SECTION IV

Cardiovascular Medicine
Chapter 15

Gp IIb/IIIa Receptor Antagonists in Intensive Coronary Care Unit

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Introduction
There has been a dramatic increase in the understanding, development, clinical evaluation and therapeutic application of platelet inhibition therapy over the last two decades. This has led to a shift from antithrombotic therapy and towards the control of platelet thrombus formation by anti-platelet agents. The wide ranging benefits of antiplatelet therapy in cardiovascular disorders are strong testimony to the central role played by platelet thrombus. Though aspirin is and may remain as the only time tested and proven anti platelet agent, thienopyridines like clopidogrel and glycoprotein IIb/IIIa receptor inhibitors have emerged as key agents in the control of arterial thrombosis.

Plaque rupture is an abrupt and catastrophic transition of a lipid laden atherosclerotic lesion. Following plaque rupture, there is exposure of substances that promote platelet activation aggregation and thrombin generation. This results in thrombus formation. The resultant thrombus interrupts blood ow and leads to an imbalance between oxygen supply and demand and if this imbalance is persistent this leads to myocardial necrosis.1,2 This highlights the importance of thrombus formation within the coronary arteries. Since thrombus is essentially an aggregate of platelets, agents that prevent the aggregation and / or adhesion of platelets play an important role in the management strategy.

Platelet Glycoprotein Receptors (Fig. 1, 2)
The process of platelet aggregation is mediated exclusively through the platelet Gp IIb/IIIa receptor.3-5 This is regardless of the pathway responsible for platelet activation. This receptor primarily binds fibrinogen. These fibrinogen molecules form cross bridges between adjacent platelets, linking them together to form a scaffold. This is the key event in the process of platelet aggregation.

Most of the platelet membrane glycoproteins belong to the integrin superfamily of adhesive receptors. Integrins are heterodimeric molecules formed by the non-covalent interaction of a series of α and β subunits. Specific α and β combinations form receptors with unique recognition specificities Integrins are found on virtually all cell types and mediate a diversity of physiologic responses.

The glycoprotein II b / III a receptor [α1bβ3] is the most prominent integrin on the platelet surface. It is found principally in cells of megakaryocytic lineage (Table 1).
Fig. 1: The molecular basis of platelet adhesions and aggregation.

REGULATION OF PLATELET AGGREGATION

ANTI-AGGREGATION

INTACT ENDOTHELIUM

Prostacyclin
Nitric oxide

INTACT ENDOTHELIUM PROJECTS

Unactivated platelets

PRO AGGREGATION

Thrombin
A-II, NE
Platelet damage

ADP
Serotonin
TXA$_2$

Activation

Ca$^{2+}$

Receptors expressed on surface

vWF
Collagen
Fibrinogen

Fig. 2: The platelet activation cycle.
Gp IIb/IIIa Receptor Antagonists

Gp IIb/IIIa receptor antagonists are potent antiplatelet agents since they block the final step in platelet aggregation triggered by endogenous platelet activators. There are several types of Gp IIb/IIIa receptor antagonists. Disintegrins are natural peptides derived from snake venom. These compete with fibrinogen for binding to Gp IIb/IIIa receptors and other members of the integrin family. Abciximab is a monoclonal antibody that belongs to this group. Based on the concept of disintegrins, synthetic peptides like Eptifibatide and non-peptides like Tirofiban were developed.

Classification of Gp IIb/IIIa Receptor Antagonists

Gp IIb/IIIa receptor inhibitors include agents with varying pharmacodynamic and pharmacokinetic properties. Greater than 80% inhibition of platelet aggregation is required for effective antiplatelet activity.

Abciximab was the first Gp IIb/IIIa receptor inhibitor to be used clinically. As highlighted previously, this is a murine monoclonal antibody that also binds the vitronectin receptor. Small molecule
Gp IIb/IIIa antagonists were developed because of concerns regarding potential immunogenicity, lack of reversibility and cost involved. Unlike abciximab, these agents are specific for Gp IIb/IIIa without any appreciable binding to other integrins like vitronectin. Because of their small size, they are less likely to induce an antibody response like Abciximab. Both Eptifibatide and Tirofiban require 100 molecules of drug per Gp IIb/IIIa receptor compared to 1.5 molecules of abciximab per Gp IIb/IIIa receptor.

Gp IIb/IIIa receptor antagonists - the Indian Scenario

Abciximab (Reopro) was the first agent available in India. Eptifibatide (Integrelin) has been available in the Indian market since the last 3 years while Tirofiban (Aggramed) has recently been launched. These 3 agents differ widely in their costs & hence a judicious decision regarding their use has to be made.

