Glycoprotein IIb/IIIa Inhibitors: Update 2009

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OUTLINE

- GP IIb/IIIa inhibitors – pharmacokinetic and pharmacodynamic properties
- Eptifibatide – history, dosing, major studies
- ACS and PCI trials
- Contemporary trials, including comparison vs. bivalirudin
- Special populations
- Conclusions and implications
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Schematic depiction of integrin $\alpha_{\text{IIb}}\beta_3$

Both subunits are a product of a single gene located on chrom. 17

Interacts with RGD sequence on ligands
GP IIb/IIIa Receptor Activation

- Fibrinogen (immobilized)
- vWF (high shear)
- Collagen
- ADP
- Thrombin
- GP IIb-IIIa
- Fibrinogen, vWF
release of over 300 proteins that act in an autocrine and paracrine fashion to modulate cell signaling. Some are pro-thrombotic, others pro-inflammatory, others regulate cell proliferation, and many are of unknown function.

Coppinger JA. Blood 2004;103:2096-2104
GP IIb/IIIa Inhibitors

- **Abciximab (ReoPro®)** – the first inhibitor developed and approved for clinical use.
  Chimeric monoclonal antibody – 7E3, the murine constant region was replaced by its human counterpart

- **Eptifibatide (Integrilin®)** – synthetic cyclic heptapeptide derived from a sequence found in the venom of the southeastern pygmy rattlesnake

- **Tirofiban (Aggrastat®)** – synthetic small molecule with structure similar to that of the RGD sequence of the snake venom echistatin
GP IIbIIIa inhibitors

**Antibody**
- abciximab

**Cyclic peptide**
- eptifibatide

**Nonpeptide**
- tirofiban HCl
  (Aggrastat®, Merck)
<table>
<thead>
<tr>
<th></th>
<th>Abciximab</th>
<th>Tirofiban</th>
<th>Eptifibatide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharma</td>
<td>Fab portion of chimeric monoclonal antibody</td>
<td>Synthetic non-peptide</td>
<td>Cyclic heptapeptide</td>
</tr>
<tr>
<td>Plasma ½ life</td>
<td>30 minutes</td>
<td>1.8 hours</td>
<td>2.5 hours</td>
</tr>
<tr>
<td>Specificity</td>
<td>Not specific</td>
<td>Highly specific</td>
<td>Highly specific</td>
</tr>
<tr>
<td>Dose</td>
<td>0.25 mcg/kg bolus followed by 0.125 mcg/kg/min drip (max 10 mcg/min) for 12-24 hours</td>
<td>0.4 mcg/kg/min for 30 minutes followed by 0.1 mcg/kg/min drip for 48-96 hours</td>
<td>180 mcg/kg bolus (x2) followed by 2.0 mcg/kg/min drip for 18-24 hours</td>
</tr>
</tbody>
</table>
COMPARE Study
– early platelet aggregation

Proportion of patients (%), in whom >80% inhibition of 20 μmol/L ADP-induced PA was achieved

73 ACS pts planned for PCI
Samples drawn in PPACK
Batchelor WB et al Circulation 2002
GOLD Study

- 485 patients undergoing a PCI with planned use of 1 of the 3 approved GP IIb/IIIa inhibitors

- Platelet function evaluated at various time points by RPFA correlated to clinical endpoints – MACE at 30 days

- Platelet inhibition at 10 min and MACE:
  \[ \geq 95\% \text{ inhibition} \Rightarrow 6.4\% \text{ MACE} \]
  \[ < 95\% \text{ inhibition} \Rightarrow 14.4\% \text{ MACE} \quad (p=0.006) \]

- Platelet inhibition at 8 hrs and MACE:
  \[ \geq 70\% \text{ inhibition} \Rightarrow 8.1\% \text{ MACE} \]
  \[ < 70\% \text{ inhibition} \Rightarrow 25\% \text{ MACE} \quad (p=0.009) \]

Steinhubl et al, Circulation 2001; 103: 2572-2578
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IMPACT – 2 - *Lancet* 1997

