Bivalirudin (Angiomax ®) vs. Heparin during Peripheral Vascular Interventions: Which is Better and How to Decide?

Vinod Nair MD FACC FSCAI
Cardiovascular Institute of the South, Houma
Financial Disclosure:
None
Percutaneous Peripheral Intervention (PPI)

Thrombosis occurs in almost all peripheral percutaneous intervention (PPI) cases.

Bleeding risks are greater in PPI than PCI.

Higher thrombus burden in PPI than PCI.

PPI requires superior anticoagulation.
PPI Vs. PCI - Procedural Differences

- Longer length diseased vessel
- Larger sheath size requirement
- Longer PTA/stented segments
- Larger acute and chronic thrombus burden
- Longer procedural times (sheath dwell times)
- Multiple catheter, guide-wire, devices, etc exchanges (oftentimes crossover techniques)
PPI Vs. PCI - Clinical Differences

“Low flow” state in peripheral versus coronary flow beds

Increased incidence of CKD (50%)

PVD- > 50-60% Diabetes: CLI -> 80% Diabetes

PVD patients are hypercoaguuble
Percutaneous Peripheral Intervention - PPI

Increased Coagulability

Significantly More Platelet Dysfunction
Ideal Anticoagulant

Reduce thrombosis risk

Reduce bleeding
Heparins

- UFH
- LMWH

Direct Thrombin Inhibitors (DTI)

- Argatroban (HIT + PCI)
- Bivalirudin
Antithrombin Agents

Heparins
- UFH
- LMWH

Direct Thrombin Inhibitors (DTI)
- Argatroban (HIT + PCI)
- Bivalirudin
Collagen

Tissue Factor

Thrombin

Thrombin - Central Role

Platelet activation

Platelet aggregation

Prothrombin

ADP

TXA2

Collagen

Tissue Factor

Plasma Clotting cascade

Prothrombin

Fibrinogen

Fibrin

THROMBUS
Peripheral Intervention and thrombosis - complementary

- Thrombin Generation
- Platelet Activation
- Vessel Wall Injury and Inflammation
- Tissue Factor
Anticoagulation in PPI

- Unfractionated heparin has been historically used
- No recommendation from ACC / AHA
- No Randomized controlled trial comparing UFH with Bivalirudin
UFH

- 5,000-30,000 Daltons

- Heterogeneous mixture of polysaccharide chains with varying effects on anticoagulant activity

- Accelerates the action of circulating antithrombin (AT), a proteolytic enzyme which inactivates factors IIa (thrombin), IXa, Xa

- Prevents thrombus propagation, but does not lyse existing thrombin
Variability of preparations

Unpredictable neutralization by PF-4

Inhibits only soluble thrombus not the fibrin bound thrombin

Binds to endothelial cells, plasma proteins, macrophages

Poor clot penetration

Indirect anticoagulant - relies on AT III levels, structure

Stimulates platelet aggregation

HIT
Unfractionated Heparin and ACT

Hemochron usually exceeds HemoTec by 30-50s (variable)
Varies substantially after fixed dose heparin
Weight adjusted dose generally preferred
ACT and ischemic complications ?
ACT and bleeding complications ?
Bivalirudin

C-terminal dodecapeptide (exosite 1-binding region)

Direct thrombin inhibitor
High specificity and potency
Lack of dependence on antithrombin-III
Effect on clot-bound & free thrombin
No platelet activation
No inhibition by PF4
No Antidote to reverse
t½ of 25 min
More than 25,000 patients randomized in clinical trials comparing bivalirudin to standard of care antithrombin therapies

- Elective PCI: REPLACE-2
- NSTE ACS: ACUITY
- STEMI: HORIZONS-MI, EUROMAX, HEAT PPCI

Overview
- Similar ischemic outcomes
- Significantly reduced bleeding (access site and non-access site)
- Reduced mortality in Primary PCI
1. Extensively investigated in PCI in ACS setting
2. Decreases death, MI & repeat revasc.
3. Bivalirudin Angioplasty Trial - n = 4000
   1. Better efficacy in preventing triple end points
   2. Lower bleeding rate
   3. FDA approval (2000)
   1. Non-Inferiority to UFH (provisional GPI)
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Comparator</th>
<th>Setting</th>
<th>Ischemic Events</th>
<th>Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>REPLACE-2</td>
<td>6002</td>
<td>UFH + GPI</td>
<td>Elective PCI</td>
<td>-</td>
<td>↓</td>
</tr>
<tr>
<td>ISAR REACT 3</td>
<td>4570</td>
<td>UFH (140 u/kg)</td>
<td>Elective PCI</td>
<td>-</td>
<td>↓</td>
</tr>
<tr>
<td>ACUITY</td>
<td>13800</td>
<td>UFH/LMWH + GPI</td>
<td>NSTEACS</td>
<td>-</td>
<td>↓</td>
</tr>
<tr>
<td>ISAR REACT 4</td>
<td>1721</td>
<td>UFH + GPI</td>
<td>NSTEACS</td>
<td>-</td>
<td>↓</td>
</tr>
<tr>
<td>BRIGHT</td>
<td>2100</td>
<td>UFH or UFH + GPI</td>
<td>STEMI &amp; NSTEMI</td>
<td>-</td>
<td>↓</td>
</tr>
<tr>
<td>HORIZONS</td>
<td>3602</td>
<td>UFH + GPI</td>
<td>STEMI</td>
<td>(-) MACE</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stent thromb</td>
<td></td>
</tr>
<tr>
<td>EUROMAX</td>
<td>2218</td>
<td>UFH ± GPI</td>
<td>STEMI</td>
<td>(-) MACE</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stent thromb</td>
<td></td>
</tr>
<tr>
<td>HEAT PPCI</td>
<td>1829</td>
<td>UFH</td>
<td>STEMI</td>
<td>↑ MACE</td>
<td>-</td>
</tr>
</tbody>
</table>
Multicenter, Prospective Study
3,277 patients randomized to Bivalirudin
Renal, Iliac and Femoral interventions
Protocol defined major bleeding occurred in 2.2% and 8.7% in favor of Bivalirudin. No difference in 30 day outcomes.
Heparin Vs. Bivalirudin

A total of 13 randomized, controlled trials involving 24,605 patients.
Heparin Vs. Bivalirudin

1. Bivalirudin resulted in a significant reduction of major bleeding as compared with heparin with routinely administered GPI but not with provisionally administered GPI.
2. Bivalirudin compared with heparin was associated with a significant increase in 30-day definite ST.
3. Overall mortality or risk of MI did not differ significantly.
PPI patients usually have higher thrombus burden compared to PCI. Bivalirudin is an alternative to UFH in PPI based on its favorable profile. No Randomized control Trial or ACC/AHA recommendation is available.
Thanks
Among patients undergoing PCI, bivalirudin + provisional GP2b3a is as effective as unfractionated heparin, but was associated with an increased hazard of stent thrombosis. Bivalirudin may be associated with a reduced hazard of major bleeding; however, this benefit was no longer apparent when compared with a dose of unfractionated heparin ≤ 75 units/kg.
Thrombin
Heparin in Peripheral Arterial Intervention - Data
Bivalirudin in Peripheral Arterial Intervention - Data
Heparin Vs. Bivalirudin