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Glycoprotein IIb/IIIa inhibitors in acute coronary syndromes

ABSTRACT

Glycoprotein (GP) IIb/IIIa inhibitors are potent antiplatelet agents and represent an exciting breakthrough in the treatment of acute coronary syndromes. However, their safety and cost-effectiveness require further investigation, and more information on risk stratification is needed to clarify which patients benefit the most from empiric use of these agents.

KEY POINTS

In a combined analysis of trials of GP IIb/IIIa inhibitors during percutaneous interventions or in non–ST-segment elevation acute coronary syndromes, the addition of these agents to standard therapy reduced the incidence of death or myocardial infarction by one fifth at 30 days.

Abciximab and eptifibatide are both approved for use during percutaneous coronary interventions; eptifibatide and tirofiban are approved as empiric therapy in patients with non–ST-segment elevation acute coronary syndromes.

During combination therapy with a GP IIb/IIIa inhibitor and heparin, the risk of bleeding can be decreased by using lower doses of heparin, with no loss of efficacy.

TREATMENT STRATEGIES for acute coronary syndromes now focus on potent agents called glycoprotein (GP) IIb/IIIa inhibitors, which block the final common pathway of platelet aggregation. This is a shift from previous strategies, which focused on fibrinolytics, antithrombins, and aspirin, a relatively weak platelet inhibitor.

ROLE OF PLATELETS IN ACUTE CORONARY SYNDROMES

Acute coronary syndromes—unstable angina, non–ST-segment elevation myocardial infarction (MI), and acute ST-segment elevation MI—all begin by a similar mechanism. First, an atherosclerotic plaque forms on a coronary artery wall. Then the plaque ruptures, exposing platelets to substances that activate them, such as collagen and von Willebrand factor. Activated platelets in turn release substances such as thromboxane A_2, serotonin, adenosine diphosphate (ADP), and thrombin, which activate more platelets.[1] Finally, activated platelets join together or "aggregate" to form a thrombus.[2] The size of the thrombus and the degree to which it disrupts coronary blood flow determine the clinical presentation of an acute coronary syndrome.[3]

Platelets join to one another via their GP IIb/IIIa receptors, found exclusively on platelets and megakaryocytes. Each platelet has up to 80,000 GP IIb/IIIa receptors. When a platelet is activated, its GP IIb/IIIa receptors undergo a conformational change and then bind circulating adhesive proteins, including fibrinogen.[4] After binding to fibrinogen, GP IIb/IIIa receptors link adjacent platelets to propagate the developing thrombus (FIGURE 1).

GP IIb/IIIa block the final common pathway of platelet aggregation

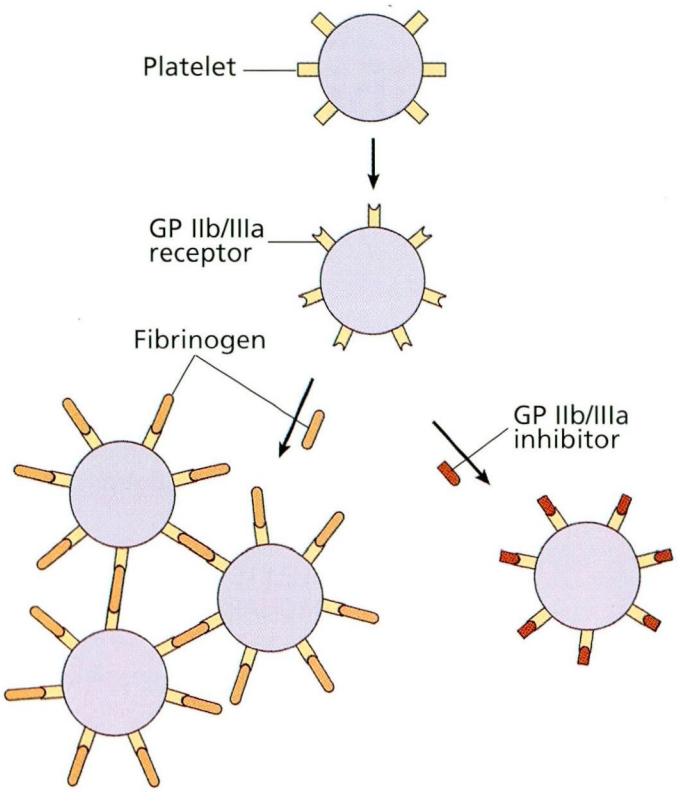

FIGURE 1. After platelets are activated by local agonists, fibrinogen binds to the platelet surface glycoprotein IIb/IIIa receptor to link adjacent platelets and cause platelet aggregation. Intraluminal coronary thrombus propagation follows platelet aggregation.

