APRIL 1998
Volume 2, Issue 4

Cardiology Rounds

AS PRESENTED IN THE ROUNDS OF THE CARDIOVASCULAR DIVISION
OF BRIGHAM AND WOMEN'S HOSPITAL, BOSTON, MASSACHUSETTS

Platelet glycoprotein IIb/IIIa inhibition in acute coronary syndromes

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Every year more than four million patients are admitted to hospitals worldwide with the diagnosis of unstable angina or acute myocardial infarction (MI). In addition, over 900,000 patients annually worldwide undergo percutaneous transluminal coronary angioplasty (PTCA) with or without stenting. The initiating event of these acute coronary syndromes is rupture of an atherosclerotic plaque followed by local thrombosis. Similar pathophysiology is present during PTCA, which is essentially a "planned" plaque disruption.

Current antiplatelet therapy

The importance of antiplatelet therapy comes from the broad experience with acetylsalicylic acid (ASA,Aspirin), which has dramatic effects in reducing both mortality and nonfatal events in patients across the spectrum of acute coronary syndromes.[1-8] In addition, the newer class of antiplatelet agents, the thienopyridines (ticlopidine and clopidogrel), is more effective than ASA. These agents have been shown to be beneficial in reducing clinical events compared with ASA alone in coronary stenting,[9-11] and in symptomatic patients with atherosclerosis.[1,12,13] This wealth of data has focused attention on the platelet as a target for more potent therapies – notably the inhibitors of the platelet glycoprotein (GP) IIb/IIIa receptor, which mediate platelet aggregation.

Platelets and acute coronary syndromes

Platelets play a key role in the transformation of a stable atherosclerotic plaque to an unstable lesion.[14,15] With rupture or ulceration of an atherosclerotic plaque, the subendothelial matrix (eg, collagen, tissue factor) is exposed to the circulating blood.[16] Platelets mediate the primary hemostasis at the site of a ruptured plaque. The first step is *platelet adhesion* with the glycoprotein Ib (GPIb) receptor and the Von Willebrand factor (figure 1a),which leads to *platelet activation* (figure 1b). This is followed in turn by several consecutive events:

• a shape change in the platelet, from a smooth disc to a spiculated form, which increases the surface area upon which thrombin generation can occur;

• degranulation of the alpha and dense granules, which releases thromboxane (Tx) A2, serotonin, and other platelet aggregatory and chemoattractant agents;

• expression of GP IIb/IIIa receptors on the platelet surface with activation of the receptor such that it can bind fibrinogen.

The final step is *platelet aggregation* (ie, the formation of the platelet plug). Fibrinogen (or Von Willebrand factor) binds to the activated IIb/IIIa receptors of two platelets, thereby creating a growing platelet aggregate (figure 1c).

Glycoprotein IIb/IIIa receptor

The platelet GP IIb/IIIa receptor is a member of the integrin receptor superfamily of complexes that mediates cell-protein and cell-cell interactions.[17] The GP IIb/IIIa receptor is a calcium-dependent heterodimer, composed of two different subunits (α_{IIb} and $ß_3$), both of which span the platelet membrane. The GP IIIa subunit contains a four-amino-acid sequence that is crucial for binding of fibrinogen and other ligands.[17] The first three amino acids are arginine-glycine-aspartic acid (letter-abbreviated RGD),while the fourth amino acid can vary. Low-molecular-weight peptides and nonpep-

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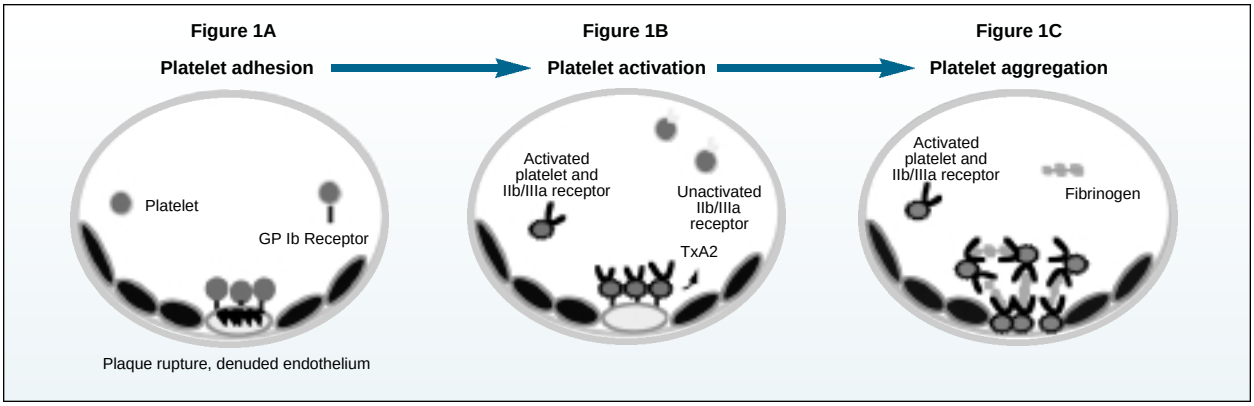
The editorial content of *Cardiology Rounds* is determined solely by the Cardiovascular Division of Brigham and Women's Hospital. This publication is made possible by an educational grant.