- 4010 patients undergoing elective, urgent, or emergency PCI
- Randomized to: placebo, eptifibatide (135 µg/kg followed by 0.75 µg/kg/min infusion for 20-24 hrs), eptifibatide (135 µg/kg followed by 0.5 µg/kg/min inf. for 20-24 hrs)
- 92% - balloon angioplasty alone (POBA)
- Mean ACT during the procedure 350-365 sec
- 84% - received heparin after the procedure
Primary endpoint: 30 day composite occurrence of death, MI, unplanned surgical or repeat PCI, or coronary stent implantation for abrupt closure
Eptifibatide with ADP / PPACK

Inhibition of platelet aggregation

Study Drug Infusion

% baseline aggregation

Eptifibatide with ADP / PPACK

IMPACT II 135 / 0.75

PURSUIT 180 / 2.0

ESPRIT 180 / 2.0 / 180

5 min, 4 hr, 8 hr, 12 hr, 16 hr, 20 hr, 24 hr, 28 hr

time

PRIDE study, Tcheng et al AJC 2001
PURSUIT – NEJM 1998

- 10,948 patients with ACS (non-ST elevation)
- Performed 1995-1997
- Eptifibatide (180 µg/kg followed by 2 µg/kg/min up to 72-96 hrs!) vs. placebo

Primary endpoint: death or non-fatal MI at 30 days

![Comparison of primary endpoints](image)

Non-CABG bleeding

![Comparison of bleeding](image)

- P<0.01

P<0.04
Aspirin – 93% of pts, heparin – 90%

Ticlopidine – used very rarely – considered for pts intolerant to aspirin

Cardiac cath – 59-60% of pts

PCI: 23-25% of pts (stents used in 50% of them)

CABG: 14% of pts

Revasc performed 72-96 hrs after enrollment

→ not really relevant for current practice

- 2064 pts planned for PCI of a native coronary artery with stenting
- Conducted 1999-2000
- Almost 20% of pts had an ACS within 48 hrs of enrollment; **rest (~80%) – stable pts**
- Eptifibatide (two 180 µg/kg boluses 10 min apart, followed by 2 µg/kg/min for 18-24 hrs) vs. placebo
- 97% had at least 1 stent placed during PCI
- 97% received a thienopyridine – mainly clopidogrel (without preloading)
- Median ACT = 268 sec
ESPRIT – 30 day results (Lancet 2000)

Death/MI

Major bleeding:
1.3% vs. 0.4%
(eptif vs. placebo)
P=0.03

Death/MI/urgent TVR
ESPRIT – 1 year results  

Hazard ratio, 0.63; \( P = .001 \)  
Hazard ratio, 0.76; \( P = .007 \)
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PCI Trials - 30-Day Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Ctrl</th>
<th>Trt</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPIC</td>
<td>2099</td>
<td>1.7</td>
<td>1.5</td>
</tr>
<tr>
<td>EPILOG</td>
<td>2792</td>
<td>0.7</td>
<td>0.4</td>
</tr>
<tr>
<td>RAPPORT</td>
<td>4833</td>
<td>2.1</td>
<td>2.5</td>
</tr>
<tr>
<td>CAPTURE</td>
<td>1265</td>
<td>1.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Impact I</td>
<td>150</td>
<td>2.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Impact II</td>
<td>4010</td>
<td>1.1</td>
<td>0.7</td>
</tr>
<tr>
<td>Restore</td>
<td>2141</td>
<td>0.7</td>
<td>0.8</td>
</tr>
<tr>
<td>Epistent</td>
<td>2399</td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Episitit</td>
<td>2064</td>
<td>0.6</td>
<td>0.4</td>
</tr>
<tr>
<td>ISAR 2</td>
<td>401</td>
<td>4.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Admiral</td>
<td>300</td>
<td>6.6</td>
<td>3.4</td>
</tr>
<tr>
<td>Cadilliac</td>
<td>2082</td>
<td>2.3</td>
<td>1.9</td>
</tr>
<tr>
<td>Combined</td>
<td>20186</td>
<td>1.3</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Odds Ratio