REPRODUCED AND ADAPTED WITH PERMISSION FROM LEFKOVITZ J ET AL. PLATELET GLYCOPROTEIN IIb/IIIa RECEPTORS IN CARDIOVASCULAR MEDICINE. N ENGL J MED 1995; 332:1553–1559.

THEORETIC ADVANTAGES OF GP IIb/IIIa INHIBITORS

Antiplatelet medications commonly used to treat acute coronary syndromes include aspirin, which blocks thromboxane A_2 production, and ticlopidine and clopidogrel, which block ADP from binding to its receptor. However, since there are other pathways for platelet activation, these medications are relatively weak and have limited efficacy. In contrast, GP IIb/IIIa inhibitors block the final common pathway of platelet aggregation, irrespective of the stimulus for platelet activation.[5]

By inhibiting platelet aggregation, GP IIb/IIIa inhibitors may "passivate" ruptured coronary plaques, perhaps by preventing platelet deposition and microaggregate formation on the disrupted arterial surface.[6] In the same way, these drugs may also promote healing of the coronary arterial surface, which in turn may limit subsequent recurrent ischemic events and reduce the likelihood of (re)infarction. Plaques may remain passivated for some time after an infusion of an intravenous GP IIb/IIIa inhibitor, but more investigation is needed regarding the mechanism and duration of plaque passivation.

ESTABLISHED AND EXPERIMENTAL USES OF GP IIb/IIIa INHIBITORS

GP IIb/IIIa inhibitors are established treatments for acute coronary syndromes:

- During percutaneous coronary interventions in patients with unstable angina or recent MI[7–9]
- Before percutaneous coronary interventions in patients with unstable angina[10]
- In patients with unstable angina or non–ST-segment elevation MI regardless of subsequent management (medical therapy or revascularization)[6,11–13]
- During primary percutaneous coronary interventions in patients with ST-segment elevation MI.[14]

In addition, preliminary evidence suggests that these drugs may be effective in two other situations, although results from phase III trials are awaited:

- As adjuncts to thrombolysis for ST-segment elevation MI
- As oral agents after hospital discharge.

INTRAVENOUS GP IIb/IIIa INHIBITORS

Abciximab, the first GP IIb/IIIa inhibitor developed, is a chimeric human-murine monoclonal antibody. It binds to the GP IIb/IIIa receptor with a high affinity and a slow dissociation rate: receptors remain occupied for up to 14 days, as shown by flow cytometry.[15] The drug reduces platelet aggregation by approximately 80% during infusion. Its serum half-life is approximately 25 minutes, but platelet aggregation remains measurably inhibited for

TABLE 1

Intravenous glycoprotein IIb/IIIa inhibitors

GENERIC NAME	BRAND NAME	APPROVED USES	DOSAGE	
			IN PERCUTANEOUS CORONARY INTERVENTIONS	IN ACUTE CORONARY SYNDROMES
Abciximab	ReoPro	Before and during percutaneous coronary interventions	0.25 µg/kg bolus, then 0.125 µg/kg/minute infusion for 12 hours*	Not approved
Eptifibatide	Integrilin	Percutaneous coronary interventions, acute coronary syndromes	135 µg/kg bolus, then 0.5 µg/kg/minute infusion for 24 hours†	180 µg/kg bolus, then 2.0 µg/kg/minute infusion for up to 72 hours‡
Tirofiban	Aggrastat	Acute coronary syndromes	Not approved	0.4 µg/kg/minute bolus for 30 minutes, 0.1 µg/kg/minute infusion for up to 72 hours§
Lamifiban	None	None	Not approved	Not approved

