
PLATELET GLYCOPROTEIN IIb/IIIa RECEPTOR ANTAGONISTS (Tables 34.15, 34.16)

Activation of the platelet glycoprotein (GP) IIb/IIIa receptor complex constitutes the final common pathway for platelet aggregation, and is a critical event in arterial thrombosis (Figure 40.4, Chapter 40). Potent GP IIb/IIIa receptor antagonists have been shown to improve event-free survival in a variety of interventional and non-interventional settings and are the focus of intensive investigation. Abciximab is a noncompetitive antagonist (monoclonal antibody) that binds 1:1 to the GP IIb/IIIa receptor molecule to induce a conformational change that renders its fibrinogen-binding site inactive. Eptifibatid and tirofiban are competitive antagonists that reversibly inhibit the binding of fibrinogen to the GP IIb/IIIa receptor by directly interacting with its RGD binding site. From a clinical standpoint, noncompetitive inhibitors (such as abciximab) have a longer biological half-life, more cross-reactivity with other cell-surface receptors, and higher dissociation constants (more permanent binding) than competitive inhibitors, which may translate into more durable clinical efficacy (in terms of reducing ischemic complications) and less restenosis (possibly due to cross-reactivity with the vitronectin receptor). Numerous studies have evaluated these agents for acute coronary syndromes and as adjuncts for percutaneous coronary intervention (Tables 34.17-34.21). The specific agents and clinical trials are detailed below.

A. ABCIXIMAB. Abciximab (ReoPro, Centocor) is the Fab fragment of the chimeric monoclonal antibody 7E3. Abciximab binds to and blocks platelet GP IIb/IIIa receptors, the vitronectin receptor ($\alpha_v\beta_3$) on smooth muscle and endothelial cells, and the Mac-1 receptor on leukocytes (Table 34.22). Interaction with these receptors may confer antiplatelet, antiproliferative (i.e., restenosis), and anti-inflammatory activity, respectively. Inhibition of clot retraction, factor XIII, and PAI-I, displacement of fibrinogen, and prolongation of the ACT may confer additional anticoagulant and thrombolytic activity unique to abciximab.

1. Abciximab Trials (Tables 34.17-34.21). Abciximab has been studied in several large-scale, placebo-controlled randomized trials¹³¹⁻¹³⁹ in PTCA (EPIC, EPILOG, CAPTURE), stenting (EPISTENT), acute MI (ADMIRAL, RAPPORT, CADILLAC), and acute coronary syndromes (GUSTO-IV ACS); a comparative trial of abciximab vs. tirofiban (TARGET) has recently been completed. EPIC, EPILOG, EPISTENT, and CAPTURE all demonstrated 35-57% reductions in the primary endpoint (death, MI, TLR) favoring abciximab,^{131,133-135} which was particularly evident in patients with unstable angina and acute MI. Although EPIC reported more bleeding complications with abciximab, EPILOG demonstrated that low-dose, weight-adjusted heparin (70 U/kg to achieve ACT 200-250 seconds) plus abciximab could significantly attenuate the risk of bleeding without sacrificing efficacy. Furthermore, benefits observed in high-risk PTCA patients in EPIC were extended to high and low-risk PTCA and stent patients in EPILOG and EPISTENT. Importantly, EPIC continues to demonstrate sustained benefit of abciximab at 30 days, 6 months, and 3 years.^{131,132,138} EPILOG has shown persistent benefit at 1 year,¹³⁷ and EPISTENT reported sustained benefit at 6 months¹³⁵ and at 1 year (mortality: 1% vs. 2.4%).¹⁴⁰ Angiographic restenosis was also lower in diabetics treated with abciximab.¹⁴¹ In contrast to the abciximab bolus and 12-

hour infusion utilized in EPIC, EPILOG, and EPISTENT, CAPTURE patients received an 18-24 infusion before and a 1-hour infusion after intervention; initial benefit at 30 days was not sustained at 6 months,¹³⁴ suggesting that a 12-hour infusion after intervention may be important for sustained clinical efficacy. Abciximab has also been studied as an adjunct to thrombolytic therapy for acute MI patients with ST-segment elevation (Table 34.21). In patients with acute MI undergoing primary PTCA or stenting, three trials of abciximab have reported divergent results (Table 34.18): In RAPPORT,¹³⁶ abciximab was associated with a nonsignificant 17% reduction in late MACE after primary PTCA ($p = 0.07$). In ADMIRAL,¹⁴² abciximab was associated with a 47% reduction in late MACE after primary stenting ($p = 0.03$). In CADILLAC,¹⁴³ patients were randomized to primary PTCA vs. stenting, and abciximab vs. no abciximab. Similar to RAPPORT, the 21% reduction in late MACE after primary PTCA was not significant, and in contrast to ADMIRAL, abciximab offered no incremental benefit after primary stenting. In patients with non-ST-segment elevation acute coronary syndromes, GUSTO-IV ACS revealed no benefit for abciximab (24 or 48-hour infusion) when added to aspirin and heparin (UFH or dalteparin).¹⁴⁴ Finally, the TARGET trial¹⁴⁵ reported better results for abciximab compared to tirofiban for stent patients (death, MI, or urgent revascularization at 30 days: abciximab 6.0% vs. tirofiban 7.5%, $p = 0.037$), especially those presenting with an acute coronary syndrome.

2. **Dosage.** The recommended dose for abciximab for percutaneous intervention is an IV bolus of 0.25 mg/kg administered 10 minutes before intervention, followed by a continuous infusion of 0.125 mcg/kg/min (to a maximum of 10 mcg/min) for 12 hours after intervention. All patients should also receive standard aspirin therapy. The recommended heparin dose is 70 U/kg to achieve an ACT 200-250 seconds; additional heparin is not recommended after intervention. Vascular sheaths should be removed when the ACT is 150-175 seconds, and there is no need to discontinue abciximab for sheath removal. When abciximab is administered after full-dose heparinization (“rescue ReoPro”), additional heparin should be used cautiously to reduce the risk of bleeding; clear guidelines have not been established, and although some suggest partial reversal of full-dose heparin with protamine, this is not routinely recommended.
3. **Limitations (Chapter 25).** A number of safety concerns have been raised about the use of IIb/IIIa antagonists in general and about abciximab in particular. Most of these concerns are related to bleeding complications, the potential requirement for emergency CABG, severe thrombocytopenia, and potential drug interactions. Virtually all of these considerations are readily prevented and/or treated, and do not constitute significant obstacles to the use of IIb/IIIa inhibitors.
 - a. **Bleeding (Table 34.23).** In most IIb/IIIa inhibitor trials,^{131-133,135,136} major bleeding was defined as a drop in hemoglobin > 5 gm/dL, an absolute drop in hematocrit $> 15\%$, or intracranial hemorrhage; minor bleeding included spontaneous gross hematuria, spontaneous hematemesis, a drop in hemoglobin > 3 gm/dL with evident blood loss, or a drop in hemoglobin > 4 gm/dL without evident blood loss. In abciximab trials utilizing standard-dose heparin to maintain high ACT levels (EPIC, EPILOG, RAPPORT), bleeding was more frequent with abciximab vs. placebo (Table 34.23); independent predictors of bleeding included acute MI, low body

weight, old age, longer procedural times, repeat PTCA, and failed intervention. In contrast, trials utilizing low-dose heparin, early sheath removal, and ACT 200-250 seconds (EPILOG, CAPTURE, EPISTENT) reported no difference in major or minor bleeding for patients treated with abciximab or placebo. These studies suggest that the risk of bleeding associated with abciximab can be minimized by low-dose heparin, early sheath removal, avoidance of venous sheaths, and fastidious post-procedure groin care (Table 34.24). Importantly, patients treated with abciximab do not have a higher incidence of intracranial hemorrhage compared to placebo.

