Medical Advisory Panel
Drug Class Review:
Glycoprotein (GP) IIb/IIIa Receptor Inhibitors For Use in Acute Coronary Syndromes (ACS) & Percutaneous Coronary Intervention (PCI)

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Purpose:

To review the safety, efficacy and administration of the available GP IIb/IIIa receptor inhibitors.

I. Indications: [1-4, 37]

Currently, there are three glycoprotein (GP) IIb/IIIa receptor inhibitors (Table 1) available in the US. The 2000 ACC/AHA unstable angina and non-ST-segment elevation myocardial infarction (MI) guidelines recommend administration of GP IIb/IIIa receptor inhibitors in patients with non-ST-segment elevation acute coronary syndromes (ACS) at high risk of death or a nonfatal myocardial infarction. Such high-risk features include positive biochemical markers of infarction (ex. troponin I), ST-segment depression on ECG, signs of left ventricular dysfunction, pulmonary edema, age greater than 75 years old, ongoing chest pain for greater than 20 minutes, or ischemia refractory to other medical therapy. Additionally, GP llb/llla inhibitors are utilized for patients who will undergo a percutaneous coronary intervention (PCI), such as balloon angioplasty, atherectomy, or stent implantation during cardiac catheterization. As demonstrated by table 2, only eptifibatide (Integrilin®) has FDA labeled support for both of these clinical indications.

Table 1. GP IIb/IIIa Receptor Inhibitors

Product	Product Availability	Product Cost (VA)[1]	Treatment Cost Per Day (VA)[#]	Manufacturer
Abciximab (ReoPro®)	Single use 5ml vial (2 mg/ml)	$249	$988*	Centocor/ Eli Lilly
Eptifibatide (Integrilin®)	a. 100 ml premixed (750 mcg/ml) b. 10 ml/vial (2000 mcg/ml) c. 100 ml/vial (2000mcg/ml)	a. $97 b. $31 c. $265	$292^	COR/Key
Tirofiban (Aggrastat®)	a. 250 ml premixed (50 mcg/ml) b. 500 ml premixed (50 mcg/ml) c. 25 ml/vial (250mcg/ml) d. 50 ml/vial (250mcg/ml)	a. $249 b. $684 c. $180 d. $250	$249^	Merck

[#]Cost estimate based upon a dose for a 70kg patient
*Abciximab cost per day calculated for bolus dose and 12-hour infusion
^Eptifibatide & tirofiban cost per day calculated for bolus dose and 24-hour infusion; usual treatment duration 72 hours for acute coronary syndromes.

Table 2. [2-4, 18-27, 36]

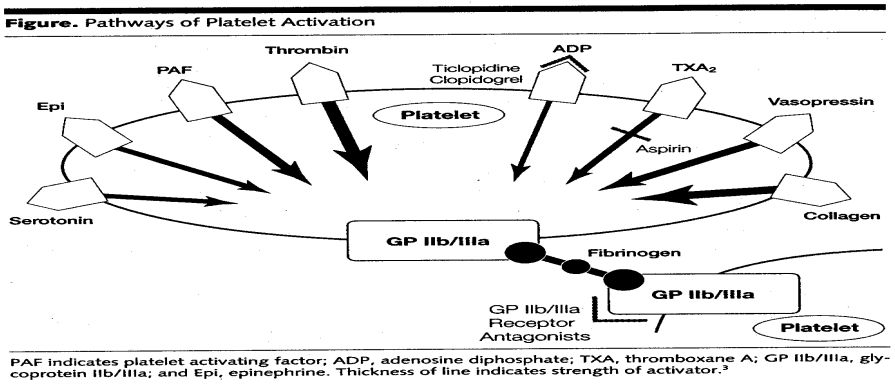
Generic Name	FDA-Approved Indications	Clinical Trial Documentation
Abciximab	PCI *only*	EPIC / EPILOG / EPISTENT
Eptifibatide	Unstable Angina / NQWMI / PCI	PURSUIT / ESPRIT / IMPACT-II
Tirofiban	Unstable Angina / NQWMI *only*	PRISM / PRISM-PLUS

PCI = Percutaneous Coronary Intervention (stent, balloon angioplasty, atherectomy, rotablation)
NQWMI = Non-Q Wave Myocardial Infarction