*The infusion can be started up to 24 hours before before percutaneous coronary interventions and continued at the same rate through the procedure
†This is the FDA-approved dosage for percutaneous coronary interventions, but pharmacodynamic data suggest that the higher dosage be used in both situations
‡No specific recommendations have been made for reducing the eptifibatide dose with renal insufficiency, but a reasonable adjustment would be to reduce the infusion rate by 50%
§If the creatinine clearance is < 30 mL/min, the tirofiban infusion rate should be reduced by 50%

18 to 36 hours after the infusion is stopped as abciximab distributes from old to new platelets entering the circulation.[16]

Abciximab is approved for use before and during percutaneous coronary interventions (TABLE 1).

Small-molecule GP IIb/IIIa inhibitors. Eptifibatide (a synthetic peptide) and tirofiban and lamifiban (which are not peptides) are highly specific for binding to the GP IIb/IIIa receptor, but rapidly dissociate from the receptor so that platelet inhibition persists for only 1 to 2 hours after stopping the infusion.[17]

Eptifibatide is approved for use during percutaneous coronary interventions and in non–ST-segment elevation acute coronary syndromes. Tirofiban is approved for use only in non–ST-segment elevation acute coronary syndromes.

CLINICAL TRIALS OF GP IIb/IIIa INHIBITORS

Topol[18] performed a meta-analysis of nine large-scale clinical trials of GP IIb/IIIa inhibitors in acute coronary syndromes and calculated that these agents reduced the 30-day incidence of death or MI by 19% when added to standard therapy. Not available at the time of Topol's analysis were the EPISTENT[9] and RAPPORT[14] trials. When the results of these trials were incorporated into the meta-analysis, the relative reduction in the risk of death or MI at 30 days was approximately 22% (FIGURE 2).

Abciximab is longer-acting than tirofiban or eptifibatide

Use during percutaneous coronary interventions

Percutaneous coronary interventions injure the vessel wall, damage the intima, and expose the subendothelium. As a result, platelets become activated and a thrombus can form. Intracoronary thrombus formation can cause abrupt vessel closure, which can lead to death or MI after percutaneous interventions.[19] In addition, many patients with acute coronary syndromes who undergo percutaneous interventions have a pre-existing intracoronary thrombus, which is a predictor of abrupt closure and other complications.[20,21]

Meta-analysis of GP IIb/IIIa inhibitors in acute coronary syndromes

STUDY	GP IIb/IIIa INHIBITOR	N	INCIDENCE OF DEATH OR MI		ODDS RATIO AND 95% CI
			PLACEBO GROUP	GP IIb/IIIa GROUP	
Studies in percutaneous coronary intervention					
EPIC	Abciximab	2,099	9.6	6.6	
EPILOG	Abciximab	2,792	9.1	4.0	
EPISTENT	Abciximab	2,399	10.2	5.2	
RAPPORT	Abciximab	483	5.8	4.6	
CAPTURE	Abciximab	1,265	9.0	4.8	
IMPACT II	Eptifibatide	4,010	8.4	7.1	
RESTORE	Tirofiban	2,141	6.3	5.1	
Total		**15,189**	**8.7**	**5.6**	$P < .001$
Studies in non–ST-segment elevation acute coronary syndromes					
PARAGON	Lamifiban	2,282	11.7	11.3	
PRISM	Tirofiban	3,231	7.0	5.7	
PRISM Plus	Tirofiban	1,570	11.9	8.7	
PURSUIT	Eptifibatide	10,948	15.7	14.0	
Total		**18,031**	**13.3**	**11.7**	$P < .001$
All Studies		**33,220**	**11.2**	**8.9**	$P < .001$