- b. Thrombocytopenia (Table 34.25).** A potential safety concern with IIb/IIIa antagonists is thrombocytopenia, which may increase bleeding complications.¹⁴⁶ The incidence of thrombocytopenia appears to be higher with abciximab than with eptifibatide or tirofiban. In the clinical trials, the incidence of mild thrombocytopenia ($< 100,000/\text{mm}^3$) was 2.6-5.6% and severe thrombocytopenia ($< 50,000/\text{mm}^3$) was 0.9-1.6%; platelet transfusions were administered in 1.6-5.5%. Unlike heparin-induced thrombocytopenia, abciximab-associated thrombocytopenia responds within days of discontinuing the drug, and responds promptly to platelet transfusions (Tables 34.24, 34.25). In contrast, severe thrombocytopenia after abciximab retreatment (which is 2-3 times more frequent than after first time use) may not respond promptly to platelet transfusions. Although abciximab is not FDA-approved for readministration, repeat use is common in clinical practice. One study of readministration of abciximab in 500 patients¹⁴⁷ reported a 3-fold higher incidence of profound thrombocytopenia than with initial administration. Although human IgG anti-chimeric antibodies (HACA) are more common after abciximab readministration,¹⁴⁸ a clear association between HACA and thrombocytopenia has not been identified. If readministration of abciximab is considered, early platelet counts should be obtained and abciximab should be discontinued immediately if the platelet counts fall (Chapter 25).
- c. Emergency CABG (Table 34.24).** The risk of bleeding during emergency CABG is potentiated by abciximab and heparin.^{149,150} The hemostatic defect due to abciximab is largely reversible with platelet transfusions, but the benefit is not immediate or complete due to persistent platelet-bound abciximab. Transfused platelets serve as “sink” to remove excess drug from affected platelets, and it may take 3 hours to completely reverse the antiplatelet effect.^{151,152} In EPIC, EPILOG, and EPISTENT,^{153,154} the risk of major bleeding or blood transfusion in emergency CABG patients receiving antecedent abciximab was similar to placebo, although abciximab patients required more platelet transfusions. Key factors in reducing the risk of bleeding during emergency CABG include careful titration of heparin dose and liberal use of platelet transfusions, especially after coming off cardiopulmonary bypass.
- d. Drug Interactions.** Potential drug interactions are described in Table 34.26.

B. EPTIFIBATIDE (Tables 34.15, 34.16). Eptifibatide (Integrilin; manufactured by COR Therapeutics, distributed by Shering-Plough) is a synthetic cyclic K-G-D (lysine-glycine-aspartic acid) heptapeptide and a competitive antagonist for the IIb/IIIa receptor. Unlike abciximab, eptifibatide has a short half-life (2.5 hours),¹⁵⁵ is very specific for the IIb/IIIa receptor, and does not cross-react with the vitronectin receptor. Platelet function returns to baseline within 4 hours after drug discontinuation.

1. Eptifibatide Trials. The use of eptifibatide during coronary intervention was studied in IMPACT-II, PURSUIT, and ESPRIT (Tables 34.17-34.21). In IMPACT-II,¹⁵⁶ there was a nonsignificant 19% reduction in the composite primary endpoint (death, MI, revascularization, or bailout coronary stent) at 30-days in the low-dose eptifibatide group (9.2% vs. 11.4%, $p = 0.063$) and in the high-dose eptifibatide group (9.9% vs. 11.4%, $p = 0.22$). There were no differences in major bleeding or blood transfusion (Table 34.23). In PURSUIT, 10,948 patients with unstable angina or non-Q-wave MI received aspirin and intravenous heparin (initial bolus of 5000 U followed by 1000 U/hr to achieve aPTT 50-70 seconds) and were randomly assigned to eptifibatide (180 mcg/kg bolus and 2.0 mcg/kg/min infusion) or placebo.¹⁵⁷ A third arm using a lower dose of eptifibatide was discontinued (as specified in the original protocol) since the higher dose did not cause more bleeding complications. In a subgroup of 1,250 patients undergoing percutaneous intervention within 72 hours of randomization, eptifibatide reduced the 30-day incidence of death and MI by 31% (11.6% vs. 16.7%, $p = 0.01$), and the incidence of the death and MI before intervention by 69% (1.7% vs. 5.5%, $p < 0.001$). In ESPRIT,¹⁵⁸ the dose of eptifibatide was further modified to include a second bolus, 10 minutes after the first. In an elective coronary stent population, this second bolus was associated with a 37% reduction in ischemic events at 48 hours, which persisted at 30 days and at 6 months.

2. Dosage. Because IMPACT II was used to support product labeling, the FDA-approved dose of eptifibatide is an IV bolus of 135 mcg/kg immediately before intervention followed by a continuous infusion of 0.5 mcg/kg/min for 12-24 hours. However, given the dosing concerns in IMPACT II and the favorable experience in PURSUIT, many physicians have adopted the higher dose employed in PURSUIT: an IV bolus of 180 mcg/kg followed by an infusion of 2 mcg/kg/min for patients with acute coronary syndromes. For therapy initiated in the cath lab (as in ESPRIT), a double bolus of eptifibatide (180 mcg/kg x 2, 10 minutes apart) is recommended, followed by an infusion of 2 mcg/kg/min.

3. Limitations. Eptifibatide did not increase the risk of major bleeding complications in IMPACT II, PURSUIT, and ESPRIT. In contrast to abciximab, there may be less need to reduce the heparin dose, there is no known immune response, and the incidence of thrombocytopenia is similar to placebo. Eptifibatide should be discontinued in patients requiring emergency CABG; antiplatelet effects will resolve in 4-6 hours and platelet transfusion is ineffective. Drug clearance is longer in patients with impaired renal function.