II. Pharmacology: [5-10]

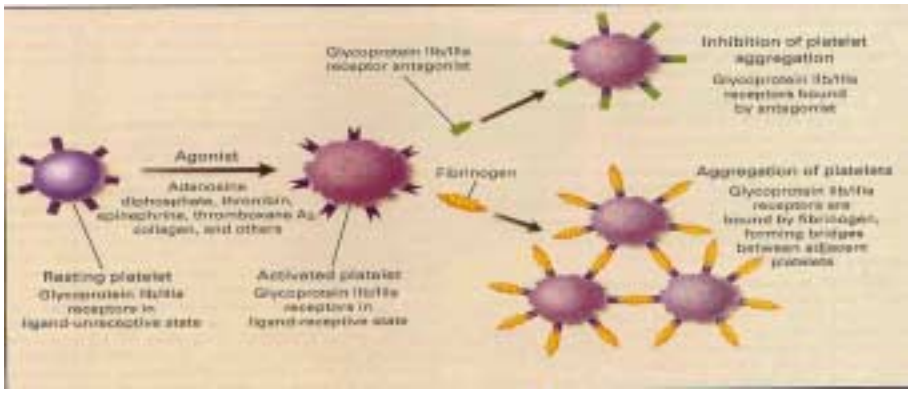
Glycoprotein IIb/IIIa receptors are the most common receptor subtypes on the platelet surface. During normal physiology, the circulating platelets do not interact with undamaged endothelium. If vessel injury occurs, the exposure of the subendothelial layer triggers adhesion of platelets surrounding the area of injury. Platelets adhere to subendothelial collagen via the glycoprotein Ia/IIa receptors and to von Willebrand factor via glycoprotein Ib receptors. Adherent platelets are activated by stimuli such as ADP, 5-HT, TXA_2, thrombin, and collagen, through receptors present on the platelet surface (figure 1). Platelet stimulation triggers a conformational change on the platelet surface, which activates nearly 80,000 GP IIb/IIIa receptors. These activated receptors bind fibrinogen to enhance platelet aggregation and facilitate the formation of a platelet plug. In turn, the platelet plug significantly contributes to the occlusion of the coronary artery and subsequent complications associated with myocardial ischemia.

Figure 1.[6]



The glycoprotein IIb/IIIa receptor inhibitors, abciximab, eptifibatide, and tirofiban, all have similar mechanisms of action to inhibit the platelet aggregation process. Abciximab is a chimeric monoclonal antibody that interferes with platelet aggregation by steric hindrance. Abciximab molecules are large and possess a high degree of platelet affinity. These molecules wrap around each platelet to prevent binding of not only glycoprotein IIb/IIIa receptors important for platelet aggregation, but also other receptors responsible for platelet adhesion to the subendothelium (ie vitronectin). By preventing both platelet adhesion *and* aggregation, abciximab may result in more bleeding complications than more specific GP IIb/IIIa inhibitors. Tirofiban and eptifibatide are small, synthetic molecular structures that have high affinity only for the glycoprotein IIb/IIIa binding site. These compounds compete with fibrinogen for the glycoprotein IIb/IIIa receptor in a concentration-dependent manner and bind in its place, preventing platelet aggregation (figure 2). The goal of all three drugs is to achieve 80% inhibition of platelet aggregation to maximize benefits and minimize adverse effects such as bleeding.

Figure 2:[10] Mechanism of action of tirofiban and eptifibatide



III. Pharmacodynamic and Pharmacokinetic Properties of GP IIb/IIIa Inhibitors: [2-4, 6, 11-13]

Pharmacological features and dosing of the GP Iib/IIIa inhibitors are provided in tables 3 and 4, respectively. Note, the extended time to normal platelet function with abciximab (correctable with platelet transfusion), recommendation to filter the admixture and administration of abciximab, and the need to renally adjust doses of eptifibatide and tirofiban. The clinical significance of the variability in other pharmacologic characteristics is unknown.

Table 3.

Property	Abciximab	Eptifibatide	Tirofiban
Chemical nature	Fab fragment of human/mouse chimeric monoclonal antibody	Cyclic heptapeptide	Nonpeptide
Size	Large (48kDa)	Small (0.8 kDa)	Small (0.5 kDa)
Antibody formation	Yes (HACA antibodies)	No	No
Binding to platelets	Activated *and* non-activated	Activated only	Activated only
Binding to other platelet receptors	Yes (vitronectin)	No	No
Time to 80% platelet inhibition	< 10 min	< 15 min (180mcg)	30 min
Half-life (plasma) Half-life (platelet-bound)	30 min 12-16 hrs	0.83-2.8 hrs Seconds	1.2-2 hours Seconds
Time to normal platelet function	Within 12 hrs*	Within 4-6 hrs	Within 4-8 hrs
Elimination	Degraded in vascular space	Renal and nonrenal	Renal

*Abciximab can be found on circulating platelets up to 15 days post-infusion

IV. Dosing and Administration: [2-4, 14-17, 22]

Table 4.