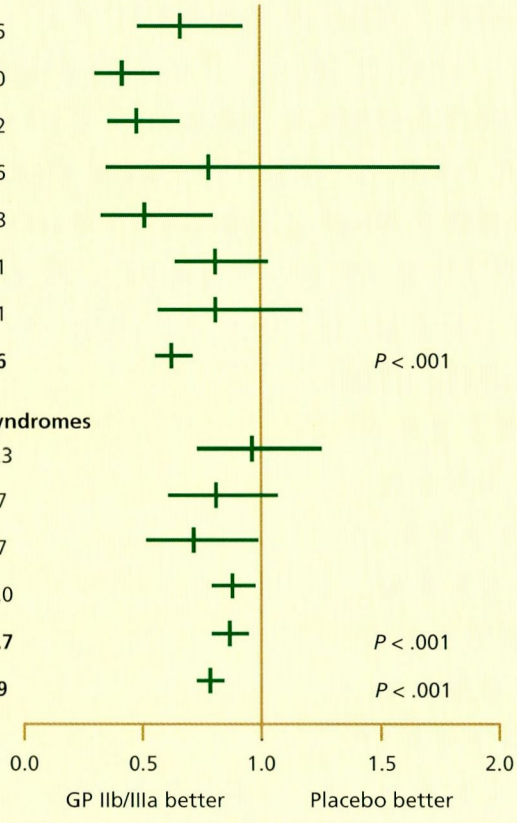

FIGURE 2. Odds ratios and 95% CI for risk of death or MI for the 11 large-scale randomized, placebo-controlled trials of platelet glycoprotein IIb/IIIa inhibitors for percutaneous coronary intervention or unstable angina/non–ST-segment elevation acute coronary syndromes. At 30 days, a highly significant 22% reduction in death or MI was noted in 33,220 patients.

For emergency CABG, abciximab can be reversed with platelet transfusions

To inhibit thrombus formation, treatments during conventional percutaneous transluminal coronary angioplasty traditionally include aspirin and heparin in high doses (100–175 U/kg).

To date, seven phase III trials have tested GP IIb/IIIa inhibitors during percutaneous interventions in patients with acute coronary syndromes or stable ischemia.[7–10,14,22–28] All trials showed a reduction in ischemic events (FIGURE 2). However, the trials of the small-molecule agents eptifibatide[26,27] and tirofiban[28] showed a proportionally smaller treatment effect than those with abciximab, at least at the doses tested.

Use as empiric therapy in non–ST-segment elevation acute coronary syndromes

Four large-scale, randomized clinical trials have evaluated small-molecule GP IIb/IIIa inhibitors in non–ST-segment elevation acute coronary syndromes (FIGURE 2).[6,11–13,29] Together, the trials demonstrated a consistent reduction in ischemic events with GP IIb/IIIa inhibitors.

Benefit in medical therapy. GP IIb/IIIa inhibitors appeared to benefit both patients

Prothrombotic effects of fibrinolytic therapy

A coronary thrombus is composed of a platelet core with a fibrin-thrombin admixture. Fibrinolytic drugs expose free thrombin and thus promote platelet aggregation. Platelets can also be resistant to fibrinolytic therapy since they secrete large quantities of PAI-1 (plasminogen activator inhibitor-1), which is a potent antagonist to fibrinolysis.

