-segment elevation MI within 12 h (Clopidogrel and Metoprolol Myocardial Infarction Trial [COMMIT])<sup>204</sup> to 24 h (Clopidogrel as Adjunctive Reperfusion Therapy [CLARITY] trial)<sup>206</sup> after the onset of symptoms. In the COMMIT trial,<sup>204</sup> the addition of clopidogrel (75 mg/d) to aspirin (162 mg/d) reduced mortality and major vascular events in the hospital by 9% (95% CI, 3%-14%), corresponding to nine fewer events per 1,000 patients with MI treated for  $\sim 2$  weeks. Overall, when all transfused, fatal, or cerebral bleeds were considered, there was no significant excess risk associated with the use of clopidogrel during the scheduled treatment period (0.58% clopidogrel plus aspirin vs 0.55% aspirin alone, P = .59), nor was there any excess of major bleeds in patients aged >70 years or in those given fibrinolytic therapy before randomization.<sup>204</sup> Clopidogrel, however, was associated with a small, but significant excess of 4.7 (95% CI, 1.4-8.0) minor bleeds per 1,000 patients treated. Taking major and minor bleeds together, there was no apparent trend with respect to age in the excess risk of bleeding.<sup>204</sup> Factors that may have contributed to the remarkable safety of dual antiplatelet therapy in the COMMIT trial include the lack of a loading dose of clopidogrel, the uniform use of low-dose aspirin (162 mg/d), and the short duration of treatment.

Evidence for a more rapid onset of action and greater platelet inhibition with the use of a 600-mg rather than a 300-mg loading dose of clopidogrel<sup>185</sup> and growing concern about the possibility that a substantial proportion of patients achieve suboptimal inhibition of platelet function with conventional doses of clopidogrel prompted the CURRENT-OASIS 7 trial. This two-by-two factorial study, which enrolled 25,086 patients with ACS who were referred for an invasive management strategy, randomized such patients to receive either double-dose clopidogrel (a

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600-mg loading dose on day 1 followed by 150 mg/d for 6 days and 75 mg/d thereafter) or standard-dose clopidogrel (a 300-mg loading dose and 75 mg/d thereafter) and either higher-dose aspirin (300-325 mg/d) or lower-dose aspirin (75-100 mg/d). The results of the aspirin dose comparison have been reviewed earlier. In the clopidogrel dose comparison, the rates of the primary outcome of MI, stroke, or vascular death were similar in patients receiving double-dose compared with standard-dose clopidogrel (4.2% vs 4.4%); HR, 0.94; 95% CI, 0.83-1.06; P = .30), but in the 17,263 patients who underwent PCI, double-dose clopidogrel reduced stent thrombosis (1.6% vs 2.3%); HR, 0.68; 95% CI, 0.55-0.85; P = .001) at the cost of an increase in major bleeding (2.5% vs 2.0%; HR, 1.24; 95% CI, 1.05-1.46).<sup>209</sup> These results suggest that there is a benefit of more rapid and complete platelet inhibition with double-dose clopidogrel during the acute phase in patients presenting with ACS.

In contrast to the consistent finding of a favorable benefit/risk profile of dual antiplatelet therapy in patients with ACS,<sup>204,206,208</sup> the same strategy was not proven successful when compared with aspirin alone in stable patients at high risk for atherothrombotic events<sup>203</sup> or with clopidogrel alone in patients after a recent ischemic stroke or TIA.<sup>205</sup> Although there might be mechanistic reasons underlying this apparent heterogeneity in treatment effects, it is important to emphasize that the size of the additional benefit associated with dual antiplatelet therapy compared with aspirin alone in patients with ACS is only a fraction (about one-third) of the benefit associated with aspirin compared with no antiplatelet therapy in this population. Perhaps more importantly, both the CURE<sup>208</sup> and the COMMIT<sup>204</sup> investigators tested realistic hypotheses of relative risk reduction (17%) and 10%, respectively) and observed reductions (20% and 9%, respectively) that were consistent with these conservative estimates. In contrast, both the Management of Atherothrombosis With Clopidogrel in High Risk Patients (MATCH)<sup>205</sup> and the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA)<sup>203</sup> investigators tested overly optimistic expectations of risk reduction and actually observed only a fraction (approximately one-third to one-half) of the expected benefit.