0.1

1

10

0.73 (0.55-0.96)
GP IIb/IIIa Inhibition in ACS

30-Day Death or MI

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Placebo</th>
<th>GP IIb-IIIa Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRISM</td>
<td>3,232</td>
<td>7.1%</td>
<td>5.8%</td>
</tr>
<tr>
<td>PRISM PLUS</td>
<td>1,915</td>
<td>11.9%</td>
<td>8.7%</td>
</tr>
<tr>
<td>PARAGON A</td>
<td>2,282</td>
<td>11.7%</td>
<td>10.6%</td>
</tr>
<tr>
<td>PURSUIT</td>
<td>9,461</td>
<td>15.7%</td>
<td>14.2%</td>
</tr>
<tr>
<td>GUSTO-IV ACS</td>
<td>7,800</td>
<td>8.0%</td>
<td>8.7%</td>
</tr>
<tr>
<td>Overall</td>
<td>26,203</td>
<td>11.9%</td>
<td>10.5%</td>
</tr>
</tbody>
</table>

0.88 (0.82, 0.94)  P < 0.001
Meta-Analysis of Risk-Adjusted Mortality in GP IIb-IIIa Inhibitor NSTE ACS Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRMI NSTEMI&lt;sup&gt;1&lt;/sup&gt; (n=60,770)</td>
<td>0.88</td>
<td>0.79, 0.97</td>
</tr>
<tr>
<td>Boersma&lt;sup&gt;2&lt;/sup&gt; (n=31,402)</td>
<td>0.91</td>
<td>0.81, 1.03</td>
</tr>
</tbody>
</table>

Boersma: NRMI=National Registry of Myocardial Infarction


Meta-Analysis of Mortality in GP IIb-IIIa Inhibitor NSTE ACS Trials

Boresma et al, Lancet 2002
ISAR-REACT 2
High-risk ACS Patients – 30 Days

**Death**
- Placebo: 1.6%
- Abciximab: 1.1%
- p = 0.34

**MI**
- Placebo: 10.5%
- Abciximab: 8.1%
- p = 0.03

**Death/MI**
- Placebo: 11.5%
- Abciximab: 8.6%
- p = 0.06

**Urg Revac**
- Placebo: 1.2%
- Abciximab: 1.0%
- p = 0.64

JAMA 2006;295:1531-38
ISAR-REACT 2 Trial: Endpoints

- Death, MI, or urgent TVR within 30 days (%):
  - Abciximab: 8.9%
  - Placebo: 11.9%
  - *p* = 0.03

- Death or MI within 30 days (%):
  - Abciximab: 8.6%
  - Placebo: 11.5%
  - *p* < 0.05

Source: JAMA 2006
4. For UA/NSTEMI patients in whom an initial invasive strategy is selected, antiplatelet therapy in addition to aspirin should be initiated before diagnostic angiography (upstream) with either clopidogrel (loading dose followed by daily maintenance dose)* or an intravenous GP IIb/IIIa inhibitor. (Level of Evidence: A) Abciximab as the choice for upstream GP IIb/IIIa therapy is indicated only if there is no appreciable delay to angiography and PCI is likely to be performed; otherwise, IV eptifibatide or tirofiban is the preferred choice of GP IIb/IIIa inhibitor. (Level of Evidence: B)
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**ACUITY** – High risk ACS, 30 days endpoint

**UFH/Enoxaparin + GPI vs. Bivalirudin Alone**

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>Risk ratio ±95% CI</th>
<th>Bival alone</th>
<th>UFH/Enox + IIb/IIIa</th>
<th>RR (95% CI)</th>
<th>p value (non inferior)</th>
<th>(superior)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net clinical outcome</td>
<td>Bival</td>
<td>10.1%</td>
<td>11.7%</td>
<td>0.86 (0.77-0.97)</td>
<td>&lt;0.001</td>
<td>0.015</td>
</tr>
<tr>
<td>Ischemic composite</td>
<td></td>
<td>7.8%</td>
<td>7.3%</td>
<td>1.08 (0.93-1.24)</td>
<td>0.01</td>
<td>0.32</td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td>3.0%</td>
<td>5.7%</td>
<td>0.53 (0.43-0.65)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Stone GW et al. NEJM 2006;355:2203-16*
ACUITY - Composite Ischemia at 1-Year
UFH/Enoxaparin + GPIIb/IIIa vs. Bivalirudin alone

