Clinical Aspects of Platelet Inhibitors and Thrombus Formation

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Abstract—The platelet, once thought to be solely involved in clot formation, is now known to be a key mediator in various others processes such as inflammation, thrombosis, and atherosclerosis. Supported by the wealth of evidence from clinical trials demonstrating their benefits in patient outcomes, antiplatelet agents have become paramount in the prevention and management of various diseases involving the cardiovascular, cerebrovascular, and peripheral arterial systems. Despite being among the most widely used and studied classes of medical therapies, new discoveries regarding important clinical aspects and properties of these agents continue to be made. As our understanding of platelet biology expands, more effective and safer novel therapies continue to be developed. The use of more refined agents in conjunction with a better understanding of their effects will further the ability to provide more optimized care on an individual basis. (Circ Res. 2007;100:1261-1275.)

Key Words: antiplatelet therapy | thrombosis | platelets | atherosclerosis | cardiovascular disease

Atherosclerosis is a systemic process that affects the cardiovascular, cerebrovascular, and peripheral arterial systems (Figure 1). Heart attacks and strokes, both clinical manifestations of acute arterial thrombosis, continue to be the most common causes of mortality and morbidity in the industrialized world. Atherosclerosis is a chronic inflammatory process that provides the underlying substrate for occlusive thrombus formation. The platelet, a mediator of various endothelial, thrombotic, immune, and inflammatory responses, is pivotal in the pathogenesis of atherothrombosis and is also involved in the initiation and progression of atherosclerosis.1–3

In response to vascular injury, platelets interact with components of the subendothelial matrix, particularly collagen and von Willebrand factor (vWF) via their respective receptors, glycoprotein (GP) VI and GPIb/V/IX.4 Various intracellular signaling reactions are then triggered, which causes inside/out activation of key integrin receptors, mainly GPIIb/IIIa and GP1a/IIa, responsible for stable platelet adhesion. This then stimulates the release and production of an array of local mediators, such as ADP, thromboxane A2 (TxA2), and thrombin that further amplify platelet activation via their interaction with their respective G protein–coupled receptors.5 The rapid recruitment and activation of surrounding platelets ultimately leads to thrombus formation, a process mainly mediated by the cross-linking of fibrinogen molecules by the GPIIb/IIIa integrin (Figure 2).
The role of platelets in atherothrombotic diseases. Platelets are pivotal to the development of atherothrombosis, which can manifest as various medical conditions in the cardiovascular, cerebrovascular, and peripheral arterial systems. Additionally, there is an array of medical interventions in which platelets are also known to be of clinical importance (noted in italics). ABI indicates ankle brachial index; CABG, coronary artery bypass grafting; CEA, carotid endarterectomy; NSTEMI, non–ST-elevation MI; STEMI, ST-elevation MI; TIA, transient ischemic attack.

Medical therapies targeting various pathways in this cascade of events have been or are currently being developed for use as antiplatelet agents. These include therapies aimed at inhibiting TxA₂, ADP, GPIIb/IIIa, thrombin, collagen, and vWF. Complex interactions between these various factors and the mechanisms involved in this process ensure redundancy in the pathways responsible for platelet activation and thrombus formation. Clinically, this limits the effectiveness of any single agent at being able to inhibit this process entirely and, as such, has spawned the use of combination therapy in many settings. Overall, there is an abundance of evidence from clinical trials supporting the broad use of antiplatelet agents in atherothrombotic disease. However, the optimal regimen for a particular individual depends on the specific disease process present and the patient characteristics. This article focuses on the clinical aspects of the available antiplatelet agents used for atherothrombotic diseases, particularly cardiovascular disease (CVD), and also highlights the more promising novel therapies being developed. A review of antiplatelet therapy in the management of cerebrovascular and peripheral arterial disease can be found in the online data supplement, available at http://circres.ahajournals.org.

Thromboxane Inhibitors

Aspirin

Aspirin, or acetylsalicylic acid, is the most widely studied of the thromboxane inhibitors and has been a mainstay in antiplatelet therapy for several decades since the discovery of its effects on platelets nearly 40 years ago6 (Figure 3a). Although not a direct inhibitor of the thromboxane receptor, aspirin indirectly inhibits the actions of thromboxane via its effects on the cyclooxygenase (COX) enzyme. Aspirin decreases platelet activity through irreversible inhibition of the prostaglandin H-synthase, or COX, enzyme involved in the arachidonic acid/prostaglandin production pathway.7 Its major effect is exerted through its relative selectivity for the COX-1, rather than COX-2, isof orm, resulting in impaired synthesis of TxA₂.8 Other purported antiplatelet effects of aspirin include a neutrophilic NO/cyclic GMP–mediated inhibition of platelets9 and various other indirect mechanisms via its effect on the coagulation cascade10 and fibrinolytic process.11

Cardiovascular Disease

The efficacy of aspirin therapy in the prevention and acute management of various CVDs is well established and supported by a wealth of clinical data12–18 (see the online data supplement for further review). However, emerging data regarding the use of aspirin for primary prevention and aspirin resistance continue to refine further aspirin’s therapeutic role in CVD.

The initial primary prevention studies, which were conducted predominantly in males, demonstrated a significant reduction in the risk of nonfatal myocardial infarction (MI), without any benefit in cardiovascular mortality with aspirin therapy19–21 (see Table I in the online data supplement). Two large-scale studies of physicians evaluated aspirin in those considered at low-risk for coronary artery disease (CAD). The larger of the two was the Physicians’ Health Study which enrolled 22 071 participants and randomized each to either aspirin (325 mg every other day) or placebo.19 A significant reduction in the risk of first MI (44%) was seen, although the benefit was apparent only in those males 50 years of age or older. However, no benefit in MI risk was seen in the British Physicians’ Study which enrolled 5139 male subjects with CVD who were randomized to aspirin (500 mg/d) versus placebo, regardless of age.20 Both of these trials failed to show any improvement in cardiovascular mortality in those receiving aspirin versus placebo. In the Physicians’ Health Study, there was a nonsignificant increase in risk of hemorrhagic stroke, and the British Physicians’ Study displayed a significant increase in disabling stroke in those randomized to aspirin therapy.

Males with a higher risk of CVD derive similar or even greater benefit with aspirin in primary prevention.22–26 In the Hypertension Optimal Treatment (HOT) trial with 18 790 participants (53% males) with 1 or more risk factors for cardiovascular events, a 36% reduction in risk of MI was observed in those patients randomized to aspirin therapy.25 Similarly, in a sex-specific metaanalysis of 6 trials with 44 114 males with various levels of cardiovascular risk, aspirin use resulted in a 32% reduction in risk of MI.27 Nonetheless, aspirin therapy had no effect on cardiovascular mortality and was associated with an increased risk of bleeding.
The first large primary prevention trial specifically aimed at evaluating aspirin therapy in women was the Women’s Health Study which randomized 39,876 healthy women to aspirin (100 mg every other day) versus placebo. There was no difference in the primary end point of the trial (cardiovascular death, MI, or stroke) in the overall population, although the subgroup of 4097 women 65 years of age or older did appear to benefit, with a significant 26% relative reduction in cardiovascular events. When examining the individual components of the trial, there was no benefit seen in MI or cardiovascular mortality in the overall trial population receiving aspirin therapy as compared with placebo. However, there was a 24% reduction in risk of ischemic stroke in the women randomized to aspirin therapy, with a nonsignificant increase in hemorrhagic stroke. One potential explanation for these negative findings in the overall population studied is that the dose of aspirin used in this study (100 mg every other day) is less effective in women than the typically prescribed low-dose aspirin regimen (81 mg daily). In one small crossover study of 49 healthy females, greater platelet inhibition with less day to day variability was obtained in those participants receiving 81 mg daily as compared with 100 mg every other day. However, this mechanism cannot entirely explain the results of the Women’s Health Study, given the significant benefit observed in the subgroup of elderly women with aspirin 100 mg every other day. For both men and women, the decision to use aspirin for primary prevention of CAD should be based on the underlying risk profile of the individual. Older patients with multiple cardiovascular risk factors who are at lower risk of bleeding are most likely to benefit from aspirin for primary prevention.

Patients with established diabetes are often prescribed aspirin to reduce the risk of MI. The American Diabetes Association recommends the use of aspirin therapy (75 to 162 mg/d) in all diabetic patients more than 40 years of age or who have additional risk factors for CVD. In diabetics between 30 and 40 years of age, the association recommends consideration for aspirin therapy especially in those with other CVD risk factors. A Study of Cardiovascular Events in Diabetes (ASCEND) is a randomized double-blind trial of 100 mg of aspirin daily versus placebo in 10,000 patients with type 1 or 2 diabetes without a history of ischemic events being coordinated by Oxford University. Once complete, this study should definitively determine the role of aspirin in diabetic patients without overt CVD.

**Aspirin Resistance**
Aspirin resistance is a loosely defined term used to describe various clinical and biochemical scenarios. Clinically, it

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**Figure 2.** The role of platelets in thrombus formation. A, At the sites of vascular injury, platelets become exposed to components of the extracellular matrix (ECM). Glycoprotein receptors on the platelet surface interact with these components, particularly collagen and vWF, resulting in platelet adherence to the subendothelium. The activated platelet begins to undergo a shape change, which causes the release of ADP and TxA2, and stimulates the formation of thrombin on the surface of the platelet and other cells. These stimuli act on surrounding platelets causing further activation and formation of these stimuli. The integrin GPIIb/IIIa also undergoes a conformational shape change, allowing it to bind adhesive proteins, particularly fibrinogen and vWF; this process causes platelet aggregation. The interaction of the platelet aggregate with fibrin and thrombin leads ultimately to thrombus formation. B, The activation of complex intracellular signaling processes causes the production and release of various stimuli, including TxA2, thrombin, and ADP, which act by binding to their respective G protein–coupled receptors. Therapies targeted at inhibiting these receptors and also the integrins and proteins involved in platelet activation include the thromboxane inhibitors, the ADP receptor antagonists, the GPIIb/IIIa inhibitors, and the novel PAR antagonists and adhesion antagonists.
refers to patients who continue to have ischemic events despite appropriate use of aspirin, which may be a manifestation of the variability among patients in response to aspirin therapy. In the laboratory, aspirin resistance indicates the inability to attain a particular level of platelet inhibition by ex vivo studies while on aspirin. Although clinical resistance or treatment failure with aspirin therapy may be present in nearly 50% of patients, true pharmacological resistance with aspirin is much less common. In a broader sense, aspirin resistance has also been used to describe those patients who are not compliant with aspirin therapy or not prescribed aspirin when clinically indicated. Despite clear evidence demonstrating its benefits, patients with atherothrombotic disease continue to be undertreated with aspirin worldwide. In the global Reduction of Atherothrombosis for Continued Health (REACH) registry containing 67,888 patients with 3

Figure 3. Chemical structures of the antiplatelet agents aspirin (A), ticlopidine (B), clopidogrel (C), prasugrel (D), AZD6140 (E), cangrelor (F), dipyridamole (G), and cilostazol (H).
or more risk factors for atherothrombosis or established CVD, only 78.6% of patients received any form of antiplatelet therapy.\textsuperscript{35} Furthermore, in the 40 258 patients with documented CAD, only 76.2% were on aspirin.