The combination of clopidogrel and aspirin has also been compared with oral anticoagulation with a vitamin K antagonist<sup>105</sup> and with aspirin alone<sup>106</sup> in the ACTIVE trial program. The primary outcome in both trials was the composite of stroke, non-CNS systemic embolism, MI, or vascular death. The 6,706-patient ACTIVE W trial was stopped early by the data monitoring committee because of clear evidence of superiority of warfarin over the combination

of clopidogrel plus aspirin for the prevention of major vascular events (3.9% vs 5.6% per year; RR, 1.44; 95% CI, 1.18-1.76), with similar rates of major bleeding.<sup>105</sup> The ACTIVE A trial, which included patients with atrial fibrillation who were deemed ineligible for warfarin therapy, demonstrated superiority of the combination of clopidogrel plus aspirin over aspirin alone for the prevention of major vascular events (6.8% vs 7.6% per year; RR, 0.89; 95% CI, 0.81-0.98). The difference was primarily due to a 28% relative reduction in the rate of stroke with clopidogrel, but this was achieved at a cost of an increase in major bleeding (2.0% vs 1.3% per year; RR, 1.57; 95% CI, 1.29-1.92), including a two per 1,000 per year increase in intracranial bleeding.<sup>106</sup> The results of the ACTIVE trial program confirm the superiority of anticoagulants over antiplatelet therapy for stroke prevention in patients with atrial fibrillation but at the same time establish the superiority of dual antiplatelet therapy with clopidogrel plus aspirin over aspirin alone for this indication, thereby supporting a mechanistic role of platelets in cardioembolic stroke.

## 4.3 Prasugrel

4.3.1 Pharmacokinetics: Prasugrel is rapidly absorbed after oral ingestion and is rapidly converted to its active metabolite, which reaches peak concentrations within 30 min of dosing. Absorption is unaffected by food. The active metabolite has a half-life of  $\sim$ 4 h, and renal excretion is the major route for elimination of the metabolites.<sup>210</sup> The prasugrel active metabolite is converted to inactive metabolites by S-methylation and cysteine conjugation.

Initial pharmacological studies with prasugrel in healthy individuals<sup>211</sup> and in patients with stable coronary artery disease<sup>212</sup> showed that prasugrel has a more rapid onset of action than clopidogrel and achieves more consistent and complete inhibition of ADPinduced platelet aggregation.<sup>211,212</sup> The more rapid onset of action of prasugrel may in part reflect the hepatic conversion to its active metabolite by CYP450 enzymes in a single step, which contrasts with that of clopidogrel, which undergoes a two-step hepatic conversion process.<sup>213</sup> No evidence exists that polymorphisms in CYP2C19 or the concomitant use of proton pump inhibitors interfere with the metabolism of prasugrel.<sup>211,214</sup>

4.3.1 Efficacy and Safety: The efficacy and safety of prasugrel have been compared with those of clopidogrel in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38).<sup>214</sup> In this

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trial, which involved 13,608 patients with ACS scheduled to undergo PCI, prasugrel (60-mg loading dose followed by 10 mg/d) was compared with standard-dose clopidogrel (300-mg loading dose followed by 75 mg/d). Compared with clopidogrel, prasugrel reduced the composite primary outcome of MI, stroke, or cardiovascular death (9.9% vs 12.1%; HR, 0.81; 95% CI, 0.73-0.90) as well as stent thrombosis (1.1% vs 2.4%, P < .001) but did not reduce overall mortality and increased major, life-threatening, and fatal bleeding. Secondary analyses suggested that the greatest benefits of prasugrel occurred in patients with ST-segment-elevation MI, a setting in which rapid and complete platelet inhibition is critical, and in those with diabetes, a patient population consistently documented to have high on-treatment platelet reactivity despite therapy with both aspirin and clopidogrel. The excess of bleeding with prasugrel reflects its more rapid onset of action; its higher potency; and, possibly, its more consistent antiplatelet effects. The FDA approval of prasugrel came with a boxed warning regarding the risk of significant or fatal bleeding. The drug is contraindicated in patients with active bleeding or with a history of stroke. The Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial is evaluating whether a more favorable benefit/risk ratio can be obtained by reducing the dose of prasugrel.<sup>215</sup>