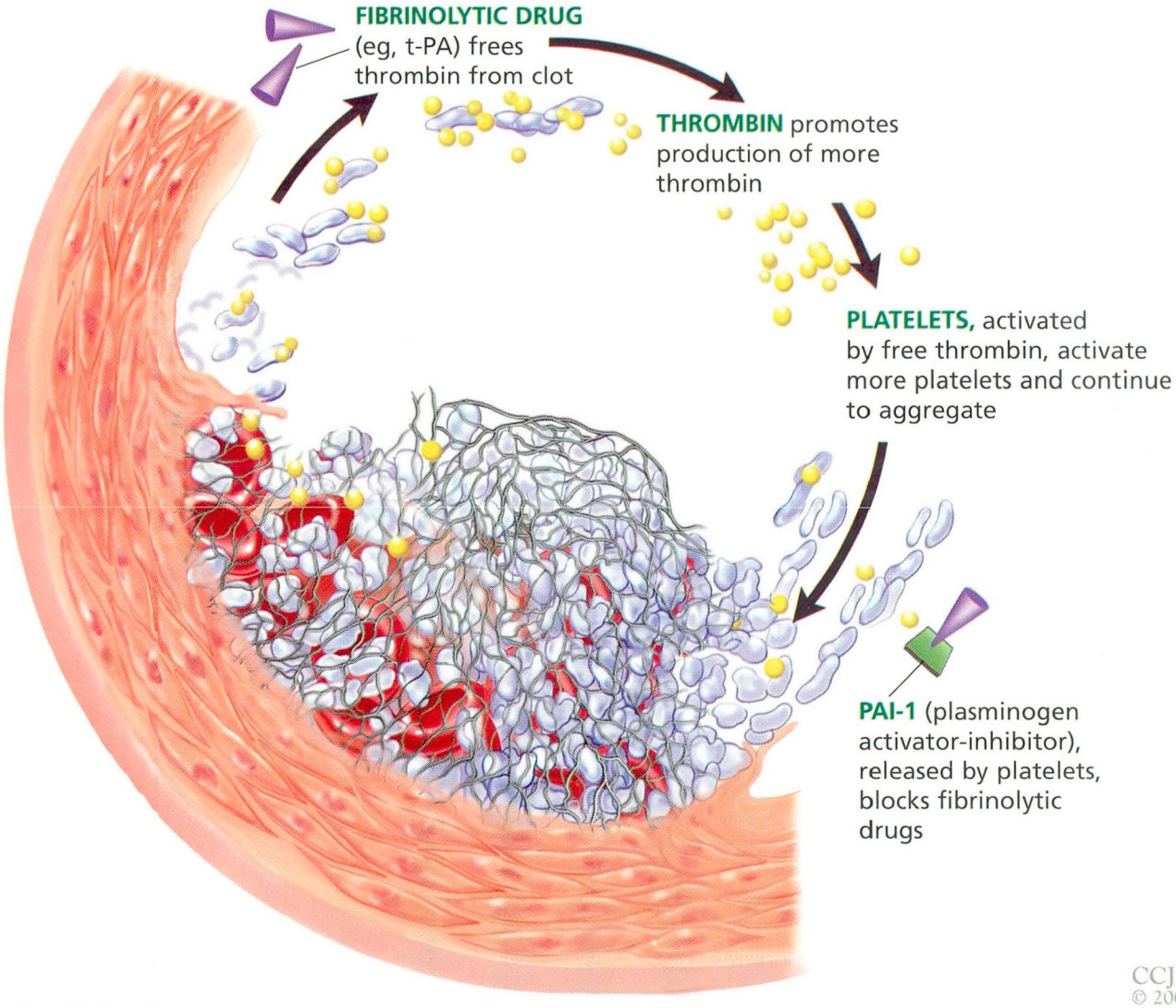

FIGURE 3

managed medically and those who underwent percutaneous interventions, although none of the trials randomly assigned patients to these management strategies. For example, patients receiving tirofiban who underwent medical management in the PRISM-PLUS trial had a reduction in the 30-day incidence of death or nonfatal MI of 2.3%; (those who underwent percutaneous interventions had a reduction of 4.3%).[12] Similarly, in the PURSUIT trial, the effect of eptifibatide was greater in patients who underwent percutaneous interventions while receiving the study drug infusion, but a sizable proportion of the treatment effect occurred before the procedure was performed, demonstrating a preprocedural stabilization effect in these patients.[13] When patients who did not undergo percutaneous or surgical

TABLE 2

Dose-ranging trials of GP IIb/IIIa inhibitors in acute ST-segment myocardial infarction

TRIAL	NO. OF PATIENTS	GP IIB/IIIA INHIBITOR	FIBRINOLYTIC AGENT
Trials of full-dose fibrinolytics plus partial-dose GP IIb/IIIa inhibitors			
TAMI-8[32]	70	Abciximab	t-PA
IMPACT-AMI[33]	132	Eptifibatide	t-PA
Ronner et al[34]	181	Eptifibatide	Streptokinase
PARADIGM[35]	345	Lamifiban	Streptokinase / t-PA
Trials of reduced-dose fibrinolytics plus full-dose GP IIb/IIIa inhibitors			
TIMI-14[36]	888	Abciximab	Streptokinase / t-PA
SPEED[37]	193	Abciximab	r-PA

revascularization in PURSUIT were separately analyzed, a significant reduction in 30-day death or nonfatal MI was still demonstrated in the eptifibatide group.[30]