There have been several small studies that have demonstrated the potential clinical significance of aspirin resistance as a risk marker. In a study of 488 patients from Heart Outcomes Prevention Evaluation (HOPE), aspirin resistance, defined as an incomplete suppression of thromboxane synthesis, was associated with a higher risk of ischemic events. In the study, those within the highest quartile of baseline urinary 11-dehydro TxB\textsubscript{2} levels, a marker of thromboxane generation, had twice the risk of MI as those in the lowest quartile.\textsuperscript{36} Similarly, in a prospective analysis of 326 patients with stable CAD, those with aspirin resistance had a three-fold increased risk of death, MI, or stroke as compared with those responsive to aspirin.\textsuperscript{37} The possible implications of aspirin resistance extend beyond just CVD. One of the initial studies to examine the correlation between clinical outcomes and aspirin resistance was done on post-stroke patients. In this pilot study of 180 patients who had experienced a recent stroke, those with persistent platelet reactivity while on aspirin therapy had a significant 10-fold increase in the risk of recurrent stroke, MI, or death at 2-year follow-up as compared with the aspirin responders (40% versus 4%, \(P<0.0001\)).\textsuperscript{32}

Although the clinical implications of aspirin resistance are now known, important questions regarding how ideally to identify those with the condition and optimally manage them remain unanswered.\textsuperscript{39} Just as there are several mechanisms, including cellular, clinical, and genetic factors, that may lead to aspirin resistance, there are also numerous ways to diagnose it. Whether bedside measurements of platelet function,\textsuperscript{39} platelet aggregometry studies, genetic testing, or some combination is the best way to identify aspirin resistance still needs to be determined. More importantly, clinical studies addressing how to manage and decrease the risk of adverse events for someone after aspirin resistance has been identified still need to be performed. There are data including that from the Blockage of the Glycoprotein IIb/IIIa Receptor to Avoid Vascular Occlusion (BRAVO) and the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) studies which suggest that simply increasing the dose of aspirin may lead to increased bleeding complications with no further clinical benefit.\textsuperscript{40–42} Although data from the CURE and Clopidogrel for the Reduction of Events During Observation (CREDO)\textsuperscript{43} trials support an approach of adding clopidogrel to aspirin therapy, there is also evidence to suggest that the addition of clopidogrel to aspirin therapy may not be entirely protective against the adverse effects of aspirin resistance.\textsuperscript{44} Despite inconsistencies in the distinction between treatment failure and true pharmacological resistance, the field of aspirin resistance remains an important area for future research.

Ridogrel

Ridogrel is a TxA\textsubscript{2} inhibitor with additional prostaglandin endoperoxide receptor antagonist properties that further enhances its antiaggregatory effects by diverting endoperoxide intermediates into the prostacyclin production pathway. Ridogrel has been studied primarily as an adjunctive agent to thrombolytic therapy in acute MI (AMI). Despite positive results from initial pilot studies,\textsuperscript{45} the largest clinical study, the Ridogrel versus Aspirin Patency Trial (RAPT) failed to demonstrate any advantage with this agent over aspirin.\textsuperscript{46} In the study of 907 patients with AMI, there was no difference in the primary end point of infarct vessel patency rate between those randomized to ridogrel (72.2%) or aspirin (75.5%). Various mechanisms are likely responsible for the results seen with ridogrel in clinical trials, including potentially ineffective thromboxane receptor inhibition with the concentrations of ridogrel used in human studies. As such, there currently are no clinical indications for preferential use of ridogrel over aspirin.

Other Thromboxane Inhibitors

Additional thromboxane inhibitors currently under investigation include a NO-releasing aspirin, NCX-4016, and a thromboxane receptor antagonist, S18886. The potential advantages of NO-releasing aspirin include all the benefits of aspirin therapy, combined with the multiple properties of NO including its gastroprotective, antithrombotic, antiatherogenic, and vasodilatory effects. NCX-4016 has been demonstrated to have beneficial effects in experimental models of restenosis\textsuperscript{47} and ex vivo studies of saphenous vein grafts of diabetic patients.\textsuperscript{48} Unlike aspirin or its derivatives, S18886 acts directly on the thromboxane receptor. Thus, it can inhibit not only TxA\textsubscript{2} but also other eicosanoids not affected by aspirin, such as hydroxyeicosatetraenoic acids (HETEs) and isoprostanes. As a reversible inhibitor of the thromboxane receptor, S18886, has been shown to prevent atherogenesis\textsuperscript{49,50} and cause plaque regression\textsuperscript{51} in animal studies, properties likely independent of any TxA\textsubscript{2} effects. In a small study of aspirin-treated patients with CAD, a single dose of S18886 (10 mg) resulted in improved endothelial function as assessed by vasodilatory response to acetylcholine.\textsuperscript{52}

ADP Receptor Antagonists

The binding of ADP to the G protein–coupled receptors P2Y\textsubscript{12} (G/adenyl cyclase pathway) and P2Y\textsubscript{1} (G\textsubscript{protein-phospholipase C/Ca\textsuperscript{2+} pathway) initiates platelet aggregation, but, more importantly, it further amplifies platelet response to other stimuli such as TxA\textsubscript{2} and thrombin.\textsuperscript{53} The ADP receptor antagonists exert their major effect by specifically inhibiting the P2Y\textsubscript{12} subtype of the purinoreceptor superfamily (Figure 2b). The currently available agents in this class include the oral thienopyridines ticlopidine and clopidogrel, which are both prodrugs requiring hepatic metabolism to form their active metabolites that irreversibly bind to the P2Y\textsubscript{12} receptor (Figure 3b and 3c). The first of these to be developed was ticlopidine in the early 1970s during efforts to discover a better anti-inflammatory compound. Despite being a poor antiinflammatory agent, ticlopidine was soon noticed to have potent antiplatelet effects.\textsuperscript{54} Efforts aimed at establishing a safer and better-tolerated medication lead to the development of the more widely used and studied thienopyridine, clopidogrel. In spite of marked improvements in clinical outcomes in atherothrombotic disease with use of these medications, the
search for an even more effective agent continues. Other novel ADP receptor antagonists currently undergoing phase II and phase III testing include prasugrel, cangrelor, and AZD6140.

**Ticlopidine**

There is older evidence available from studies regarding the use of ticlopidine therapy in CAD. There has been one large-scale randomized trial that examined the use of ticlopidine in the management of unstable angina. In this study of 652 patients, those receiving ticlopidine versus conventional therapy had a 46.8% relative reduction in the combined rate of vascular death or nonfatal MI at 6 months. This benefit is comparable to that seen with aspirin in unstable angina. In 1470 patients with AMI treated with thrombolytics who were randomized to daily ticlopidine (500 mg) versus daily aspirin (160 mg), at 6 months follow-up, there was no significant difference between the 2 treatment groups in the combined primary end point of recurrent AMI, stroke, angina with evidence of myocardial ischemia, or death.

There have been several trials examining the use of ticlopidine in conjunction with aspirin in patients treated with percutaneous coronary intervention (PCI). These studies predate those performed with clopidogrel, and they were the first to demonstrate the synergistic benefit of thienopyridine and aspirin therapy. These trials also confirmed the superiority of dual antiplatelet therapy over aspirin alone or aspirin with warfarin in the prevention of stent thrombosis, along with less major bleeding. Later, the CLASSICS (Clopidogrel Aspirin Stent International Cooperative Study) trial compared the safety of ticlopidine against clopidogrel, with and without loading doses, in patients after coronary stenting. Of the 1020 patients in total, those randomized to clopidogrel as compared with ticlopidine had a significant 50% reduction in major peripheral or bleeding complications, neutropenia, thrombocytopenia, or early discontinuation of study drug (4.6% versus 9.1%, \( P = 0.005 \)). In a pooled analysis of 13,995 patients from studies comparing the use of ticlopidine against clopidogrel after coronary stenting, clopidogrel therapy was associated with a significant decrease in major adverse cardiac events (2.10% versus 4.04%, \( P = 0.002 \)) and mortality (0.48% versus 1.09%, \( P = 0.003 \)) at 30 days. Thus, the use of ticlopidine in PCI has been largely supplanted by clopidogrel given the adverse effects and potential decreased efficacy seen with ticlopidine.

**Clopidogrel**

**Cardiovascular Disease**

There is an abundance of clinical evidence supporting the benefit of clopidogrel in the treatment of various cardiovascular conditions (see supplemental Table II). This includes the use of clopidogrel as adjunct therapy in the acute management of ST-elevation MIs, the invasive and conservative management of acute coronary syndromes without ST-segment elevation, and as lone therapy in the secondary prevention of atherothrombotic heart disease. Recently published evidence, however, suggests that dual antiplatelet therapy with combination aspirin and clopidogrel for primary prevention of atherothrombotic events is of no benefit and only increases the risk of bleeding.

The first large randomized clinical trial to evaluate the effectiveness and safety of clopidogrel was the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) study, which was a secondary prevention study comparing clopidogrel (75 mg/d) versus aspirin (325 mg/d) therapy in patients with recent MI, ischemic stroke, or symptomatic peripheral arterial disease. In this study of 19,185 subjects, clopidogrel use was associated with an 8.7% relative risk reduction for the composite outcome of vascular death, MI, or stroke. Clopidogrel also reduced rehospitalization for ischemic events to a greater extent than aspirin. Clopidogrel was shown to be similar to aspirin in safety as there were no major differences in adverse events between the two therapies. In subgroup analyses, clopidogrel was shown to have an even greater efficacy in those patients with diabetes mellitus, prior coronary artery bypass surgery, and those with a prior history of MI or ischemic stroke. Based on the CAPRIE study, clopidogrel has become the alternative antiplatelet agent of choice for those patients with aspirin intolerance. Were it not for issues of cost, it would likely be used more broadly instead of aspirin in secondary prevention.

There has been one large-scale study demonstrating the effectiveness of clopidogrel in the acute management of non-ST-segment elevation acute coronary syndrome. In the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial of 12,562 patients with unstable angina/non–ST-elevation MI, randomization to clopidogrel (300-mg load +75 mg/d) plus aspirin therapy versus aspirin plus placebo resulted in a highly significant 20% reduction in the combined end point of cardiovascular death, MI, or stroke (9.3% versus 11.4%, \( P = 0.00005 \)). Similar efficacy was seen with clopidogrel irrespective of patient risk profile and therapeutic benefit was sustained at 1 year of follow up.

In a substudy of the CURE trial, clopidogrel therapy was shown to have an even greater magnitude of benefit in those patients treated with PCI. In the 2658 patients of PCI-CURE randomized to preprocedural clopidogrel plus aspirin versus aspirin plus placebo, there was a 30% reduction in the combined end point of cardiovascular death, MI, or urgent target vessel revascularization within 30 days of intervention (4.5% versus 6.4%, \( P = 0.03 \)). Long-term clopidogrel therapy (mean duration of 8 months) resulted in a relative reduction of 31% in the risk of cardiovascular death or MI.