C. TIROFIBAN (Tables 34.15, 34.16). Tirofiban (Aggrastat; Merck) is a synthetic, small-molecule nonpeptide competitive antagonist of the IIb/IIIa receptor. As with eptifibatide, it is rapidly reversible,

highly selective, and does not cross-react with the vitronectin receptor.

- 1. Tirofiban Trials.** In RESTORE,^{159,160} 2,139 patients with acute coronary syndromes undergoing PTCA or DCA receiving aspirin and heparin were randomized to tirofiban (10 mcg/kg bolus and 0.15 mcg/kg/min infusion) or placebo for 36 hours. There was a 40% reduction in death, MI, and urgent revascularization (5.2% vs. 8.7%, $p = 0.002$) at 2 days, 30% reduction at 7 days (6.9% vs. 9.8%, $p = 0.016$), and 24% reduction at 30 days (8.0% vs. 10.5%, $p = 0.16$). The composite endpoint (death, MI, and revascularization) at 6 months was similar (24.1% with tirofiban vs. 27.1% with placebo, $p = 0.11$), and follow-up angiography in 417 patients showed no difference in restenosis (Tables 34.17-34.20).¹⁶⁰ In PRISM-PLUS,¹⁶¹ patients with acute coronary syndromes were randomized to tirofiban, heparin, or tirofiban plus heparin for 48-96 hours; the tirofiban-only arm was dropped because of excess mortality at 7 days. The study was completed with 773 patients receiving tirofiban plus heparin and 797 patients receiving heparin plus placebo. The primary endpoint (death, MI, or refractory ischemia within 7 days) was significantly lower in the heparin plus tirofiban group (12.9% vs. 17.9%, $p = 0.004$). The composite of death and MI was also significantly lower in the heparin plus tirofiban group at 7 days, 30 days, and 6 months. The incidence of major bleeding was similar in the two groups. The recently reported TARGET trial¹⁴⁵ was a direct head-to-head comparison of tirofiban vs. abciximab in 4812 stent patients. Overall, tirofiban was less effective than abciximab, with a 26% relative increase in the primary endpoint of death, MI, or urgent revascularization at 30 days (7.5% vs. 6.0%, $p = 0.037$). In TACTICS-TIMI-18,¹⁶² 2,220 patients with unstable angina or non-ST-elevation MI received aspirin, heparin, beta-blockers and tirofiban upon hospital admission, followed by randomization to invasive management (cath within 4 to 48 hours and revascularization where feasible) vs. conservative management (cath only for spontaneous or provokable ischemia). The primary endpoint of the trial (death, MI, or rehospitalization for ACS at 6 months) was reduced by 18% in the invasive arm (15.9% vs. 19.4%, $p = 0.025$); the beneficial effect was most pronounced in patients with positive troponins (14% vs. 24%).
- 2. Dosage.** The dose of tirofiban used in RESTORE and TARGET was a 10 mcg/kg bolus followed by an infusion of 0.15 mcg/kg/min. In PRISM-PLUS, the dose was slightly different, a 0.4 mcg/kg/min loading infusion for 30 minutes, followed by a 0.1 mcg/kg/min maintenance infusion. In practice, physicians favor the high-dose regimen for patients undergoing coronary intervention. Therapy is usually continued for 18-24 hours after completion of the case.
- 3. Limitations.** There was no increase in major bleeding complications with tirofiban in the clinical trials (Table 34.23),^{159,161} and like eptifibatide, there is no known immune response and the overall incidence of thrombocytopenia is low. If patients require emergency CABG, tirofiban should be discontinued; antiplatelet effects will resolve in 6 hours, but platelet transfusion is ineffective. Clearance is longer in patients with renal failure.

D. OTHER IIb/IIIa INHIBITORS. Lamifiban, another intravenous GP IIb/IIIa antagonist, showed benefit for reducing ischemic complications in unstable angina patients in one study,¹⁶³ but was less

efficacious in others.^{164,165} Lamifiban is not currently under investigation as an adjunct to interventional procedures. Trials of oral GP IIb/IIIa antagonists have been disappointing (Tables 34.17, 34.20, 34.26). In EXCITE,¹⁶⁶ 7,232 patients undergoing coronary intervention were randomized to xemilofiban or placebo. The primary endpoint (death, MI and urgent intervention) was similar at 30 days and 6 months, although there appeared to be a benefit in diabetics. In OPUS-TIMI 16,¹⁶⁷ 10,302 patients with unstable ischemic syndromes were randomized to oral orofiban or placebo. Enrollment was terminated because of excess 30-day mortality in the low-dose orofiban group, although patients who underwent PCI appeared to benefit from orofiban. In SYMPHONY¹⁶⁸ and 2nd SYMPHONY¹⁶⁹ there was a trend toward higher mortality in patients with acute coronary syndromes receiving sibrafiban. The BRAVO¹⁷⁰ trial with lotrifiban was also terminated because of concerns about excess mortality.

- E. RECOMMENDATIONS FOR USE OF GP IIb/IIIa INHIBITORS.** GP IIb/IIIa inhibitors have been extensively studied in a variety of clinical settings (Tables 34.17, 34.28). There are compelling data to support their routine use in patients undergoing percutaneous intervention and in patients with acute coronary syndromes. Recommendations in these and other clinical setting are described in Table 34.28.

Table 34.15. Platelet Glycoprotein IIb/IIIa Receptor Antagonists

Class	Agent	Route	Type of Inhibition
Monoclonal antibody	Abciximab (ReoPro)	IV	Noncompetitive
Cyclic peptides			
RGD sequence	MK-852	IV	Competitive
KGD sequence	Eptifibatide (Integrilin)		
Nonpeptide inhibitors	Tirofiban (Aggrastat), fradafiban, lamifiban	IV	Competitive
Oral agents	Xemilofiban, orofiban, sibrafiban, lefradafiban, lotrifiban	Oral	Competitive

Table 34.16. Comparison of Noncompetitive and Competitive Glycoprotein IIb/IIIa Inhibitors

	Noncompetitive*	Competitive**
Biological half life	Long	Short
Duration of effect	Continues after infusion	During infusion
Plasma half-life	Short	Short
GP IIb/IIIa specificity	Cross-reactivity with other receptors	Highly specific
GP IIb/IIIa binding	Permanent	Reversible