Drug	Unstable Angina (UA) / NQWMI	Percutaneous Coronary Intervention (PCI)	Filtration required	Renal adjustment
Abciximab	0.25mg/kg IV bolus over 1 min, then IV infusion at 0.125mcg/kg/min for 24 hours[+$]	0.25mg/kg IV over 1 min (10-60 min prior to PCI) then IV infusion at 0.125mcg/kg/min for 12 hours Max: 10mcg/min	Admixture & administration through 0.2-0.22 micron filter	Not necessary*
Eptifibatide	180mcg/kg IV bolus over 1-2 min, & infusion of 2mcg/kg/min up to CABG or 72 hours	180mcg/kg IV over 1-2 min before PCI, start IV infusion of 2 mcg/kg/min, then rebolus 180mcg/kg 10 min after initial bolus[#]	No	If SCr 2 - 4mg/dl, give 135mcg/kg bolus and 0.5mcg/kg/min infusion Avoid use if SCr >4 mg/dl or in hemodialysis* patients
Tirofiban	0.4mcg/kg/min IV for 30 min, then 0.1 mcg/kg/min IV infusion for 48-72hr	10mcg/kg IV infused over 3 minutes, then 0.15 mcg/kg/min infusion for 36 hours^[$] or 10mcg/kg IV infused over 3 minutes, then 0.15 mcg/kg/min infusion for 18-24 hours^^[$]	No	If ClCr < 30 mL/min, reduce dose to half the usual rate of infusion Avoid use if SCr > 2.5mg/dL*

*Patients on continuous or intermittent hemodialysis have not been studied
[+]GUSTO IV ACS trial dosing strategy[16,17]
^RESTORE trial dosing strategy[14]; ^^TARGET trial dosing strategy[15]
[#]ESPRIT trial dosing strategy[22]; recommended dosing higher than PCI dose listed package insert[3]
[$]**Not FDA-approved for this indication**

V. Clinical Efficacy of Glycoprotein IIb/IIIa Inhibitors: [14, 18-24]

A. Percutaneous Coronary Intervention FDA approval: abciximab, eptifibatide

Table 5.

