Updated Guideline of Glycoprotein IIb/IIIa Inhibitor for Acute Coronary Syndrome

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Disclosure Information

Honorarium from Handok Corp
Clinical Classification of ACS

Acute Coronary Syndrome

No ST Elevation

- Unstable Angina
- Non-STEMI

ST Elevation

- STEMI
Platelet Activation

- Epinephrine
- Collagen
- Thrombin
- ADP

Platelet

- AA
- TxA₂

Platelet Membrane

GP IIb/IIIa

Fibrinogen

Aspirin

Thienopyridines

GPIIb/IIIa inhibitors
Target Sites of Antiplatelet Therapy

- Prostaglandins
- GPIb/vWF Antagonists, Dipyridamole
- Aspirin, TxsS Inhibitors
- GPIIb/IIIa Antagonists
- Disruption of Endothelium
- Platelet Adhesion
- Platelet Activation
- Platelet Release
- Platelet Aggregation
- Shear Stress, Binding of Agonists:
  - Thrombin
  - Serotonin
  - ADP
  - $\text{TXA}_2$
  - Others

GP = Glycoprotein
vWF = von Willebrand factor
TxsS = Thromboxane synthase
$\text{TXA}_2$ = Thromboxane $A_2$

Parenteral GP IIb/IIIa inhibitors

**Antibody**
- abciximab
  (ReoPro®, Centocor/Lilly)

**Cyclic peptide**
- eptifibatide
  (INTEGRILIN®, COR/Key)

**Nonpeptide**
- tirofiban HCl
  (Aggrastat®, Merck)
# GP IIb/IIIa Receptor Antagonists

<table>
<thead>
<tr>
<th>Pharma</th>
<th>Abciximab (ReoPro®)</th>
<th>Tirofiban (Aggrastat®)</th>
<th>Eptifibatide (Integrilin®)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fab portion of chimeric monoclonal antibody</td>
<td>Synthetic non-peptide</td>
<td>Cyclic heptapeptide</td>
</tr>
<tr>
<td></td>
<td>30 minutes</td>
<td>1.8 hours</td>
<td>2.5 hours</td>
</tr>
<tr>
<td>Renal Adj.</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Dosage</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>
Early AbciximabPCI Trials

Death, MI, Urgent Revascularization – 30 Days

**EPIC**
- Placebo: 12.8
- Bolus: 12.8
- Bolus + Infusion: 8.3

**EPILOG**
- Placebo: 11.7
- Abciximab: 5.2

**EPISTENT**
- Placebo + Stent: 10.8
- Abciximab + PTCA: 6.9
- Abciximab + Stent: 5.3

**Statistics**
- **EPIC**
  - Absolute: 4.5%
  - Relative: 35%
  - \( p = 0.008 \)
- **EPILOG**
  - Absolute: 6.5%
  - Relative: 55%
  - \( p < 0.001 \)
- **EPISTENT**
  - Absolute: 5.5%
  - Relative: 51%
  - \( p < 0.001 \)

**References**
- NEJM 1994; 330:956-61
- NEJM 1997; 336:1689-96
For STEMI
All-cause mortality; rehospitalization or ED visit for CHF; VF >48 hours after randomization; cardiogenic shock. N=2452.

**FINESSE – 90-Day Endpoints**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Composite*</th>
<th>Death</th>
<th>MI Comp</th>
<th>CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary PCI (806)</td>
<td>10.7%</td>
<td>4.5%</td>
<td>8.9%</td>
<td>2.2%</td>
</tr>
<tr>
<td>PCI+Abcix (818)</td>
<td>10.5%</td>
<td>5.5%</td>
<td>7.5%</td>
<td>2.9%</td>
</tr>
<tr>
<td>PCI+Abcix+Reteplase (828)</td>
<td>9.8%</td>
<td>5.2%</td>
<td>7.4%</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

*All-cause mortality; rehospitalization or ED visit for CHF; VF >48 hours after randomization; cardiogenic shock. N=2452.
## FINESSE – 90-Day Bleeding

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>TIMI Major</th>
<th>TIMI Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary PCI (806)</td>
<td>6.9</td>
<td>2.6</td>
<td>4.3</td>
</tr>
<tr>
<td>PCI+Abcix (818)</td>
<td>10.1</td>
<td>4.1</td>
<td>6</td>
</tr>
<tr>
<td>PCI+Abcix+Reteplase (828)</td>
<td>14.5</td>
<td>4.8</td>
<td>9.7</td>
</tr>
</tbody>
</table>

* p = 0.025, ** p < 0.01, *** p < 0.001

Ellis S. ESC N Engl J Med 2008;358:2205
CARESS
Abciximab with ½ Dose Reteplase

Composite = 30-day Death, Re-MI, Refractory ischemia. N=600

Immediate PCI (N=298) Rescue PCI (N=300)

Percent

<table>
<thead>
<tr>
<th>Condition</th>
<th>Immediate PCI</th>
<th>Rescue PCI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>4.1</td>
<td>3.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Re-MI</td>
<td>4.4</td>
<td>1.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Ischemia</td>
<td>5</td>
<td>0.7</td>
<td>0.032</td>
</tr>
<tr>
<td>Bleed</td>
<td>12.2</td>
<td>7.4</td>
<td></td>
</tr>
<tr>
<td>Transfuse</td>
<td>3.7</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>
On-TIME 2: Study Design

STEMI diagnosed in ambulance or referral center
ASA + 600 mg clopidogrel + UFH

N=984
Jun 2006–Nov 2007

Placebo

Angiogram

Provisional HDB Tirofiban

HDB Tirofiban*

Transportation

PCI center

PCI

Angiogram

Tirofiban cont’d

*Bolus: 25 µg/kg and 0.15 µg/kg/min infusion.

