

Chapter 15

Glycoprotein IIb/IIIa Antagonists

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INTRODUCTION

GP IIb/IIIa Receptors

- The GP IIb / IIIa receptors (Fibrinogen or aggregation receptors), belong to the family of integrins which are membrane bound adhesion molecules and are made of two glycoprotein sub-units (α and β).
- GP IIb / IIIa receptors are only restricted to blood platelets and they bind fibrinogen and adhesion proteins such as fibronectin, vitronectin, von Willebrand factor to form cross bridges between adjacent platelets.
- GP IIb / IIIa receptors recognize an Arginine - Glycine - Aspartic acid (R-G-D) amino acid sequence in several adhesion proteins which binds to the recognition site in the extracellular domain of the receptor.
- GP IIb / IIIa receptors remain unable to bind fibrinogen unless the platelet is in active and binding mode. Platelet activation by agonists or adhesion to extracellular matrix proteins brings a conformational change in the platelet that exposes the R-G-D binding site which recognizes the peptide sequence R-G-D.
- If two activated platelets with functional GP IIb / IIIa each bind to the same fibrinogen molecule, a fibrinogen bridge is created between the two platelets producing platelet aggregation.
- The binding of fibrinogen to activated platelets is the final step in platelet aggregation and is completely mediated by GP IIb / IIIa. Blocking the GP IIb / IIIa receptors will interfere with all signals that produce platelet aggregation (Figure 15-1).

Pharmacologic Approaches

There are three current pharmacologic approaches that interfere with GP IIb / IIIa receptor function.

1. *Antibodies* against the receptor glycoprotein which forms a cap that covers the receptor and interfere with fibrinogen binding, e.g., Abciximab (Reo Pro).
2. *Peptides* that have the same RGD sequence like the adhesion proteins (fibrinogen and vWF) and compete with fibrinogen for receptor binding, e.g., Eptifibatide (Integrilin).
3. *Nonpeptide molecules*, usually derivatives of amino acids that mimic the geometric, stereotactic and charge characteristics of the RGD sequence and interfere with platelet aggregation. Examples of this rapidly growing group are :

a. Intravenous agents : Tirofiban, lamifiban

b. Oral agents : Xemilofiban, orofiban, sibrafiban, lefradafiban.

Table : Properties and Dosage of Intravenous GP IIb/IIIa Antagonists

	Abciximab	Eptifibatide	Tirofiban
Commercial Name	Reo P/o	Integrilin	Aggrastat
Structure	Anti-body Fab fragment	Cyclic heptapeptide	Synthetic nonpeptide
Plasma half-life	8-12 hs	Approx. 2.5 h	Approx. 2 h
Approved Indications	- PCI - Refractory UA if PCI to be performed within 24 hours.	- NSTE - ACS - PCI	NSTE - ACS
Approved Dose	-PCI: Bolus: 0.25mg/kg Infusion: 0.125 µg/kg/min (max 10 µg/min) - ACS+PCI (within 24h) Same as above, for 12-24 h	- ACS: Bolus: 180 mg/kg Infusion: 2 µg/kg/min for 72-96h - PCI: Bolus: 135 mg/kg Infusion: 0.5 µg/kg/min for 20-24h	- ACS: 0.4 µg/kg/min for 30 min then 0.1 µg/kg/min for 24-108h

NSTE: non ST elevation.

MECHANISMS OF ACTION

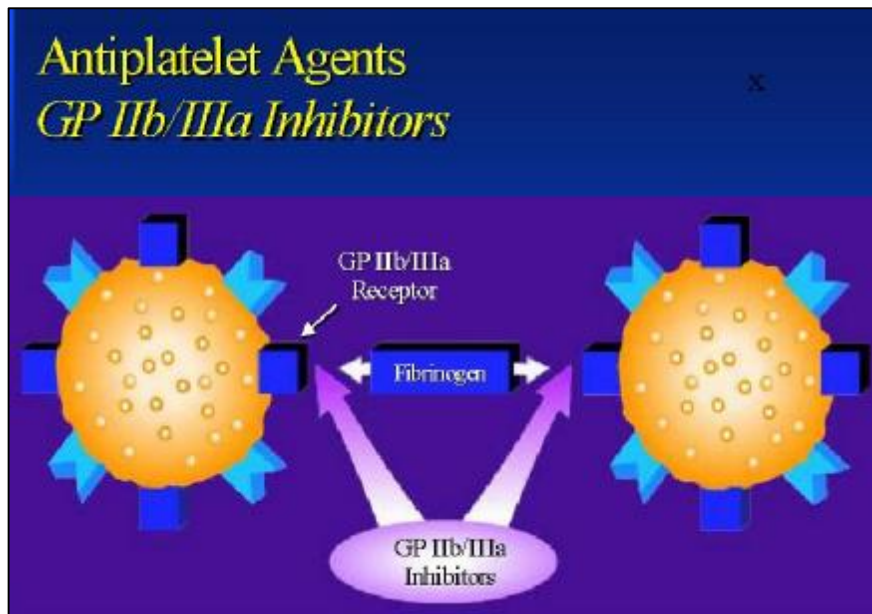


Figure (15-1): Antiplatelet Agents (GP IIa/IIIa inhibitors)