Trial	EPIC[18]	EPILOG[19]	CAPTURE[20]	IMPACT-II[21]	ESPRIT[22-24]	RESTORE[14]
Treatment	Abciximab vs. placebo	Abciximab vs. placebo	Abciximab vs. heparin	Eptifibatide vs. placebo	Eptifibatide vs. placebo	Tirofiban vs. placebo
Study design	Randomized, double-blind, multicenter	Randomized, double-blind, multicenter	Randomized, double-blind, multicenter	Randomized, double-blind, multicenter	Randomized, double-blind, multicenter	Randomized, double-blind, multicenter
# patients	2099	2792	1265	4010	2064	2141
Indication	High risk for abrupt closure (includes peri-MI pts)	Elective or urgent intervention	Intervention for unstable angina not responding to medical tx	Any elective or urgent percutaneous intervention	Elective PCI for stent implantation	Intervention within 72hrs of unstable angina, MI
Aspirin (ASA) regimen	ASA 325mg within 2hr of PCI & daily	ASA 325mg within 2hr of PCI & daily	ASA 325mg within 2hr of PCI & daily	ASA 75mg-325mg 1-24h before PCI	ASA before PCI	ASA 325mg within 12hrs of PCI
Heparin regimen	Bolus to ACT 300-350 sec, then PTT 1.5-2.5x control for 12 hrs	Standard dose bolus to ACT 300 sec vs. Low dose bolus to ACT 200	Infusion to ACT 300 sec or PTT 2-2.5x control	Bolus to ACT 300-350 sec	Bolus to ACT 200-300 sec	Bolus to ACT 300-400 sec
Heparin bolus	10,000 – 12,000 U	Std 100U/kg Low 70U/kg	100 U/kg (≤ 10,000 U)	100 U/kg	60 U/kg (≤ 6,000 U)	150 U/kg (≤ 10,000 U)
GP IIb/IIIa treatment arms	AB1 0.25 mcg/kg bolus vs. AB2 0.25 mcg/kg bolus & 10mcg/min infusion vs. placebo	0.25mcg/kg bolus & 0.125 mcg/min infusion vs. placebo	0.25mcg/kg bolus & 10 mcg/min infusion vs. placebo	135 mcg/kg bolus & 0.5 mcg/kg/min infusion vs. 135 mcg/kg & 0.75 mcg/kg/min vs. placebo	180mcg/kg bolus x2, & 2 mcg/kg/min infusion vs. placebo	10mcg/kg bolus & 0.15 mcg/kg /min infusion vs. placebo
Recommended duration (avg / median)	12 hours (12 hours)	12 hours (12 hours)	18-24 hours	20-24 hours	18-24 hours (18.3 hrs)	36 hours (36 hours)
Use and timing of invasive procedures	AB bolus 10-60min before PCI	AB bolus 10-60min before PCI	AB bolus & infusion 18-24 hrs prior to PCI until 1 hr after PCI	EP bolus 20min before PCI	EP bolus #1 & infusion immediately before PCI & bolus #2 10 min later	TIR bolus immediately before PCI
% PTCA* % stents placed % no intervention	95% 0% 5%	98.6% 13.5% 1.4%	98.1% 7.6% 1.9%	96.9% 4.1% 3.1%	3% 96% 1%	99% 0% 1%
Primary end-point	Composite 30-d death / MI / revasc. for acute ischemia	Composite 30-d death / MI / revasc. for ischemia	Composite 30-d death / MI / urgent revasc.	Composite 30-d death / MI / urgent revasc.	Composite 48-h death/ MI/ target vessel revasc.	Composite 30-d death / MI / revasc. for recurrent ischemia
Trial arms showing no statistical difference from placebo	AB1 0.25 mcg/kg bolus without infusion p=0.43	none	none	EP2 135 mcg/kg & 0.75 mcg/kg/min p=0.179 vs. placebo	none	TIR 10mcg/kg & 0.15 mcg/kg/min P=0.16 vs. placebo

*PTCA = percutaneous transluminal coronary angioplasty (“balloon” angioplasty”), OR atherectomy

V. Clinical Efficacy of Glycoprotein IIb/IIIa Inhibitors: [14,15 18-24]

A. Percutaneous Coronary Intervention FDA approval: abciximab, eptifibatide

Several trials have been conducted to evaluate the role of glycoprotein IIb/IIIa inhibitors during percutaneous coronary intervention, the most significant of which are summarized in table 5 and table 6. The TARGET trial is a landmark study that has recently been presented but has yet to be published.[15] The TARGET trial is a randomized, double-blind, double-dummy, head-to-head comparison trial the large molecule abciximab, which acts by steric hindrance of the GP receptors, to a smaller, competitive inhibitor of fibrinogen binding to the GP IIb/IIIa receptor. TARGET was designed to evaluate the efficacy of tirofiban in PCI when stent implantation was utilized, since tirofiban had not yet been studied in this population. The results are listed in table 6 and suggest that tirofiban is not as effective as abciximab in PCI. There is much speculation as to why this finding occurred. One theory is that the dosing strategy may not have lead to 80% inhibition of platelet aggregation throughout the entire study period, and a double-bolus regimen, such as is utilized in the ESPRIT trial may show more benefit. Another theory is that the small molecular agents, tirofiban and eptifibatide, may not be as effective in the PCI setting as abciximab. Since abciximab works to block platelet aggregation in both activated and non-activated platelets, it may be more beneficial in the setting of elective PCI, since platelets may not be already activated in this scenario. Tirofiban and eptifibatide only bind to activated platelets, such as existing in the acute coronary syndromes setting.

Table 6. Clinical Trial Results for GPIIb/IIIa Inhibitors for Percutaneous Coronary Intervention[14,15,18-24]