BRAVE-3
Abciximab before Primary PCI
30-day Death, MI, Revas, and Stroke

Mehilli et al. Circulation. 2009;119
Pre-hospital High Dose Tirofiban

ST Resolution Time

Composite: death, recurrent MI, urgent revascularization

Pre-treated with aspirin, heparin & 600 mg clopidogrel

On-TIME 2

Lancet. 2008;372:537
**IIB/IIIa Meta-regression**

**30-Day Mortality**

# GP IIb/IIIa Guideline for STEMI 2009

<table>
<thead>
<tr>
<th>Early invasive / PCI</th>
<th>Medical Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC / AHA</td>
<td>ESC</td>
</tr>
<tr>
<td>Class IIa Abciximab</td>
<td>Class I Without stenting</td>
</tr>
<tr>
<td>Class IIb Tirofiban, eptifibatide</td>
<td>Class IIa With stenting</td>
</tr>
<tr>
<td></td>
<td>ACC / AHA</td>
</tr>
<tr>
<td></td>
<td>ESC</td>
</tr>
<tr>
<td>Class IIb Abciximab</td>
<td>Class IIb Abciximab with half-dose lytic for patients age &lt; 75 years</td>
</tr>
<tr>
<td></td>
<td>Class III</td>
</tr>
</tbody>
</table>

GPI = glycoprotein IIb/IIIa inhibitor
For UA / NSTEMI
Medical vs Interventional Therapy
30-day Death or MI – No Early PCI

<table>
<thead>
<tr>
<th>Trial</th>
<th>Placebo</th>
<th>2b3a Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>PURSUIT</td>
<td>15.6%</td>
<td>14.5%</td>
</tr>
<tr>
<td>PRISM PLUS</td>
<td>10.1%</td>
<td>7.8%</td>
</tr>
<tr>
<td>PARAGON B</td>
<td>11.3%</td>
<td>10.8%</td>
</tr>
<tr>
<td>GUSTO-IV ACS</td>
<td>8.0%</td>
<td>8.7%</td>
</tr>
</tbody>
</table>

p=NS
Medical vs Interventional Therapy
30-day Death or MI – Early PCI

- **PURSUIT**: 16.7% (Placebo), 11.6% (2b3a Inhibitor)
  - 16.7% in Placebo, p=0.01
  - 11.6% in Inhibitor, p=NS

- **PRISM PLUS**: 10.2% (Placebo), 5.9% (2b3a Inhibitor)
  - 10.2% in Placebo
  - 5.9% in Inhibitor, p=NS

- **PARAGON B**: 18.5% (Placebo), 11.6% (2b3a Inhibitor)
  - 18.5% in Placebo, P<0.05
  - 11.6% in Inhibitor, p=0.03

- **CAPTURE**: 9.0% (Placebo), 4.8% (2b3a Inhibitor)
  - 9.0% in Placebo
  - 4.8% in Inhibitor, p=0.03
ISAR-REACT
PCI for Low-risk SA Patients – 30 Days

Death

MI

Death/MI

Urg Revac

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Abciximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0.3%</td>
<td>0.3%</td>
</tr>
<tr>
<td>MI</td>
<td>3.8%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Death/MI</td>
<td>4.0%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Urg Revac</td>
<td>0.6%</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

p=NS

NEJM 2004;350:232-8
ISAR-REACT 2
PCI for Higher-risk ACS Patients – 30 Days

- **Death**: Placebo (1012) 1.6%, Abciximab (1010) 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
Higher-risk Patients (ACS) – 30 Days

JAMA 2006;295:1531-38
EVEREST: Study Design

- Angina at rest within 12 h of admission
- Unequivocal changes on ECG during angina
- cTnI elevation

High-risk NSTEMI ACS

“In-Lab” Abciximab

ASA/heparin thienopyridine

Intent to PTCA/stent 24 - 48 hours + Abciximab

“In-Lab” HDB Tirofiban

ASA/heparin thienopyridine

Intent to PTCA/stent 24 - 48 hours + HDB tirofiban

“Upstream” Tirofiban

ASA/heparin thienopyridine tirofiban

Intent to PTCA/stent 24 - 48 hours

HDB, high dose bolus
**EVEREST**
**Tissue-Level Perfusion by TMPG**

<table>
<thead>
<tr>
<th></th>
<th>Pre-PCI</th>
<th>Post-PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upstream</td>
<td>28.1</td>
<td>6.2</td>
</tr>
<tr>
<td>Tirofiban</td>
<td>66.7</td>
<td>20.0</td>
</tr>
<tr>
<td>HDB</td>
<td>71.0</td>
<td>35.5</td>
</tr>
<tr>
<td>Abciximab</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TMPG, TIMI perfusion grade