## 5.0 GLYCOPROTEIN IIB/IIIA ANTAGONISTS

The pharmacologic characteristics of the three approved IV glycoprotein IIb/IIIa (GpIIb-IIIa) inhibitors abciximab, tirofiban, and eptifibatide are summarized in Table 7.

## 5.1 Abciximab

Abciximab is a humanized version of a Fab fragment of a murine antibody directed against GpIIb-IIIa. Blockade of GpIIb-IIIa with abciximab produces a

Table 7—Comparison of Glycoprotein	IIb/IIIa
Inhibitors in Clinical Use	

	Abeiximab	Tirofiban	Eptifibatide
Structure	Antibody Fab fragment	Nonpeptide	Cyclic heptapeptide
Molecular weight	48 kDa	<1 kDa	<1 kDa
Onset	Rapid	Rapid	Rapid
Reversibility of platelet inhibitory effects	Slow	Rapid	Rapid
Drug half-life	10-30 min	2 h	2.5 h
Excretion	Unknown	40%-70% renal	50% renal

phenotype similar to that of Glanzmann thrombasthenia.<sup>216</sup> Approximately 40,000 antibody molecules bind to the surface of each platelet, but because they likely bind in a bivalent fashion, there are probably 80,000 GpIIb-IIIa receptors per platelet.<sup>217</sup> 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 with ~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 markedly prolonged.<sup>217</sup>

After IV bolus administration, pharmacokinetic data indicate that free plasma abciximab concentrations decrease rapidly (initial half-life of about 30 min), reflecting the rapid binding of the antibody to GpIIb-IIIa, with  $\sim 65\%$  of the antibody becoming attached to platelets in the circulation and spleen.<sup>218</sup> A bolus dose of 0.25 mg/kg blocked > 80% of the receptors and reduced platelet aggregation in response to 20  $\mu$ mol/L ADP to < 20% of baseline.<sup>218</sup> Peak effects on receptor blockade, platelet aggregation, and bleeding time were observed at 2 h, the first sampling time. This was followed by gradual recovery of platelet function, with bleeding times returning to near-normal values by 12 h.<sup>218</sup> ADP-induced platelet aggregation returns to at least 50% of the baseline level within 24 h. Small amounts of abciximab can be detected on circulating platelets for up to 14 days, presumably reflecting antibody redistribution from platelet to platelet.<sup>219</sup>

The receptor blockade, inhibition of platelet aggregation, and prolongation of the bleeding time achieved with a 0.25-mg/kg bolus dose of abciximab could be maintained by administering the drug at a dose of 10 µg/min over 12 h.<sup>218</sup> This regimen was chosen for the Evaluation of 7E3 for the Prevention of Ischaemic Complications (EPIC) trial,<sup>220</sup> which demonstrated the efficacy of abciximab when added to conventional antithrombotic therapy for reducing the incidence of ischemic events in patients undergoing percutaneous transluminal coronary angioplasty (PTCA). Subsequently, the dose was modified to 0.125 µg/kg per min (to a maximum of 10 µg/min) to adjust for differences in body weight.

Thrombocytopenia occurs in 1% to 2% of patients treated with abciximab. The risk of thrombocytopenia appears to be increased with abciximab readministration.<sup>221,222</sup> Typically, the decrease in platelet count occurs within 24 h of initiation of treatment but may begin to fall as early as 2 h after treatment starts. Consequently, the abciximab package insert specifies that a platelet count should be obtained 2 to 4 h after initiating therapy. The thrombocytopenia is believed to be antibody mediated.<sup>223</sup> In most cases, the

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thrombocytopenia resolves when the drug is stopped. If necessary, platelet transfusions can be given.  $^{220,224,225}$ 

## 5.2 Tirofiban

Tirofiban is a nonpeptide tyrosine derivative that selectively binds to GpIIb-IIIa.<sup>226,227</sup> The plasma half-life of tirofiban is 1.5 to 2 h, and both renal and biliary excretion contribute to tirofiban clearance, with unchanged tirofiban found in urine and feces.<sup>228</sup> Dose adjustment is required in patients with renal insufficiency but not in patients with hepatic disease.