Hazard ratio ±95% CI

Bivalirudin alone
UFH/Enoxaparin + IIb/IIIa
HR (95% CI) P_int

1 yr KM estimate

Biomarkers (CK/Trop)
- Elevated (n=5072)
  - 17.7% 16.4% 1.14 (0.99-1.30) 0.11
  - 14.6% 16.1% 0.95 (0.80-1.14)
- Normal (n=3402)
  - 9.0% 9.6% 0.97 (0.76-1.24)

Pre Thienopyridine
- Yes (n=5751)
  - 16.2% 17.2% 0.97 (0.86-1.11) 0.07
  - 16.4% 14.3% 1.20 (1.01-1.44)
- No (n=3305)
  - 17.7% 16.4% 1.14 (0.99-1.30)

Actual Treatment
- PCI (n=5179)
  - 19.8% 19.2% 1.09 (0.96-1.23) 0.67
- CABG (n=1040)
  - 21.1% 20.7% 1.04 (0.79-1.36)
- Medical (n=2994)
  - 9.0% 9.6% 0.97 (0.76-1.24)

Stone GW et al. NEJM 2006;355:2203-16
## HORIZONS: STEMI pts, 30 days endpoint

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Bivalirudin (%)</th>
<th>Heparin+GP IIb/IIIa blocker (%)</th>
<th>Relative risk (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>4.9</td>
<td>8.3</td>
<td>0.60 (0.46–0.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Net adverse clinical events</td>
<td>9.2</td>
<td>12.1</td>
<td>0.76 (0.63–0.92)</td>
<td>0.005</td>
</tr>
<tr>
<td>MACE</td>
<td>5.5</td>
<td>5.5</td>
<td>1.00 (0.75–1.32)</td>
<td>0.98</td>
</tr>
<tr>
<td>Death from cardiac causes</td>
<td>1.8</td>
<td>2.9</td>
<td>0.62 (0.40–0.95)</td>
<td>0.03</td>
</tr>
<tr>
<td>Death from all causes</td>
<td>2.1</td>
<td>3.1</td>
<td>0.66 (0.44–1.00)</td>
<td>0.047</td>
</tr>
</tbody>
</table>

HORIZONS 30 Day Mortality:
Cardiac and Non Cardiac

<table>
<thead>
<tr>
<th>Time in Days</th>
<th>Cardiac Death (%)</th>
<th>Non Cardiac Death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.9%</td>
<td>1.8%</td>
<td></td>
</tr>
</tbody>
</table>

- Heparin + GPIIb/IIIa inhibitor (n=1802)
- Bivalirudin monotherapy (n=1800)

HR [95%CI] = 0.62 [0.40, 0.96]
P = 0.029

Stone et al, NEJM 2008
### HORIZONS: Stent thrombosis results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Bivalirudin (%)</th>
<th>Heparin+GP IIb/IIIa blocker (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent thrombosis within 30 d</td>
<td>2.5</td>
<td>1.9</td>
<td>0.30</td>
</tr>
<tr>
<td>Acute (&lt;24 h)</td>
<td>1.3</td>
<td>0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Subacute (24 h–30 d)</td>
<td>1.2</td>
<td>1.7</td>
<td>0.28</td>
</tr>
</tbody>
</table>

BRIEF-PCI Rationale

- Dual anti-platelet oral therapy with aspirin and clopidogrel – almost 100% of pts undergoing PCI
- High dose clopidogrel loading (600 mg) is often used, well tolerated and has rapid onset of action
- Routine use of coronary stents reduces abrupt vessel closure
- Prolonged 18-hour eptifibatide infusion may not be necessary

Fung et al, JACC 2009
BRIEF-PCI

- 624 pts with ACS > 48 hrs or stable angina (non emergent pts)
- Uncomplicated PCI with stenting, performed under the coverage of eptifibatide
- TIMI-3 flow, no dissection or thrombus post procedure
- Randomization after successful PCI
- 67% pts received clopidogrel pre-treatment - dose dependent on timing
- Randomized to brief (< 2hrs) vs. 18 hrs of eptifibatide maintenance