* Abciximab

** Eptifibatide, tirofiban

Table 34.17. Overview of Clinical Trials of GP IIb/IIIa Inhibitors

Trial	IIb/IIIa Inhibitor	Setting
ACUTE MI - ADJUNCT TO LYTIC THERAPY		
TAMI-8	M7E3	t-PA
IMPACT-AMI	Eptifibatide	t-PA
PARADIGM	Lamifiban	t-PA, SK, r-PA
TIMI-14A	Abciximab	t-PA, SK
SPEED	Abciximab	r-PA
GUSTO-IV MI	Abciximab	r-PA
INTRO-AMI	Eptifibatide	t-PA
ACUTE MI - ADJUNCT TO PRIMARY PTCA/STENT		
GRAPE	Abciximab	Primary PTCA
RAPPORT	Abciximab	Primary PTCA
ADMIRAL	Abciximab	Primary PTCA
CADILLAC	Abciximab	Primary stenting or PTCA
STOP-AMI	Abciximab	Stent/abciximab vs. t-PA
ISAR-2	Abciximab	Primary stenting*
PERCUTANEOUS CORONARY INTERVENTION		
EPIC	Abciximab	PTCA, DCA
EPILOG	Abciximab	PTCA, DCA
IMPACT-II	Eptifibatide	PTCA, DCA, ROTA, ELCA
RESTORE	Tirofiban	High-risk PTCA, DCA
EPISTENT	Abciximab	PTCA, PS stent
ESPRIT	Eptifibatide	Elective stent
TARGET	Tirofiban vs. abciximab	Stent (elective and ACS)
EXCITE	Xemilofiban	All percutaneous devices
ERASER	Abciximab	Stent (IVUS to assess restenosis)
UNSTABLE ANGINA/NON-ST-ELEVATION MI		
CAPTURE	Abciximab	ACS with intervention
PURSUIT	Integrilin	ACS with/without intervention
PARAGON A	Lamifiban	ACS with/without intervention
PARAGON B	Lamifiban	ACS with/without intervention
PRISM	Tirofiban	ACS: tirofiban vs. UFH
PRISM-PLUS	Tirofiban	ACS with/without intervention
GUSTO-IV ACS	Abciximab	ACS without intervention
ACUTE II	Tirofiban	ACS: LMWH vs. UFH
TACTICS (TIMI 18)	Tirofiban	ACS: conservative vs. invasive

Abbreviations: ACS = acute coronary syndromes; DCA = directional coronary atherectomy; ELCA = excimer laser coronary angioplasty; LMWH = low-molecular-weight heparin; PS = Palmaz-Schatz; r-PA = reteplase; ROTA = Rotablator; SK = streptokinase; t-PA = tissue plasminogen activator; UFH = unfractionated heparin

* Included patients with acute MI < 48 hours

Acronyms: See Table 34.31, p. 803

Table 34.18. Major Trials of IIB/IIIa Antagonists for Coronary Intervention in Acute MI

Study	Antagonist	1° Endpoint	Result	Comments
CADILLAC ¹⁴³ (n = 2082)	Abciximab (PTCA vs. stent)	Death, MI, or ischemia-driven TVR at 6 months	PTCA: 19.3% PTCA/abcix: 15.2% Stent: 10.9% Stent/abcix: 10.8% (p < 0.0001)	Stenting superior to PTCA; adverse effects of stents on TIMI flow and late mortality in PAMI-STENT not observed in CADILLAC. Abciximab was associated with a trend toward better event-free survival in PTCA patients, but no benefit in stent patients
RAPPORT ¹³⁶ (n = 483)	Abciximab (primary PTCA)	Death, MI, or revascularization at 6 months	Placebo: 16.1% Abciximab: 13.3% (p = 0.32)	No benefit for abciximab in primary PTCA patients
ADMIRAL ¹⁴² (n = 299)	Abciximab (stent 85%, PTCA 15%)	Death, MI, or ischemia-driven TVR at 30 days	Placebo: 20% Abciximab: 10.7% (p < 0.03)	Substantial benefit for abciximab in primary stent patients
Munich Trial ²²² (n = 200)	Abciximab (primary stenting)	Hospital death, MI, revascularization	Placebo: 9.2% Abciximab: 2.0% (p < 0.05)	Abciximab group also had better regional wall motion, global LV function, and peak coronary blood flow. Short-term benefits on primary endpoint were no longer significant at 30 days (p = 0.16)
ISAR-2 ¹⁸⁰ (n = 401)	Abciximab (primary stenting)	Angiographic restenosis	No effect on restenosis	Abciximab led to reduction in 30-day MACE (5.0% vs. 10.5%). No additional benefit over time
EPIC ¹⁸¹ (n = 64)	Abciximab (direct or rescue PTCA)	Death, MI, or urgent revascularization at 30 days	30-day: Placebo 26.1% vs. abciximab ⁺ 4.8% (p = 0.06) 6-month: Placebo 47.8% vs. abciximab ⁺ 4.5% (p = 0.002)	Study group represented 64 of 2099 patients in EPIC with acute MI; 42 direct PTCA, 22 rescue PTCA
GRAPE ¹⁶³ (n = 60)	Abciximab (PTCA)	Infarct artery patency	TIMI-3: 18%	Abciximab before primary PTCA is safe
RESTORE ^{159,160} (n = 134)	Tirofiban (primary PTCA)	Death, MI, or any revascularization	56% reduction at 7 days and 22% reduction at 30 days (p = NS)	Study group represented 134 of 2141 patients in RESTORE with acute MI

Abbreviations: IVUS = intravascular ultrasound; MI = myocardial infarction; TVR = target vessel revascularization
+ Bolus plus infusion

Acronyms: See Table 34.31, p. 803

Table 34.19. Major Trials of IIb/IIIa Antagonists for Acute Coronary Syndromes

Study	Antagonist	Setting	Composite Events (30 days)	Result (Drug vs. Placebo)	RRR (%)
PURSUIT ¹⁵⁷ (n = 10,984)	Eptifibatide	ACS	Death, MI	14.2% vs 15.7% (p = 0.04)	10
CANADIAN LAMIFIBAN STUDY ¹⁶³ (n = 365)	Lamifiban	ACS	Death, MI	3.7% vs 8.1% (p = 0.07)	54
PARAGON A ^{164,189} (n = 2282)	Lamifiban	ACS	Death, MI	Placebo: 11.7% Low-dose lamifiban: 10.6%* High-dose lamifiban: 12.0%*	-
PARAGON B ¹⁹⁰ (n = 5225)	Lamifiban	ACS	Death, MI, refractory ischemia	11.8% vs. 12.8%*	8
PRISM ¹⁹¹ (n = 3232)	Tirofiban	ACS	Death, MI, recurrent ischemia	36% risk reduction (p = 0.007) at 48 hours was not maintained at 30 days (15.9% vs. 17.1%*)	7
PRISM-PLUS ¹⁶¹ (n = 1915)	Tirofiban	High-risk ACS	Death, MI, recurrent ischemia	18.5% vs 22.3% (p = 0.03)	17
TACTICS ¹⁶² (n = 2220)	Tirofiban (all pts)	ACS: invasive vs. conservative	Death, MI, rehospitalization	Invasive 7.4% vs. conservative 10.5% (p < 0.001); benefit persisted at 6 months (18% risk reduction, p = 0.025)	30
CAPTURE ¹³⁴ (n = 1265)	Abciximab	ACS	Death, MI, rehospitalization	11.3% vs. 15.9% (p = 0.012)	29
GUSTO-IV ACS ¹⁴⁴ (n = 7800)	Abciximab	ACS	Death, MI	Placebo: 8.0% Abciximab (24-hr): 8.2%* Abciximab (48-hr): 9.1%*	-
ACUTE-II ⁷⁵	Tirofiban	ACS: LMWH vs. UFH	Death, MI, recurrent ischemia, ischemic CVA	Tirofiban, LMWH: 11.7 Tirofiban, UFH: 16.7	30