Figure 1: The central role of platelets in the formation of thrombi (TxA2 = thromboxane A2)



tide GP IIb/IIIa inhibitors have been developed to bind to the RGD sequence of the receptor, thereby interfering with the binding of fibinrogen to the GP IIb/IIIa receptor.

Mechanisms of inhibition

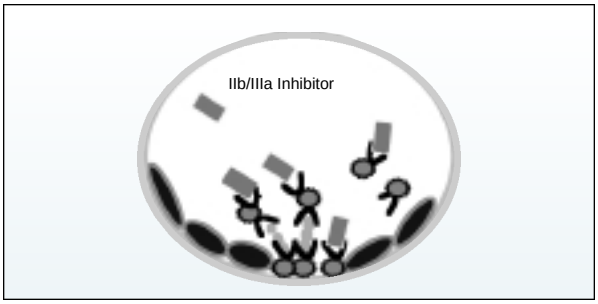
The currently available antiplatelet agents – ASA and the thienopyridines (ticlopidine and clopidogrel) – and GP IIb/IIIa inhibitors have quite distinct mechanisms of action.

ASA permanently acetylates cyclooxygenase, thereby blocking the synthesis of thromboxane A2 (TxA2) by the platelet.[18] TxA2 stimulates other platelets; by decreasing the TxA2, overall platelet aggregation is decreased. Because ASA's inhibition of cyclooxygenase is permanent, its antiplatelet effect lasts for the lifetime of the platelets – approximately 7-10 days.

The thienopyridine class of agents (ticlopidine and clopidogrel) is thought to act by blocking the ADP receptor.[19,20] These drugs might also inhibit intracellular processing of activation of the ADP pathway but have no effect on the numerous other stimulants to platelet aggregation, such as thrombin and collagen. The thienopyridine's onset of antiplatelet effect is delayed, between 2-4 days after the start of therapy.

In contrast, GP IIb/IIIa inhibitors bind to the IIb/IIIa receptor and thereby block the final common pathway of platelet aggregation. By binding to the receptor, they prevent the binding of fibrinogen to the platelet and thereby prevent formation (or progression) of a platelet plug (figure 2). Thus, no matter what stimuli there are for platelet activation, the process is affected by the IIb/IIIa inhibitor, making it an order of magnitude more effective than ASA (or ticlopidine). Laboratory tests show that ASA inhibits ADP-induced platelet aggregation by approximately 10%; ticlopidine and clopidogrel reduce it approximately 30%;[21] and the doses of the IIb/IIIa inhibitors being tested clinically inhibit platelet aggregation by approximately 80%.[22]

Figure 2: Inhibition of aggregation by glycoprotein IIb/IIIa inhibitors.



Types of GP IIb/IIIa inhibitors

There are three broad categories of GP IIb/IIIa inhibitors (table 1): the monoclonal antibody to the IIb/IIIa receptor, abciximab (ReoPro™); the intravenous peptide and non-peptide small molecule inhibitors, such as eptifibatide and tirofiban; and the oral IIb/IIIa inhibitors such as xemilofiban, orbofiban, and sibrafiban.

Abciximab, the monoclonal antibody, binds very tightly to the IIb/IIIa receptor.[23] Thus the antiplatelet effect lasts much longer than the infusion period – a potential benefit on improving efficacy. On the other hand, if bleeding occurs, stopping the drug will not immediately reverse the antiplatelet effect; however, transfusion of platelets will redistribute the antibodies among all the platelets, thereby reducing the level of platelet inhibition. Abciximab also binds to other integrins on the platelet receptor, such as the vitronectin receptor,[17] but the clinical significance of this cross-reactivity is not yet established.