In a pilot study, 73 patients undergoing PTCA were treated with aspirin, heparin, and bolus doses of tirofiban of 5, 10, or 15  $\mu$ g/kg followed by an infusion of 0.05, 0.10, or 0.15  $\mu$ g/kg per min, respectively.<sup>229</sup> Tirofiban produced rapid and dose-dependent inhibition of platelet aggregation and prolonged the bleeding time. After stopping tirofiban, platelet aggregation recovered to 50% of the baseline value within 4 h.

In patients with a creatinine clearance < 30 mL/min, the half-life of tirofiban is prolonged more than three-fold.<sup>230</sup> Although the manufacturer recommends a 50% reduction in both the bolus and the infusion doses in such patients, the pharmacokinetic basis for this recommendation has been challenged.<sup>230</sup> In the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial, the 40 patients with a creatinine clearance < 30 mL/min had an increased risk of bleeding.<sup>231</sup>

Severe, but reversible thrombocytopenia has been reported in a small percentage of patients treated with tirofiban. Thrombocytopenia is believed to be immune mediated; tirofiban binding induces a conformational change in GpIIb-IIIa, and antibodies are generated against the newly exposed epitope.<sup>225,232</sup> No data are available on the safety of tirofiban readministration, but high antibody titers have been found in patients who developed thrombocytopenia after tirofiban exposure.<sup>233</sup>

## 5.3 Eptifibatide

Eptifibatide is a synthetic disulfide-linked cyclic heptapeptide. It is patterned after the KGD sequence found in the snake venom disintegrin obtained from *Sistrurus miliarius barbouri* (barbourin), and has high specificity for GpIIb-IIIa.<sup>234,235</sup> Although preliminary reports have suggested that eptifibatide produces less prolongation of the bleeding time than other GpIIb-IIIa inhibitors at doses producing comparable inhibition of platelet aggregation, it is likely that collection of the blood samples into citrate resulted in an overestimate of the inhibitory effects of eptifibatide,<sup>236</sup> Because the drug is cleared by the kidneys, patients with renal impairment exhibit prolonged inhibition of platelet function after receiving eptifibatide. The proper dose of eptifibatide in patients with modest to moderate renal insufficiency is uncertain.<sup>230</sup> In the ESPRIT trial, patients with a creatinine clearance <60 mL/min had increased major and minor bleeding rates compared with those with higher creatinine clearances, and eptifibatide treatment increased major and minor bleeding in both groups of patients.<sup>237</sup>

With an infusion rate of 2  $\mu$ g/kg per min, the steady-state level of eptifibatide is ~1,900 ng/mL, suggesting that > 50 molecules of eptifibatide bind to each GpIIb-IIIa.<sup>238</sup> Consequently, platelet transfusion may not reverse the effects of the drug.<sup>239</sup> Based on the results of phase 2 studies, two bolus doses of 180  $\mu$ g/kg per min given 10 min apart followed by a 2  $\mu$ g/kg per min infusion was selected for the phase 3 trials.