Abbreviations: ACS = acute coronary syndromes; LMWH = low-molecular-weight heparin; MI = myocardial infarction; PCI = percutaneous coronary intervention ; RRR = relative risk reduction; UFH = unfractionated heparin

Acronyms: See Table 34.31, p. 803

* p = NS

Table 34.20. Major Trials of IIb/IIIa Antagonists for Coronary Intervention in Acute Coronary Syndromes or Elective Indications

Study	Antagonist	1° Endpoint	Result	Comments
EPIC ^{131,132,138} (n = 2099)	Abciximab (high risk; PTCA or atherectomy)	Death, MI, or urgent TVR at 30 days	Placebo: 12.8% Bolus alone: 11.4% Bolus/infusion: 8.3% (p = 0.008)	Short-term benefits persisted at 6 months (RRR 23%) and 3 years (RRR 13%); first trial to show improved survival by decreasing risk of post-procedural CK elevation. Increased bleeding with abciximab
EPILOG ^{133,136,137} (n = 2792)	Abciximab (PCI)	Death, MI, or urgent TVR at 30 days	Placebo: 11.7% SD heparin: 5.2% LD heparin: 5.4% (p < 0.001)	Persistent benefit at 6 months (RRR 43%, p < 0.05). This study extended the benefits of abciximab to low-risk patients and proved that a reduction in heparin dose reduced bleeding complications without sacrificing efficacy
CAPTURE ¹³⁴ (n = 1265)	Abciximab (PCI for refractory unstable angina)	Death, MI, or urgent TVR at 30 days	Placebo: 15.9% Abciximab: 11.3% (p = 0.012)	More major bleeding with abciximab; no difference in outcome at 6-months, suggesting the need for 12-hour drug infusion post-intervention
EPISTENT ¹³⁵ (n = 2399)	Abciximab (stent)	Death, MI, or urgent TVR at 30 days	Stent alone: 10.8% PTCA/abcix: 6.9% Stent/abcix: 5.3% (p < 0.001)	No increase in bleeding; significant benefit as an adjunct to stenting; mortality benefit at 1 year
ERASER ¹³⁹ (n = 225)	Abciximab (elective stent)	In-stent restenosis at 6 months (by IVUS)	Placebo: 32.4% 12-hr abcix: 37.7% 24-hr abcix: 34.2% (p = NS)	No restenosis benefit for abciximab after stenting using IVUS criteria
IMPACT-II ¹⁵⁶ (n = 4010)	Eptifibatide (PCI)	Death, MI, or urgent TVR at 30 days	Placebo: 11.4% LD eptifib: 9.2% (p = 0.062) HD eptifib: 9.9% (p = 0.22)	No difference in bleeding; insignificant trend toward benefit with low-dose eptifibatide may have been due to inadequate drug dose
ESPRIT ¹⁵⁸ (n = 2064)	Eptifibatide (elective stent)	Death, MI, or urgent TVR at 48 hours	Placebo: 10.4% Eptifibatide: 6.8% (p = 0.0015)	Slight increase in bleeding; modified double bolus effective in reducing short-term events in low-risk patients (RRR 35% at 30-days, p = 0.003). Long-term data not yet available
RESTORE ^{159,160} (n = 2141)	Tirofiban (PCI for unstable angina)	Death, MI, or any TVR at 48 hours	Placebo: 8.7 % Tirofiban: 5.4% (p = 0.005)	No difference in bleeding; used different endpoints than abciximab trials; tirofiban with persistent (but not significant) benefit at 30-days (RRR 16%)
TARGET ¹⁴⁵ (n = 4802)	Tirofiban vs. abciximab (stent)	Death, MI, or ischemia-driven TVR at 30 days	Tirofiban: 7.6% Abciximab: 6.0% (p = 0.037)	Comparable bleeding. Tirofiban was inferior to abciximab, but may be an alternative in low-risk patients without acute coronary syndromes
EXCITE ¹⁶⁶	Xemilofiban (PCI)	Death, MI, or urgent TVR at 30 days	Placebo: 8.1% 10 mg: 8.1% 20 mg: 7.3% (p = NS)	Oral xemilofiban had no benefit; diabetics had slight benefit with xemilofiban

Abbreviations: HD = high-dose; IVUS = intravascular ultrasound; LD = low-dose; MI = myocardial infarction; RRR = relative risk reduction; SD = standard dose; TVR = target vessel revascularization

Acronyms: See Table 34.31, p. 803

Table 34.21. Major Trials of IIb/IIIa Antagonists as Adjuncts to Lytics for Acute MI

Study	Antagonist	Setting	Composite Events	Results (Drug vs. Placebo)
TAMI-8 ¹⁸³ (n = 70)	Abciximab	Acute MI (with t-PA)	Rest angina, ECG changes, reinfarction, urgent revascularization, and death at 30 days	13% vs 20%; no excess bleeding in patients receiving t-PA and abciximab
TIMI 14 ¹⁸⁵ (n = 681)	Abciximab	Acute MI (with SK or t-PA)	TIMI-3 flow at 90 minutes	t-PA + abciximab: 72% Lytic therapy alone: 43%
SPEED ¹⁸⁶ (n=305)	Abciximab	Acute MI (with r-PA)	TIMI-3 flow at 60-90 minutes	Abciximab alone: 28% r-PA + abciximab: 63%
GUSTO-IV MI	Abciximab	Acute MI	—	Pending
STOP-AMI ¹⁸⁸ (n = 140)	Abciximab	Acute MI (stent + abciximab vs. t-PA)	Death, MI, stroke at 6 months; infarct size	8.5% vs. 23.2% (p = 0.02); smaller infarct size with stent/abciximab (14.3% vs. 19.4% of LV)
Intro-AMI ¹⁸⁷ (n=342)	Eptifibatide	Acute MI (with t-PA)	TIMI-3 flow at 60 minutes	Better results when eptifibatide given after t-PA; more complete lysis with 50 mg t-PA
IMPACT-AMI ¹⁸⁴ (n = 180)	Eptifibatide	Acute MI (with t-PA)	TIMI-3 flow at 90 minutes	66% vs 39% (p = 0.006)
PARADIGM ¹⁶⁵ (n = 353)	Lamifiban	Acute MI (with t-PA)	Reperfusion (by continuous ECG at 90 minutes)	80.1% vs 62.5% (p = 0.005)