- The glycoprotein IIb/IIIa receptor (GP IIb/IIIa) is member of the integrin superfamily of heterodimeric adhesion molecules that are found on platelets (see section on platelet structure and function).

- GP IIb/IIIa is unable to bind fibrinogen unless the platelet is first activated by an agonist, which then induces a conformational change in GP IIb/IIIa receptor, exposing the binding domain and rendering the molecule a competent fibrinogen binder.
- GP IIb/IIIa antagonists block the final step in platelet aggregation triggered by all platelet activators.
- There are currently four intravenous GP IIb/IIIa antagonists available commercially (Table 15-1).
 1. *Abciximab*: the first to be developed, is a chimeric monoclonal antibody derived from the murine antibody against the GP IIb/IIIa receptor. It acts like a cap over the entire GP IIb/IIIa integrin. It is commercially known as Reo Pro.
 2. *Eptifibatide* is a cyclic heptapeptide. It binds competitively the arginine-glycine-aspartate (RGD) recognition site of the GP IIb/IIIa molecule.
 3. *Tirofiban* and *lamifiban* are small molecule peptidomimetic agents that occupy the fibrinogen-binding site of GP IIb/IIIa. They mimic the geometric, stereotactic and charge characteristics of the RGD sequence and thus interfere with platelet aggregation.
- There are several important differences in the pharmacokinetics and pharmacodynamics of the currently available GP IIb/IIIa antagonists.
 - Abciximab has a very high affinity for GP IIb/IIIa and a long half life (8-12 hours). After discontinuation of the infusion, platelet function returns gradually.
 - Abciximab has low specificity and binds to other integrins, including the vitronectin receptor , which is found on endothelial cells. Abciximab has been associated with profound thrombocytopenia in 0.5-1% of cases.
 - Small molecule antagonists eptifibatide and tirofiban have short half-lives, and platelet function returns quickly after discontinuation of the infusion.

GP IIb/IIIa INHIBITORS in ACS

- Benefit more in troponin positive pts
- Benefit more in pts referred to angioplasty
- Risk of moderate to severe bleeding increased by 32%

CLINICAL EFFICACY

Table (15-2): Major Trials of IV GP IIb/IIIa Receptor Antagonists:
(Completed, Placebo-Controlled RCTs)

PCI Trials	NSTE-ACS Trials	STE-ACS Trials
- EPIC	- PRISM	- GUSTO-V
- EPILOG	- PRISM-PLUS	- ASSENT 3
- CAPTURE	- PURSUIT	- RAPPORT
- EPISTENT	- PARAGON A	- ISAR
- IMPACT-II	- PARAGON B	- ADMIRAL
- ESPRIT	- GUSTO-IV	- CADILLAC
- RESTORE		

- Available GP IIb/IIIa antagonists require intravenous administration, beginning with a loading dose.
- The use of GP IIb/IIIa antagonist in coronary artery disease was examined in the following situations (Table 15-2):
 1. *Unstable angina and non ST elevation MI*: tested in the PURSUIT, PRISM, PRISM PLUS and PARAGON trials.
 2. *Percutaneous revascularization in ACS*: tested in the EPIC, EPILOG, EPISTENT, CAPTURE, IMPACT II, RESTORE, RAPPORT, ISAR2, ADMIRAL, and CADILLAC trials.
 3. *Adjunct to thrombolytic therapy*: tested in IMPACT-AMI, TIMI-8, SPEED, TIMI-14, ASSENT III, INTRO-AMI, INTEGRITI, SK-eptifibatide and GUSTO V trials.