The peptide and peptidomimetic inhibitors, (eg, tirofiban and eptifibatide) are competitive inhibitors of the IIb/IIIa receptor;[24,25] thus, the level of platelet inhibition is directly related to the drug level in the blood. Since both inhibitors have short half-lives, when the drug infusion is stopped,[24,25] the antiplatelet activity reverses after a few hours – a potential benefit for avoiding bleeding complications. On the other hand, for prolonged antiplatelet effect, the drug must be given

Table 1: Types of glycoprotein IIb/IIIa inhibitors

Monoclonal antibody	
	abciximab
Peptide inhibitor	
	eptifibatide
Non-peptide inhibitors	
	tirofiban, lamifiban
Oral agents	
	xemilofiban, orbofiban, sibrafiban, fradifiban

Table 2: Major clinical trials of GP IIb/IIIa inhibitors

Trial	Agent	Study cohort	N	Endpoint	Primary result
EPIC	abciximab	high-risk PTCA	2,099	D/MI/Urg Rev	35% reduction (p=0.007)
EPILOG	abciximab	high/low-risk PTCA	2,792	D/MI/Urg Rev	56% reduction (p<0.001)
CAPTURE	abciximab	PTCA for UA	1,265	D/MI/Urg Rev	29% reduction
RAPPORT	abciximab	PTCA for ST-elevation MI	483	D/MI/target-vessel Rev at 6 months	No significant difference
EPISTENT	abciximab	stent/PTCA	2,399	D/MI/Urg Rev	57% reduction (p<0.001)
IMPACT-II	eptifibatide	PTCA	4,010	D/MI/Urg Rev/stent	21% reduction, (p = 0.06)
RESTORE	tirofiban	high-risk PTCA	2,139	D/MI/Any TV Rev	16% reduction (p=0.16)
PRISM	tirofiban	UA/NQWMI	3,231	D/MI/Ref Ang 48 h	36% reduction p=0.007
PRISM-PLUS	tirofiban	UA/NQWMI	1,915	D/MI/Ref Ang 7 days	34% reduction (p=0.004)
PURSUIT	eptifibatide	UA/NQWMI	10,948	Death or MI	10% reduction (p = 0.042)
IMPACT-AMI	eptifibatide	ST-elevation MI	188	TIMI 3 flow	66% vs.39%
TIMI-14	abciximab	ST-elevation MI	>700	TIMI 3 flow	79% vs.57% (for tPA)

EPIC = Evaluation of c7E3 in Preventing Ischemic Complications
EPILOG = Evaluation of PTCA to Improve Long-term Outcome by 7E3 GP IIb/IIIa Receptor Blockade
IMPACT II = Integrilin to Minimize Platelet Aggregation and Prevent Coronary Thrombosis II
RESTORE = The Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis
PRISM = Platelet Receptor Inhibition for Ischemic Syndrome Management
PRISM-PLUS = Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited to very Unstable Signs and Symptoms
CAPTURE = The Chimeric 7E3 Anti-Platelet Therapy in Refractory Unstable Angina

Abbreviations:

Ang = angina
Rev = revascularization
TIMI = Thrombolysis in Myocardial Infarction
PTCA = percutaneous transluminal coronary angioplasty
MI = myocardial infarction
SK = streptokinase
UA = unstable angina
D= Death
NQWMI = non-Q-wave myocardial infarction
tPA = tissue plasminogen activator
Urg = urgent
Ref = refractory
TV = target vessel

intravenously for a longer period. The inhibitors developed to date have been specifically targeted to the GP IIb/IIIa receptor and not to cross-react other integrins.

The third group of GP IIb/IIIa inhibitors are the oral agents. These agents are also competitive inhibitors, and are usually prodrugs, which are absorbed and then converted to active compounds in the blood.[26-28] The oral agents all have longer half-lives, such that they can be given twice or three times daily to achieve relatively steady levels of IIb/IIIa inhibition. With oral dosing, long-term therapy (ie, >1 year) is possible. However, the long half-life also means that if bleeding occurs, the drug must be removed from the circulation in order to reduce the antiplatelet effect. At present, this can be accomplished acutely by hemodialysis or charcoal hemoperfusion. The development of specific antidotes may be produce an attractive alternative method for quickly removing the drug from the circulation.

Potential mechanisms for benefit from IIb/IIIa inhibition

Several potential mechanisms explain how GP IIb/IIIa inhibition can improve clot resolution and clinical outcome in patients with acute coronary syndromes.

First, by blocking platelet aggregation in the platelet-rich arterial thrombus, GP IIb/IIIa inhibition prevents propagation of the thrombus. It might also be that IIb/IIIa inhibitors can disaggregate a recently-formed platelet plug.

Second, by preventing accumulation of a large number of platelets at the lesion, GP IIb/IIIa inhibition decreases the amount of platelet phospholipid membrane, a co-factor for thrombin generation and of the clotting cascade.

Third, a thrombus rich in platelets can resist thrombolysis (either thrombolytic therapy or endogenous thrombolysis) owing in part to the increased presence of plasminogen activator inhibitor (PAI-1), a potent natural inhibitor of fibrinolysis that exists in high concentrations in platelets.