Indications

Based on various clinical trials conducted worldwide, the indications for use may be summarised as:

Drug | Abciximab | Eptifibatide | Tirofiban
--- | --- | --- | ---
Adjunct to Percutaneous Coronary Intervention (PCI) | · Adjunct to PCI | · ACS
ACS when PCI planned in next 24 hours | · ACS | · Facilitated thrombolysis
Facilitated thrombolysis | | |

Contraindications

• Hypersensitivity to any component agent.
• Active internal bleed.
• History of bleeding diathesis.
• Severe uncontrolled hypertension.
• Major surgery or trauma within past 4-6 weeks.
• Platelet count <1 lac/mm³.
• History of CVA within 1 year or hemorrhagic stroke at any time.
• History of intracranial bleed, intracranial neoplasm, AV malformation or aneurysm.
• History of vasculitis (Abciximab).
• Acute pericarditis (Tirofiban)
• S. creatinine > 4 mg/dl (Eptifibatide, Tirofiban)
• Use of I.V. dextran before procedure or intent to use during procedure (Abciximab).
• Administration of oral anticoagulant within previous 7d unless PT <1.2 times control.
Table 3: Adverse effects of Gp IIb/IIIa receptor inhibitors

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Abciximab</th>
<th>Eptifibatide</th>
<th>Tirofiban</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10% of patients</td>
<td>Minor bleed, Hypotension</td>
<td>Minor bleed, Hypotension</td>
<td>Minor bleed</td>
</tr>
<tr>
<td>1-10% of patients</td>
<td>Major bleed, Bradycardia, Thrombocytopenia, Abdominal Pain, Headache, Pleurisy, Anaphylaxis, Human Antichimeric - Antibody Development</td>
<td>Major bleed, Bradycardia, Thrombocytopenia</td>
<td>Major bleed, Bradycardia, Thrombocytopenia, Vasovagal reaction, Coronary artery dissection, Dizziness, Acute pericarditis</td>
</tr>
</tbody>
</table>

Table 4: Approved dosing and administration guidelines for Gp IIb/IIIa receptor inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Abciximab</th>
<th>Eptifibatide</th>
<th>Tirofiban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>PCI: 0.25 mg/kg iv bolus pre-PCI, then 0.125 µg/kg/min (max. 10 µg/min) iv infusion and 12h post PCI</td>
<td>PCI: 180 µg/kg iv bolus pre PCI, then 2 µg/kg/min iv infusion, with a second 180 µg/kg bolus 10 minutes after first bolus infusion for 18-24 h post PCI</td>
<td>PCI: 0.4 µg/kg/min iv infusion x 30 mins, then 0.1 µg/kg/min x 48 - 108h</td>
</tr>
<tr>
<td></td>
<td>ACS with planned PCI 0.25 mg/kg iv bolus, then 10 µg/min iv infusion 18-24 hrs pre-PCI and 12 hr post PCI</td>
<td>ACS 180 µg/kg iv bolus, then 2 µg/kg/min (max. 15 mg/hr for 72 - 96h)</td>
<td></td>
</tr>
<tr>
<td>Dosage adjustment</td>
<td>Not required</td>
<td>If Serum Creatinine &gt; 2 mg% - decrease bolus to 135 µg/kg and infusion to 1.4 µg/kg/min. C/I if S. Creatinine &gt; 4 mg%</td>
<td>If S. Creatinine &gt; 3 mg% - decrease bolus rate and infusion by 50%</td>
</tr>
</tbody>
</table>

Glycoprotein IIb/IIIa receptor antagonists in ICCU care

Indications for use in ICCU

a. Acute Coronary Syndrome
   i. Unstable angina / NSTEMI
      - Small molecule agents like Eptifibatide & Tirofiban
   ii. STEMI - Facilitated Thrombolysis - combination of half dose thrombolytic with Abciximab or Eptifibatide

b. Primary Angioplasty in Myocardial Infarction (PAMI)
   - Abciximab as an adjuvant to PCI

c. When PCI is planned following an ACS - Facilitated PCI
   - Abciximab or Eptifibatide
When should we use GpIIb/IIIa receptor Inhibitors in the ICCU?
GpIIb/IIIa receptor inhibitors reduce the occurrence of death / MI in patients of ACS not routinely scheduled for an early revascularization. Event reduction is greatest in patients at high risk of thrombotic complications. Treatment with these agents should be considered early after admission and continued till a decision about early revascularization is made.