Use in acute ST-segment elevation MI

Fibrinolytic therapy is a well-established method of reperfusion for acute ST-segment elevation MI and reduces mortality by 25% to 30% compared with placebo. However, even ideal fibrinolytic regimens restore complete perfusion (TIMI grade 3 flow) in only approximately half of patients, and half of patients who initially achieve reperfusion subsequently experience reocclusion or intermittent patency of the infarct vessel. Thus, fibrinolytic therapy alone establishes and maintains reperfusion in only approximately one fourth of patients with acute ST-segment elevation MI.[31]

Monitor the platelet count for 24 hours after starting a GP IIb/IIIa inhibitor

Why does fibrinolysis so often fail? Fibrinolytic agents break down fibrin in a coronary thrombus, but also increase thrombin generation by exposing underlying clot-bound thrombin. Since thrombin is a potent platelet activator, fibrinolytic therapy can paradoxically make a ruptured plaque more prothrombotic. In addition, platelets are rich in PAI-1 (plasminogen activator inhibitor-1), so the expanding platelet thrombus may resist fibrinolysis by inhibiting tissue plasminogen activator (t-PA) with PAI-1 (FIGURE 3).[18]

With these limitations of fibrinolytic therapy in mind, investigators hope that the combination of GP IIb/IIIa inhibitors plus fibrinolytic agents will produce better results. So far, four dose-ranging trials[32–35] evaluated combination therapy with GP IIb/IIIa inhibitors and full doses of fibrinolytic agents for acute ST-segment elevation MI. Subsequently, two trials[36,37] used partial doses of fibrinolytics with GP IIb/IIIa inhibitors (TABLE 2).

The collective results suggest that adding a GP IIb/IIIa inhibitor increases the percentage of patients who achieve patency of the infarct-related artery. This combined approach appears safe and did not substantially increase the rate of bleeding complications except when streptokinase was used with full doses of GP IIb/IIIa inhibitors.[34,36] Intracranial hemorrhage rates did not appear to increase, although trials to date included too few patients to assess this infrequent complication. Also, the ideal dose of heparin to use with combination reperfusion therapy has not yet been established. The ongoing GUSTO IV trial will determine if combination therapy with reteplase and abciximab will improve clinical outcomes in a large-scale, definitive study.

SAFETY ISSUES

The safety profile of intravenous GP IIb/IIIa inhibitors evaluated in phase III clinical trials has generally been favorable.

Periprocedural bleeding. When abciximab was first used with standard, high-dose heparin during percutaneous coronary inter-

ventions, bleeding complications increased, mostly at the puncture site.[38] When the heparin dose used with abciximab was decreased and weight-adjusted, bleeding complications decreased without a loss in efficacy.[8] Minor bleeding complications were increased when the small-molecule GP IIb/IIIa inhibitors were used with weight-adjusted heparin, and major bleeding requiring transfusion occurred in 0.7% to 1.5% of patients.[6,11–13] Intracranial hemorrhage has rarely been seen with GP IIb/IIIa inhibitors, alone or in combination with heparin.[39,40]

Bleeding during surgery. In theory, patients who receive abciximab may be at increased risk of bleeding during any subsequent emergency coronary artery bypass grafting (CABG). However, patients in the EPILOG and EPISTENT trials who underwent emergency CABG after receiving abciximab did not have a higher incidence of bleeding complications than did placebo-treated patients.[41] If a patient needs emergency CABG, abciximab can be reversed with platelet transfusions. Increased bleeding during emergency CABG is not an issue with eptifibatide or tirofiban, since their antiplatelet effect rapidly decreases after they are stopped.

