

Chapter

17

Gp2b/3a Inhibitors

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INTRODUCTION

Platelet glycoprotein IIb/IIIa (GP2b/3a) receptor inhibitors are the most recent addition to medical therapy for acute coronary events and percutaneous coronary interventions. These agents have demonstrated reductions in the combined endpoint of death, myocardial infarction and urgent coronary revascularization in several cardiovascular settings¹. There are three parenteral agents currently available: abciximab, eptifibatide and tirofiban.

Comparative Pharmacology and Pharmacokinetics

Platelet aggregation is a crucial step in the pathogenesis of ACS, including unstable angina and myocardial infarction. Atherosclerotic plaque rupture initiated by several physiologic causes, as well as mechanical injury which may occur during PCI, leads to coronary vessel injury. Injury to the vascular endothelium triggers platelet aggregation and subsequent thrombosis. The final step in platelet aggregation is the binding of fibrinogen between two platelets at the GP2b/3a receptor. GP2b/3a receptor inhibitors block this final pathway and abolish platelet aggregation regardless of the mechanism by which the platelets are activated.

Although the GPIIb/IIIa receptor inhibitors inhibit platelet aggregation by the same mechanism, several differences exist between the three agents. Table 1 summarizes the pharmacokinetic properties for each agent².

Adjunctive Therapy During Revascularization (PCI)

The role of the GP2b/3a receptor inhibitors (Table 1) in conjunction with PCI have been evaluated

although abciximab has been most thoroughly studied. The durations of infusion post-PCI varied, with shorter durations used for abciximab (12 hours), compared to eptifibatide (18-24 hours) and tirofiban (18-36 hours). The primary clinical endpoint in these trials was the impact on the incidence of a "composite endpoint" at 30 days following treatment. This composite endpoint included the clinical endpoints of death, myocardial infarction, and need for urgent repeat revascularization procedures.

Abciximab. In the EPIC³, EPILOG⁴ and EPISTENT⁵ trials, abciximab showed a 4.5-6.5% absolute reduction in the risk for the 30-day composite endpoint. This reduction in absolute risk translated to a 35-56% reduction in the relative risk for the composite endpoint. Benefit was seen regardless of the method of revascularization (PTCA versus stent placement versus directional atherectomy). The effect on the composite endpoint was durable and maintained for 3 years in the EPIC trial, and for 1 year in the EPISTENT trial. High-risk patients (unstable angina or acute MI) in the EPIC trial derived the greatest benefit. The majority of the impact on the composite endpoint was due to a reduction in nonfatal MI and the need for urgent revascularization. Although there was a trend towards reduction of overall mortality in EPIC and EPILOG trials, only the EPISTENT trial showed a statistically significant reduction in mortality with prolonged follow-up. In the EPISTENT study, there was a 60% relative risk reduction in mortality in the abciximab plus stent group at 1 year as compared to the other treatment groups. Unfortunately, this mortality benefit was not maintained at 3 years of follow-up. Thus, the long-term benefit of abciximab on mortality remains to be proven.

Table 1: Pharmacokinetic properties of Gp2b/3a receptor inhibitors

Properties	Abciximab (ReoPro®)	Eptifibatide (Integrilin®)	Tirofiban (Aggrastat®)
Type of agent	Monoclonal antibody (MoAb)	Peptide	Non-peptide
Mechanism of 2b/3a receptor inhibition	MoAb binds to receptor causing steric hindrance and conformational changes	Mimics native protein sequence in receptor	Mimics native protein sequence in receptor
Binding to receptors	Long-acting, high-affinity receptor blocker	Short-acting, dose-dependent binding	Short-acting, dose-dependent binding
Reversible with Platelet infusions?*	Yes	No. (Platelet function returns to normal in 4 hours)	No. (Platelet function returns to normal in 4 hours)
Speed of reversibility	Slow (> 48 hours; due to prolonged binding to platelets)	Fast (2-4 hours)	Fast (2-4 hours)
Half-life	30 minutes	2.5 hours	2 hours
Elimination	Protease degradation	Renal	Renal

* Note : Reversibility of the effects of eptifibatide and tirofiban with platelet transfusions has not been specifically studied in humans

In the CAPTURE⁶ trial, high-risk patients with unstable angina were started on abciximab 18-24 hours prior to PCI, following cardiac catheterization. Although this trial is often presented as an ACS trial, all patients received PCI. This trial showed similar benefit on the 30-day composite endpoint, but the statistical significance of the benefit was not maintained at 6 months follow-up. This may be due to either the sicker patient population enrolled on this study (more severe, refractory unstable angina as compared to other abciximab trials) or the short duration of post-PCI abciximab therapy. The results of this trial formed the basis for the expanded indication of abciximab to include patients with unstable angina and planned PCI within 24 hours.