Potential risks

The major concerns with any antithrombotic agent are increased potential for bleeding and, with platelet inhibitors, thrombocytopenia. The initial EPIC study (table 2) showed increased bleeding with the combination of abciximab and heparin during angioplasty compared with heparin alone;[29] however, a strong interaction with the dose of heparin was observed such that, in the EPILOG trial, the rate of major bleeding was identical between heparin control patients and those receiving abciximab and low-dose heparin.[30] Similarly, the rate of major bleeding has generally not been significantly increased in other trials with the intravenous[31,32] or oral IIb/IIIa inhibitors.[27] Thus, use of lower doses of heparin and careful monitoring of the degree of anticoagulation will prevent bleeding complications in patients receiving IIb/IIIa inhibitors. With regard to monitoring the degree of platelet inhibition,

trials to date are using fixed dosing, but investigation is currently under way to determine when and where monitoring of platelet function can be clinically useful.[33]

Thrombocytopenia is the other major side effect of IIb/IIIa inhibition. Platelet counts falling below 100,000 occur in approximately 1-2% of patients treated with IIb/IIIa inhibitors, and platelet counts falling to <50,000 occur in <0.5% of patients.[30,32,34] In the initial trials, thrombocytopenia generally occurred either on the first day after beginning therapy or after approximately two weeks of therapy. The mechanism by which it occurs is not well understood. Fortunately, it is nearly always reversible, with platelet counts returning to normal after a few days.

IIb/IIIa inhibition during coronary angioplasty

Initial testing of the IIb/IIIa hypothesis began in patients undergoing PTCA. The EPIC trial (table 2) studied 2,099 patients undergoing high-risk PTCA, all treated with heparin and ASA, and all randomized to receive either a placebo, an abciximab bolus, or an abciximab bolus plus a 12-hour infusion.[29] The primary endpoint of the trial was a composite of death,MI, or urgent need for revascularization at 30 days. The group treated with the abciximab bolus and infusion had a significantly lower composite event rate at 30 days compared to the placebo group (8.3% vs 12.8%), a risk reduction of 35.2% (p=0.008). In long-term follow-up, benefit has been observed at six months,[35] and up to three years.[36]

Similarly dramatic reductions in death or MI were observed in the EPILOG trial, which studied 2,792 patients undergoing elective or urgent PTCA. Patients were randomized to either standard heparin alone, abciximab plus standard heparin, or abciximab plus low-dose heparin. Death, MI, or urgent revascularization at 30 days for the abciximab plus low-dose heparin group was 5.2% vs 11.7% for heparin alone, a 58% risk reduction (p<0.001).[30] The abciximab plus standard-dose heparin group also had a significant reduction in ischemic complications to 5.4% (p<0.001).[30] When using a lower dose of heparin with abciximab, investigators found no difference in the incidence of major bleeding or the need for transfusion between abciximab-treated patients and the placebo group. Thus, a low-dose heparin regimen can be recommended with abciximab (70 U/kg initial bolus with an additional 20 U/kg if the activated clotting time is <200 seconds).

The CAPTURE trial, which studied 1,265 patients with refractory angina undergoing PTCA, also found abciximab to be beneficial when started 24 hours prior to PTCA.[37] All subjects had undergone cardiac catheterization and had a planned PTCA the following day. Death, MI, or urgent revascularization was reduced by abciximab from 15.9% to 11.3% (p=0.012).[37] As in all the trials, the major benefit was in reductions of periprocedural MI as well as the need for urgent revascularization. However, a recent meta-analysis has shown that there is also a significant reduction in mortality when GP IIb/IIIa inhibition is used.[38]

These data highlight the clinical importance of thrombosis and effective antithrombotic therapy in PTCA.

IIb/IIIa inhibition with stenting

Most recently, the EPISTENT trial has addressed the role of abciximab with coronary stenting.[39] A total of 2,399 patients were randomized between July 1996 and September 1997 to stent with placebo, stent with abciximab, or balloon angioplasty with abciximab. All patients received ASA and heparin, followed by ticlopidine if a stent was placed.

Compared with stenting alone, the rate of death, MI, or urgent revascularization at 30 days was significantly reduced in both abciximab groups, from 10.8% to 5.3% for stent plus abciximab (p<0.001), and to 6.9% for balloon angioplasty with abciximab (p=0.007). Thus, abciximab has beneficial effects in reducing ischemic complications even when "state-of-the-art" coronary interventions are used.

