The Role of Glycoprotein IIb/IIIa Inhibitors During Peripheral Intervention with No Reflow

Pradeep K. Nair, MD, FACC, FSCAI
Interventional Cardiology
Cardiovascular Institute of the South
Houma, Louisiana
Disclosures

Speaker’s Bureau:
• None

Honorarium:
• Medicure

Consultant:
• Medicure

Stockholder:
• None

Grant/Research Support:
• LumenRECON principal investigator

Medical/ Scientific Boards:
• None
The Scenario...
Endovascular Intervention
Outcome 1: Restoration of Flow
Outcome 2: No Reflow
What is no-reflow?

Vasoconstrictor (vasoconstriction)

Thrombotic (microvascular occlusion)

Mechanical (mechanical occlusion)

Platelet activation
Serotonin release

Aggregates of platelets, neutrophils, RBCs, cellular and interstitial edema

Distal embolization
No Reflow in Acute Myocardial Infarction

- Incidence 2.3%
- Risk Factors:
  - older age
  - late presentation
  - cardiogenic shock
  - bifurcation lesions
  - longer lesion length
  - type C lesions


No Reflow in PAD interventions

Mean Embolic Signal Frequency During Intervention

Clinically relevant: 1-5%
No-reflow: 1-2%
Any embolization: 63-100%

No Reflow in PAD Interventions: Risk Factors

<table>
<thead>
<tr>
<th>Lesion Specific Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic total occlusions</td>
</tr>
<tr>
<td>Long lesions</td>
</tr>
<tr>
<td>In stent restenosis</td>
</tr>
<tr>
<td>Acute or sub-acute occlusions</td>
</tr>
<tr>
<td>Infrapopliteal disease (outflow)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Procedure Related Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ↑ equipment exchanges</td>
</tr>
<tr>
<td>• ↑ procedure time</td>
</tr>
<tr>
<td>• Suboptimal anticoagulation</td>
</tr>
<tr>
<td>• PTA</td>
</tr>
<tr>
<td>• Stenting</td>
</tr>
<tr>
<td>• Atherectomy</td>
</tr>
<tr>
<td>• Thrombolysis</td>
</tr>
</tbody>
</table>
Intracranial Bleed

Thrombolytics

- Increase cost
- Higher bleeding risk
Prevention
+ Therapy

No Reflow

• Embolic protection devices
• Therapeutic activated clotting times
• Peri-procedural aspirin therapy
• Surgical bypass or embolectomy

Thrombolytic therapy
• Vasodilator therapy
• Surgical bypass or embolectomy

Glycoprotein (GP) IIb/IIIa Inhibitors
Thrombus Generation
Platelets: Thrombus Generation Begins Here

- Anucleate cytoplasmic fragments derived from megakaryocytes
- Size 1-2 µm
- Lifetime 7-10 days

Mechanism of Thrombosis

1. Endothelial/vascular injury
2. Platelet adhesion, activation, aggregation, and stabilization
3. Activation of the coagulation cascade
Platelet Ligand Interactions

Platelet adhesion: 1 minute
Thrombus formation: 3 minutes

vorapaxar

José Rivera et al.
Haematologica
2009;94:700-711


GP 2b/3a inhibitors
aspirin

High Shear Rates

Platelet adhesion: 1 minute
Thrombus formation: 3 minutes

vorapaxar

José Rivera et al.
Haematologica
2009;94:700-711


GP 2b/3a inhibitors
aspirin

High Shear Rates
GP IIb/IIIa Inhibitors
Mechanism of Thrombus Dissolution

1. Ligand Binding to Activated GP IIb/IIIa is Reversible.
2. Ligands Are Replaced by Anti-GP IIb/IIIa.
3. Platelet Thrombi Start to Dissolve.
• Heparin
• Thrombolytics
• …and every wire, catheter, balloon, stent or atherectomy device introduced into the vessel

Iatrogenic Platelet Activation (leading to clot)…it’s not just plaque rupture
### Glycoprotein 2b/3a Inhibitors (60,000-80,000 receptors/platelet)