GpIIb/IIIa Receptor Inhibitors in STEMI

Rationale for use of Gp IIb/IIIa receptor inhibitors in STEMI.
Fibrinolytic therapy has substantially reduced mortality following MI by promoting early patency of the infarct-related artery. However, TIMI III ow is established in only 20 to 45% of the patients. Thrombolysis exposes the underlying disrupted plaque and releases various pro-aggregatory agents into the circulation. This leads to platelet activation and a paradoxical hypercoagulable state. The combination with Gp IIb/IIIa receptor inhibitor reduces platelet activation. The addition of a Gp IIb/IIIa receptor inhibitor facilitates the action of a thrombolytic agent - hence the concept of FACILITATED THROMBOLYSIS. However, there was always a concern for an excess incidence of bleed.

Table 5 : Comparison of the various Gp IIb/IIIa receptor inhibitors available in India

<table>
<thead>
<tr>
<th>Property</th>
<th>Abciximab</th>
<th>Eptifibatide</th>
<th>Tirofiban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td>Antibody</td>
<td>Peptide</td>
<td>Non peptide</td>
</tr>
<tr>
<td>Size</td>
<td>Large</td>
<td>Small</td>
<td>Small</td>
</tr>
<tr>
<td>Onset</td>
<td>Rapid</td>
<td>Rapid</td>
<td>Rapid</td>
</tr>
<tr>
<td>Reversibility</td>
<td>Slow</td>
<td>Rapid</td>
<td>Rapid</td>
</tr>
<tr>
<td>Binding to integrins</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Antibody response</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Costs</td>
<td>Rs.54,000/-</td>
<td>Rs.24,000/-</td>
<td>Rs.18,000/-</td>
</tr>
</tbody>
</table>

When should we use GpIIb/IIIa receptor Inhibitors in the ICCU?
GpIIb/IIIa receptor inhibitors reduce the occurrence of death / MI in patients of ACS not routinely scheduled for an early revascularization. Event reduction is greatest in patients at high risk of thrombotic complications. Treatment with these agents should be considered early after admission and continued till a decision about early revascularization is made.

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Table 6 : Gp IIb/IIIa Receptor Inhibitors as the Sole Reperfusion Agent

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Agent</th>
<th>TIMI ow</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRAPE</td>
<td>1998</td>
<td>Abciximab</td>
<td>40% TIMI II</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18% TIMI III</td>
</tr>
<tr>
<td>TIMI 14</td>
<td>1999</td>
<td>Abciximab</td>
<td>32% TIMI III</td>
</tr>
<tr>
<td>SPEED</td>
<td>2000</td>
<td>Abciximab</td>
<td>27% TIMI III</td>
</tr>
</tbody>
</table>
Gp IIb/IIIa receptor inhibitors as the sole repurfusion agents, have been studied in 3 trials. These agents cannot be used alone an alternative to a thrombolytic agent, since they have a reduced incidence of TIMI III ow. Hence the combination of these drugs with a thrombolytic agent is more logical and would be more effective in the management of a STEMI.

Table 7 : Combination Therapy Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Fibrinolytic</th>
<th>Gp IIb/IIIa inhibitor</th>
<th>IRA patency</th>
<th>Bleeding rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAMi - 8</td>
<td>t-PA</td>
<td>m 7E3 Fab</td>
<td>56% v/s 92%</td>
<td>Equivalent</td>
</tr>
<tr>
<td>IMPACT - AMI</td>
<td>t-PA</td>
<td>Eptifibatide</td>
<td>69% v/s 87%</td>
<td>4% v/s 5%</td>
</tr>
<tr>
<td>PARADIGM</td>
<td>t-PA or STK</td>
<td>Lamifiban</td>
<td>Equivalent</td>
<td>More in Lamifiban arm</td>
</tr>
</tbody>
</table>

A review of these three trials revealed that there was a higher risk of bleeding in the combination arm with full dose therapy. Hence, the need for reduced dose combination trials.

Table 8 : Dose ranging combination therapy trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Fibrinolytic</th>
<th>Reduced dose Gp IIb/IIIa</th>
<th>IRA patency</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI 14</td>
<td>tPA or STK</td>
<td>Abciximab</td>
<td>78% v/s 93%</td>
</tr>
<tr>
<td>SPEED</td>
<td>Reteplase</td>
<td>Abciximab</td>
<td>47% v/s 54%</td>
</tr>
<tr>
<td>INTRO - AMI</td>
<td>tPA</td>
<td>Eptifibatide</td>
<td>73% v/s 83%</td>
</tr>
</tbody>
</table>

There was a reduced incidence of bleed with a combination of reduced dose Gp IIb/IIIa receptor inhibitor and a thrombolytic agent. A higher rate of infarct related artery patency was also seen.