Eptifibatide. The IMPACT II⁷ trial documented the benefit of eptifibatide as an adjunct to PCI. In the intent-to-treat analysis of IMPACT II, eptifibatide was found to reduce the incidence of the composite endpoint at 24 hours, but benefit was not maintained at 30 days. The study design allowed patients who gave informed consent to be randomized prior to the decision to perform PCI. When the results of patients who actually received treatment are analyzed separately, there is a statistically significant reduction in the composite endpoint at 24 hours and 30 days. A subgroup analysis found high risk patients (those enrolled within 24 hours of onset of AMI or who had rescue PTCA) to have a greater benefit from eptifibatide. However, the magnitude of observed treatment effects at 30 days was lower than the seen in the abciximab trials. One possible reason is due to the dosing of eptifibatide. Due to problems with the laboratory methods used to measure the drug's antiplatelet activity, a lower than optimal dose of eptifibatide was recommended for the study, and may

have limited the magnitude of the observed clinical benefit. This was confirmed in the ESPRIT trial, which studied eptifibatide in patients undergoing PCI with coronary stent placement. The dose of eptifibatide in this study was fourfold higher than in the IMPACT II study, with two intravenous boluses of 180mcg/kg followed by a continuous infusion of 2 mcg/kg/min for 18-24 hours post-intervention. In this trial, patients who received eptifibatide were found to have a significant reduction in the incidence of the composite endpoint at 48 hours, 30 days, 6 months, which was durable at 1 year. The majority of the benefit was derived from reduction in myocardial infarction. Although there was a trend toward reduction in mortality, the results did not achieve statistical significance.

Tirofiban. In the RESTORE⁸ trial, patients receiving tirofiban experienced a significant decrease in the composite endpoint at 48 hours and 7 days, but this difference was not maintained at 30 days. The investigators attributed this loss of effect to the inclusion of low risk patients that were undergoing non-emergent coronary artery bypass graft (CABG) and PTCA. When the 30-day composite endpoint was reanalyzed with only urgent procedures (as in EPIC and IMPACT II), there was a 24% reduction in the relative risk of the composite endpoint, that did not reach statistical significance (10.5% versus 8%, $p = 0.052$). The TACTICS trial evaluated the effect of early PCI versus a more conservative strategy where intervention was reserved for patients with recurrent ischemia or an abnormal stress test. Clinical trials conducted prior to the availability of the GP2b/3a receptor inhibitors and intracoronary stenting had not shown a difference in clinical outcomes for the two interventional strategies.

In this trial, all patients received aspirin, heparin, and tirofiban; there was no placebo group. For patients at intermediate high risk for complications, the early intervention group had a significantly lower incidence of the composite endpoint of death, non-fatal MI and rehospitalization within 6 months than the conservative strategy group of 6 months follow-up (15.9% versus 19.4%, respectively, $p=0.025$). Low-risk patients had similar outcomes regardless of the strategy employed. While this trial implied that the improved results were due to incorporation of a GP2b/3a receptor inhibitor, it is impossible to specifically determine the explanation for the benefit, since there was no placebo group. The early timing of revascularization and the use of intracoronary stents could also explain the improved outcomes for early invasive strategy group.

Comparative studies. Until recently, there were no clinical trials available which directly compared the efficacy of the GP2b/3a receptor inhibitors. The results of the multinational TARGET⁹ trial consisted of patients with planned PCI and intended stent placement were randomized to tirofiban or abciximab. Patients who received abciximab had a significantly lower incidence of the composite endpoint at 30 days, but no difference in mortality. The majority of the difference in the composite endpoint was due to a lower incidence of MI. Patients treated with abciximab experienced more minor bleeding (5.59% versus 3.54%, $p = 0.001$) and more thrombocytopenia (2.44% versus 0.54%, $p < 0.001$), but there was no difference in major bleeding complications between the two groups.

Treatment of Acute Coronary Syndromes (ACS)

The effect of the three approved GP2b/3a receptor inhibitors has been investigated in over 16,000 patients with ACS. The design of the clinical trials in ACS differ in several aspects, especially in the types of patients enrolled, the use of revascularization procedures and the use of heparin.