Primary Endpoint 30-Day Death, MI, or Urgent Revascularization^							
Trial	**GP IIb/IIIa**	**GP IIb/IIIa % pts achieving primary endpoint**	**Control % pts achieving primary endpoint**	**P value**	**Absolute Risk Reduction ARR (%)**	**Relative Risk Reduction RRR (%)**	**Odds Ratio (95% CI)**
EPIC*	Abciximab	8.3%	12.8%	0.008	4.5%	35%	Not available
EPILOG	Abciximab	5.2%	11.7%	< 0.001	6.5%	55%	0.43 (0.30-0.60)
CAPTURE	Abciximab	11.3%	15.9%	0.012	4.6%	29%	Not available
IMPACT-II[#]	Eptifibatide	9.2%	11.4%	0.063	2.5%	22%	Not available
ESPIRIT^	Eptifibatide	6.6%	10.5%	0.0015	3.9%	37%	0.95 (0.47-0.84)
RESTORE	Tirofiban	10.3%	12.2%	0.16	1.9%	16%	Not available
TARGET**	Tirofiban	7.6%	6%	0.037	1.6%	21%	Not available

*p=0.008 Abciximab bolus + infusion vs. placebo
[#]p=0.035 Eptifibatide 135/0.5 vs. placebo
^ESPRIT trial used 48-hr composite primary endpoint of death, MI, or urgent revascularization
**All trials were placebo-controlled except TARGET, which was abciximab-controlled; all patients in both treatment & control groups received heparin & aspirin. Statistical significance, absolute, and relative risk reductions are all in favor of abciximab over tirofiban.

B. Treatment of Acute Coronary Syndromes FDA approval: eptifibatide, tirofiban

Since acute coronary syndromes, including unstable angina and myocardial infarction, are the result of plaque rupture, subsequent platelet aggregation, and thrombus formation, GP IIb/IIIa inhibitors were studied in this scenario to prevent aggregation, thrombus extension, and occlusion of the coronary artery. In combination with aspirin and heparin, glycoprotein (GP) IIb/IIIa inhibitors have shown a significant reduction in composite morbidity and mortality rates. Published trials demonstrating these effects in unstable angina and NQWMI are summarized in table 7.

V. Clinical Efficacy of Glycoprotein IIb/IIIa Inhibitors:[2-4,16,17,25-27]

B. Treatment of Acute Coronary Syndromes FDA approval: eptifibatide, tirofiban

Table 7.

Trial	PRISM[# 25]	PRISM-PLUS[26]	PURSUIT[27]	GUSTO IV ACS^[16,17]
Treatment	Tirofiban vs. heparin	Tirofiban vs. heparin vs. tirofiban + heparin	Eptifibatide vs. placebo	Abciximab vs. placebo
Study design	Randomized, double-blind, multicenter	Randomized, double-blind, multicenter	Randomized, double-blind, multicenter	Randomized, double-blind, multicenter
# patients	3232	1915	10948	7800
Indication	Unstable angina / NQWMI within 24hrs of chest pain onset	High risk unstable angina / NQWMI within 12 hrs of chest pain	Unstable angina / NQWMI within 24hrs of chest pain onset	Unstable angina / NQWMI
% Unstable angina % NQWMI % ST depression on EKG	75.1% 24.9% 31.5%	55% 45% 58.5%	Not available Not available 50%	71.7% 28.3% 80%
Glycoprotein IIb/IIIa treatment arms	TIR 0.6mcg/kg/min bolus x30min & 0.15 infusion alone + placebo-heparin vs. heparin	TIR 0.6mcg/kg/min bolus & 0.15 infusion alone vs. UFH + TIR 0.4mcg/kg/min bolus & 0.10 infusion, vs. UFH + placebo	High-dose EP 180mcg/kg bolus & 2 mcg/kg/min infusion vs. low-dose EP 180mcg/kg & 1.3 mcg/kg/min	AB 0.25mcg/kg & 0.125mcg/kg/min x24h vs. AB 0.25mcg/kg & 0.125mcg/kg/min x48h vs. placebo
Aspirin (ASA) Regimen	ASA 300-325mg at randomization & daily	ASA 325mg at randomization & daily	MD discretion (93% received ASA 80-325mg)	Not available
Unfractionated Heparin (UFH) Regimen	Control arm *only* *	Control arm & tirofiban/UFH arm	MD discretion (89.8% received UFH)	Not available
Heparin dosing	Heparin 5000U bolus & 1000U/hr infusion to PTT 2x control	Heparin 5000U bolus & 1000U/hr infusion to PTT 2x control	Heparin 5000U bolus & 1000U/hr to maintain PTT 50-70	Not available
Recommended duration (avg/median)	48 hours (45.6h ± 8.7)	48 hours, unless PCI, then continue through PCI & 12-24hrs after (71.3h ± 20)	72 hours, unless discharged prior, or unless PCI, then continue up to 96hrs (72h)	24 hours in one group, 48 in the other
Use and timing of invasive procedures	Discouraged during first 48 hours, infusion discontinued if proceeded to PCI	Discouraged during first 48 hours, recommend at 48-96 h	Recommended, at MD discretion	Revascularization procedures only performed in ~30% of pts in each group
% Angiography % PTCA % stents placed % CABG % no intervention	5.7% 1.9% 0% 0.5% 93.8%	90% 30.5% NA 23.3% 46.2%	59% 23.3% 11.7% 13.9% 62.8%	Info not available ~70%
Primary Endpoint	Composite 48-hr death / MI / refractory ischemia	Composite 7-d death / MI / refractory ischemia	Composite 30-d death / MI *only*	Composite 30-d death / MI *only*
Trial arms discontinued early	None	Tirofiban-alone arm due to excess 7-d deaths, risk ratio 4.11	Low-dose EP arm after safety analysis found high dose safe	None

