Efficacy and safety of early versus late glycoprotein IIb/IIIa inhibitors in ACS patients undergoing PCI

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Disclosures: NONE
ACS: Causes & Solutions

The cause
Ruptured TCF and luminal thrombus

The solution
Revascularization with stenting (in most pts) to stabilize the ruptured plaque
STEMI: PCI ~90%
NSTE-ACS: PCI~70%
ACS: What is the role of PCI?

- TIMI Flow
- Limit Infarct Size
- ST Resolution
- Myocardial Blush Grade
- Limit case complications
ACS: What really matters to the patient?

To survive

To have a high quality of life

Bleeding, Stroke, MI
pruritis/rash, depression, hepatitis
Dyspnea, Hospitalization
claudication, arrhythmias, convenience
Fatigue, Unplanned revasc
sleep, infections, myalgias
Renal insufficiency, cost
Angina, headaches
Thrombocytopenia
Platelet activation

- Epinephrine
- Collagen
- Thrombin
- ADP
- Thienopyridines
- Platelet
- Platelet Membrane
- TxA₂
- Aspirin
- GP IIb/IIIa
- GPIIb/IIIa inhibitors
- Fibrinogen
## Parenteral GP IIB/IIA Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Abciximab (ReoPro®)</th>
<th>Tirofiban (Aggrastat®)</th>
<th>Eptifibatide (Integrilin®)</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>Half-life</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>
Rationale of GP IIb/IIIa Inhibitors use in ACS

- Early potent antiplatelet therapy
- Adjunctive use in PCI improves outcomes
- May improve flow
- May limit infarct size (and thus complications)
ACS: Impact of MI and bleeding on mortality

24,112 patients from GUSTO IIb, PURSUIT, and PARAGON B

![Graph showing the impact of transfusion on cumulative mortality over time. The graph compares transfusion and no transfusion groups, with a Log Rank p-value of <0.001.]

Rao et al, JAMA 2004
GP IIb/IIa Inhibitors in STEMI / pPCI
Several trials performed before the routine use of stenting/DAPT, mostly using abciximab, had documented clinical benefits but increased bleeding with GP IIb/IIIa inhibitors in unselected pts undergoing primary PCI with UFH.
Trials performed before the routine use of DAPT documented no clinical benefits and increased bleeding of GP IIb/IIIa inhibitors (mostly abciximab) in unselected pts undergoing primary PCI with UFH.

*De Luca et al, Eur Heart J 2009*
In high-risk pts undergoing primary PCI with UFH, a mortality benefit of GP IIb/IIIa inhibitors (mostly abciximab) was documented.

De Luca et al, Eur Heart J 2009
Upstream vs. downstream use of GP IIB/IIA Inhibitors in primary PCI

EUROTRANSFER Registry of 1,086 pts
Only ~25% received >300 mg clopidogrel before cath lab

Compared to downstream use of abciximab, upstream abciximab before pPCI (>30 min before balloon) is associated with improved outcomes in pts>65y, without increasing bleeding

Dziewiertz et al, Int J Cardiol 2010
Upstream vs. downstream use of GP IIb/IIa Inhibitors in primary PCI

EGYPT-ALT

An individual patients data meta-analysis of 722 pts

Early upstream use of abciximab before pPCI improves mortality

De Luca et al, J Thromb Hemost 2011
Upstream vs. downstream use of GP IIb/IIa Inhibitors in primary PCI