**GUSTO V**

![Fig. 4](image_url)

GUSTO V in 2001 has been one of the largest trials to date that has studied the combination of reteplase and Abciximab. This combination was superior to reteplase alone. Combination therapy led to a consistent reduction in key secondary end points including reinfarction, but there is a evidence of increased rate of non-intracranial bleeding.

ASSENT - 3 trial compared the efficacy of tenecteplase when used in combination with either LMWH, UFH or Abciximab. These trials showed results similar to GUSTO - V. No benefits were seen with combined therapy in patients older than 75 years and in diabetics, but were more effective in younger patients who are likely candidates for a PCI.
Benefits from Combination Therapy

- Medical management with a combination of reduced dose Gp IIb/IIIa inhibitor and thrombolytic agent in the setting of a STEMI serves as a facilitator of thrombolysis and primary angioplasty.
- Leads to more complete ST-segment resolution.
- Lower rates of reinfarction and urgent revascularization.

**Gp IIb/IIIa Receptor Inhibitor as an adjunct to PCI in AMI**

![Graphs showing benefits of combination therapy](image)

Fig. 5:
The RAPPORT Trial revealed that the addition of Abciximab as an adjuvant to PCI in patients of AMI reduced the secondary end points by 50% as compared to placebo. Similarly, the key secondary end point were also reduced by a similar magnitude when stents were deployed (ADIMARAL Trial). However the CADILLAC Trial revealed discrepant results. The combination of stent with Abciximab was only marginally better than the deployment of stent alone. Plain balloon with Abciximab fared worse off than stent without Abciximab.

**Who benefits by a Gp IIb/IIIa receptor inhibitor in UA/NSTEMI?**
A meta-analysis revealed that treatment is most beneficial when tailored to the patients’ risk profile. Patients with active ongoing ischaemia, raised Troponin levels or ST segment deviation defines a group who benefit the most. These agents are equally effective in diabetic subset.

<table>
<thead>
<tr>
<th>Table 9: Trials for UA/NSTEMI&lt;sup&gt;18-22&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial</strong></td>
</tr>
<tr>
<td>PRISM</td>
</tr>
<tr>
<td>PRISM-PLUS</td>
</tr>
<tr>
<td>PARAGON</td>
</tr>
<tr>
<td>PURSUIT</td>
</tr>
<tr>
<td>GUSTO IV ACS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 10: Trials for PCI&lt;sup&gt;23-26&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trials</strong></td>
</tr>
<tr>
<td>EPIC</td>
</tr>
<tr>
<td>EPILOG</td>
</tr>
<tr>
<td>EPISTENT</td>
</tr>
<tr>
<td>CAPTURE</td>
</tr>
<tr>
<td>IMPACT II</td>
</tr>
<tr>
<td>RESTORE</td>
</tr>
<tr>
<td>ESPRIT</td>
</tr>
</tbody>
</table>

**Trials for PCI**

**Fig. 6:**

Gp IIb/IIIa Receptor Antagonists in Intensive Coronary Care Unit
These agents have consistently shown benefit in patients who are taken for a PCI at 30 days at 6 months.

**CRUSADE Trial** (Can Rapid Risk Stratification of Unstable Angina Patients Suppress ADverse Outcome with Early Implication of ACC/AHA guidelines)

This trial included who have ischemic symptoms lasting more than 10 minutes and < 24 hours, CK-MB or TnI / TnT above normal. Dynamic ST-segment ECG changes: ST-segment depression > 0.5 mm, transient ST-segment elevation of 0.6-1.0 mm (lasting < 10 mins). This trial included 31,257 patients.

![CRUSADE Trial Graph]

**Fig. 7:**

There was a significant reduction in mortality when Gp IIb/IIIa inhibitor was administered within 24 hours of onset of chest pain. Patients with the highest risk profile benefitted the most with early catheterization. Thus, patients at highest risk tend to benefit the most from aggressive interventions.