GP IIb/IIIa INHIBITORS ACS 32,125 Patients Meta-analysis , 16 Randomized Trials		
Reduction (within)	Mortality	Death/MI
48-96 hs	30%	-
30 days	NS	24%
6 mon	NS	18%

Unstable angina and Non-ST-elevation MI (UA/NSTEMI)

- GP IIb/IIIa antagonists has been proven to be a clinically effective adjunct therapy in the treatment of patients with non-ST-elevation ACS.
- The use of these agents has resulted in an approximate 12% risk reduction in 30-day death or MI. However, there has been significant heterogeneity in trials results (Figure 15-1).
- Reduction in the endpoints of death or nonfatal MI considered individually did not achieve statistical significance (meta-analysis).
- In individual trials there is a wide range of relative risk reduction in 30-day death or MI varying from 8% to 27%.
- Abciximab has limited or no value and is not indicated in the management of patients with UA or NSTEMI in whom an early invasive management is not planned.
- Treatment effects of GP IIb/IIIa antagonists are more evident in patients who are troponin-positive. Such patients have been shown to have more extensive coronary artery disease, with more complex lesions and often containing thrombus.
- Use of GP IIb/IIIa antagonists in troponin-positive patients resulted in relative risk reduction of the composite of death or MI by 42 to 74%.
- There is limited or no benefit in troponin-negative patients.

- *The benefit of GP IIb/IIIa antagonists is primarily seen in high risk patients. (patients with TIMI risk score ≥ 4 , patients with continuing ischemia or elevated troponin).*

- There is a need for appropriate risk stratification to determine who would benefit from this therapy and who would not.

- There is a strong relation between the level of inhibition of platelet aggregation and clinical outcomes.
- Increased risk of bleeding associated with GP IIb/IIIa antagonists is reduced with the use of reduced dosing, weight adjusted heparin and avoidance of post-procedural heparin.

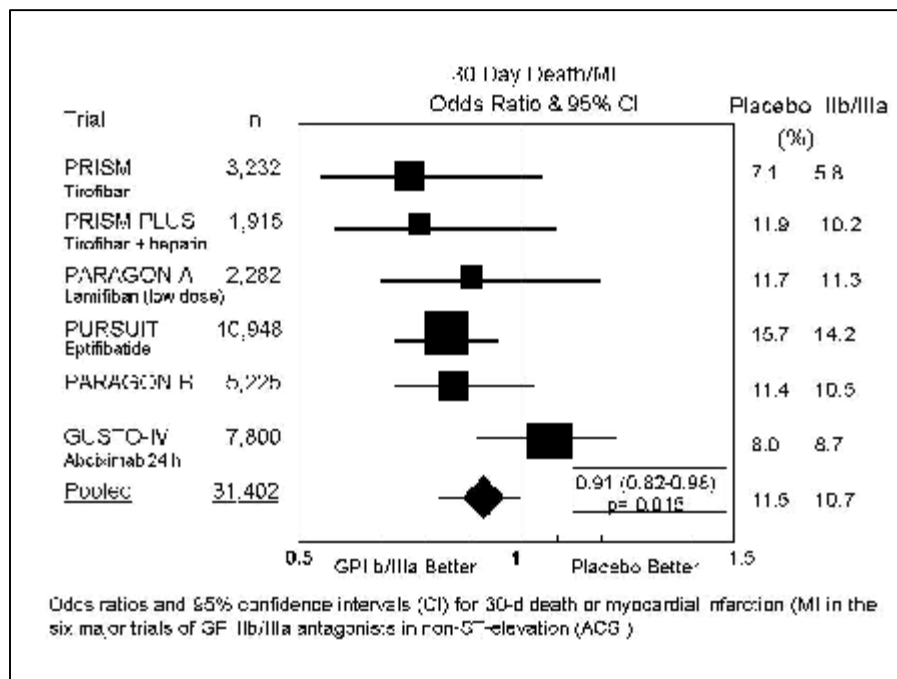


Figure 15-1: GPIIb/IIIa Antagonists in non ST-elevation ACS

ST-Elevation MI: Combined Therapy with Fibrinolytics

Combination therapy with a reduced-dose fibrinolytic (reteplase, tenecteplase, streptokinase, alteplase) and a GP IIb/IIIa antagonists (abciximab, eptifibatid) results in:

- Improvement in infarct-related artery patency.
- Higher rates of better perfusion (TIMI flow grade).
- Reduction in non-fatal ischemic events.
- No improvement in mortality.
- Increased bleeding complications.

Percutaneous Revascularization in ACS (PCI)

- All the GP IIb/IIIa antagonists (abciximab, eptifibatid and tirofiban) have been tested extensively in patients undergoing PCI (table 15-2).
- There was a 33% reduction in the composite of death, MI or the need for urgent revascularization through 30 days.
- The available GP IIb/IIIa antagonists are probably equally effective when given after PCI, if similar degree of platelet inhibition is attained
- Comparison of abciximab and tirofiban in stent-based PCI (TARGET trial) immediately before revascularization showed that at 30 days abciximab was superior to tirofiban in the composite endpoint of both infarction or the need for urgent revascularization but this was limited only to patients undergoing stenting for ACS and to non-diabetics. There was no significant difference after 6 months.