The benefit of clopidogrel pretreatment in PCI was further evaluated in the Clopidogrel for the Reduction of Events During Observation (CREDO) trial. Additionally, this trial addressed one other important issue: the optimal length of post-PCI clopidogrel therapy. In the trial, 2116 subjects were randomized to either a loading dose (300 mg) of clopidogrel plus 1 year of therapy (75 mg/d) or 28 days of clopidogrel without any loading dose. At 1 year, there was a significant 26.9% reduction in the combined end point of death, nonfatal MI, or stroke seen with long-term clopidogrel therapy. Overall, a loading dose of clopidogrel did not result in any significant reduction in death, MI, or urgent target vessel revascularization at 28 days. However, there was a statisti-
cally significant reduction in these events in those patients who received a loading dose more than 6 hours before intervention.\textsuperscript{43} Despite the observed favorable effects in CREDO and PCI-CURE, the actual benefit of long-term clopidogrel therapy after PCI, particularly after bare-metal stenting, has been questioned by some.\textsuperscript{77,78} However, in the contemporary era of drug-eluting stents and the evolving relationship between clopidogrel therapy cessation and stent thrombosis, any questions regarding the interpretation of these 2 trials may become even less pertinent.

The use of clopidogrel in addition to standard therapy for the management of AMI has been investigated in 2 recently published studies and was shown to provide further reduction in mortality and ischemic events.\textsuperscript{67,68} In the COMMIT trial (Clopidogrel and Metoprolol in Myocardial Infarction Trial) of 45,852 patients with suspected AMI, dual antiplatelet therapy with clopidogrel and aspirin resulted in a 7% relative reduction in death (7.5% versus 8.1%, \textit{P}=0.03) and a 9% relative reduction in the risk of death, reinfarction, or stroke as compared with aspirin plus placebo (9.2% versus 10.1%, \textit{P}=0.002).\textsuperscript{67} Similarly, the CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy Thrombolysis in Myocardial Infarction 28) trial with 3491 patients demonstrated a 20% relative reduction in the combined end point of cardiovascular death, MI, or urgent revascularization at 30 days with the addition of clopidogrel to aspirin and fibrinolytic therapy in patients presenting within 12 hours after initial onset of ST-segment-elevation MI.\textsuperscript{68}

Given the synergistic benefits of clopidogrel and aspirin combination therapy in acute coronary syndromes and after PCI, the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization Management and Avoidance) trial was conducted to investigate the primary and secondary prevention of atherothrombosis with use of long-term dual antiplatelet therapy in patients deemed high-risk.\textsuperscript{69} A total of 15,603 patients were randomized to clopidogrel (75 mg) plus aspirin therapy (75 to 162 mg) daily or aspirin plus placebo. In the overall trial population, dual antiplatelet therapy did not result in a significant reduction in the primary efficacy end point of MI, stroke, or cardiovascular death at follow-up (6.8% in clopidogrel+aspirin therapy versus 7.3% in aspirin therapy+placebo, \textit{P}=0.22). In the 3284 patient primary prevention subgroup, dual antiplatelet therapy provided no benefit, although it did still significantly raise the risk of moderate bleeding as compared with placebo plus aspirin. In the subgroup of 12,153 patients with established CVD, randomization to clopidogrel was associated with a significant 12.5% relative risk reduction in the composite end point of MI, stroke, or cardiovascular death. This benefit was most notable in those patients with a prior MI, prior stroke, or symptomatic peripheral arterial disease.\textsuperscript{79}

Drug-eluting stents have become quite popular in certain parts of the world. They have been shown in randomized clinical trials to reduce restenosis effectively compared with bare-metal stents, with no excess death or MI rates noted in the lesion types and patient populations studied to date.\textsuperscript{80} However, there are emerging reports of late stent thrombosis on discontinuation of clopidogrel and/or aspirin. In a recent metaanalysis of 6675 patients from 14 randomized trials, there was a 4- to 5-fold relative increase in the rate of late stent thrombosis with use of drug-eluting stents as compared with bare-metal stents, although the absolute risk excess of approximately 0.5% was small. Notably, the median time to late stent thrombosis was 15.5 to 18 months.\textsuperscript{81} Thus, the optimal duration of dual antiplatelet therapy after drug-eluting stents remains uncertain, with observational data suggesting a benefit of therapy for more than 1 year.\textsuperscript{82} Additionally, there is also evidence suggesting that a higher dose of clopidogrel maintenance therapy with 150 mg/d provides more effective platelet inhibition than the currently recommended dose of 75 mg/d.\textsuperscript{83} Whether this will further reduce thrombotic events including late stent thrombosis is yet to be determined. The CURRENT/OASIS 7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/ Optimal Antiplatelet Strategy for Interventions) trial is an ongoing study evaluating the clinical effects of higher loading and early maintenance doses of clopidogrel against lower doses of both in patients presenting with unstable angina and non–ST-elevation MI with planned early invasive therapy.\textsuperscript{84}

Although dual antiplatelet therapy with aspirin and a thienopyridine, usually clopidogrel, has salutary effects in patients with CAD, particularly those with acute coronary syndromes and PCI, these must be balanced against the increased risk of bleeding associated with this therapy.\textsuperscript{85} In patients with non-ST elevation acute coronary syndromes, data from the CURE trial demonstrated a significantly increased risk in both major bleeding (relative risk, 1.38; 95% confidence interval, 1.38 to 1.40; \textit{P}=0.001) and minor bleeding (relative risk, 2.12; 95% confidence interval, 1.75 to 2.56; \textit{P}<0.001) in those receiving clopidogrel plus aspirin as compared with aspirin alone.\textsuperscript{66} In patients with STEMI, there was no difference in overall bleeding noted with dual antiplatelet therapy in patients from the CLARITY-TIMI 28\textsuperscript{71} and the COMMIT\textsuperscript{67,68} trials; however, there was a significant increase in minor bleeding with clopidogrel use in the COMMIT study. Additionally, the CHARISMA trial demonstrated a significant increase in GUSTO-defined moderate bleeding with use of long-term combination aspirin and clopidogrel therapy in both those at risk and those patients with documented atherothrombotic disease.\textsuperscript{69} As such, the risk/benefit ratio favors the use of dual antiplatelet therapy in patients with acute coronary syndromes or post-PCI; however, this does not appear to be true for primary preventive therapy for those at risk for CAD.

\textbf{Clopidogrel Resistance}

Just as there has been interest in aspirin resistance, clopidogrel resistance has been a source of controversy and confusion. Because of problems with inconsistent nomenclature, the generic term “clopidogrel resistance” has been used to describe many processes such as interindividual response variability to clopidogrel, clinical failure of therapy, or a combination thereof.\textsuperscript{86} Although qualitatively different, these processes are potentially interrelated given that patients with low responses to clopidogrel have been demonstrated to be at increased risk for ischemic events. Patient variability to clopidogrel has been demonstrated in several studies and has been generally shown to follow a normal bell-shaped curve.
distribution. A host of factors, commonly divided into those intrinsically or extrinsically related to the platelet, are responsible for this phenomenon. Examples of intrinsic factors include the variability in P2Y$_2$ receptor number and its affinity for the active metabolite of clopidogrel, as well as the variability in internal signaling pathways and glycoprotein Iib/IIIa receptor activation after binding. Absorption and metabolism variability, drug–drug interactions, under-dosing, and noncompliance are all potential extrinsic factors responsible for response variability to clopidogrel. As in the case of aspirin, clopidogrel resistance portends worse clinical outcomes, particularly in those patients who undergo stenting. In a small study of 60 patients placed on clopidogrel therapy after PCI for AMI, those within the lowest quartile of responsiveness to clopidogrel had a marked increase in the rate of recurrent cardiovascular events during 6 months follow-up as compared with those in the other three quartiles (40% versus 6.7%, $P=0.007$). Of course, this could just reflect that activated platelets are the causal factor, rather than clopidogrel variability per se.

The most suitable approach in managing patients deemed to have response variability to clopidogrel has not been defined. One of the first studies to support the notion of using larger doses of clopidogrel to achieve higher blood levels was the ARMYDA-2 (Antiplatelet Therapy for Reduction of Myocardial Damage during Angioplasty) trial. In this trial, the use of a 600 mg loading dose of clopidogrel as opposed to 300 mg significantly reduced the incidence of periprocedural MI by 50% in patients undergoing PCI ($P=0.041$). Additionally, in the ISAR-CHOICE (Intracoronary Stenting and Antithrombotic Regimen: Choose Between 3 High Oral Doses for Immediate Clopidogrel Effect) trial and the ALBION (Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation and Ongoing Necrosis) trial, pretreatment with 600 mg of clopidogrel was associated with a more rapid and greater degree of platelet inhibition than a 300 mg loading dose in patients undergoing PCI. Whether any additional benefit is gained with use of loading doses higher than 600 mg is yet to be determined as ALBION and ISAR-CHOICE yielded somewhat discordant results in this matter. As previously stated, among the aims of the CURRENT/OASIS 7 trial is to investigate the effects of a 600 mg clopidogrel loading dose as compared with 300 mg on clinical outcomes in patients undergoing PCI. In addition to simply increasing the dose of clopidogrel, another option in the future may be to switch to another ADP receptor antagonist. Currently, there are several novel ADP receptor antagonists, such as prasugrel, cangrelor, and AZD6140, still undergoing study that may serve as alternative therapeutic options in the future for those patients with low response to clopidogrel.

**Other ADP Receptor Antagonists**

Despite better tolerability than ticlopidine, important issues such as variability of response, irreversible inhibitory effects, and the length of time required for maximum platelet inhibition with clopidogrel have served as an impetus for the investigation of newer antiplatelet agents. The ADP receptor antagonists currently being studied in phase II and III trials include the third oral thienopyridine prasugrel (Figure 3d) and 2 reversible nonthienopyridine agents, AZD6140 (Figure 3e) and cangrelor (Figure 3f).

In preclinical studies, prasugrel has been shown to have the most potent antiplatelet effect of all the thienopyridines. In animal studies, it was shown to be 10 times more potent than clopidogrel. Similar to clopidogrel and ticlopidine, prasugrel is a produg whose active metabolite irreversibly binds to the P2Y$_{12}$ receptor. In the Joint Utilization of Medications to Block Platelets Optimally (JUMBO)-TIMI 26 trial, a double-blind safety trial of prasugrel in a PCI population, a loading dose followed by 1 month of maintenance therapy with prasugrel was just as safe as clopidogrel. There was no significant difference in the incidence of non-CABG, TIMI major, or minor bleeding in the prasugrel-treated patients as compared with those who received a 300 mg loading dose with 75 mg maintenance dose of clopidogrel (1.7% versus 1.2%, $P=0.59$). Although not specifically designed to assess efficacy, there was a nonsignificant decrease in the incidence of death, MI, stroke, or target vessel thrombosis at 30-day follow-up in the prasugrel-treated patients as compared with those assigned to clopidogrel. Prasugrel is currently being evaluated against clopidogrel as adjuvant therapy in patients presenting with acute coronary syndromes with planned PCI in the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel) phase III study. The PRINCIPLE-TIMI 44 (Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation) study is assessing the effect on platelet inhibition of a prasugrel 60 mg loading dose followed by 10 mg daily versus a clopidogrel 600 mg loading dose followed by 150 mg daily. This study will help determine whether higher loading and maintenance dosing of clopidogrel overcomes its more variable response compared with prasugrel. In addition to evaluating the efficacy and safety of prasugrel versus clopidogrel, TRITON-TIMI 38 will either validate or invalidate the concept that greater platelet inhibition improves clinical outcomes.