**RAPIER Trial** (Rapid Administration of Platelet Inhibitors in the Emergency Room)

The rationale for this trial is that the potential benefit of primary angioplasty over fibrinolytic therapy is limited by a narrow time window (60-120 minutes) and the lack of availability of around the clock primary angioplasty facilities in most institutions. Restoration of coronary ow prior to successful primary angioplasty improves LV function and survival. The objective of this study were to improve coronary blood ow at initial angiography, decrease the time from baseline angiography to first balloon inflation and the total procedure time. 30 consecutive patients with STEMI were treated in the ICCU with eptifibatide : 180 µg/kg bolus followed by 2 µg/kg infusion. The 2nd bolus of 180 µg/kg was given in the cath lab.
Baseline coronary flow was fully (TIMI III) or partially restored (TIMI II) more frequently in the study group. Time to access the lesions and complete the procedure was significantly less for the study group. However there was no difference on the overall procedural success or in hospital outcome of death, MI, repeat revascularization. Thus a facilitated primary angioplasty strategy utilizing ICCU, with administration of eptifibatide prior to angiography widens the time window for treatment results more often in TIMI III flow and simplifies the PTCA procedure.

Oral GP IIb/IIIa receptor inhibitors

Table 11: Randomized Trials of Oral Agents

<table>
<thead>
<tr>
<th>Trials</th>
<th>Agent</th>
<th>Target Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPUS - TIMI 16</td>
<td>Orofiban</td>
<td>UA/NSTEMI</td>
</tr>
<tr>
<td>SYMPHONY I</td>
<td>Sibrafiban</td>
<td>UA/NSTEMI</td>
</tr>
<tr>
<td>SYMPHONY II</td>
<td>Sibrafiban</td>
<td>UA/NSTEMI</td>
</tr>
<tr>
<td>BRAVO EXCITE</td>
<td>Xemilofiban</td>
<td>PCI</td>
</tr>
</tbody>
</table>

Randomized Trials of Oral Agents

Fig. 8

Fig. 9
Oral agents were developed with the hope of replicating the success of parenteral agents. However randomized trials of these agents showed, that despite a promise of long term oral therapy, the results have been disappointing and most of these trials were stopped prematurely due to an excess of adverse effects, including prothrombotic tendencies.

Are all Gp IIb/IIIa receptor inhibitors equivalent in efficacy?

There have been 3 trials that have compared these trials.

1. TARGET Trial: Compared Abciximab with Tirofiban in 4812 elective PCI patients. At 30 days, there was a 1.6% excess of adverse events in the Tirofiban arm. The advantage of Abciximab is possibly due to this effect on vitronectin. An additional bolus of Tirofiban may help establish the efficacy of this drug.

2. COMPARE Trial: Compared Abciximab, Eptifibatide and Tirofiban in 70 patients undergoing PCI. The Tirofiban regimen produced less inhibition at 30 mins but with continued infusion, an equivalent platelet inhibition was achieved by Tirofiban as the other two. Eptifibatide produced consistent platelet inhibition throughout infusion while platelet recovery was seen after 4-12 hours of Abciximab infusion.

3. TEAM Trial: Compared Abciximab, Eptifibatide and Tirofiban. All three were equally effective. It was more important to achieve an adequate platelet inhibition of >90% in high risk PCI by adequate dosing rather than debating which agent to use.

The Final Analysis - A Meta-analysis of All Clinical Trials

![Graphs showing initial medical therapy and after PCI](image-url)
A meta-analysis of all trials with a Gp IIb/IIIa receptor inhibitor reveals that these agents are conclusively better than placebo when used as the initial medical therapy or as an adjuvant to PCI. These beneficial effects are also seen at 30 days. Similarly, they have been found to be effective in all subsets of patient, irrespective of age, gender or diabetic status.

Conclusion
There are 3 Gp IIb/IIIa receptor inhibitors presently available in India. Though they all have a common mode of action, they differ in their pharmacodynamic and pharmacokinetic properties. These agents have been consistently shown to be superior to placebo in all subsets and their beneficial effects have been shown at 6 months and 1 year of follow-up. Oral agents have shown no beneficial effect. Facilitated thrombolysis with reduced dose thrombolytic and Gp IIb/IIIa receptor inhibitor in the ICCU has shown an efficacy better than the thrombolytic agent alone with equivalent rates of bleeding. The rapid administration of these agents in the ICCU prior to a percutaneous coronary intervention has been shown to establish a better TIMI flow. However, the limiting factor in India is the cost involved. However, considering the benefits accrued, these expenses may be justified. Concerns regarding a higher incidence of fatal bleed are misplaced. Event reduction is maximum in patients at highest risk of thrombotic complications. Hence, we strongly advocate the aggressive use of these agents in the intensive coronary care unit, especially so in patients with high risk features.

References
20. PARAGON-B Investigators: Randomized, Placebo-controlled trial of titrated intravenous lamifiban for Acute
coronary syndrome circulation.