Acronyms: See Table 34.31, p. 803

Table 34.22. Effects of Abciximab

Effect	Mechanism
Antiplatelet activity	Inhibits platelet cross-linking by fibrinogen
Anticoagulant activity	Inhibits clot retraction; prolongs ACT
Thrombolytic activity	Inhibits factor XIII and PAI-1; displaces fibrinogen
Antiproliferative activity	Nonselective binding to vitronectin receptor
Anti-inflammatory activity	Nonselective binding to Mac-1 receptor on white blood cells

Abbreviations: ACT = activated clotting time; PAI = plasminogen activator inhibitor; Mac-1 = CR3 integrin

Table 34.23. Bleeding Complications in Trials of GPIIb/IIIa Inhibitors

Trial	Agent	Bleeding		
		Major	Minor	Transfusion
EPIC ¹³¹ (n = 2099)	Abciximab (bolus + infusion)	14.0	16.9	15.0
	Abciximab (bolus)	11.1	15.4	13.0
	Placebo	6.6	9.8	7.0
	<i>p-value</i>	< 0.001	< 0.001	< 0.01
IMPACT-II ¹⁵⁶ (n = 4010)	Eptifibatide (135/0.5)*	5.1	11.7	5.6
	Eptifibatide (135/0.75)*	5.2	14.2	5.9
	Placebo	4.8	9.3	5.2
	<i>p-value</i>	NS	NS	NS
CAPTURE ¹³⁴ (n = 1265)	Abciximab	3.8	4.8	7.1
	Placebo	1.9	2.0	3.4
	<i>p-value</i>	0.04	< 0.01	< 0.01
RESTORE ¹⁵⁹ (n = 2139)	Tirofiban	2.4	-	-
	Placebo	2.1	-	-
	<i>p-value</i>	NS		
EPILOG ¹³³ (n = 2792)	Abciximab (std. dose heparin)	3.5	7.4	3.3
	Abciximab (low-dose heparin)	2.0	4.0	1.9
	Placebo	3.1	3.7	3.9
	<i>p-value</i>	NS	< 0.001	NS
EPISTENT ¹³⁵ (n = 2399)	Stent (placebo)	2.2	1.7	2.2
	Stent (abciximab)	1.5	2.9	2.8
	PTCA (abciximab)	1.4	2.9	3.1
	<i>p-value</i>	NS	NS	NS

Acronyms: See Table 34.31, p. 803

Table 34.24. Safety Issues Related to I Ib/IIIa Inhibitors

Issue	Recommendations
Bleeding	<p>Reduce Preprocedural Risk Factors:</p> <ul style="list-style-type: none"> • Identify clinical risk factors (acute MI, low body weight, advanced age). • Identify contraindications (stroke within 2 years, neurosurgery within 6 months, clinically significant GI or GU bleeding with 6 weeks, active internal bleeding, bleeding diathesis, intracranial neoplasm, AV malformation, or aneurysm, severe uncontrolled hypertension, major surgery or trauma within 6 weeks) • For warfarin patients, INR should be < 1.5 <hr/> <p>Enhance Procedural Safety:</p> <ul style="list-style-type: none"> • Use weight-adjusted heparin (70 U/kg) and abciximab to keep ACT 200-250 seconds; for other I Ib/IIIa inhibitors, see Figure 34.1 • Single-wall arterial puncture • Avoid venous sheaths if possible • Use different arterial access site if recent arterial access was achieved (< 2 weeks) • Avoid lytic therapy if possible <hr/> <p>Postprocedure Care:</p> <ul style="list-style-type: none"> • Avoid post-procedural heparin • Sheaths may be removed during infusion of the I Ib/IIIa inhibitor when aPTT \leq 50 seconds or ACT \leq 175 seconds. Apply pressure to access site for at least 30 minutes; check site and distal pulses every 15 minutes for 1 hour, then hourly for 6 hours. Keep patient at complete bed rest with head elevated < 30° for 6-8 hours after discontinuation of I Ib/IIIa infusion • Nursing care: Avoid IM injections, Foley catheters, NG tubes, and non-compressible sites (e.g., subclavian or jugular vein) for venous access if possible; consider heparin locks for blood drawing
Emergency CABG	<ul style="list-style-type: none"> • Discontinue infusion of drug and heparin • Obtain ACT in operating room; adjust heparin dose to target ACT (400 sec). Heparin bolus based on ACT: ACT < 200 sec (heparin 4000 U); ACT 200-250 sec (heparin 3500 U); ACT 250-300 sec (heparin 2500 U); ACT 300-350 sec (heparin 1500 U); ACT 350-400 sec (heparin 1000 U); ACT > 400 sec (no additional heparin) • Prophylactic platelet transfusion (6-10 units) • Liberal platelet transfusions after separation from cardiopulmonary bypass
Major hemorrhage	<ul style="list-style-type: none"> • Discontinue drug and heparin • Platelet transfusions (6-10 units) for abciximab patients • Blood transfusions as necessary • Identify and correct cause
Thrombocytopenia	<p>Platelets > 20,000/mm³ and no Bleeding (Figure 25.1, Table 25.19):</p> <ul style="list-style-type: none"> • Stop drug and other agents • Repeat platelet count every 6 hours • If platelet count is not normal within 2-3 days, evaluate other causes <p>Platelets < 20,000/mm³:</p> <ul style="list-style-type: none"> • Stop drug and other agents • Consider prophylactic platelet transfusion (6-10 units) • Repeat platelet counts every 6 hours

Table 34.25. Thrombocytopenia Due to Abciximab or Heparin

	Abciximab (First Exposure)	Abciximab (Re-exposure)	Heparin
Onset	Acute; onset within hours of exposure	Immediate onset within hours of exposure	Subacute; onset within days of exposure
Platelet count	Frequently 20,000-50,000/mm ³ ; sometimes < 20,000/mm ³	Frequently < 20,000/mm ³	Usually > 50,000/mm ³ (except HIT-2)
Clinical sequelae	Bleeding, particularly when platelet count < 20,000/mm ³	Bleeding is common if not identified early	Thrombosis with HIT-2; bleeding is less common
Recovery	Immediate increase in platelet count 20,000/mm ³ per day after drug discontinuation	Initial increase may be followed by subsequent decrease in platelet count after drug discontinuation	Slow recovery is common after drug discontinuation
Treatment	Stop abciximab; platelet transfusions are indicated for bleeding or platelet count < 20,000/mm ³ ; IgG does not enhance recovery of platelet count	May not be immediately responsive to initial platelet transfusion; repeat transfusions may be needed; the role of IgG has not been evaluated	Stop heparin; platelet transfusions are not useful.
Laboratory evaluation	Serial platelet counts; identification of abciximab antibodies can be arranged through manufacturer; HACA antibodies may identify patients at risk for thrombocytopenia during readministration	Serial platelet counts; identification of abciximab antibodies can be arranged through manufacturer	Serial platelet counts (Chapter 25)