Fung et al, JACC 2009
BRIEF-PCI - cont

Composite Triple End-points @ 30 Days

No differences in markers of myonecrosis
BRIEF-PCI - cont

Bleeding & Quadrupple End-points

P = NS

2° end-point

P = 0.02

REPLACE-2 criteria
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GP IIb/IIIa Inhibitors Reduce Mortality in Pts With Diabetes

30-Day Mortality – Diabetic Patients

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Odds Ratio &amp; 95% CI</th>
<th>Placebo</th>
<th>IIb/IIIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>PURSUIT</td>
<td>2163</td>
<td></td>
<td>6.1%</td>
<td>5.1%</td>
</tr>
<tr>
<td>PRISM</td>
<td>687</td>
<td></td>
<td>4.2%</td>
<td>1.8%</td>
</tr>
<tr>
<td>PRISM-PLUS</td>
<td>362</td>
<td></td>
<td>6.7%</td>
<td>3.6%</td>
</tr>
<tr>
<td>GUSTO IV</td>
<td>1677</td>
<td></td>
<td>7.8%</td>
<td>5.0%</td>
</tr>
<tr>
<td>PARAGON A</td>
<td>412</td>
<td></td>
<td>6.2%</td>
<td>4.6%</td>
</tr>
<tr>
<td>PARAGON B</td>
<td>1157</td>
<td></td>
<td>4.8%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Pooled</td>
<td>6458</td>
<td></td>
<td>6.2%</td>
<td>4.6%</td>
</tr>
</tbody>
</table>

Roffi et al, Circulation 2001
GP IIB/IIIA inhibitors and Diabetes

- Meta-analysis of non-STEMI ACS trials with GP IIb/IIIa inhib. (PRISM, PRISM-PLUS, PARAGON, PURSUIT, GUSTO-IV)

- 6,458 diabetic pts → significant mortality reduction at 30 dys: 6.2% vs. 4.6% (placebo vs. IIb/IIIA, P=0.007)

- 23,072 non diabetic pts → no survival benefit (3% vs. 3%)

- Main benefit in diabetics among those who underwent PCI (4% vs. 1.2%, P=0.002)

Roffi et al, Circulation 2001
STEMI

- Majoraty of large GP IIb/IIIa trials with abciximab
- In all trials early administration preferable to late

Primary PCI 30 Day Death, MI or Urgent TVR

- **RAPPORT**
  - Placebo: 11.2%
  - Abciximab: 5.8%
  - **↓ 48%**, p = 0.03

- **ISAR-2**
  - Placebo: 10.5%
  - Abciximab: 5.0%
  - **↓ 52%**, p = 0.04

- **ADMIRAL**
  - Placebo: 14.6%
  - Abciximab: 6.0%
  - **↓ 52%**, p = 0.01

- **CADILLAC**
  - Placebo: 6.9%
  - Abciximab: 4.5%
  - **↓ 30%**, p = 0.02

- **ACE**
  - Placebo: 10.5%
  - Abciximab: 4.5%
  - **↓ 57%**, p = 0.02

References:
GP IIb/IIIa Inhibitors - Abciximab

Only trials of PCI with stenting that included long-term follow-up

Death or re-infarction over 3 yrs of f/u

3 year mortality

---


P = 0.008

P = 0.052
GP IIb/IIIa inhibitors still have an important role and are beneficial in **high risk patients**

Patient groups who appear to benefit the most from GP IIb/IIIa inhibitor therapy:

1. ACS troponin+ (especially STEMI) who undergo PCI
2. Patients with diabetes
3. Patients with ACS who were not preloaded with clopidogrel before the PCI
Bleeding complications are definitely an important issue when compared to bivalirudin (or heparin alone). Increase in major bleeding offsets advantages in ischemic complications and can translate to mortality differences (e.g. HORIZONS).

Bleeding can be reduced by:
- Shorten infusion time
- Lower heparin dose
- Better adjustment for CrCl