Eptifibatide treatment has been associated with thrombocytopenia,<sup>240,241</sup> and an immunologic mechanism has been identified in some patients.<sup>233</sup> No data are available about the safety of reinfusing eptifibatide, but high levels of antibody have been found in patients who develop thrombocytopenia after reexposure to eptifibatide.<sup>233</sup>

## 5.4 Efficacy and Safety of IV GpIIb-IIIa Antagonists

5.4.1 ACS, ST-Segment Elevation MI, and Coronary Revascularization: The efficacy and safety of GpIIb-IIIa antagonists were initially evaluated in patients undergoing PCI. The first of these phase 3 trials, the EPIC trial,<sup>220</sup> resulted in approval of abciximab in 1994 for PCI patients at high risk of developing ischemic complication. Eptifibatide was studied in the Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis-II (IMPACT-II)<sup>242</sup> and ESPRIT trials,<sup>243,244</sup> whereas tirofiban was studied in the Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) trial.245 Although neither the IMPACT-II nor the RESTORE trials achieved their predefined efficacy end points, there was a positive trend in each case. Eptifibatide received approval from the FDA for PCI in 1998 based on data from the IMPACT-II and PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) trials, and the dosing was modified based on the efficacy demonstrated in the ESPRIT trial.243,244 The CAPTURE (Chimeric c7E3 AntiPlatelet Therapy in Unstable Angina Refractory to Standard Treatment trial)<sup>246</sup> demonstrated the efficacy of an 18- to 24-h infusion of abciximab prior to PCI in patients with unstable angina refractory to conventional antithrombotic and antianginal therapy. The Evaluation in

PTCA to Improve Long-term Outcome with Abciximab Glycoprotein IIb/IIIa Blockade (EPILOG) trial<sup>224</sup> demonstrated the efficacy of abciximab in a broad patient population undergoing PCI, not just high-risk patients as enrolled in the EPIC and CAPTURE trials. The Evaluation of Platelet IIb/IIIa Inhibitor for Stenting Trial (EPISTENT) demonstrated that abciximab decreases the frequency of ischemic complications associated with stent insertion during the first 30 days.<sup>247</sup> Furthermore, the 1-year mortality difference was statistically significant between stent alone (2.4%) and stent plus abciximab (1%), and this mortality difference was sustained for longer periods of time.<sup>248</sup> Both abciximab and stenting were studied in the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial, which enrolled patients with MI.<sup>249</sup> In this group of patients who appeared to be at relative low risk, abciximab had a beneficial effect in the PTCA group but did not affect death or reinfarction in the stent group.<sup>249</sup>

Abciximab was compared with tirofiban in patients undergoing PCI in the Do Tirofiban and ReoPro Give Similar Efficacy Trial (TARGET). Abciximab treatment was found to be associated with a statistically significant lower rate of ischemic complications after 30 days.<sup>250,251</sup>

A series of randomized clinical trials conducted by the ISAR (Intracoronary Stenting and Antithrombotic Regimen) group have reexamined the efficacy and safety of GpIIb-IIIa blockade in a broad range of patients undergoing PCI who also were receiving aspirin and clopidogrel.<sup>252-255</sup> Using a 600-mg clopidogrel loading dose given at least 2 h prior to PCI in all patients, the ISAR investigators evaluated the effects of adjunctive abciximab in low- to intermediate-risk patients,<sup>254</sup> in patients undergoing revascularization of small-diameter vessels,252 in patients with diabetes mellitus,<sup>255</sup> and in patients with non-STsegment elevation ACS.<sup>253</sup> In stable patients undergoing elective PCI, pretreatment with 600 mg of clopidogrel provides platelet inhibition sufficient to enable a safe procedure without the need for GpIIb-IIIa blockade. 252,254,255 However, the same abciximab regimen was associated with a statistically significant 25% relative risk reduction in the 30-day combined end-point of death, MI, or urgent target vessel revascularization in patients with ACS.<sup>253</sup> Although the additional benefit of GpIIb-IIIa blockade appeared to be confined to patients with an elevated troponin level (>0.03  $\mu$ g/L), the *P* value for the interaction was not statistically significant.