AZD6140 is a cyclopentyl triazolopyrimidine, and it offers potential therapeutic advantages when contrasted to the thienopyridines. AZD6140 is an orally active, direct-acting reversible inhibitor of the P2Y$_{12}$ receptor that provides a more rapid and complete antiplatelet effect than clopidogrel because of its distinct pharmacodynamic and pharmacokinetic properties. In the DISPERSE (Dose Confirmation Study Assessing Anti-Platelet Effects of AZD6140 Versus Clopidogrel in NSTEMI) trial, a phase II study of patients with atherosclerosis, AZD6140 (100 and 200 mg BID) with concomitant aspirin therapy had peak inhibition of ADP-induced platelet aggregation within 2 hours as compared with only minimal inhibition seen with clopidogrel (with no loading dose) at 24 hours. Additionally, more potent inhibition of platelet aggregation was seen at days 14 and 28 in those receiving AZD6140 as compared with clopidogrel. Whether more potent ex vivo platelet inhibition with AZD6140 will translate into better clinical outcomes for patients is still to be determined. The DISPERSE-2 trial was a phase II study that evaluated the clinical safety of 90 mg BID and 180 mg BID of AZD6140 versus clopidogrel in patients presenting with
non-ST elevation acute coronary syndromes and found similar rates of bleeding. There was no significant difference in ischemic events, although numerically the lowest rates were with 180 mg BID of AZD6140.100 The ongoing PLATO (Platelet Inhibition and Patient Outcomes) trial is a phase III study with an expected total enrollment of 18,000 patients which is comparing the efficacy of AZD6140 against clopidogrel in patients with non-ST or ST elevation acute coronary syndromes.101

Cangrelor is an intravenous direct-acting reversible inhibitor of the P2Y12 purinoreceptor whose very short half-life offers a potential safety advantage over the currently available thienopyridines.102 Cangrelor, as an adjunct to aspirin and anticoagulation therapy, has been shown to be well tolerated and safe in phase II studies performed in patients with ischemic heart disease, acute coronary syndromes, and those undergoing PCI.103–105 In a phase II study of PCI patients, cangrelor dosed at 4 μg/kg per minute was shown to achieve almost complete platelet inhibition at a time interval comparable to that seen with the glycoprotein IIb/IIIa inhibitor abciximab. However, a return to baseline platelet function was more rapidly obtained after discontinuation of cangrelor therapy than after abciximab.103 The CHAMPION-PCI106 and CHAMPION-PLATFORM107 (Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition) trials, both multicenter prospective randomized studies, will assess the clinical effectiveness of cangrelor in comparison to clopidogrel in patients requiring PCI. If these 2 studies reach completion, taken together, they would constitute the largest drug evaluation in PCI.

**Glycoprotein IIb/IIIa Inhibitors**

The GPIIb/IIIa receptor is vital to the process of platelet activation and aggregation. There are numerous stimuli known to bind to specific receptors on the platelet cell surface and cause activation of intracellular signaling pathways within the platelet (Figure 2a). The resting GPIIb/IIIa receptor, in response to these intracellular reactions, undergoes a conformational change allowing it to bind its most important ligand, fibrinogen. Once this occurs, platelet aggregation ensues via the cross-linking of 2 separate platelets by fibrinogen. Irrespective of the initial agonist, the effects of the intracellular signaling processes are mainly mediated through the GPIIb/IIIa receptor complex. Hence, the GPIIb/IIIa receptor is among the key integrins involved in platelet aggregation and thrombus formation. By inhibiting the action of this integrin, the GPIIb/IIIa receptor antagonists provide potent antiplatelet activity, much more than that seen with aspirin or the oral ADP receptor antagonists clinically evaluated to date.

The GPIIb/IIIa receptor antagonists have been extensively investigated, particularly in the area of CVD (see supplemental Table III). Abciximab, a chimeric monoclonal antibody that binds nonspecifically to the GPIIb/IIIa receptor was the first of these agents to be developed. Next, the small molecule GPIIb/IIIa receptor inhibitors were developed in response to concerns related to abciximab including possible immunogenicity, irreversibility, and nonspecificity for the GPIIb/IIIa receptor. These agents include eptifibatide, a cyclic heptapeptide, and tirofiban and lamifiban, both of which are nonpeptide antagonists of the GPIIb/IIIa receptor. Unlike abciximab, all of these agents are highly specific for the GPIIb/IIIa receptor and each act at the arginine–glycine–aspartic acid (RGD) ligand-binding sequence site. All of the small molecule agents have a shorter biological half-life and a weaker affinity for the GPIIb/IIIa receptor than abciximab.

The intravenous GPIIb/IIIa receptor inhibitors have been established as effective therapy for the reduction of ischemic events when used in both the management of acute coronary syndromes and as adjunctive therapy during PCI108 (see the online data supplement for further review). In a pooled analysis of 32,135 patients from 16 randomized trials in ischemic CVD, a significant reduction in the combined end point of death or MI was demonstrated within 48 to 96 hours, and this persisted at 30 days and 6 months.108

The role of GPIIb/IIIa inhibitors as adjuncts to either thrombolytic therapy or primary PCI in patients with AMI has not been completely elucidated. In the ADMIRAL (Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long Term Follow-Up) trial of 300 patients, those randomized to abciximab plus PCI as compared with PCI alone had a significant 59% reduction in the rate of death, recurrent MI, or urgent target vessel revascularization at 30 days (6% versus 14.6%, P=0.01).109 and a significant mortality benefit that persisted at three year follow-up.110 However, these results were not substantiated in the larger, multicenter Controlled Abciximab Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial of 2082 patients with AMI, in which abciximab therapy provided no significant additive clinical benefit to primary stenting.111 Despite these contrasting results, the majority of trials indicate a significant benefit with use of adjunctive GPIIb/IIIa inhibitor therapy during primary PCI reperfusion for AMI.112

Additionally, there have been extensive studies investigating the use of combination GPIIb/IIIa receptor antagonists and reduced-dose fibrinolytic therapy in the management of AMI. Despite the promising results of earlier pilot studies, the results of the GUSTO V113 study failed to demonstrate any mortality benefit with use of abciximab and half-dose reteplase, and the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT-3)114 trial also showed no mortality benefit with abciximab and half-dose tenecteplase as compared with standard dose thrombolytics. The efficacy of GPIIb/IIIa receptor antagonists with or without combination thrombolytics before planned PCI, or “facilitated” PCI, is yet to be determined. A recent metaanalysis was performed on the trials thus far completed, and it indicated no benefit with facilitated PCI as compared with primary PCI in the management of AMI.115 Overall, there was no short-term mortality benefit over primary PCI with either GPIIb/IIIa inhibitor alone facilitated PCI (3% versus 3%, P=0.94) or combination GPIIb/IIIa inhibitors plus thrombolytics facilitated PCI (1% versus 4%, P=0.44). Noteworthy, the majority of trials included in this analysis were underpowered for detection of clinical outcomes. Ongoing studies such as the FINESSE (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events) trial116...
hope to provide further insight into the role of combination GPIIb/IIIa inhibitor and thrombolitics and GPIIb/IIIa inhibitor alone facilitated PCI for management of AMI. In contrast to the observed efficacy of intravenous GPIIb/IIIa inhibitors in the management of acute coronary syndromes and as adjunctive therapy in PCI, the trials with oral GPIIb/IIIa inhibitors have failed to demonstrate any benefit. In a pooled analysis of over 33 000 patients, the use of oral GP IIb/IIIa inhibitors was associated with a significant increase in mortality (odds ratio, 1.37; 95% confidence interval, 1.13 to 1.67). As a result, the oral GPIIb/IIIa inhibitors are not available for clinical use. Efforts to explain these findings have provided further insight into the complexity of platelet biology and the pharmacology of these agents. One potential mechanism responsible for these findings is the presence of partial agonist activity with these agents, resulting in an increase in intracellular responses, adhesion molecule expression, and fibrinogen binding and platelet aggregation. Other possible explanations include phospholipase A2 polymorphism and other genetic factors, augmented cardiomyocyte apoptosis via caspase 3 activation, and suboptimal dosing with inadequate inhibition of platelet aggregation, although significant increases in major bleeding were observed in the trials.

### Other Antiplatelet Agents

#### Dipyridamole

Although once thought to be only an inhibitor of the cAMP phosphodiesterase enzyme, dipyridamole is now known to have a multitude of biochemical properties responsible for its antiplatelet effects (Figure 3g). Possibly the most important is its ability to selectively inhibit the cyclic GMP phosphodiesterase type V enzyme, thereby enhancing the antiplatelet effects of the NO/cyclic GMP signaling pathway. Other potential inhibitory effects on platelets result from its inhibitory action on adenosine deaminase resulting in increased concentrations of adenosine, its inhibition of adenosine uptake, and also from its ability to increase the release of prostanooids from the endothelium.

Although primarily studied for use in cerebrovascular disease, there have been investigations of dipyridamole with or without aspirin as a therapeutic modality for secondary prevention of MI. In the Persantine-Aspirin Reinfarction Study (PARIS) of more than 2000 patients with history of MI, no further benefit in death or MI prevention was gained with the addition of dipyridamole to aspirin therapy. In the subsequent Persantine-Reinfarction Study Part II (PARIS II) trial, dual therapy with dipyridamole and aspirin significantly reduced the composite end point of MI or death at one year as compared with placebo.

#### Cilostazol

Cilostazol reversibly inhibits platelets via its selective antagonism of the cyclic nucleotide phosphodiesterase type 3 enzyme, and it is also known to inhibit adenosine uptake (Figure 3h). Its ability to inhibit platelets in vivo, however, is uncertain. Additionally, cilostazol is known to promote arterial vasodilatation. Since the discovery of its abilities to suppress vascular smooth muscle proliferation and intimal hyperplasia, several trials have also investigated the use of cilostazol in the setting of PCI. Cilostazol appears to reduce the rate of restenosis after balloon angioplasty and directional coronary atherectomy. Pilot studies demonstrated similar or even better efficacy with cilostazol than with aspirin, ticlopidine, or clopidogrel in preventing restenosis after coronary stent implantation. In the Cilostazol for Restenosis Trial (CREST), 705 patients undergoing PCI with stent implantation were randomized to cilostazol (100 mg BID) or placebo in addition to aspirin and clopidogrel (75 mg daily for 1 month) therapy. There was a significant 36% reduction in the rate of restenosis in those randomized to cilostazol as compared with placebo (22% versus 34.5%, P = 0.002). Further large randomized studies are necessary to determine whether triple therapy with aspirin, clopidogrel, and cilostazol will translate into better clinical outcomes.