Primary PTCA

The current Food and Drug Administration (FDA) indication for abciximab includes its use as an adjunct to percutaneous coronary intervention (PCI) balloon angioplasty, atherectomy, and stent placement to prevent cardiac ischemic complications in patients undergoing PCI (urgent or elective), and in patients with unstable angina not responding to conventional medical therapy when PCI is planned within 24 hours.

Similarly, two other intravenous IIb/IIIa inhibitors have been shown to be effective during PTCA. In the IMPACT II trial of patients undergoing elective or urgent PTCA, eptifibatide was given as a bolus plus either a low-dose or high-dose infusion for 20-24 hours. The primary endpoint of the trial was a composite of death, MI,urgent need for revascularization, or stent placement for abrupt vessel closure at 30 days. There was a trend towards a lower composite event rate in the low- and high-dose eptifibatide-treated groups vs placebo, 9.2% and 9.9% vs 11.4%, respectively (p=0.063).

In the RESTORE trial involving 2,139 patients undergoing high-risk PTCA, tirofiban given for 36 hours tended to reduce the primary composite endpoint of death, MI, and revascularization for target-vessel ischemia. It also reduced stent placement for abrupt vessel closure at 30 days (10.3% vs 12.2%, a 16% risk reduction, p=0.16). Tirofiban therapy reduced death, MI, or urgent revascularization within 30 days by 24% (8.0% vs 10.5%, p=0.052).[31] This broad experience with IIb/IIIa inhibitors in PTCA has produced a new therapeutic standard for coronary intervention.

The final area of coronary intervention that has been tested is for primary PTCA – ie, for acute ST elevation infarctions. After favorable results were observed in a subgroup of the EPIC trial,[40] the RAPPORT trial was conducted to compare abciximab with placebo. Although the prespecified six-month endpoints (death, MI, or any target-vessel revascularization) were not significantly reduced, abciximab was able to reduce the 30-day incidence of death, MI, or urgent revascularization by 62%, from 11.2% to 5.8% (p=0.005).[41]

IIb/IIIa inhibition in unstable angina and non-Q-wave MI

Two agents, tirofiban and eptifibatide, have been tested in large phase-III trials specifically for the initial treatment of unstable angina and non-Q-wave MI. PRISM PLUS studied 1,915 patients; all had unstable angina and non-Q-wave MI documented by either electrocardiographic changes or positive enzymes.[34] The combination of tirofiban, heparin, and ASA significantly lowered the rate of death, MI, or recurrent refractory ischemia at 7 days (primary endpoint) compared with heparin plus ASA: 12.9% vs 17.9%, respectively, a 34% risk reduction (p=0.004) (table 2). The 30-day rate of death or MI was also reduced by 31%, from 11.9% to 8.7% (p=0.031).

The rate of major hemorrhage was not significantly increased for patients treated with tirofiban/heparin/ASA vs heparin plus ASA (1.8% vs 1.3%, p=NS).

A beneficial effect of tirofiban was also observed in the PRISM study, which randomized 3,231 patients with unstable angina and non-Q-wave MI to therapy with either heparin or tirofiban; all patients received ASA.[42] The primary endpoint was a composite of death, MI, and refractory ischemic conditions at 48 hours. Tirofiban-treated patients had a significantly lower composite event rate (3.8%) than the placebo group (5.9%), a 36% risk reduction (p=0.007).[42] No significant benefit on the composite endpoint or on death or MI was observed at 30 days.

It should be noted that the tirofiban-alone arm in the PRISM-PLUS trial (N=345) was discontinued early due to increased 7-day mortality at an interim analysis, although no difference in 30-day mortality or the composite endpoint at either time point was observed. Since a beneficial effect of tirofiban alone was observed in the parallel PRISM trial (N=1,616),the probable "true" effect of tirofiban alone is that it is clinically equivalent to heparin alone. Thus, IIb/IIIa inhibition with tirofiban appears to have greater long-term effects when used in conjunction with heparin.

Eptifibatide was studied in the PURSUIT trial, involving 10,948 patients with unstable angina and non-Q-wave MI.[43] Patients received ASA and heparin, and were randomized to one of three arms: eptifibatide high-dose, eptifibatide low-dose, or placebo. By study design, the low-dose was dropped because of a reasonable safety profile of the high-dose. Eptifibatide reduced the rate of death or MI at 30 days from 15.7% to 14.2% (p=0.042). Although on first look these results are not as dramatic as in the PRISM-PLUS trial, it should be noted that this was a very large, international trial (28 countries) that included various management strategies for unstable angina, which might influence the overall relative benefit of the drug.