Abciximab has been studied in two clinical trials. The CAPTURE trial was summarized in the PCI section above. Although all patients ultimately underwent PCI, the benefit of abciximab began to appear prior to PCI with decreased rates of MI in the first 24 hours (2.1 vs 0.6%, $p = 0.029$). Unfortunately, the results of the GUSTO IV ACS trial failed to demonstrate any benefit of abciximab therapy in the medical management of unstable angina. This trial was designed to test the effect of abciximab without concomitant revascularization interventions. There was no difference in the incidence of the composite endpoint at 30 days.

The PURSUIT¹⁰ trial was designed to allow investigators to treat patients according to institutional standard practice without mandated revascularization protocols. At 30 days, the composite endpoint (death or MI) was significantly lower in the eptifibatide arm versus placebo. Of the 1,228 patients who underwent PCI within the first 72 hours, there was a decreased risk of MI prior to PCI (5.5% versus 1.7%, $p < 0.001$) and also a decrease in the composite endpoint at 30 days (16.7% versus 11.6%, $p = 0.01$). Similar benefit was demonstrated in patients who underwent CABG surgery during the first 72 hours. At 30 days, eptifibatide had no significant effect over placebo in patients who did not undergo early revascularization (within 72 hours). The treatment effect seen in this trial was not as marked as in the CAPTURE trial, possibly due to the higher risk patients in the CAPTURE trial, all of whom underwent PCI.

In the PRISM¹¹ and PRISM-PLUS¹² trials, the effect of tirofiban in patients with ACS was studied. In the PRISM trial, revascularization procedures were discouraged. Tirofiban produced superior effects on the composite endpoint at 48 hours (end of infusion) compared to heparin alone, but the benefit was lost at 7 and 30 days. In the PRISM-PLUS trial, PCI was not allowed in the first 48 hours, but encouraged at 48-96 hours. Tirofiban in combination with heparin produced a significantly lower incidence of the composite endpoint at both 7 and 30 days versus heparin alone. The tirofiban alone group had an increase in mortality and was discontinued early. Investigators have attributed this effect to possible "heparin rebound".

Use in ST-Segment Elevation Myocardial Infarction (STEMI)

The principal goal of reperfusion procedures in the management of STEMI is to achieve a high rate of "TIMI 3 flow", defined as complete perfusion of the affected coronary arteries. Each absolute increase of 20% in TIMI 3 flow is known to decrease mortality related to STEMI by 1%. Although thrombolytics have become the mainstay of treatment, their use is associated with an increase in thrombin activity and activation of platelets. The GPIIb/IIIa receptor inhibitors could potentially enhance clot dissolution, and decrease the risk for re-occlusion of the treated vessel.

Results of the ADMIRAL¹³ trial provide evidence of benefit for abciximab when used with coronary stenting. This trial randomized 300 patients to coronary stenting and placebo or stenting plus abciximab prior to cardiac catheterization. At 30 days, the composite endpoint of

death, myocardial reinfarction and urgent revascularization of the target vessel had occurred in 6% of the abciximab-treated patients compared to 14.6% of the placebo group ($p = 0.01$). The positive impact on the composite endpoint was maintained at 6 months follow-up (7.4% vs 15.9%, respectively, $p = 0.02$). Bleeding complications were not significantly different between the groups. Thus, abciximab in combination with coronary stenting is an acceptable option for patients with acute STEMI.

Several preliminary dose finding studies showed promise in reduction of cardiac events when GPIIb/IIIa receptor inhibitors were given in combination with a thrombolytic agent. The largest of these were the TIMI 14¹⁴ and SPEED¹⁵ trials. Although the results of these early trials were promising, they were not powered to adequately address the safety of the drug combinations. The results of GUSTO V AMI which enrolled 16,588 patients included patients who were randomized to receive standard-dose tereplase, or half-dose reteplase and abciximab. There was no difference in the primary endpoint of mortality at 30 days between the reteplase alone group and the combination group (5.9% vs 5.6%, $p = 0.43$). Compared to reteplase alone, the combination group did have a lower incidence of the composite endpoint of death and non-fatal reinfarction (8.8% vs 7.4%, $p = 0.0011$), and less need for urgent revascularization (8.6% vs 5.6%, $p = 0.001$). These beneficial effects were offset by a higher incidence of non-intracranial bleeding complications, such as spontaneous hemorrhage (4.3% vs 1.9%, $p < 0.0001$), need for transfusions (5.7% vs 4.0%, $p < 0.0001$), and thrombocytopenia (2.9%

vs 0.1%, $p < 0.0001$) in the combination group. Thus, at this time, combination therapy does not seem warranted in the routine management of STEMI.