- Eptifibatide is generally preferred for a non-ST elevation ACS because its cost is substantially lower than abciximab and its optimal dosing regimen is more clearly defined than with tirofiban.
- *Primary angioplasty (acute ST-elevation MI)*
 - Abciximab treatment resulted in 48% reduction in death, reinfarction or need for urgent revascularization in 30 days. The majority of this benefit was derived from a reduction in the need for urgent revascularization.
- *PCI with stenting*
 - Use of GP IIb/IIIa antagonists was associated with reduction in rate of deaths, reinfarction or target lesion revascularization at 30 days (ISAR2, ADMIRAL, CADILLAC trials). Angiographic studies showed improved rates of TIMI flow grade 3 in the culprit artery both before and after stenting (ADMIRAL trial).
- GP IIb/IIIa antagonists are of great benefit in patients with UA/NSTEMI who undergo PCI.

- It is recommended (ACC /AHA guidelines) to use eptifibatide or tirofiban in combination with aspirin and heparin for the treatment of the following groups:
 1. Patients with ongoing ischemia.
 2. Patients with high risk features.
 3. Patients in whom PCI is planned.

Acute STEMI without perfusion

- Patients who did not undergo perfusion therapy with either a thrombolytic or primary PCI, because of late presentation or lack of catheterization laboratory did not benefit from GP IIb/IIIa (tirofiban) therapy.

LIMITATIONS AND ADVERSE EFFECTS

- Available GP IIb/IIIa antagonists require intravenous administration, beginning with a loading dose. Oral preparation were ineffective and hazardous.
- Side effects are uncommon and anaphylaxis is extraordinary rare.
- *Bleeding* is the main complication regarding the safety of these agents. Transfusion is required for bleeding side effects. It is frequently associated with invasive procedures. After diagnostic angiography the major bleeding risk is about 1% which rises to about 10% when revascularization procedure is performed. Intracranial hemorrhage is rare.
- Tirofiban and lambifiban are cleared by the kidney, their half-life is prolonged in renal failure.

- Blood hemoglobin and platelet counts should be monitored and patient's surveillance for bleeding should be carried out daily.
- Thrombocytopenia occurs in 0.3-0.5% of patients treated with abciximab.
- There is a significant inter-individual variability in the response to GP IIb/IIIa antagonists regarding platelet inhibition and clinical outcome.

GP IIb/IIIa Receptor Blockers

- ✓ Proven efficacy:
 - PTCA. Unstable angina. Non- ST elevation MI.
 - ↓ Mortality, ↓ MI.
 - ↓ Recurrent ischemia.
 - Useful adjuncts to thrombolytics in acute MI.
- ✓ Limitations:
 - Long term benefit is variably sustained. Need long term oral treatment.
 - Hemorrhage.
 - Variable heterogenous effect. All GPIIb/IIIa blockers are not the same (some block α V β ₃: vitronectin-receptor).
 - Not potent anti thrombins. Need to combine IIb/IIIa blockers with antithrombins.

Table (15-3): Antiplatelet Agents in Patients with Acute Coronary Syndromes

Treatment	ST-segment elevation ACS	Non ST-segment elevation ACS	PCI procedure (coronary angioplasty and stent)		
			Before	During	After
Aspirin	Load + maintenance dose for long-term	Load + maintenance dose for long-term	Aspirin 160-325 mg daily > 2 hours prior	-	75-150 mg daily: long term
Clopidogrel	Could be used in place of aspirin	Load + maintenance dose for 1 year (add to aspirin)	clopidogrel 300 mg load at least 6 hours prior (+ ASA)	-	75 mg daily for 12 months
GPIIb/IIIa inhibitors (dose of heparin to be reduced when given together)	Use in primary PCI No clear indication with thrombolysis	If high risk * (+ ASA + Clopidogrel)	If high risk * (+ ASA + Clopidogrel)	If high risk * (+ ASA + Clopidogrel)	+ for 12 hours for abciximab and 24 hours for tirofiban and eptifibatide, if high risk *

* High risk includes: recurrent or persistent chest pains + associated electrogram changes (ST-segment depression or transient ST-segment elevation) despite anti-ischemic treatment; elevated troponin concentrations; diabetes; age >65 years; cardiac failure; major arrhythmias

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