Abbreviations: HACA = human anti-chimeric antibodies; HIT = heparin-induced thrombocytopenia

Table 34.26. Drug Interactions with Abciximab

Drug	Clinical Impact	Recommendations
Aspirin	No increase in risk of bleeding	Routinely administered with abciximab; no dose adjustment required
Warfarin	About 40% of patients with intracranial hemorrhage while on abciximab occurred in patients on warfarin with INR \geq 1.5	Avoid abciximab in warfarin-treated patients with INR \geq 1.5. If abciximab is mandatory, use FFP (2 units) before abciximab administration
Heparin	Potentiates bleeding, particularly at vascular access sites	Use low-dose weight-adjusted heparin (70 U/kg) and prophylactic (rather than "rescue") abciximab; maintain ACT 200-250 seconds. Avoid post-procedural heparin
Thrombolytics	Potentiates bleeding	Avoid intraprocedural thrombolytic agents, if possible. For lytic patients with acute MI or rescue-PTCA patients after failed lytics, follow heparin recommendations above
Ticlopidine	Weak experimental synergy, but bleeding is not increased	No dose adjustment
Clopidogrel	Clopidogrel monotherapy probably does not increase risk of bleeding. When clopidogrel is given with aspirin, the risk of bleeding is somewhat increased with abciximab	No dose adjustment. Routinely administered with aspirin and abciximab in stent patient

Abbreviations: ACT = activated clotting time; FFP = fresh frozen plasma; INR = international normalized ratio

Table 34.27. Major Trials of Oral GP IIb/IIIa Antagonists

Study	Drug	Setting	Endpoints	Results
Kereiakes ¹⁹² (n = 17)	Xemilofiban up to 4 weeks (procedural heparin, aspirin, abciximab)	PCI	Platelet inhibition; safety	Magnitude and extent of platelet inhibition enhanced with combination therapy; no increase in major bleeding
Simpendorfer ¹⁹³ (n = 30)	Xemilofiban up to 30 days (procedural heparin and aspirin)	PCI for unstable angina	Platelet inhibition; safety	Mucocutaneous bleeding. Severe bleeding in 4 patients (1 death after emergency CABG)
Muller ¹⁹⁴ (n = 104)	Fradafiban or lefradafiban up to 7 days (no aspirin)	Healthy volunteers	Platelet inhibition	Continued profound platelet inhibition with oral drug administration
TIMI-12 ¹⁹⁵ (n = 329)	Sibrafiban up to 28 days (no aspirin)	ACS	Platelet inhibition; safety	Dose-related increase in platelet inhibition; high incidence of minor bleeding
ORBIT ¹⁹⁶ (n = 549)	Xemilofiban up to 4 weeks (with aspirin)	After PCI	Platelet inhibition; safety	Dose-related increase in platelet inhibition; no intracranial hemorrhage; low incidence of major bleeding
SOAR ^{197,198} (n = 259)	Orbofiban up to 3 months (with aspirin)	ACS	Platelet inhibition; safety	Dose-related increase in platelet inhibition; no increase in major bleeding; frequent insignificant/minor bleeding
TIMI-15 ¹⁹⁹ (n = 192)	Klerval (IV for 24-96 hrs, oral up to 4 weeks)	ACS	Platelet inhibition; safety	Relatively high incidence of thrombocytopenia (13%); limited dose response. Less inhibition with oral drug despite similar receptor occupancy
EXCITE ¹⁶⁶ (n = 7232)	Xemilofiban up to 6 months (procedural heparin and aspirin)	PCI	Death, MI, urgent intervention	Placebo vs. xemilofiban 10 mg vs. xemilofiban 20 mg: 30 days (8.1% vs. 8.1% vs. 7.3%, p = NS); 6 months (13.6% vs. 14.1% vs. 12.6%, p = NS). Trend towards higher mortality in low-dose xemilofiban group
OPUS-TIMI 16 ¹⁶⁷ (n = 10,302)	Orbofiban up to 7 months (with aspirin)	ACS	Death, MI, ischemia- driven or urgent TVR, stroke	Placebo vs. orofiban 50/30 vs. orofiban 50/50: 30 days (10.7% vs. 9.7% vs. 9.3%, p = NS); 7 months (20.5% vs. 20.2% vs. 19.5%, p = NS). Trial halted because of significant excess mortality in low-dose group (1.4% vs. 2.3% vs. 1.6%)

Table 34.27. Major Trials of Oral GP IIb/IIIa Antagonists

Study	Drug	Setting	Endpoints	Results
FROST ²⁰⁰ (n = 531)	Lefradafiban up to 1 month (with heparin, aspirin)	ACS	Bleeding, death, MI, ischemia-driven TVR	High dose (45 mg TID) stopped because of excess major bleeding; no significant difference in composite events; trend toward fewer recurrent ischemic events with 30 mg TID dose
SYMPHONY ¹⁶⁸ (n = 9233)	Sibrafiban up to 3 months (without aspirin)	ACS	Death, MI, revascularization	Aspirin: 9.8% Low-dose sibrafiban: 10.1% High-dose sibrafiban: 10%
2 nd SYMPHONY ¹⁶⁹ (n = 6671)	Aspirin vs. aspirin plus low- dose sibrafiban vs. high-dose sibrafiban alone	ACS	Death, MI, severe recurrent ischemia	[Trial discontinued after SYMPHONY results available] Aspirin: 9.2 % Aspirin + sibrafiban: 9.3% Sibrafiban alone: 10.5%
BRAVO ¹⁷⁰ (n = 9200)	Lotrifiban vs. placebo (with aspirin)	Recent ACS; recent neurologic event	Death, MI, stroke, recurrent ischemic TVR	Trial discontinued because of excess mortality (2.7% vs. 2.0%, p = 0.022)

Abbreviations: ACS = acute coronary syndromes; CABG = coronary artery bypass surgery; MI = myocardial infarction; PCI = percutaneous coronary intervention; TVR = target vessel revascularization