EVEREST
Tissue-Level Perfusion by Myocardial Contrast Echocardiography

MCE score index

\[ P = .012 \]

Normal tissue-level perfusion by MCE

\[ P = .04 \]

ACUITY Timing

Moderate-high risk ACS undergoing invasive strategy (N=13,800)
PCI in 57%

JAMA. 2007;297:591
ACUITY Timing
Ischemic Composite

30 day events (%)

- Routine Upstream IIb/IIIa (N=4605)
  - Ischemic composite: 7.1%
  - Death: 1.3%
  - MI: 4.9%
  - Unplanned rev for ischemia: 2.1%

- Deferred PCI IIb/IIIa (n=4602)
  - Ischemic composite: 7.9%
  - Death: 1.5%
  - MI: 5.0%
  - Unplanned rev for ischemia: 2.8%

JAMA. 2007;297:591
ACUITY Timing
Major Bleeding

<table>
<thead>
<tr>
<th>Group</th>
<th>Estimate</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine Upstream IIb/IIIa (N=4605)</td>
<td>6.1%</td>
<td></td>
</tr>
<tr>
<td>Deferred PCI IIb/IIIa (n=4602)</td>
<td>4.9%</td>
<td>0.009</td>
</tr>
<tr>
<td>Bivalirudin alone (N=4612)</td>
<td>3.0%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Days from Randomization vs Cumulative Events (%)

JAMA. 2007;297:591
EARLY-ACS: Primary Endpoint
Invasive Strategy
Death, MI, Urgent revasc., Thrombotic events


Delayed provisional eptifibatide
Early routine eptifibatide

N
4684
4722

# Events
469
439

10.0%

P = 0.23 (stratified for intended early clopidogrel use)
Early-ACS: 30-day Death or MI

Delayed provisional eptifibatide

Early routine eptifibatide

P = 0.079

(stratified for intended early clopidogrel use)

39% use of eptifibatide

12.4%

11.2%

N# Events
4684 578
Days to Event
2.1 (1.0, 5.8)

Early routine eptifibatide

N# Events
4722 528
Days to Event
2.7 (1.0, 4.9)

Early invasive / PCI | Medical Management

<table>
<thead>
<tr>
<th>ACC / AHA</th>
<th>ESC</th>
<th>ACC / AHA</th>
<th>ESC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I</strong> Either GPI or clopidogrel in addition to aspirin should be initiated before angiography</td>
<td><strong>Class I</strong> If subsequent recurrent symptom/ischemia, heart failure, or serious arrhythmia occur, angiography should be performed with upstream use of either clopidogrel or GPI</td>
<td><strong>Class I</strong></td>
<td><strong>Class II</strong> (high risk)</td>
</tr>
<tr>
<td><strong>Class IIa</strong> Reasonable to initiate antiplatelet therapy with both GPI and clopidogrel</td>
<td><strong>Class IIa</strong> If recurrent ischemic discomfort with clopidogrel, it is reasonable to add a GPI before angiography</td>
<td><strong>Class IIb</strong> May be reasonable to add GPI to oral antiplatelet and anticoagulant therapy</td>
<td></td>
</tr>
</tbody>
</table>

GPI = glycoprotein IIb/IIIa inhibitor
ICE Trial
Intracoronary Injection of Eptifibatide
180-g/kg eptifibatide IC bolus

Pre-PCI  Post-PCI

Circulation. 2010;121:784
Conclusion

• Extensive data support the use of IV GPIs in the setting of moderate- or high-risk NSTE-ACS, particularly if an early invasive strategy is planned.

• Patients who present with STEMI who are undergoing primary PCI also appear to benefit; however, the benefit is less evident.

• In the setting of low-risk ACS, GPIs may not be useful.

• In spite of extensive studies, open questions remain, including the timing of initiation, their clinical utility in combination with and compared with newer antithrombotics, and optimal dosing in certain patient populations (i.e., the elderly, patients with renal insufficiency).
## Reimbursement Policy in Korea

<table>
<thead>
<tr>
<th>Abciximab</th>
<th>Tirofiban</th>
</tr>
</thead>
<tbody>
<tr>
<td>o High risk PCI</td>
<td>o High risk ACS with elevated troponin or change of EKG</td>
</tr>
<tr>
<td>o PCI for high risk AMI</td>
<td></td>
</tr>
<tr>
<td>o Acute closure due to thrombus</td>
<td></td>
</tr>
<tr>
<td>o No reflow after stenting</td>
<td></td>
</tr>
<tr>
<td>o Threatening of acute closure due to no reflow, new thrombus,</td>
<td></td>
</tr>
<tr>
<td>intramural haziness during PCI</td>
<td></td>
</tr>
</tbody>
</table>