Figure 3 shows a meta-analysis of all the large IIb/IIIa inhibitor trials in PTCA or unstable angina.[44,45] There was a consistent benefit on death or MI at 30 days that is highly statistically significant (p<0.0000002).[44,45] Although some differences exist in the relative benefits, the general thought is that this is a "class effect" of all the IIb/IIIa inhibitors. Direct comparisons among the agents must be conducted to determine the relative benefits of one agent versus another.

In patients with unstable angina and non-ST-elevation MI (and PTCA),IIb/IIIa inhibition reduced death or MI at 30 days. This is a significant advance in treatment. These data highlight the importance of acute thrombosis and of platelet inhibition in acute coronary syndromes, and they establish IIb/IIIa inhibition as a new standard of care in the treatment of such conditions.

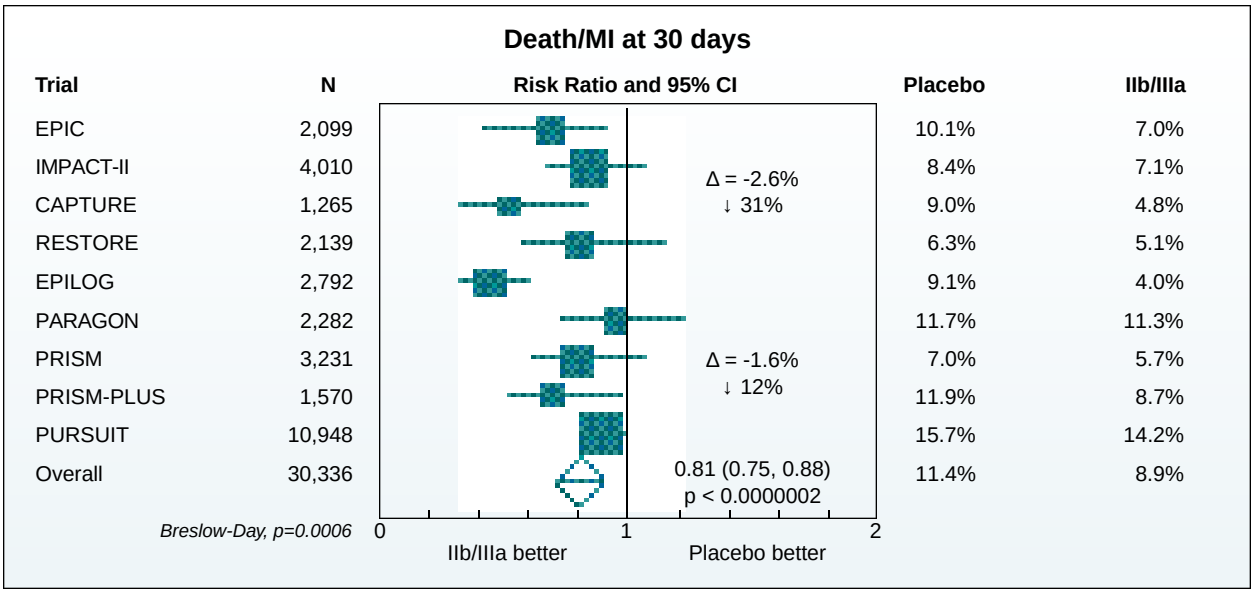
Potential role for IIb/IIIa inhibition with thrombolysis in acute MI

Thrombolytic therapy has dramatically reduced mortality following acute MI. Its benefit is due to *early* achievement of infarct-related artery patency, which limits myocardial infarct size, decreases left ventricular dysfunction, and improves survival.[46,47] While thrombolytic therapy has proven to be a major advance in the treatment of patients with acute myocardial infarction, current regimens are limited by failure of initial reperfusion, inadequate perfusion with delayed flow (TIMI grade-2 flow),[48] reocclusion, and reinfarction in significant percentages of patients.[48,49] Because these problems are associated with increased subsequent mortality,[50-52] and because platelets play a central role in failed reperfusion, reocclusion, and reinfarction, attention has turned to the promising glycoprotein IIb/IIIa inhibitors.

Clinical trials of IIb/IIIa inhibition with thrombolysis

In the setting of ST-elevation MI, IIb/IIIa inhibition was first used following thrombolysis in the Thrombolysis and Angioplasty in Myocardial Infarction-8 (TAMI-8) trial. Subjects received the monoclonal antibody to the IIb/IIIa receptor following tissue plasminogen activator (t-PA) therapy.[53] A consistent dose-dependent inhibition of platelet aggregation was observed,and major bleeding was not increased.