### Novel Antiplatelet Agents

#### Protease-Activated Receptor Antagonists

Thrombin, an essential component of the coagulation cascade, is also a potent stimulus for platelet activation. Thrombin formation occurs on the surface of activated platelets after the exposure of tissue factor to coagulation factors in the plasma. Its actions are partly mediated through 2 specific protease-activated receptors (PARs), PAR1 and PAR4, both of which are G protein–coupled receptors. PAR1 is a high-affinity receptor and the major effector of thrombin signaling in the platelet, whereas PAR4 supplements its actions in the later stages of platelet activation. This property difference likely results from the absence of a hirudin-like sequence near the C-terminal thrombin cleavage site of PAR4, making thrombin binding less effective. There is much interest in the clinical development of both PAR1 and PAR4 antagonists as novel antiplatelet therapeutic modalities (Figure 2b). Thus far, there have been several peptide and nonpeptide antagonists of PAR1 developed, but only 2 PAR4 antagonists. Recent studies suggest that simultaneous PAR1 and PAR4 antagonism is synergistic and provides more effective inhibition of thrombin-induced platelet activation than with either PAR1 or PAR4 antagonism alone. Two of the orally administered PAR1 antagonists currently undergoing evaluation in phase II studies are E5555 and SCH530348. A randomized, double-blind, placebo-controlled study of the safety and tolerability of E5555, and its effects on markers of intravascular inflammation in subjects with coronary artery disease, with an expectant enrollment of 600 subjects, will evaluate the efficacy and safety of E5555 in patients with CAD. The TRANSCENDENCE (Thrombin Receptor Antagonist for Clinical Event Reduction Over Standard Concomitant Therapies) PCI trial is a multicenter randomized study enrolling 1600 patients and is investigating the safety of various doses of SCH530348 when used in the nonemergent PCI setting; initial reports suggest excellent safety.

#### Platelet Adhesion Antagonists

Platelet adhesion is not only the primary step in thrombogenesis but emerging evidence continues to highlight the importance of this process in the initiation and progression of
atherosclerosis. As such, there is much interest in developing therapeutic modalities aimed at inhibiting the critical interactions between platelets and subendothelial components of the damaged vessel wall, thus preventing platelet adhesion altogether. One agent undergoing investigation is the collagen inhibitor, C1qTNF-related protein-1, which has been shown to inhibit platelet aggregation by blocking the ability of vWF to bind to collagen, thereby interrupting platelet adhesion and thrombogenesis. Similarly, the compound DZ-697b has been shown to selectively inhibit collagen- and vWF-induced platelet aggregation in human ex vivo studies. In animal studies, it also has been shown to have a more potent antiplatelet and antithrombotic effect with less bleeding risk than aspirin. Additional therapies in the early stages of development include monoclonal antibodies against GP Ib, GP VI, and vWF, all of which have been shown to prevent thrombus formation in animal studies. The use of therapies targeted toward inhibition of platelet adhesion appears to be a promising approach.

Conclusion
Atherothrombosis is the downstream aftermath of atherosclerosis with clinical ramifications that continue to be a huge burden globally. The platelet, once thought to have minor involvement in this process, is now recognized as a critical link between thrombus formation, inflammation, and atherosclerosis. Antiplatelet therapies such as thromboxane inhibitors, ADP receptor antagonists, and GPIIb/IIIa inhibitors have proven to be very effective in the treatment and prevention of atherothrombotic disease. Ongoing efforts to refine these current agents are underway and hopefully will bring more effective and safer drugs to fruition. Some of the more promising antiplatelet therapies with this potential include the newer ADP antagonists and the PAR receptor antagonists. Given the redundant pathways present for platelet activation and subsequent thrombogenesis, there is a continued need to develop additional therapies with novel molecular targets. Potential attractive therapies include those aimed at preventing platelet adhesion, such as those targeting collagen, vWF, GP VI, or GPIIb/V/IX. A greater understanding of platelet biology, and the factors and pathways involved in platelet adhesion, activation, and aggregation, will only further our ability to develop additional novel therapies for use in the management of atherothrombotic diseases.

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References


Clinical Aspects of Platelet Inhibitors and Thrombus Formation Online Supplement

Antiplatelet Agents and Cerebrovascular Disease

Aspirin

There have been two large randomized trials examining the use of aspirin for management of acute ischemic stroke. In the International Stroke Trial (IST), which enrolled 19,435 patients, there was a significant reduction in recurrent stroke (2.8% vs. 3.9%, 2P < 0.001) at 14 days in those patients randomized to aspirin therapy versus placebo.\(^1\) Likewise, the Chinese Acute Stroke Trial (CAST) of 21,106 subjects found a significant reduction in the incidence of recurrent ischemic stroke (1.6% vs. 2.1%, 2P = 0.01) at 4 weeks with aspirin as compared to placebo.\(^2\) In neither of the trials was there a significant increase in hemorrhagic stroke with aspirin therapy. From a pooled analysis, there was a trend toward decreased mortality and disability at 4 weeks with aspirin use.\(^3\)

The results of initial trials regarding the overall effectiveness of aspirin therapy for secondary prevention in patients with a prior history of transient ischemic attacks (TIA) or stroke were not conclusive.\(^4-10\) However, the results of more recent studies have indicated a definite benefit of aspirin therapy in reducing the risk of recurrent stroke.\(^9-11\) In the updated ATC meta-analysis of 21 trials composed of over 18,000 patients with prior history of stroke or TIA, antiplatelet therapy (predominantly aspirin with or without other antiplatelet agents) resulted in a significant reduction in non-fatal stroke recurrence (25 fewer/1000 patients) and vascular death.\(^12\) In another meta-analysis of 10 trials with over 9,000 patients, a similar reduction (13%) in the risk of recurrent stroke was observed
in those randomized to low-dose aspirin as compared to placebo.\textsuperscript{13} Another important cause of TIA and stroke is intracranial arterial stenosis and aspirin has been shown to be safe and beneficial in this setting. The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial compared the safety and efficacy of aspirin (1300 mg per day) against warfarin (target international normalized ratio of 2 to 3) in patients with a history of TIA or stroke due to angiographically confirmed stenosis of a major intracranial artery. The trial was prematurely stopped due to an increased risk of adverse events including death, MI, and major hemorrhage in those patients randomized to warfarin therapy. There was no difference between the two therapies in the rate of the combined endpoint of ischemic stroke, brain hemorrhage, or death from vascular causes other than stroke (22.1\% vs. 21.8\%, \(P = 0.83\)).\textsuperscript{14}

Patients with non-valvular atrial fibrillation have a known five to sevenfold increase in the risk of stroke. Several randomized studies have investigated the effectiveness of aspirin for stroke prevention in this unique population.\textsuperscript{15-19} In a meta-analysis of six randomized trials with over 3,000 subjects, aspirin (dose range: 50 to 1300 mg/day) resulted in a significant 22\% reduction in the incidence of stroke.\textsuperscript{20} However, in this same review and in a more recent meta-analysis, aspirin therapy was shown to be less efficacious than warfarin in this particular setting.\textsuperscript{20,21}

**ADP receptor antagonists**

**Ticlopidine**

One of the earliest investigational studies demonstrating the benefit of ticlopidine focused on its use for secondary prevention in patients with prior stroke.\textsuperscript{22} In the Canadian American Ticlopidine Study (CATS) trial with 1,072 participants, ticlopidine-
treated patients had a 30% relative reduction in stroke, myocardial infarction, or vascular
death as compared to those given placebo. Subsequently, ticlopidine was shown also to
be superior to aspirin in patients at high-risk for stroke. In the multicenter Ticlopidine
Aspirin Stroke Study (TASS), 3,069 patients with recent transient cerebral or retinal
ischemia were randomized to daily ticlopidine (500 mg) or aspirin (1300 mg) and
followed for two to six years. Ticlopidine therapy resulted in a significant 12% reduction in stroke or death with a 3-year event rate of 17% in the ticlopidine-treated
group and 19% in the aspirin-treated group (P = 0.048). However, the superiority of
ticlopidine over aspirin may not be generalizable to all ethnic groups. The African
American Antiplatelet Stroke Prevention Study (AAASPS) randomized 1,809 black men
and women with history of noncardioembolic ischemic stroke to ticlopidine (500 mg/day)
or aspirin (650 mg/day). There was no difference in the primary endpoint of recurrent
stroke, MI, or vascular death within 2-year follow-up between those randomized to
ticlopidine versus aspirin therapy (14.7% vs. 12.3%, P = 0.12).

**Clopoidogrel**

The results of clinical trials investigating the role of clopidogrel therapy in
patients at high-risk or with a history of cerebrovascular events are inconclusive. In the
CAPRIE trial of over 19,000 patients with prior history of atherothrombosis, clopidogrel
was shown to be superior to aspirin in the reduction of future ischemic events, one of
which included ischemic stroke. However, the patients with prior stroke in this study
had a reduction in the composite endpoint of cardiovascular death, MI, or stroke that was
not statistically significant. In ex-vivo platelet activation studies, clopidogrel and aspirin
combination therapy provides greater platelet inhibition than aspirin alone in patients
with recent ischemic stroke. Dual aspirin and clopidogrel therapy when compared to aspirin alone has also been shown to further reduce asymptomatic embolization, a proposed surrogate for antiplatelet efficacy, in patients with symptomatic carotid stenosis at high-risk for stroke. Hence, the Management of ATherothrombosis with Clopidogrel in High-risk patients with recent transient ischemic attack, or ischemic stroke (MATCH) trial was designed to determine if greater platelet inhibition would translate into better clinical outcomes in patients with a recent history of TIA or ischemic stroke. The study randomized 7,599 subjects with recent TIA or stroke to daily clopidogrel (75 mg) and either aspirin (75 mg/day) or placebo. At 18 months follow-up, dual antiplatelet therapy did not result in a significant reduction in the combined end point of ischemic stroke, myocardial infarction, vascular death, or rehospitalization for acute ischemia (15.7% ASA + clopidogrel vs. 16.7% clopidogrel, RRR 6.4%, [95% CI -4.6 to 16.3]).

Furthermore, the addition of aspirin to clopidogrel significantly increased the risk of life-threatening bleeding (2.6% ASA + clopidogrel vs. 1.3% clopidogrel, absolute risk increase 1.3%, [95% CI 0.6 to 1.9]).