Thrombocytopenia occurs in 0.5% to 1.0% of patients treated with intravenous GP IIb/IIIa inhibitors. The mechanism has not been clearly delineated.[42] Severe thrombocytopenia (platelet count $< 20 \times 10^9$/L) has occurred within 24 hours of receiving abciximab.[43,44] In the EPIC and CAPTURE trials, severe thrombocytopenia occurred in 0.3% of patients.[10,45] Thrombocytopenia resolved with platelet transfusions and stopping antiplatelet therapy and heparin, and no major complications were reported. Thus, platelet counts should be closely monitored for 24 hours after starting a GP IIb/IIIa inhibitor. If bleeding and severe thrombocytopenia occur, platelet transfusions should be given and the GP IIb/IIIa inhibitor, heparin, and aspirin should be stopped.

Efficacy and safety of repeated use. Whether GP IIb/IIIa inhibitors remain safe and effective with repeated use is important, since many patients who undergo percutaneous interventions or fibrinolytic therapy ultimately require further interventions. Approximately 6% of patients develop antibodies to abciximab after the first dose.[7] Recent data from the Abciximab Readministration Registry[46] showed no cases of allergic, hypersensitivity, or anaphylactic reactions among 329 patients who received abciximab a second time. In addition, the clinical efficacy and level of platelet inhibition was similar the second time. There was, however, a moderate increase in thrombocytopenia. No antibodies have been detected after use of the synthetic agents eptifibatide or tirofiban.

COST-EFFECTIVENESS

The high cost of GP IIb/IIIa inhibitors (abciximab costs $1,407 per dose) has limited their widespread use, but given their substantial benefit, they may be cost-effective.

A formal economic analysis of the EPIC trial[47] concluded that abciximab paid for itself during percutaneous coronary interventions by reducing ischemic events that necessitated readmission to the hospital and urgent revascularization procedures. Other analyses[48,49] concluded that abciximab is approximately as cost-effective as other widely used therapies. In addition, trials performed after the EPIC trial showed markedly fewer bleeding events, making the cost-benefit ratio of GP IIb/IIIa inhibitors more favorable. Economic analyses from the PURSUIT and PRISM-PLUS trials are expected soon and will help to determine the cost-effectiveness of empiric use of IIb/IIIa inhibitors for acute coronary syndromes.

Though costly, GP IIb/IIIa inhibitors may be cost-effective

UNRESOLVED ISSUES

Several issues require further research.

Which GP IIb/IIIa inhibitor should be used in a given situation? The answer is not clear, since these agents have not been directly compared in clinical trials. Overwhelming data support the efficacy of abciximab during percutaneous coronary interventions over the short and long term. Abciximab appears more potent than the doses of eptifibatide or tirofiban that have been used during percutaneous interventions.

On the other hand, there are no apparent differences between eptifibatide and tirofiban when used for empiric treatment of unstable angina, although more patients were enrolled in trials of eptifibatide (ie, the PURSUIT trial) than in trials of tirofiban.

What if a patient starts out receiving eptifibatide or tirofiban as empiric treatment and then undergoes angioplasty? One may be tempted to change to abciximab, which seems to be more beneficial during angioplasty than the other agents. We cannot recommend this, however, since eptifibatide and tirofiban also are beneficial during percutaneous coronary interventions, and we have no data on whether changing to abciximab is safe or effective.

What is the proper eptifibatide dosage in percutaneous coronary interventions? As shown in TABLE 1, the Food and Drug Administration recommends a lower dose of eptifibatide during percutaneous coronary interventions than in acute non–ST-segment elevation coronary syndromes, because the lower dose was used in the IMPACT-II trial. However, we suspect that the higher dose should be used in both situations: a 180 µg/kg bolus followed by a 2.0 µg/kg/min infusion. Clinical trials are underway to examine this issue.

Inability to titrate low-molecular-weight heparins is a barrier to use with GP IIb/IIIa inhibitors

What is the proper dosage of heparin to use with GP IIb/IIIa inhibitors? No clear recommendations have emerged despite the multiple clinical trials completed.