[#] PRISM pts were low-risk (30% had no ECG evidence of cardiac ischemia); similar baseline characteristics for PRISM-PLUS & PURSUIT

*Heparin not used concomitantly with tirofiban

^Trial not yet published & information limited to currently available resources

V. Clinical Efficacy of Glycoprotein IIb/IIIa Inhibitors:[2-4,16,17,25-27]

B. Treatment of Acute Coronary Syndromes FDA approval: eptifibatide, tirofiban

Of note, there are no head-to-head evaluations of GP Iib/IIIa inhibitors in this setting. Despite variability when comparing the trials (definition of acute coronary syndromes, application of PCI, primary endpoint definition), current data supports the use of eptifibatide and tirofiban in the treatment of non-ST-segment-elevation ACS (synonymous with UA/NQWMI). Preliminary data from GUSTO IV ACS does not appear to support the abciximab dosing strategy utilized in the trial, and therefore, until further data can be obtained, the use of abciximab for ACS should be avoided, unless PCI is planned immediately upon presentation.

Table 8. Clinical Trial Results for GPIIb/IIIa Inhibitors in Acute Coronary Syndromes [2-4,16,17, 25-27]

Primary Endpoint Composite Death, MI, and/or Urgent Revascularization^							
Trial	**GP IIb/IIIa**	**GP IIb/IIIa % pts achieving primary endpoint**	**Control* % pts achieving primary endpoint**	**P value**	**Absolute Risk Reduction ARR (%)**	**Relative Risk Reduction RRR (%)**	**Odds Ratio (95% CI)**
PRISM	Tirofiban	3.8%	5.9%	p=0.007	2.1%	32%	0.67 (0.48-0.92)
PRISM-PLUS	Tirofiban	12.9%	17.9%	p=0.004	5%	28%	0.68 (0.53-0.88)
PURSUIT	Eptifibatide	14.2%	15.7%	p=0.04	1.5%	9.6%	0.89 (0.56-0.85)
GUSTO IV ACS	Abciximab	8.2%	8%	Not available	0.2%*	2%*	Not available

^Primary endpoints differed between trials. PRISM trial primary endpoint 48-hr death/MI/revascularization, PRISM-PLUS trial 7-d death/MI/revascularization, PURSUIT 30-d death/MI only, GUSTO IV ACS 30-d death/MI only.
*ARR & RRR in favor of placebo over abciximab; 9.1% of 48hr abciximab patients achieved primary endpoint, leading to 1.1% ARR & 12% RRR in favor of placebo over abciximab.

VI. Bleeding Complications: [2-4,11, 13, 18, 29-29]

Data from acute coronary syndrome trials with GP IIb/IIIa inhibitors identified no significant differences in major bleeding events between those treated with heparin versus a parenteral GP IIb/IIIa inhibitor, with or without heparin. Most studies have demonstrated higher rates of minor bleeding in patients treated with GP IIb/IIIa inhibitors plus heparin, versus those treated with heparin alone. Rates of minor bleeding are highest at the site of arterial access for cardiac catheterization. The dose of heparin utilized during percutaneous coronary intervention was a significant risk factor for major bleeding in early trials, such as the EPIC trial.[18] Since then, heparin doses during PCI have been reduced.

Bleeding severity is most commonly defined based on TIMI criteria. Major bleeding is defined as intracranial bleeding, a decrease in hemoglobin more than 5 g/dL, or a decrease in hematocrit of more than 15%. Minor bleeding is defined as spontaneous gross hematuria or hematemesis, a decrease in hemoglobin greater than 3 gm/dL with observed bleeding, decrease in hemoglobin greater than 4 gm/dL with no observed bleeding, and all other observed bleeding.