<table>
<thead>
<tr>
<th>GP IIb/IIIa antagonist</th>
<th>Abciximab (ReoPro®)</th>
<th>Tirofiban (Aggrestat®)</th>
<th>Eptifibatide (Integrilin®)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structure</strong></td>
<td>Humanized mouse monoclonal Ab fragment</td>
<td>Non-peptide (mimic natural ligand)</td>
<td>Cyclic hexapeptide (derivative of pigmy rattlesnake venom)</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td>Large (47,615 Da)</td>
<td>Small (495 Da)</td>
<td>Small (832 Da)</td>
</tr>
<tr>
<td><strong>Receptor Affinity</strong></td>
<td>+++ Kd = 5 nmol/L</td>
<td>++ Kd = 15 nmol/L</td>
<td>+ Kd = 120 nmol/L</td>
</tr>
<tr>
<td><strong>Anti-platelet aggregation</strong></td>
<td>Long-acting (24-48 hrs)</td>
<td>Short-acting (2-4 hrs)</td>
<td>Short-acting (4-8 hours)</td>
</tr>
<tr>
<td><strong>Duration of platelet binding</strong></td>
<td>Up to 21 days</td>
<td>seconds</td>
<td>Seconds</td>
</tr>
<tr>
<td><strong>Plasma half life</strong></td>
<td>10-30 mins</td>
<td>1.5-2 hrs</td>
<td>2.5 hrs</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>Reticuloendothelial system</td>
<td>Renal</td>
<td>Renal</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>7.2</td>
<td>5.5-6.5</td>
<td>5.35</td>
</tr>
<tr>
<td><strong>Approved Indications</strong></td>
<td>PCI/UA</td>
<td>UA/NSTEMI</td>
<td>PCI/UA/NSTEMI</td>
</tr>
</tbody>
</table>
GP 2b/3a Inhibitors: Weight of Evidence

- Randomized controlled data
- FDA labelling and guidelines
- ↓ combined endpoint CV death, nonfatal MI, urgent revascularization
- Improved microperfusion

Peripheral Interventions
- Paucity of data
- No FDA labelling or clear guidelines
- Use is inconsistent between operators and centers
Impact of glycoprotein IIb/IIIa inhibitors use on outcomes after lower extremity endovascular interventions from nationwide inpatient sample (2006–2011)

* = $P<0.001$
Clinical Cases:
No-reflow treated with local deliver of **multi-bolus** (supra-therapeutic) tirofiban
Case 1: 73-yo female with stage 4 CKD, anemia, and infection of left knee prosthesis s/p explant and recent re-do surgery presents for non-healing wounds and limb salvage.
Laser atherectomy and angioplasty → No Reflow
Flow Restoration

“Cardiovascular Institute of the South”
Treatment Algorithm

1. Low pressure balloon inflation just proximal to zone of no-reflow

2. Vasoactive medications administered via the balloon
   A. Tirofiban 25 mcg/kg bolus ± peripheral drip
   B. Vasodilators (nipride and NTG)
   C. Balloon deflated after 5 minutes
   D. Re-angio

3. Process repeated if needed to achieve adequate result
• 59-yo male with HIT, extensive PAD history, AAA s/p EVAR, CAD presents for limb salvage after developing ischemic rest pain over the last week.

• PAD history includes left femoral-AT bypass, distal graft to AT stenting, and several prior limb salvage procedures requiring catheter-directed thrombolysis.
Laser atherectomy + angioplasty + bivalirudin + GPI 2b/3a → No Reflow
“Cardiovascular Institute of the South” Treatment Algorithm with tirofiban bolus x 5 (AT proximal and distal)
Clinical Case:
Thrombus dissolution with locally delivered multi-bolus (supra-therapeutic) tirofiban
Initial Angiogram: 66-yo female smoker with CAD and PAD s/p multiple prior interventions presents with Rutherford 3 claudication.
Atherectomy $\rightarrow$ Thrombus $\rightarrow$ “CIS Algorithm” x 3 $\rightarrow$ Thrombus Dissolution $\rightarrow$ Flow
“Dethrombosis” with GP 2b/3a Inhibitors


Conclusion

• No reflow during peripheral interventions occurs from the culmination of vasoconstrictive, thrombotic, and embolic events that can lead to serious clinical sequelae.

• Prevention of no reflow (with devices or pharmaceuticals) in peripheral interventions is not standardized and typically operator and center specific.

• Thrombolytic agents are commonly used for treatment of no reflow, but can yield significant morbidity and mortality.

• Pre-clinical studies demonstrate that GP IIb/IIIa antagonism induce dissolution of platelet-rich clot, or dethrombosis, by disrupting fibrinogen-platelet interaction.

• Our understanding of the ideal route of administration and dose for GP IIb/IIIa antagonists in peripheral interventions with (and without) no reflow continues to evolve.
Thank You
The Role of Glycoprotein IIb/IIIa Inhibitors During Peripheral Intervention with No Reflow

Pradeep K. Nair, MD, FACC, FSCAI
Interventional Cardiology
Cardiovascular Institute of the South
Houma, Louisiana