Can low-molecular-weight heparin be used with GP IIb/IIIa inhibitors? Although enoxaparin reduced ischemic events when compared with unfractionated heparin in the ESSENCE trial, it has not been tested in combination with GP IIb/IIIa inhibitors.[50]

A problem with low-molecular-weight heparins is that we cannot monitor their anticoagulant effect closely with tests such as the activated clotting time assay.[51] Given the known risk of hemorrhage when excessive doses of unfractionated heparin are used with GP IIb/IIIa agents during coronary intervention, the inability to titrate the dosage of low-molecular-weight heparins poses a barrier to using them with GP IIb/IIIa inhibitors.

Other issues. Ongoing trials are addressing specific questions regarding the optimal dose and duration of GP IIb/IIIa inhibitor therapy (PARAGON-B and SYMPHONY, respectively), the safety and efficacy of combination reperfusion therapy with fibrinolytics and GP IIb/IIIa inhibitors (GUSTO-IV), and the ideal balance between antiplatelet therapy and percutaneous revascularization for non–ST-segment elevation acute coronary syndromes (TACTICS-TIMI 18).

ORAL GP IIb/IIIa INHIBITORS

After initially being treated with fibrinolytics and antithrombins, patients with acute MI and unstable angina can remain in a prothrombotic state for several months.[52] In addition, the underlying ruptured plaque may take weeks to months to heal.[53] Further, many of the trials of intravenous GP IIb/IIIa inhibitors showed a large benefit early on but a smaller benefit at 30 days. With these observations in mind, investigators hope to extend the benefits of GP IIb/IIIa blockade by giving oral agents.[54]

Sibrafiban in varying doses was compared with aspirin in 329 patients with acute coronary syndromes in the TIMI-12 trial.[55] Sibrafiban produced a rapid and sustained inhibition of platelet aggregation at the expense of a moderate increase in "nuisance" bleeding at the highest dose studied. However, a sizable percentage of patients had to stop taking the drug because of such "nuisance" bleeding (eg, epistaxis, gum bleeding), suggesting that intense inhibition of platelet aggregation may not be tolerated in the long term. Adverse ischemic events were rare in both the aspirin and sibrafiban groups. Sibrafiban was compared with aspirin for the treatment of acute coronary syndromes in the phase III SYMPHONY trial among 9,000 patients, but no consistent benefit was demonstrated.[56]

Xemilofiban was tested in 549 patients after elective percutaneous coronary intervention in the ORBIT trial; sustained platelet inhibition was seen after 1 month of therapy.[57] The agent was also tested in the large-scale EXCITE trial in patients undergoing coronary intervention, but no treatment benefit was seen.[58]

Orofiban was tested in patients with acute coronary syndromes in the SOAR trial; sustained platelet inhibition for 12 weeks was demonstrated.[59] The agent was also tested in

the large-scale OPUS TIMI 16 trial, which was prematurely halted because of unfavorable results. Excess mortality was demonstrated in the orofiban arms, but a mechanistic explanation for this finding has not been elucidated.[58]

Other oral GP IIb/IIIa inhibitors being evaluated include **lotrifiban**, **lefradifiban**, and **roxifiban**.

Therefore, multiple questions remain regarding oral GP IIb/IIIa inhibitors: Are these agents safe? Is there synergistic benefit with concomitant aspirin therapy? Will oral GP IIb/IIIa inhibitors cause unacceptable rates of bleeding or thrombocytopenia?[60,61] Also unknown are the optimal dosage and the necessary duration of treatment.

RECOMMENDATIONS

Consider treatment with a GP IIb/IIIa inhibitor in:

- All patients undergoing percutaneous revascularization (although patients with unstable angina or an evolving or recent acute MI may derive more benefit).
- Patients with non–ST-segment elevation acute coronary syndromes who have high-risk characteristics, regardless of the intended management strategy. High-risk characteristics include dynamic ST-segment electrocardiographic changes, positive cardiac markers, postinfarction angina, prolonged chest pain refractory to other medications, hemodynamic instability, and previous revascularization procedures. In addition, patients with elevated troponin levels appear to derive more benefit from GP IIb/IIIa inhibitors.[62]

Aspirin and heparin should be given with eptifibatide or tirofiban for empiric treatment of unstable angina unless specific contraindications exist.

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