Figure 3: Meta-analysis of large GP IIb/IIIa trials (Adapted from data presented by Moliterno[44])



Eptifibatide,was tested in the Integrilin to Minimize Platelet Aggregation and Combat Thrombosis in Acute Myocardial Infarction (IMPACT-AMI) trial.[54] Subjects received accelerated full-dose t-PA,ASA, and heparin; they were also randomized to receive eptifibatide (at one of six doses) or placebo. The highest dose of eptifibatide appeared to improve the 90-minute rate of TIMI grade-3 flow (66% vs 39% for placebo,p=0.006).[54]

More recently, a pilot study combined full-dose streptokinase (1.5 million U/h) and three doses of eptifibatide (180 µg/kg bolus and either 0.75,1.33, or 2.0 µg/kg/min infusion for 24 hours) or placebo.[55] Adding the IIb/IIIa inhibitor led to a modest improvement in early complete reperfusion (TIMI grade-3 flow at 90 minutes) from 38% with placebo to approximately 50% with eptifibatide.[55] The highest dose of eptifibatide was associated with increased bleeding and was discontinued. Further testing of eptifibatide is planned with reduced-dose thrombolytic agents.

Reduced-dose thrombolysis plus IIb/IIIa inhibition

The combination of a reduced-dose thrombolytic agent and a GP IIb/IIIa inhibitor is being tested in the TIMI-14 trial (using t-PA, streptokinase, and reteplase) and in the GUSTO-IV pilot trial, SPEED (using reteplase). TIMI-14 has been designed to determine the percentage of patients with TIMI grade-3 flow in the infarct-related artery at 90 minutes after one of four infusion regimens: accelerated t-PA (control); standard full-dose abciximab with reduced doses of t-PA; abciximab with reduced doses of streptokinase; and abciximab alone. All patients received ASA and low-dose heparin.

Interim results show that abciximab alone produced 32% TIMI grade-3 flow,[56] which is similar to that previously reported for streptokinase.[56] Streptokinase plus abciximab produced modest improvements in the rates of TIMI grade-3 flow. Low-dose t-PA plus abciximab was tested initially at doses ranging from 20-50 mg given as a single bolus or as a bolus plus 30- or 60-minute infusion. In the dose-ranging phase, the 50-mg dose given over 60 minutes produced substantial improvement in TIMI grade-3 flow, 79% compared with 57% for t-PA alone.[56] Overall patency of the infarct-related artery was achieved in 94% of patients taking the combination of abciximab and t-PA compared with 79% for patients on t-PA only. Major hemorrhage was similar among all groups (5-8%) with the exception of the two higher streptokinase plus abciximab groups.

Thus, in the initial phase, abciximab plus t-PA was able to increase the rate of TIMI grade-3 flow by approximately 20% (absolute rate), a relative 35% improvement. These results are now being confirmed in trials with larger numbers of patients. The combination of reteplase and abciximab will also be studied.

Preliminary results from the SPEED trial of reteplase therapy show similar improvements in early TIMI grade-3 flow, indicating that the combination of low-dose thrombolytic therapy with t-PA or reteplase appears to be a promising new regimen for achieving reperfusion in acute MI.

Potential need for long-term GP IIb/IIIa inhibition

Intravenous platelet GP IIb/IIIa receptor antagonists have been proven effective in reducing ischemic complications following angioplasty and in unstable angina/non-Q-wave MI. However,in many of the trials, the relative benefit observed at the later time points is lower than that at earlier time points, suggesting a need for prolonged oral GP IIb/IIIa inhibition. For example, when contrasting the statistically significant results obtained in angioplasty with abciximab[29,30,37] and the loss of the early benefit seen after the shorter infusions (24-36 hours) of eptifibatide and tirofiban,[31,32] we see that the former therapy has a very long duration of action on the platelet, with antiplatelet activity detected up to one week following administration of abciximab. This suggests that the prolonged antiplatelet effect of abciximab is responsible for some of its sustained beneficial effect.

Furthermore, in the trials of unstable angina and non-Q-wave MI, all the benefit in reducing ischemic complications occurs during infusion of the IIb/IIIa inhibitor. The benefits are preserved, but no added benefit is achieved after the infusion is stopped. Thus, one can hope that if IIb/IIIa inhibition is continued, using an oral IIb/IIIa inhibitor, there might be continued reduction in recurrent events. This has been seen in trials with beta-blockers: reductions in death or MI continue the longer patients are on beta-blockers.