Given the superiority of anticoagulation over aspirin therapy for the prevention of stroke in patients with non-valvular atrial fibrillation, the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE) trial was designed to compare the efficacy of clopidogrel against various therapies in the prevention of stroke, MI, vascular death, and systemic embolism. The results of ACTIVE W, which evaluated clopidogrel plus aspirin against warfarin, were recently published after early termination of the trial due to the clear advantage of oral anticoagulation over dual antiplatelet therapy. Of the 6,706 patients randomized to clopidogrel and aspirin
therapy, there was a significant 44% relative increase in the risk of the composite endpoint of first occurrence of stroke, non-CNS systemic embolus, MI, or vascular death as compared to those receiving warfarin (5.60% vs. 3.93%, P = 0.0003). Many patients, however, have contraindications to oral anticoagulation therapy and the ACTIVE A trial is assessing if additional benefit is gained with adding clopidogrel to aspirin in these particular patients versus aspirin alone.29

**Glycoprotein IIb/IIIa inhibitors**

The glycoprotein IIb/IIIa receptor antagonists are currently in the early stages of investigation for use as both primary medical therapy and as adjunctive therapy to pharmacologic and mechanical reperfusion modalities for acute ischemic stroke. Preclinical studies have demonstrated an improvement in microvascular patency,31 a reduction in ischemic brain injury32 and thrombolytic induced intracerebral hemorrhage,33 and a prolongation of the therapeutic time window for thrombolytics34 with use of glycoprotein IIb/IIIa antagonists in animal stroke models. In the Abciximab in Emergent Stroke Treatment Trial (AbESTT) phase 2 study of 400 patients, intravenous abciximab given within 6 hours of stroke onset resulted in a nonsignificant trend toward improved clinical outcomes as assessed by clinical rating scores without any significant increase in bleeding.35 In a small pilot study of 19 patients, tirofiban and reduced-dose recombinant tissue plasminogen activator combination therapy were demonstrated to safely and effectively provide middle cerebral artery recanalization as assessed by magnetic resonance angiography.36 In a recent single center retrospective analysis, combination intra-arterial and GPIIb/IIIa inhibitor therapy was shown to be an independent predictor
of successful vessel recanalization in 168 consecutive acute ischemic stroke patients treated with various reperfusion modalities.\textsuperscript{37}

**Other antiplatelet agents**

*Dipyridamole*

The use of dipyridamole alone or in combination with aspirin for secondary prevention of recurrent strokes in patients with a history of ischemic cerebrovascular disease has been studied extensively and has yielded conflicting results.\textsuperscript{38-42} However, in the largest trial conducted, the European Stroke Prevention Study II (ESPS II), dipyridamole with or without aspirin therapy effectively prevented stroke recurrence. The trial enrolled 6,602 subjects with a prior history of stroke or TIA and randomized each to either aspirin alone (50 mg daily), modified-release dipyridamole alone (400 mg daily), combination ASA plus dipyridamole, or placebo.\textsuperscript{38} As compared to placebo, dipyridamole alone resulted in a 16% ($P = 0.039$) reduction in the risk of stroke, and there was an additive 24% ($P < 0.001$) risk reduction seen with use of aspirin plus dipyridamole. The benefit of dipyridamole alone was comparable to that of aspirin alone (16% vs. 18%). The results of a pooled analysis of 11,459 patients from seven randomized trials were consistent with those from ESPS II.\textsuperscript{43} Dipyridamole alone was shown to reduce effectively future strokes in those with a prior history of ischemic cerebrovascular disease (OR 0.82; 95% CI 0.68 – 1.0) when compared to placebo and this benefit was further magnified with the addition of aspirin therapy (OR 0.61; CI 0.51 – 0.71). In addition, combination dipyridamole plus aspirin therapy was shown to be more effective then either agent alone.
Results from the recently published European/Australian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) suggest that combination dipyridamole plus aspirin therapy may not only provide protection against stroke recurrence but also against other vascular events such as MI or death from vascular causes.\textsuperscript{44} In the study of 2,739 patients, those randomized to combination therapy versus aspirin alone had a significant reduction in the composite outcome of death from all vascular causes, stroke, MI, or major bleeding event (hazard ratio 0.80, 95\% CI 0.66 – 0.98). The Prevention Regimen for Effectively Avoiding Second Strokes (ProFESS) trial is a large ongoing study of over 15,000 patients that is comparing clopidogrel versus extended-release dipyridamole plus aspirin in patients with a history of TIA or ischemic stroke. The results of this study will further determine the most effective antiplatelet regimen for secondary prevention in cerebrovascular disease.

\textbf{Antiplatelet Agents and Peripheral Arterial Disease}

\textit{Aspirin}

The aim of medical therapy in the management of peripheral arterial disease (PAD) is two-fold. One goal is to prevent disease progression while providing symptom relief. Aspirin therapy has been shown to decrease angiographic progression of PAD in a small study of 240 subjects.\textsuperscript{45} In a subset of low-risk subjects from the Physicians’ Health Study, low-dose aspirin therapy was also shown to decrease the need for peripheral arterial surgery.\textsuperscript{46} However, aspirin has not been shown to improve claudication symptoms. Another important objective in the management of PAD is reducing the associated cerebrovascular or cardiovascular complications. The ATC meta-analysis contained 9,214 patients from 42 trials with PAD and it demonstrated a significant 23\%
reduction in the risk of myocardial infarction, stroke, or cardiovascular death with antiplatelet therapy.\textsuperscript{12}

**ADP receptor antagonists**

**Ticlopidine**

Ticlopidine has been shown to be efficacious in the secondary prevention of vascular events in patients with PAD. In a trial of 687 participants with a history of intermittent claudication, treatment with long-term ticlopidine (250 mg bid) as compared to placebo resulted in a significant 34% reduction in the incidence of myocardial infarction, stroke, or TIA.\textsuperscript{47} Furthermore, long-term ticlopidine therapy also reduced the need for future vascular surgery in this same population by approximately 50%.\textsuperscript{48} In those patients requiring surgical intervention, the initiation of ticlopidine as soon as possible after intervention has been shown to further reduce thrombotic events and claudication symptoms.\textsuperscript{49} Ticlopidine has also been demonstrated to improve the long-term patency of saphenous vein grafts in those patients who undergo peripheral vein bypass surgery.\textsuperscript{50}

**Clopidogrel**

The CAPRIE trial established the superiority of clopidogrel over aspirin in secondary prevention of ischemic events in a diverse group of high-risk patients, but the greatest benefit was seen in the subset of patients with an established history of peripheral arterial disease. In the 6,452 subjects with PAD, randomization to clopidogrel as compared to aspirin resulted in a significant 23.8% (95% CI 8.9% - 36.2%) relative reduction in the risk of MI, stroke, or cardiovascular death.\textsuperscript{25} Dual antiplatelet therapy with clopidogrel and aspirin therapy did not appear to provide any statistically significant
benefit compared with aspirin alone in the subset of 3,531 patients with PAD in CHARISMA trial, though event rates were numerically lower.\textsuperscript{51} Two other trials were planned to help define the role of clopidogrel and aspirin combination therapy in PAD. The Clopidogrel and Aspirin in Surgery for Peripheral Arterial Disease (CASPAR) trial is currently enrolling patients undergoing vascular surgery. The intent of the Clopidogrel and Aspirin in the Management of Peripheral Endovascular Revascularization (CAMPER) trial had been to study dual antiplatelet therapy in patients undergoing endovascular procedures, but because use of dual antiplatelet therapy at least early after these procedures had become so common, enrollment was sluggish, and the trial was terminated.\textsuperscript{52}

**Glycoprotein IIb/IIIa inhibitors**

The use of GPIIb/IIIa inhibitors as adjunctive therapy in catheter-directed thrombolysis in peripheral arterial occlusive disease (PAOD) has been evaluated in several small pilot studies.\textsuperscript{53-56} In The Platelet Receptor Antibodies in Order to Manage Peripheral Artery Thrombosis (PROMPT) pilot study of 70 patients, the addition of abciximab to urokinase therapy significantly increased both the rapidity of thrombus dissolution and the incidence of 90-day amputation free survival at the expense of a slightly higher bleeding rate.\textsuperscript{53} The efficacy and safety of combination GPIIb/IIIa inhibitors and third generation thrombolytics was studied in the Reteplase Monotherapy and Reteplase/Abciximab Combination Therapy in Peripheral Arterial Occlusive Disease (RELAX) trial and combination therapy was associated with a decreased rate of distal embolic events with no further increase in hemorrhagic complications.\textsuperscript{54} In the Antibodies of Platelet Receptors and Reteplase for Thrombolysis (APART) study directly
comparing combination abciximab plus urokinase versus abciximab plus reteplase, there
was no difference in efficacy or safety between the two treatment modalities. Although
the preliminary trials results are promising, larger clinical studies with long-term
outcomes still need to be performed to establish definitively the role of combined
GPIIb/IIIa inhibitors and reduced-dose thrombolytic therapy in PAOD.

Other antiplatelet agents

Cilostazol

Given the properties of cilostazol, including its ability to promote peripheral
arterial dilatation, numerous trials have evaluated the efficacy of this agent in patients
with symptomatic claudication. In a pooled analysis of eight randomized trials with
2,702 patients, cilostazol significantly increased maximal and pain-free walking distances
by 50% and 67%, respectively, regardless of gender, age or presence of diabetes
mellitus.

Aspirin in the Acute Management and Secondary Prevention
of CAD

The Second International Study of Infarct Survival (ISIS-2) was the first large
prospective randomized trial to establish conclusively the beneficial effects of aspirin in
the management of acute myocardial infarction (AMI). In this trial of 17,187 patients
presenting a median of 5 hours after the onset of suspected AMI, one month of aspirin
therapy versus placebo resulted in a significantly decreased incidence of ischemic events
at 5 weeks and a survival benefit sustained at 10 years of follow-up. Additionally, the
ISIS-2 trial established the role of aspirin as an adjunct to thrombolytic therapy in AMI as
there was an additive effect in mortality reduction seen in those patients who received
streptokinase plus aspirin as compared to streptokinase alone. Aspirin’s beneficial role as adjunctive therapy to thrombolytics has been further confirmed by a meta-analysis of 32 trials showing a significant decrease in reocclusion rates (11% vs. 25%, P < 0.001) and recurrent ischemic events (25% vs. 41%, P < 0.001) in those receiving concomitant aspirin therapy.

Aspirin is just as efficacious in the treatment of the other acute coronary syndromes: acute non ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA) (see Table 1B). Randomized studies examining aspirin therapy versus placebo in unstable angina have shown a significant decrease of approximately 50% in the incidence of nonfatal MI or death. The original Antiplatelet Trialists’ Collaboration (ATC, later renamed Antithrombotic Trialists’ Collaboration) meta-analysis containing nearly 4,000 patients with unstable angina showed a significant reduction in vascular events which were defined as nonfatal MI, stroke, or vascular death (9% vs. 14%) in those treated with aspirin as compared to placebo. This treatment effect has recently been re-confirmed in the updated ATC meta-analysis examining antiplatelet therapy, predominantly aspirin, in high-risk patients.