Bleeding complications in ACS trials of GP IIb/IIIa inhibitors: [2-4,11,13, 16-17, 25-28, 30]

Table 9.

Trial	PRISM	PRISM-PLUS	PURSUIT[#]	GUSTO IV ACS
Treatment	Tirofiban vs. UFH	Tirofiban + UFH vs. UFH	Eptifibatide + UFH vs. placebo + UFH	Abciximab x24h + UFH vs. abciximab x48h +UFH vs. placebo + UFH
Major bleeding	0.4% vs. 0.4%^^	4% vs. 3% (p = 0.34) 1.4% vs. 0.8%^^ (p = 0.23)	10.8% vs. 9.3%^^ (p=0.02)	0.6% vs. 1% vs. 0.3% (p<0.001)
Minor bleeding	2% vs. 1.9%	Not available	12.9% vs. 7.4%	2.5% vs. 3.6% vs. 1.5% (p<0.001)
Blood transfusion	2.4% vs. 1.4%	4% vs. 2.8% (p=0.21)	11.6% vs. 9.2%	0.8% vs. 1.3% vs. 0.7% (p<0.001)

^^bleeding according to TIMI criteria

[#]PURSUIT also included bleeding related to CABG surgery; if CABG bleeding is subtracted, the major bleeding rates become 1.1% for placebo and 2.6% for eptifibatide

VII. Adverse Reactions: [2-4]

The most common adverse drug reactions associated with GP IIb/IIIa inhibitor are both major and minor bleeding and acute profound thrombocytopenia. Acute profound thrombocytopenia is defined as a platelet count dropping to less than 50,000/mm^3 within 24 hours of infusion. This type of thrombocytopenia is reversible by platelet transfusion when it occurs after abciximab administration. Due to their differing pharmacokinetic properties, acute profound thrombocytopenia with eptifibatide or tirofiban is most easily managed by discontinuing the infusion. Platelet count usually returns to baseline within 24 to 48 hours.

GP IIb/IIIa inhibitors share a number of contraindications with thrombolytic agents, due to their bleeding risks. GP IIb/IIIa inhibitors are contraindicated in the following situations: active internal bleeding or history of bleeding within 30 days, history of intracranial hemorrhage, intracranial neoplasm, arteriovenous malformation or aneurysm, history of thrombocytopenia following previous exposure to GP IIb/IIIa inhibitors, history of ischemic stroke within 30 days or *any* history of hemorrhagic stroke, major surgery or severe trauma within the previous 30 days, history, symptoms, or findings suggestive of aortic dissection, severe hypertension (SBP > 180 mmHg and/or DBP > 90 mmHg), unless corrected prior to administration, acute pericarditis, or concomitant use of GP IIb/IIIa inhibitor. Caution should also exercised in patients who are already thrombocytopenic prior to GP IIb/IIIa administration (platelet count < 150,000/mm^3).

Table 10. [2-4, 18-20, 27]

Drug	Bleeding	Thrombocytopenia	Anaphylaxis	Hypotension
Abciximab	Major bleeding 1.9-10.6%	Acute profound thrombocytopenia <1.5% Plts <100,000: 2.6-5.2%	Could potentially occur if re-administered due to anti-chimeric antibodies, however, not reported	14.4% seen with rapid IV injection and continuous infusion (EPIC, EPILOG, CAPTURE trials)
Eptifibatide	Major bleeding 10.8%*; minor bleeding 13.1%	Acute profound thrombocytopenia with platelets <90,000 0.5-1%.	None reported	7% (PURSUIT trial)
Tirofiban	Major bleeding 1.4-2.2%; minor bleeding 10.5-12.0%	Acute profound thrombocytopenia <0.5%; platelets <90,000 <1.9%	None reported	None reported

VIII. Monitoring Parameters: [2-4]

Before infusion of any glycoprotein IIb/IIIa inhibitor, baseline laboratory monitoring of aPTT, Hgb, Hct, and platelet count should be performed to detect any underlying abnormalities. Recommendations for monitoring individual agents during infusion vary significantly. Platelet counts should be obtained 2 to 4 hours after bolus dose of abciximab and at 24 hours or prior to discharge. Platelet counts should be evaluated within 6 hours of the start of tirofiban infusion and at least daily for the duration of treatment. Although no formal monitoring recommendations exist for eptifibatide after the baseline parameters, if platelet count decreases below 100,000/mm^3 at any time during infusion, eptifibatide should be discontinued. If a patient on any glycoprotein Iib/IIIa inhibitor experiences a platelet count decrease to less than 90,000/mm^3, additional platelet counts should be performed to exclude pseudothrombocytopenia. If thrombocytopenia is confirmed, the infusion should be discontinued. Patients should be observed frequently during infusion for overt signs or symptoms of bleeding.