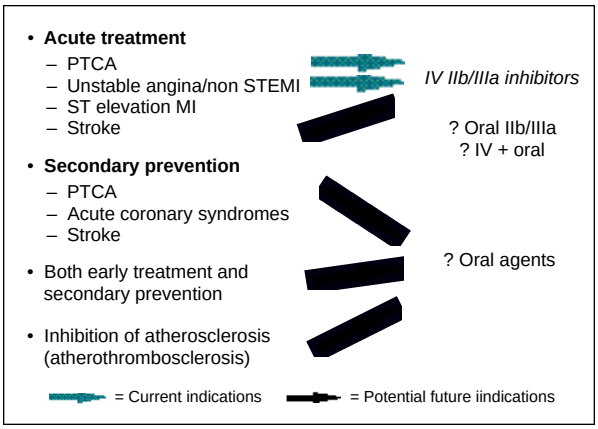
In addition, active thrombus activity has been observed by coronary angioscopy even as late as one month after acute coronary syndromes occurred.[57] This indicates that the long period of treatment is necessary for complete antithrombotic treatment of a culprit lesion. Similarly, in the TIMI-12 trial of an oral IIb/IIIa inhibitor given to patients stabilized after an acute coronary syndrome, the subjects had high levels of activated platelets at baseline but also one month later, despite oral IIb/IIIa treatment.[58] Thus there is an active, prothrombotic "milieu" in patients following acute coronary syndromes that might benefit from antithrombotic therapy more aggressive than just ASA.

Oral IIb/IIIa inhibition

Oral IIb/IIIa receptor antagonists offer the potential for long-term treatment, which has many possible applications (table 3) such as during the early phase of acute coronary syndromes. In addition, oral IIb/IIIa inhibitors could be used for secondary prevention after stabilization from an acute coronary syndrome, or for *both* acute treatment and secondary prevention. Extending these benefits, oral IIb/IIIa inhibitors could potentially prevent the process of athero(thrombo)-sclerosis (table 3). Such therapy might also be useful for percutaneous coronary intervention and for patients with stroke,for both early treatment and secondary prevention.

However, many questions remain. Variability in drug level and degree of platelet inhibition is one potential issue. In the TIMI 12 trial, a considerable amount of variability in both was observed,[27] although it should be noted that intravenous IIb/IIIa inhibitors also produce variable results.[59] The peak (and trough) levels of platelet inhibition appear to be related to clinical effects such as bleeding.[27] With doses producing high peaks in the level of inhibition, the rate of bleeding was higher than with doses producing lower "peak-to-trough" ratios. In addition, the absolute degree of inhibition achieved appeared to be related to minor bleeding,[27] raising the important issue of what level of platelet inhibition will be tolerable for long-term treatment. Another issue is the degree of platelet inhibition: Should one target the full 80-90% inhibition that has been used for short-term treatment with the intravenous

Table 3: Current and potential future indications for IIb/IIIa inhibition



compounds, or use lower levels of platelet inhibition that might be better tolerated.

Great potential exists for oral IIb/IIIa inhibitors to be a major advance in the treatment of acute coronary syndromes, percutaneous coronary interventions, and stroke. They might play a role both in early treatment (either as a substitute for intravenous compounds or as follow-up to IV treatment) and in secondary prevention. To date, only minimal data are available on their pharmacokinetic and pharmacodynamic effects. Numerous questions remain, such as optimal levels of platelet inhibition, the balance between efficacy and safety, the need for adjunctive ASA, and whether monitoring platelet function is useful. Ongoing large-scale clinical trials are assessing many of these issues.

Current status

For the practicing physician, it is an exciting time: this important new therapy can significantly reduce death, MI, refractory ischemia, and urgent revascularization. The benefits apply to just about every type of patient undergoing PTCA or stenting, thereby setting a new standard of care for such cases.

For the large number of patients with unstable angina and non-Q-wave MI, IIb/IIIa inhibition will significantly reduce recurrent ischemic events. The trials to date have studied the higher-risk unstable angina patients – those with ECG changes or positive cardiac enzymes – and thus, in clinical practice, these patients should be targeted for early use of IIb/IIIa inhibitors.

In cases of thrombolysis and of oral long-term therapy, the pilot trials show great promise, and large phase-III trials are under way to determine the clinical benefits of this important class of drugs.

Glycoprotein IIb/IIIa inhibition is a rapidly evolving field. Its many significant advances should translate into improved clinical outcomes for patients with acute coronary syndromes in 1998 and into the next millennium.

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Dr. Cannon is currently the principal investigator of the international OPUS-TIMI 16 trial (which will study the oral IIb/IIIa inhibitor orbofiban in 12,000 patients with acute coronary syndromes) and the TACTICS-TIMI 18 trial (which will compare the efficacy and cost-effectiveness of an invasive vs. conservative strategy in patients with unstable angina, all of whom receive treatment with aspirin,heparin, and the new intravenous IIb/IIIa inhibitor, tirofiban). Dr. Cannon also is a member of the TIMI Study Chairman's office, and serves as a co-investigator on all other ongoing TIMI trials.

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