Patients with an acute coronary syndrome or symptomatic obstructive atherosclerotic disease often undergo some form of revascularization as part of their management. Aspirin reduces the incidence of ischemic complications after revascularization in both percutaneous coronary interventions (PCI) and surgical bypass grafting. In PCI, aspirin therapy decreases the risk of acute ischemic events, but it does not have any affect on the incidence of restenosis. Early use of aspirin therapy after
coronary artery bypass grafting (CABG) leads to improvement in both short- and long
term-graft patency rates.\textsuperscript{71}

The overwhelming evidence also indicates a benefit with aspirin in secondary
prevention in patients with a prior history of myocardial infarction. There have been five
large randomized trials demonstrating a trend toward mortality benefit in patients
receiving aspirin therapy after AMI.\textsuperscript{72-76} The Aspirin Myocardial Infarction Study was the
one large-scale trial, randomizing 4,524 patients to daily aspirin versus placebo that
showed no difference in mortality (10.8\% vs. 9.7\%, respectively). However, there was a
trend toward decreased incidence in nonfatal MI seen in patients randomized to aspirin.\textsuperscript{77}
In the ATC meta-analysis of approximately 20,000 patients with a prior history of MI,
antiplatelet therapy, predominantly in the form of aspirin, resulted in a significant
reduction of nonfatal MI, stroke, or vascular mortality as compared to control (17.1\% vs.
13.5\%, \(P < 0.0001\)).\textsuperscript{65}

**Glycoprotein IIb/IIIa Inhibitors and Cardiovascular Disease**

The earliest phase 3 study with the GPIIib/IIIa inhibitors was conducted with
c7E3, later named abciximab, in patients undergoing balloon angioplasty. In The
Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC) trial of 2,099
high-risk patients, including those with complex angiographic lesions, unstable angina, or
evolving MI, there was a significant 35\% reduction in the composite primary end point of
death, nonfatal MI, or recurrent ischemia at 30 days in patients randomized to c7E3 bolus
plus infusion as compared to placebo (12.8\% vs. 8.3\%, \(P = 0.008\)).\textsuperscript{78} An even greater
magnitude of benefit was seen in those patients who had presented with unstable angina,
as there was a 62\% reduction in death, MI, or recurrent ischemia at 30 days in this
particular subgroup. Similar benefits with abciximab therapy were further confirmed in a low-risk patient population undergoing PCI and in those patients receiving PCI with stenting. The Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trial demonstrated an additive effect with combination abciximab and stenting and it also showed a consistent benefit with abciximab irrespective of angiographic lesion type. In a pooled analysis of five trials evaluating abciximab therapy in PCI, there was a significant reduction in the 30-day incidence of death or MI regardless of the particular interventional device used (hazard ratio 0.52, \( P < 0.001 \)).

The initial study to investigate the use of eptifibatide as adjunctive therapy in PCI was the Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis-II (IMPACT-II) trial. In this study of 4,010 subjects with wide-ranging indications for PCI, those randomized to 135 micrograms/kg bolus and 0.5 micrograms/kg infusion of eptifibatide as compared to placebo had a modest reduction (11.6% vs. 9.1%, \( P = 0.04 \)) in the rate of death, MI, urgent revascularization, or bailout stenting. Later, the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial demonstrated that higher dosing eptifibatide provided an even greater degree of efficacy. The Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) trial investigated the use of adjunctive tirofiban in PCI in 2,139 patients presenting with unstable angina or MI. Treatment with tirofiban resulted in a significant 38% relative reduction in ischemic events at 48 hours; however, this effect was attenuated and no longer significant at 30 days. The one phase 3 trial conducted that directly compared the relative efficacy of two GPIIb/IIIa inhibitors was the Do Tirofiban and Reopro Give Similar Efficacy Trial (TARGET). In this study of 4,809 patients
undergoing non-emergent PCI, treatment with abciximab as opposed to tirofiban significantly reduced the incidence of death, MI, or urgent target vessel revascularization by 27% at 30 days follow-up (6.0% vs. 7.6%, P = 0.038).

Additional studies have provided further insight into the mechanistic effect and applicability of the GPIIb/IIIa receptor inhibitors when used as adjunctive therapy in PCI. The c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) trial evaluated the use of abciximab, given 18 to 24 hours prior to PCI, in 1,265 patients with medically refractory unstable angina. Randomization to abciximab resulted in a significant reduction in ischemic events both prior to and after PCI, a benefit attained by its ability to potentiate thrombus resolution as was seen on angiographic analysis. Furthermore, the subgroup of patients that derived the most benefit from abciximab therapy was that with elevated serum troponin levels. This appears to be applicable in the contemporary era of dual antiplatelet therapy as evident from the Intracoronary Stenting and Antithrombotic Regimen Rapid Early Action for Coronary Stenting 2 (ISAR-REACT 2) trial. In this study, 2,022 patients with non-ST-segment elevation ACS undergoing PCI were randomized to abciximab or placebo in addition to pretreatment with 600 mg of clopidogrel at least 2 hours prior to procedure. Overall, there was a significant 25% reduction in the rate of death, MI, or urgent target vessel revascularization in those randomized to abciximab versus placebo (8.9% vs. 11.9%, P = 0.03). However, subgroup analysis revealed that abciximab provided benefit only in those patients with an elevated serum troponin level. Consequently, serum troponin levels continue to be used as a risk stratification tool to determine those patients most likely to obtain clinical benefit from GPIIb/IIIa inhibitors.
Another specific patient population that has been shown to derive particular benefit with adjunctive GPIIb/IIIa inhibitors is those with diabetes mellitus. In the EPISTENT trial, diabetic patients treated with abciximab versus placebo had a significant reduction in the rate of death or MI at 6 months.92 Similarly, in a pooled analysis of 1,462 diabetic patients undergoing PCI, there was a significant reduction in the one-year mortality rate in those randomized to abciximab as compared to placebo (2.5% vs. 4.5%, P = 0.031) with an even more impressive benefit in those undergoing multivessel intervention (7.7% vs. 0.9%, P = 0.018).93 However, the benefit with GPIIb/IIIa inhibitors in both diabetic and non-diabetic patients appears to be attenuated when concomitant clopidogrel therapy is used during PCI.94, 95 For instance, in the Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment (ISAR-REACT) Study, abciximab, in addition to 600 mg pretreatment with clopidogrel at least two hours prior to the procedure, provided no further reduction in the combined endpoint of death, MI, or urgent revascularization at 30 days than placebo in low-risk, elective PCI (4% vs. 4%, P = 0.82).94 The Intracoronary Stenting and Antithrombotic Regimen-Is Abciximab a Superior Way to Eliminate Elevated Thrombotic Risk in Diabetics (ISAR-SWEET) study also demonstrated no additional benefit in death or MI at one year, rather only a decreased incidence of angiographic restenosis at a median of seven months (28.9% vs. 37.8%, P = 0.01), with the addition of abciximab to loading dose clopidogrel 600 mg given at least two hours prior to the procedure in diabetics undergoing elective PCI.95

In addition to adjunctive therapy during PCI, the GPIIb/IIIa inhibitors have also been established as effective therapy in the initial medical management of unstable
angina and non-ST-elevation MI. In The Platelet Glycoprotein IIb/IIIa in Unstable Angina Receptor Suppression Using Integrlin Therapy (PURSUIT) trial of 10,948 patients with unstable angina or ST elevation MI, there was a significant reduction in the composite endpoint of death or MI at 30 days in those randomized to eptifibatide bolus and infusion as compared to placebo (14.2% vs. 15.7%, P = 0.04). Accordingly, in a similarly high-risk population of 1,915 patients with acute coronary syndromes without ST-segment elevation in the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) study, the addition of tirofiban to heparin was demonstrated to significantly decrease the 7-day composite endpoint of death, MI, or refractory ischemia from 17.9% to 12.9% (P = 0.004). In this study, there was a tirofiban-only arm that was stopped prematurely due to excess mortality when compared to heparin alone suggesting the need for concomitant anticoagulant use with GPIIb/IIIa inhibitors.

As is the case with PCI, the particular patients likely to derive the maximal benefit from GPIIb/IIIa inhibitor therapy in acute coronary syndromes are those at increased risk of ischemic complications identified by the presence of elevated serum troponin levels or ST-segment depression on the electrocardiogram. However, the one trial whose results contradict this generalization is the Global Utilization of Strategies To open Occluded coronary arteries trial IV in Acute Coronary Syndromes (GUSTO IV-ACS). In this trial of 7,800 high-risk patients with unstable angina or non-ST elevation MI being medically treated, the addition of abciximab to standard medical therapy provided no further benefit than placebo, regardless of the presence of ST-segment depression or troponin elevation. As a result of this trial, the use of abciximab should be
limited to adjunctive therapy in PCI and in those patients with non ST-segment elevation ACS with a definite plan for PCI. Despite the negative results with abciximab in the GUSTO-IV ACS trial, GPIIb/IIIa inhibitors justifiably remain an important modality of therapy in patients with non-ST-elevation ACS, especially those undergoing PCI. In a pooled analysis of the six trials examining the use of GPIIb/IIIa inhibitors for therapy in non ST-segment elevation ACS, which includes GUSTO IV ACS, there was a significant, though modest, reduction in the rate of MI or death at 30 days with GPIIb/IIIa inhibitors as compared to placebo (10.7% vs. 11.5%, P = 0.04).\textsuperscript{102}
## Online Table I

### Trials of aspirin in primary prevention

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population</th>
<th>Treatment Dose</th>
<th>Mortality, Relative Risk</th>
<th>MI/Stroke, Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physicians’ Health Study&lt;sup&gt;103&lt;/sup&gt;</td>
<td>22,071 males</td>
<td>325 mg every other day</td>
<td>0.96</td>
<td>0.59 / 1.22</td>
</tr>
<tr>
<td>British Doctors’ Trial&lt;sup&gt;104&lt;/sup&gt;</td>
<td>5,139 males</td>
<td>500 mg daily</td>
<td>0.89</td>
<td>0.97 / 1.15</td>
</tr>
<tr>
<td>Swedish Angina Pectoris Aspirin Trial&lt;sup&gt;105&lt;/sup&gt;</td>
<td>2,035 males and females</td>
<td>75 mg daily</td>
<td>0.78</td>
<td>0.61 / 0.75</td>
</tr>
<tr>
<td>Thrombosis Prevention Trial&lt;sup&gt;106&lt;/sup&gt;</td>
<td>5,085 males</td>
<td>75 mg daily</td>
<td>1.06</td>
<td>0.68 / 0.98</td>
</tr>
<tr>
<td>Hypertension Optimal Treatment Study&lt;sup&gt;107&lt;/sup&gt;</td>
<td>18,790 males and females</td>
<td>75 mg daily</td>
<td>0.93</td>
<td>0.64 / 0.98</td>
</tr>
<tr>
<td>Primary Prevention Project&lt;sup&gt;108&lt;/sup&gt;</td>
<td>4,495 males and females</td>
<td>100 mg daily</td>
<td>0.81</td>
<td>0.69 / 0.67</td>
</tr>
<tr>
<td>Women’s Health Study&lt;sup&gt;109&lt;/sup&gt;</td>
<td>39,876 healthy females</td>
<td>100 mg every other day</td>
<td>0.95</td>
<td>1.02 / 0.83</td>
</tr>
</tbody>
</table>