IX. Clinical Applications [3-4, 30-35]

Three trials, PRISM, PRISM-PLUS, and PURSUIT, have demonstrated reductions in the composite endpoint of death and/or MI when GP IIb/IIIa inhibitors are used in the setting of unstable angina or NQWMI with potential percutaneous revascularization. A recent meta-analysis of these three studies by Kong et al. has revealed an odds ratio (OR) of 0.88 (95% CI, 0.81 to 0.97) or 13 fewer events per 1000 patients treated, based on a 30-day composite endpoint of death or MI. For the composite endpoint of death, MI, or revascularization at 30 days, there was also a statistically significant benefit with an OR of 0.86 (95% CI, 0.8 to 0.93) or 22 fewer events per 1000 patients treated. Therefore, GP IIb/IIIa inhibitors, along with aspirin and heparin, should be used for intermediate to high-risk patients with non-ST-segment elevation acute coronary syndromes when percutaneous coronary intervention is planned. GP IIb/IIIa inhibitors should be administered as soon as the diagnosis is made. Based on clinical trials, tirofiban or eptifibatide, with a concomitant heparin infusion, should be continued for up to 72 hours or until percutaneous coronary intervention can be completed (not to exceed 96 hours).[3,4,26,27]

A recently presented trial added to the body of literature supporting the use of GP IIb/IIIa inhibitors in the acute coronary syndromes setting combined with aggressive management by taking patients early for percutaneous coronary intervention. The TACTICS-TIMI 18 trial[34] examined an early aggressive versus early conservative strategy in managing patients admitted for unstable angina or NQWMI. In this randomized, multi-center trial, all patients received aspirin, heparin 5000U bolus and 1000U/hr infusion, and tirofiban 0.4mcg/kg/min loading infusion for 30min, then 0.1mcg/kg/min. The primary endpoint was composite death, MI, or rehospitalization for acute coronary syndromes at 6 months. In patients randomized to the early aggressive arm, who were taken for PCI within 4 to 48 hours of randomization, there was a statistically significant benefit over those in the conservative medical treatment strategy only, 15.9% versus 19.4% (p=0.025). These results suggest that greater benefit is achieved when glycoprotein IIb/IIIa inhibitors are combined with early cardiac catheterization & intervention following acute coronary syndromes.

X. Formulary Considerations [2-4, 34, 38-44]

Further subanalysis of published data has not provided clear evidence to support additional prescribing stratification of the GP IIb/IIIa inhibitors, based upon gender, comorbidities such as diabetes, or smoking status.[38-44] Early initiation of PCI directly influences positive treatment outcomes (TACTICS-TIMI 18)[34] and can significantly affect the total dose of GP IIb/IIIa inhibitor utilized. Cost assessments should be individualized to accurately reflect the clinical application of these products within each institution.

To date, the clinical data supports the superiority of abciximab (Reopro®) as the agent of choice for patients with scheduled PCI. Eptifibatide (Integrilin®) and tirofiban (Aggrastat®) trials support their preference in the treatment of unstable angina and NQWMI. Eptifibatide has FDA indications for both applications of GP IIb/IIIa inhibitors (UA/NQWMI/PCI). Product superiority, in the treatment of ACS or PCI, has not been demonstrated through rigorous, comparative trials. The VA National Formulary will include abciximab as an agent available at all facilities. The formulary

status of eptifidibate and tirofiban will be made at a VISN level due to differences in pharmaceutical preparation and patient type treated. Each VISN will be requested to have one of the latter two agents on its formulary.

XI. Future Applications

At this time, glycoprotein IIb/IIIa inhibitors are *not* indicated for use in ST-segment elevation MI with complete coronary artery occlusion. Initial investigations with the combined use of GP IIb/IIIa inhibitors with thrombolytics appear promising and may affect future prescribing of this class. Larger scale dose-finding and safety trials in combination with thrombolytic agents are ongoing.

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