DOSING AND ADMINISTRATION OF Gp2b/3a INHIBITORS IS PROVIDED IN TABLE 2

Adverse Effects

Bleeding is a primary safety concern with the GP2b/3a receptor inhibitors. The incidence of bleeding in the clinical trials of these agents is difficult to compare, as the studies used different criteria to define major and minor bleeding. Thus, it is easy to misinterpret safety data when comparing agents. Overall, the incidence of life-threatening bleeding complications with the GP2b/3a receptor inhibitors is $<0.2\%$, which is lower than that reported with traditional thrombolytic therapy (0.8-1.0%). The high bleeding rates in the EPIC trial led to re-evaluation of heparin dosing in this setting. In subsequent studies, heparin has been dosed based on patient weight and has been discontinued immediately after the PCI procedure. In addition, the practice of early removal of the vascular access sheath following PCI has been adopted. These interventions together have resulted in a reduced incidence of bleeding complications.

Contraindications

Contraindications, warning and precautions are similar for the three agents. In general, the following contraindications apply to each GP2b/3a receptor inhibitor:

Table 2: Dosing and administration

FDA-approved dosing and administration guidelines for the Gp 2b/3a receptor inhibitors

Drug	Abciximab (ReoPro)	Eptifibatide (Integrilin)	Tirofiban (Aggrastat)
Dose	PCI: 0.25 mg/kg IV bolus pre-PCI, then 0.125 mcg/kg/min (max. 10 mcg/min) IV infusion x 12 hours post-PCI. ACS with planned PCI: 0.25 mg/kg IV bolus, then 10 mcg/min IV infusion x 18-24 hours pre-PCI and x 1 hour post-PCI	PCI: 180 mcg/kg IV bolus pre-PCI, then 2.0 mcg/kg/min IV infusion with a second 180 mcg/kg bolus 10 minutes after the first bolus. Infusion continues until hospital discharge or for 18-24 hours post PCI (whichever comes first), (ESPRIT dose)** ACS: 180 mcg/kg IV bolus, then 2 mcg/kg/min (max. 15 mg/hr) x 72-96 hours	— ACS: 0.4 mcg/kg/min IV infusion x 30 min, then 0.1 mcg/kg/min x 48-108 hours
Dosage adjustments	N/A	SCr > 2.0 mg/dl-decrease infusion to 1.0 mcg/kg/min SCr > 4.0 mg/dl or requires hemodialysis - CI	CrCl < 30 ml/min-decrease bolus rate and infusion rate by 50%

CI = contraindicated

* FDA approved dose-for PCI, a 12 hour duration post-PCI is recommended.

** The initial FDA approved dose was according to IMPACT II, which has since been found to be a suboptimal dose. Therefore, the ESPRIT dosing regimen is recommended.

Hypersensitivity to any agent component

Active internal bleeding or recent (within 6 months) clinically significant gastrointestinal or genitourinary bleeding

History of bleeding diathesis with previous 30 days

Severe uncontrolled hypertension

Major surgery or trauma within previous four weeks (tirofiban) or six weeks (abciximab, eptifibatide)

Thrombocytopenia defined as a platelet count $< 100,000/\text{mm}^3$ (abciximab, eptifibatide)

History of cerebrovascular accident (CVA) within previous two years, or CVA with neurologic deficit at any time (abciximab)

History of stroke within 30 days or hemorrhagic stroke at any time (eptifibatide, tirofiban)

History of intracranial hemorrhage, intracranial neoplasm, arteriovenous malformation or aneurysm.

History of vasculitis (abciximab)

History of symptoms suggestive of aortic dissection (tirofiban)

Concomitant use of another GP2b/3a inhibitor

Acute pericarditis (tirofiban)

Renal dialysis or serum creatinine ≥ 4.0 mg/dl or requiring hemodialysis (eptifibatide)

Use of IV dextran before procedure or intent to use during procedure (abciximab). Administration of oral anticoagulant within previous seven days unless prothrombin time ≤ 1.2 times the control (abciximab)

Emergency coronary artery bypass surgery. There has been concern regarding the risk of excessive perioperative bleeding among patients who require urgent coronary artery bypass surgery after administration of a glycoprotein IIb/IIIa inhibitor. In this regard, the rapidly reversible agents eptifibatide and tirofiban present little in the way of bleeding risk. With abciximab, platelet transfusions (after discontinuation of abciximab infusion) appear to reduce hemorrhagic risk (48, 49), and blood loss was only modestly increased among patients who required emergency surgery in the EPILOG and EPISTENT trials.