### Trials of aspirin in unstable angina

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population</th>
<th>Treatment Dose</th>
<th>Treatment Duration</th>
<th>Death or MI Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA Cooperative Study&lt;sup&gt;62&lt;/sup&gt;</td>
<td>1,266</td>
<td>325 mg daily</td>
<td>12 weeks</td>
<td>51%</td>
</tr>
<tr>
<td>Canadian Multicenter Trial&lt;sup&gt;64&lt;/sup&gt;</td>
<td>555</td>
<td>325 mg 4 x daily</td>
<td>18 months (mean)</td>
<td>51%</td>
</tr>
<tr>
<td>Theroux et al&lt;sup&gt;63&lt;/sup&gt;</td>
<td>479</td>
<td>325 mg twice daily</td>
<td>6 days</td>
<td>72%</td>
</tr>
<tr>
<td>RISC Study&lt;sup&gt;61&lt;/sup&gt;</td>
<td>796</td>
<td>75 mg daily</td>
<td>90 days</td>
<td>62%</td>
</tr>
</tbody>
</table>

MI, myocardial infarction
### Online Table II.  *Randomized studies of clopidogrel therapy in CAD*

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population</th>
<th>Follow-up</th>
<th>Primary Endpoint</th>
<th>RRR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPRIE</td>
<td>19,185 with</td>
<td>1 to 3 years (mean 1.91</td>
<td>Vascular death, MI, or ischemic stroke</td>
<td>8.7%</td>
</tr>
<tr>
<td></td>
<td>MI/stroke/PAD</td>
<td>years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CURE</td>
<td>12,562 NSTEMI-ACS</td>
<td>3 to 12 months</td>
<td>CV death, MI, or stroke</td>
<td>20%</td>
</tr>
<tr>
<td>PCI-CURE</td>
<td>2,658 NSTEMI-ACS</td>
<td>Within 30 days from PCI</td>
<td>CV death, MI, or urgent TVR</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>undergoing PCI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CREDO</td>
<td>2,116 with PCI or</td>
<td>1 year</td>
<td>Death, MI, or stroke</td>
<td>26.9%</td>
</tr>
<tr>
<td></td>
<td>high likelihood of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PCI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLARITY</td>
<td>3,491 STEMI +</td>
<td>Median 48 hours (angiography)</td>
<td>Death, recurrent MI, or occluded infarct-related artery</td>
<td>36%</td>
</tr>
<tr>
<td></td>
<td>lytics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI-CLARITY</td>
<td>1,863 STEMI +</td>
<td>30 days from PCI</td>
<td>Death, MI, or stroke</td>
<td>42%</td>
</tr>
<tr>
<td></td>
<td>lytics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COMMIT</td>
<td>45,852 suspected</td>
<td>Mean 15 days</td>
<td>Death, re-infarction, or stroke</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>acute MI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHARISMA</td>
<td>15,603 with CV</td>
<td>Median of 28 months</td>
<td>CV death, MI, or stroke</td>
<td>7%*</td>
</tr>
<tr>
<td></td>
<td>disease or multiple risk factors for CV disease</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome; CV, cardiovascular; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; RRR, relative risk reduction; TVR, target vessel revascularization

*P = 0.22
**Online Table III. Randomized studies of glycoprotein IIb/IIIa inhibitors in CAD**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Treatment</th>
<th>Endpoint</th>
<th>Follow-up</th>
<th>RRR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPIC78</td>
<td>2,099</td>
<td>Abciximab</td>
<td>Death, MI, urgent revascularization, stent or balloon pump placement</td>
<td>30 days</td>
<td>35%</td>
</tr>
<tr>
<td>EPILOG80</td>
<td>2,792</td>
<td>Abciximab</td>
<td>Death, MI, or urgent revascularization</td>
<td>30 days</td>
<td>~ 55%</td>
</tr>
<tr>
<td>CAPTURE88</td>
<td>1,265</td>
<td>Abciximab</td>
<td>Death, MI, or urgent revascularization</td>
<td>30 days</td>
<td>29%</td>
</tr>
<tr>
<td>EPISTENT81</td>
<td>2,399</td>
<td>Abciximab</td>
<td>Death, MI, or urgent revascularization</td>
<td>30 days</td>
<td>51%</td>
</tr>
<tr>
<td>IMPACT-II84</td>
<td>4,010</td>
<td>Eptifibatide</td>
<td>Death, MI, urgent revascularization, or unplanned stenting</td>
<td>30 days</td>
<td>22%</td>
</tr>
<tr>
<td>RESTORE86</td>
<td>2,139</td>
<td>Tirofiban</td>
<td>Death, MI, urgent revascularization, or unplanned stenting</td>
<td>30 days</td>
<td>16%</td>
</tr>
<tr>
<td>ESPRIT85</td>
<td>2,064</td>
<td>Eptifibatide</td>
<td>Death, MI, urgent revascularization, or need for GP IIb/IIIa inhibitor</td>
<td>48 hours</td>
<td>37%</td>
</tr>
<tr>
<td>ISAR-REACT94</td>
<td>2,159</td>
<td>Abciximab</td>
<td>Death, MI, or urgent TVR</td>
<td>30 days</td>
<td>---†</td>
</tr>
<tr>
<td>ISAR-REACT291</td>
<td>2,022</td>
<td>Abciximab</td>
<td>Death, MI, or urgent TVR</td>
<td>30 days</td>
<td>25%</td>
</tr>
</tbody>
</table>

**Non-ST-Elevation Acute Coronary Syndromes Trials**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Treatment</th>
<th>Endpoint</th>
<th>Follow-up</th>
<th>RRR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PURSUIT96</td>
<td>10,948</td>
<td>Eptifibatide</td>
<td>Death or MI</td>
<td>30 days</td>
<td>10%</td>
</tr>
<tr>
<td>PRISM116</td>
<td>3,232</td>
<td>Tirofiban</td>
<td>Death, MI, or refractory ischemia</td>
<td>48 hours</td>
<td>32%</td>
</tr>
<tr>
<td>PRISM-PLUS97</td>
<td>1,915</td>
<td>Tirofiban</td>
<td>Death, MI, or refractory ischemia</td>
<td>7 days</td>
<td>28%</td>
</tr>
<tr>
<td>PARAGON-A117</td>
<td>2,282</td>
<td>Lamifiban</td>
<td>Death or MI</td>
<td>30 days</td>
<td>---§</td>
</tr>
<tr>
<td>PARAGON-B118</td>
<td>5,225</td>
<td>Lamifiban</td>
<td>Death, MI, or recurrent ischemia</td>
<td>30 days</td>
<td>7.8%</td>
</tr>
<tr>
<td>GUSTO-IV ACS101</td>
<td>7,800</td>
<td>Abciximab</td>
<td>Death or MI</td>
<td>30 days</td>
<td>---**</td>
</tr>
</tbody>
</table>

**ST-Elevation Acute Coronary Syndrome Trials**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Treatment</th>
<th>Endpoint</th>
<th>Follow-up</th>
<th>RRR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAPPORT119</td>
<td>483</td>
<td>Abciximab (PTCA)</td>
<td>Death, reinfarction or urgent TVR</td>
<td>30 days</td>
<td>48%</td>
</tr>
<tr>
<td>ADMIRAL120</td>
<td>300</td>
<td>Abciximab (stenting)</td>
<td>Death, reinfarction or urgent TVR</td>
<td>30 days</td>
<td>59%</td>
</tr>
<tr>
<td>CADILLAC121</td>
<td>2,082</td>
<td>Abciximab (stenting or PTCA)</td>
<td>Death, reinfarction, disabling stroke, or TVR due to ischemia</td>
<td>6 months</td>
<td>---§</td>
</tr>
<tr>
<td>ACE122</td>
<td>400</td>
<td>Abciximab (stenting)</td>
<td>Death, reinfarction, TVR or stroke</td>
<td>1 month</td>
<td>57%</td>
</tr>
<tr>
<td>ISAR-2123</td>
<td>401</td>
<td>Abciximab (stenting)</td>
<td>Death, reinfarction or target lesion revascularization</td>
<td>30 days</td>
<td>52%</td>
</tr>
<tr>
<td>TETAMI124</td>
<td>1,224</td>
<td>Tirofiban</td>
<td>Death, MI or recurrent angina</td>
<td>30 days</td>
<td>---††</td>
</tr>
<tr>
<td>ASSENT 3125</td>
<td>6,095</td>
<td>Abciximab + half dose tenecteplase</td>
<td>Death, MI or refractory ischemia</td>
<td>30 days</td>
<td>28%</td>
</tr>
<tr>
<td>GUSTO V126</td>
<td>16,588</td>
<td>Abciximab + half dose reteplease</td>
<td>Death</td>
<td>30 days</td>
<td>5%</td>
</tr>
</tbody>
</table>

**Oral Glycoprotein IIb/IIIa Inhibitors Trials**
### Study Patient Treatment Follow-up Mortality, MI, Odds Ratio (P) Odds Ratio (P)

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient</th>
<th>Treatment</th>
<th>Follow-up</th>
<th>Odds Ratio (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXCITE127</td>
<td>7,232</td>
<td>Xemilofiban</td>
<td>30 days</td>
<td>2.14 (0.048)</td>
</tr>
<tr>
<td>OPUS-TIMI-16128</td>
<td>10,288</td>
<td>Orbofiban</td>
<td>30 days</td>
<td>1.40 (0.049)</td>
</tr>
<tr>
<td>SYMPHONY129</td>
<td>9,233</td>
<td>Sibrafiban</td>
<td>30 days</td>
<td>1.14 (0.42)</td>
</tr>
<tr>
<td>2nd SYMPHONY130</td>
<td>6,671</td>
<td>Sibrafiban</td>
<td>30 days</td>
<td>1.55 (0.038)</td>
</tr>
<tr>
<td>BRAVO131</td>
<td>9,200</td>
<td>Lotrafiban</td>
<td>Median 366 days</td>
<td>1.33†† (0.026)</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome; CV, cardiovascular; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; RRR, relative risk reduction; TVR, target vessel revascularization

* Not statistically significant, P = 0.16
† Incidence of 1° endpoint: abciximab 4% vs. placebo 4%
‡ 30-day risk reduction of 17%
§ Incidence of 1° endpoint: low dose lamifiban (10.6%), high dose lamifiban (12.0%) and standard therapy (11.7%); P = 0.67
¶ Not statistically significant, P = 0.33
** Incidence of 1° endpoint: 24 hr abciximab (8.2%), 48 hr abciximab (9.1%) and placebo (8%)
†† Incidence of 1° endpoint: tirofiban (16.6%) and placebo (16.4%)
¶¶ No statistically significant difference with addition of abciximab to PTCA compared to PTCA alone or with the addition of abciximab to stenting as compared to stenting alone
††† Not statistically significant, P = 0.43
§§§ Reported value is a hazard ratio instead of odds ratio.
References


79. Lincoff AM, Califf RM, Anderson KM, Weisman HF, Aguirre FV, Kleiman NS, Harrington RA, Topol EJ. Evidence for prevention of death and myocardial infarction


98. Heeschen C, Hamm CW, Goldmann B, Deu A, Langenbrink L, White HD. Troponin concentrations for stratification of patients with acute coronary syndromes in relation to