Acronyms: See Table 34.31, p. 803

Table 34.28. Results of Rescue IIB/IIIa Inhibitors and Hirulog for Thrombus

Series	N	Adjunctive Therapy	Results
ESPIRT ²²³ (2001)	77	Rescue eptifibatide for thrombotic complications (42%)	Bailout therapy was associated with more MI (30% vs. 7%, $p = 0.01$) and urgent PCI at 48 hours (14% vs. 0%, $p = 0.03$) compared to “no bailout”
Fuchs ²²⁸ (2000)	298	Rescue abciximab for thrombus, dissection Type $\geq C$, no-reflow, suboptimal result, or distal embolization	Stents in 73%. In-hospital results: death (1.3%); Q-MI (0.7%); non-Q-MI (31%); TLR (4.6%). Late events: death (1.7%); MI (2.7%); TVR (15.1%); EFS at 1-yr (83%)
Velianou ²²⁴ (2000)	186	Abciximab (planned 45%; rescue for threatened or acute closure 55%)	In-hospital results (planned vs. rescue): death (1.2% vs. 1.0%); Q-MI (2.4% vs. 2.0%); non-Q-MI (7% vs. 12.9%); TLR (1.2% vs. 0%). 6-month results (planned vs. rescue): death (2.3% vs. 4.0%); MI (9.4% vs. 14.9%); TVR (4.7% vs. 20.8%, $p = 0.001$)
de Lemos ²²⁵ (2000)	92	Rescue abciximab ($n = 29$) vs. no abciximab ($n = 63$); TIMI 14 substudy	Abciximab group had greater ST-segment resolution 90-180 minutes after PCI
Piamsomboon ²²⁶ (1999)	73	Abciximab (planned 74%; rescue 26%) in acute coronary syndromes with thrombus-containing lesions	Death (1.4%); Q-wave MI (1.4%); non-Q-wave MI (18%). No subacute thrombosis, emergency CABG, or repeat PTCA
Ahmed (1999)	45	Rescue abciximab in degenerated SVG	No benefit on procedural success or major ischemic complications compared to “no-abciximab”; more non-Q-MI in rescue group (40.5% vs. 17.7%)
Fuchs ²⁰⁶ (1999)	186	Rescue abciximab for thrombus and suboptimal PTCA	Procedural success (95.3%); in-hospital MACE (4.7%); non-Q-MI (24.7%); 1-year TLR (24.9%) and EFS (71%)
Haase ²⁰⁸ (1999)	63	Rescue abciximab for thrombus and threatened or acute closure	Repeat PTCA 2 minutes after abciximab. Marked improvement in thrombus score and TIMI flow; MACE (2%); late TVR (15%)
Sullebarger ²⁰⁷ (1999)	17	Planned abciximab and TEC in SVG	Abciximab was associated with higher procedural success (100% vs. 50%) and less distal embolization/no-reflow (0% vs. 30%) compared to “no abciximab”
Barsness (1998)	58	Local delivery of abciximab in thrombotic SVG	Significant improvement in thrombus score and stenosis severity, but not TIMI flow. Adjunctive stent (88%)
Garbarz ²¹⁴ (1998)	138	Rescue abciximab for thrombus and suboptimal PTCA	Angiographic success in 84% (100% success for stent thrombosis); adjunctive PTCA or stent (100%); MACE (17%); bleeding and vascular complications (27%); transfusion (5%)
Grantham ²²⁷ (1998)	185	Planned and unplanned (rescue) abciximab in thrombotic SVG	Procedural success higher with planned abciximab; no impact of abciximab on angiographic (distal embolization, no-reflow) or clinical complications
Henry ²¹³ (1998)	16	Rescue abciximab for acute stent thrombosis	Recurrent thrombosis after PTCA for stent thrombosis may respond to abciximab
Muhlestein ²¹² (1997)	29	Rescue abciximab for thrombus after PCI	Procedural success (97%), clinical success (93%). Significant improvement in thrombus score and TIMI flow, without distal embolization or no-reflow
Shah ²¹⁵ (1997)	567	Hirulog vs. heparin for thrombus-containing lesions (Hirulog Angioplasty Study)	Thrombus-containing lesions were associated with more MI (5.1% vs. 3.2%) and abrupt closure (13.6% vs. 8.3%); no difference between hirulog and heparin in acute or late outcomes

Abbreviations: SVG = saphenous vein graft; Q-MI = Q-wave myocardial infarction; MACE = major adverse cardiac events; TLR = target lesion revascularization; EFS = event-free survival; PCI = percutaneous coronary intervention; TIMI = Thrombolysis in Myocardial Infarction

Table 34.29. Recommendations for Platelet Glycoprotein II/IIIa Antagonists

Clinical Setting	Recommendations
Acute MI (lytic therapy)	Abciximab (TIMI-3 flow, ischemic events at 30-days), eptifibatide (TIMI-3 flow, ischemic events at 30-days), and lamifiban (clinical reperfusion but not TIMI flow) all show modest benefit as adjuncts to lytic therapy for ST-elevation acute MI. Further study is needed before GP IIb/IIIa antagonists are routinely used as adjuncts to lytic therapy for acute MI. GUSTO-IV MI results pending.
Acute MI (primary PTCA/Stent)	Trials of abciximab as an adjunct to primary PTCA (RAPPORT, CADILLAC) and stenting (ADMIRAL, CADILLAC) demonstrated variable benefit. In stent patients, data from ADMIRAL are favorable, while data from CADILLAC are not. In PTCA patients, data from CADILLAC are favorable, while data from RAPPORT are not. I Ib/IIIa inhibitors reduce acute thrombotic events, but routine use in acute MI is controversial.
Acute MI (rescue PTCA after failed lytic therapy)	Available anecdotal data in small numbers of patients suggest potential benefit for abciximab; further study is needed.
Unstable angina, non-Q-wave MI	There are compelling data to support the routine use of abciximab, eptifibatide, and tirofiban in patients with acute coronary syndromes without ST-elevation referred for PCI. As adjuncts to heparin, aspirin, and β -blockers, these agents decrease early (30-day) cardiac event rates. Benefits are established for tirofiban and eptifibatide in patients not undergoing PCI, but GUSTO-IV ACS failed to show benefit for abciximab.
Percutaneous coronary intervention	There are compelling data to support the routine use of abciximab, eptifibatide, or tirofiban as an adjunct to heparin and aspirin in patients undergoing PCI. Only abciximab has shown long-term (≥ 1 year) mortality benefit in stent patients. Eptifibatide was effective in ESPRIT in reducing short- and mid-term (48-hour, 30-day, 6-month) events. Tirofiban was inferior to abciximab in TARGET.
Rescue use after failed or suboptimal intervention	The value of GP IIb/IIIa antagonists as pretreatment before percutaneous intervention is irrefutable; post-hoc use has not been prospectively studied. Several reports in small numbers of patients suggest potential benefit for "rescue" use in thrombus-containing lesions, stent thrombosis, and abrupt closure, but less benefit in degenerated vein grafts. Disadvantage of "rescue" or post-hoc use is that antecedent high-dose heparin may increase bleeding complications.
Readministration	Readministration is not a concern with tirofiban or eptifibatide. Modest experience with abciximab suggests readministration is feasible, but the risk of severe thrombocytopenia may be higher than after initial exposure. Readministration within 2 weeks of initial exposure is probably safe (before development of HACA). For later re-exposure, H ₂ -blockers and steroids are not necessary, but close monitoring of platelet counts is recommended to identify thrombocytopenia. Anaphylactic reactions have not been reported.

Acronyms: See Table 34.31, p. 803