Thrombocytopenia. Thrombocytopenia occurs infrequently with glycoprotein IIb/IIIa inhibition but may be precipitous and profound (platelet count $< 50,000 \text{ mm}^{-3}$); the excess risk of profound thrombocytopenia associated with abciximab (0.4% to 1.1%) is higher than with eptifibatide (0%-0.2%), tirofiban (0.1% to 0.3%) or lamifiban (0% to 0.1%). The mechanism of thrombocytopenia is unknown, but there is little evidence of ongoing

platelet clearance after discontinuation of the glycoprotein IIb/IIIa antagonist. Platelet transfusions are protective for profound thrombocytopenia with or without serious bleeding induced by glycoprotein IIb/IIIa inhibitors. Platelet counts should, therefore, be measured early (within the first 2 to 4 h) after administering these agents and followed for the duration of therapy.

Conjunctive Heparin

During coronary intervention, the low-dose, weight-adjusted heparin regimen (initial bolus of 70 U/kg, maximum 7000 U, adjusted to maintain in activated clotting time ≥ 200 s) is safe and effective with abciximab therapy. Postprocedural heparin likely provides no additional benefit, even in patients with acute ischemic syndromes, and vascular access sheaths can typically be removed 2 to 6 h after the procedure. Optimal heparin dosing during coronary intervention in patients receiving eptifibatide or tirofiban has not been investigated, but a dose of 100 U/kg (maximum 10,000 U) adjusted to an activated clotting time ≥ 300 s is currently recommended. The role of heparin among patients receiving glycoprotein IIb/IIIa antagonists during the medical management of unstable angina remains unresolved. Evidence from the randomized trials¹⁶ and other studies suggests that heparin likely adds clinical benefit to glycoprotein IIb/IIIa blockade in the acute ischemic syndromes although the optimal intensity and duration of therapy has not been defined.

Readministration. The development of a human antichimeric antibody (HACA) response in approximately 5% to 6% of patients within the first month after receiving abciximab raises the question of safety of readministration of this agent. No antibodies have been observed to develop in response to treatment with eptifibatide, tirofiban or lamifiban. A prospective abciximab readministration registry of 500 patients¹⁷ found no instances of hypersensitivity or anaphylactic reactions after abciximab readministration, and efficacy of the agent in reducing ischemic complications appears to be similar with readministration as with first-time use. Rates of thrombocytopenia after readministration were somewhat higher, however, than those seen with first time administration, although the presence or absence of a positive HACA titer was not predictive of a lack of clinical effectiveness, development of thrombocytopenia or other sequelae in patients undergoing readministration.

Indications for therapy and choice of agent. Although trial data support the use of glycoprotein IIb/IIIa

inhibitors in virtually all patients undergoing percutaneous coronary revascularization, these agents are not universally employed in clinical practice due, in part, to economic considerations and concerns regarding safety issues.

The benefits of this therapy should certainly be provided to patients at elevated risk for periprocedural complications, such as those with unstable angina or acute MI, complex lesion morphology, extensive myocardium at jeopardy, multivessel or multilesion interventions or diabetes mellitus. The current efficacy standard during and after percutaneous coronary intervention is abciximab administered as a bolus followed by a 12-h infusion. Aspirin, heparin and ticlopidine or clopidogrel (in patients receiving stents) should also be administered. A pretreatment regimen of abciximab is effective in stabilizing patients before coronary revascularization, but offers no clear advantage in stable patients or even in unstable patients for whom revascularization can be immediately performed. Regardless of whether or not a period of pretreatment with abciximab is used, the 12-h postprocedural infusion appears to be necessary for optimal clinical benefit.

Eptifibatide or tirofiban are effective as empiric therapy among patients with unstable ischemic symptoms associated with either electrocardiographic or enzymatic evidence of myocardial ischemia or necrosis, particularly if revascularization is subsequently performed. Given the heterogeneity of acuity and risk for complications of patients admitted with the diagnosis of "unstable angina," these agents will likely prove most beneficial if focused on those with high risk features such as recurrent or prolonged rest symptoms, ischemic heart failure, dynamic electrocardiographic changes, hemodynamic instability, elevated troponin or creatine kinase or prior aspirin use. Treatment with abciximab in this setting has not yet been evaluated and cannot be recommended. Once a course of empiric therapy with eptifibatide or tirofiban is initiated, it should be continued for 24 h after percutaneous coronary intervention (if performed).

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