Randomized trials have examined the efficacy and safety of tirofiban, lamifiban (a nonpeptide GpIIb-IIIa blocker whose development has been discontinued), eptifibatide, and abciximab in patients

with ACS without persistent ST-segment elevation randomized to receive a GpIIb-IIIa antagonist or placebo in addition to conventional antithrombotic therapy.<sup>240,256-259</sup> These studies demonstrated a 0% to 27% relative risk reduction in MI or death at 30 days. Both eptifibatide and tirofiban have received approval from the FDA for the treatment of ACS, including patients who are to be managed medically and those undergoing PCI. However, in the Global Utilization of Strategies to Open Occluded Arteries (GUSTO) IV-ACS trial,<sup>256</sup> abciximab for 24 h (0.25-mg/kg bolus followed by a 0.125-µg/kg per min infusion) or 48 h was not beneficial as first-line medical treatment in patients with ACS. A meta-analysis of all major randomized clinical trials of GpIIb-IIIa antagonists in patients with ACS who were not routinely scheduled to undergo early coronary revascularization suggests a 9% reduction in the odds of death or MI at 30 days.<sup>260</sup> However, the true size of the additional benefit resulting from short-term, high-grade blockade of GpIIb-IIIa combined with standard antithrombotic therapy is somewhat uncertain because the 95% CI ranged from 2% to 16%. Moreover, the 1% absolute difference in death or MI was balanced by an absolute excess of 1% in major bleeding complications associated with GpIIb-IIIa antagonists compared with controls.<sup>260</sup>

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

Phase 2 trials in acute MI with abciximab and eptifibatide suggested potential benefits of GpIIb-IIIa blockade as an adjunct to thrombolysis. The GUSTO V trial compared the efficacy and safety of half-dose reteplase and full-dose abciximab vs standard-dose reteplase in 16,588 patients in the first 6 h of evolving ST-segment elevation MI.<sup>261</sup> The primary end point of 30-day mortality was similar in the two treatment groups (5.6% vs 5.9%). Combination therapy led to a consistent reduction in secondary complications of MI, including reinfarction, which was partly counterbalanced by increased extracranial bleedings. There was no mortality benefit of combined therapy after 1 year, and thus, there appears to be little or no net benefit in combined therapy.<sup>261</sup>

The failure of several more recent randomized trials to demonstrate benefits of GpIIb-IIIa blockade among patients with ST-segment elevation MI treated with primary angioplasty and in patients treated with clopidogrel<sup>262,263</sup> has prompted critical reevaluation of the benefits and risks of this approach in an updated meta-analysis.<sup>264</sup> Pooled data from a meta-analysis of 16 randomized trials involving 10,085 patients undergoing primary PCI demonstrated that adjunctive GpIIb-IIIa blockade did not reduce 30-day mortality (2.8% vs 2.9%, P = .75) or reinfarction (1.5% vs 1.9%, P = .75)P = .22) and increased major bleeding (4.1% vs 2.7%), P = .0004). However, meta-regression analysis demonstrated a relation between risk profile and adjunctive GpIIb-IIIa blockade and suggested a mortality benefit among those at highest risk, supporting the use of GpIIb-IIIa blockade at the time of primary PCI in selected high-risk patients with ST-segment elevation MI.

5.4.2 Cerebrovascular Disease: Despite reassuring data from a phase 2 trial of abciximab in patients with acute ischemic stroke,<sup>265</sup> a phase 3 trial has been stopped because of safety concerns.<sup>266</sup> A phase 2 trial of eptifibatide has also yielded promising results,<sup>267</sup> and a further phase 2 trial with this agent is ongoing.

6.0 CONCLUSION

Antiplatelet therapies are effective for prevention of platelet-rich arterial thrombi that form under high-shear conditions. Antiplatelet therapies are also effective for the prevention of fibrin-rich thrombi that form under low-shear conditions, such as VTE and left atrial appendage thrombi that form in patients with atrial fibrillation, but for these indications, antiplatelet drugs are less effective than anticoagulants. The efficacy of antiplatelet drugs for thrombosis prevention is explained by their ability to block well-characterized pathways involved in platelet activation and aggregation. It is these actions that also lead to the major side effect of antiplatelet therapy, which is bleeding. The efficacy of antiplatelet therapy can be improved by increasing the intensity of therapy by using more-potent antiplatelet drugs or combinations of antiplatelet drugs but at the cost of an increase in bleeding. Under certain circumstances, efficacy can also be improved by using more rapidly acting drugs.

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