EGYPT-ALT

An individual patients data meta-analysis of 722 pts

<table>
<thead>
<tr>
<th>Study</th>
<th>Period</th>
<th>Study design (number of patients)</th>
<th>Symptom duration (h)</th>
<th>Stent</th>
<th>Primary endpoints</th>
<th>Definition major bleeding complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>ReoPro-BRIDGING [22]</td>
<td>2003-2004</td>
<td>Early (n = 28) vs. late (n = 27) abciximab</td>
<td>&lt; 6</td>
<td>Yes</td>
<td>Preprocedural TIMI 3 flow, cTFC and MACE</td>
<td>TIMI major</td>
</tr>
<tr>
<td>Relax-MI [17]</td>
<td>2003-2004</td>
<td>Early (n = 105) vs. late (n = 105) abciximab</td>
<td>&lt; 6</td>
<td>Yes</td>
<td>Preprocedural TIMI 3 flow, ST resolution, myocardial salvage</td>
<td>TIMI major</td>
</tr>
<tr>
<td>Rakowski et al. [18]</td>
<td>2004</td>
<td>Early (n = 25) vs. late (n = 30) abciximab</td>
<td>&lt; 12</td>
<td>Yes</td>
<td>Preprocedural TIMI 3 flow, ST resolution, LVF</td>
<td>Intracranial bleeding or haemoglobin loss &gt; 5 g TIMI major</td>
</tr>
<tr>
<td>ERAMI [20]</td>
<td>2001-2002</td>
<td>Early (n = 36) vs. late (n = 38) abciximab</td>
<td>&lt; 12</td>
<td>NA</td>
<td>Preprocedural TIMI flow</td>
<td>TIMI major</td>
</tr>
<tr>
<td>Zorman et al. [16]</td>
<td>1998-2001</td>
<td>Early (n = 56) vs. late (n = 56) abciximab</td>
<td>&lt; 12</td>
<td>Yes</td>
<td>Early (60 min) ST-segment resolution, preprocedural 3 TIMI flow</td>
<td>TIMI major</td>
</tr>
<tr>
<td>REOMOBILE [19]</td>
<td>2001-2002</td>
<td>Early (n = 52) vs. late (n = 48) abciximab</td>
<td>&lt; 6</td>
<td>Yes</td>
<td>Preprocedural TIMI flow</td>
<td>TIMI major</td>
</tr>
<tr>
<td>Petronio et al. [21]</td>
<td>2006-2008</td>
<td>Early (n = 55) vs. late (n = 55) abciximab</td>
<td>&lt; 6</td>
<td>Yes</td>
<td>Infarct size at 6 months</td>
<td>TIMI major</td>
</tr>
</tbody>
</table>

Early upstream use of abciximab before pPCI improves mortality

De Luca et al, J Thromb Hemost 2011
Routine upstream use of bolus abciximab before pPCI did not yield clinical benefit compared with routine use in the catheterization laboratory

Ellis et al, NEJM 2008
Routine upstream use of bolus abciximab before pPCI increased bleeding compared with routine use in the catheterization laboratory.

Ellis et al, NEJM 2008
Upstream vs. downstream use of GP IIb/IIa Inhibitors in primary PCI (high-risk pts)

FINESSE Trial
90-day MACE

FINESSE Trial
1-year mortality

Routine upstream use of abciximab before pPCI in high risk STEMI pts (TIMI risk score>3) who present within 4 h of symptom onset to non-PCI hospitals might derive a survival benefit.

Herrmann et al, JACC Cardiovasc Interv 2009
# Upstream vs. downstream use of GP IIb/IIa Inhibitors in primary PCI

On -TIME 2 Trial

## ST resolution

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 493)</th>
<th>HBD Tirofiban (n = 491)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residual ST-segment deviation &gt;3 mm</td>
<td>205/455 (45.1%)</td>
<td>172/451 (38.1%)</td>
<td>0.035</td>
</tr>
<tr>
<td>Cumulative ST-segment deviation 1-h post-PCI, mm</td>
<td>4.8 ± 6.3</td>
<td>3.6 ± 4.6</td>
<td>0.003</td>
</tr>
<tr>
<td>ST-segment resolution 1 h post-PCI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>264/440 (60.0%)</td>
<td>286/436 (65.6%)</td>
<td>0.033</td>
</tr>
<tr>
<td>Partial</td>
<td>104/440 (23.6%)</td>
<td>100/436 (22.9%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>72/440 (16.4%)</td>
<td>50/436 (11.5%)</td>
<td></td>
</tr>
<tr>
<td>30 days</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Early, pre-hospital initiation of high bolus tirofiban + infusion for up to 18h (vs provisional use of tirofiban in the cath lab), in addition to high-dose clopidogrel, improves the markers of reperfusion after pPCI in patients with STEMI.

Ten Berg et al, JACC 2010
Upstream vs. downstream use of GP IIB/IIA Inhibitors in primary PCI

On-TIME 2 Trial
30-day MACE

Early, pre-hospital initiation of high bolus tirofiban + infusion for up to 18h (vs provisional use of tirofiban in the cath lab), in addition to high-dose clopidogrel, improves the clinical outcome after pPCI in patients with STEMI.

Ten Berg et al, JACC 2010
Upstream vs. downstream use of GP IIB/IIA Inhibitors in primary PCI

On-TIME 2 Trial
30-day bleeding

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Clinical Outcome and Safety-Related Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo/No Tirofiban Infusion</td>
</tr>
<tr>
<td>30 days</td>
<td>(n = 662)</td>
</tr>
<tr>
<td>Death, re-MI, or urgent TVR</td>
<td>57 (8.6%)</td>
</tr>
<tr>
<td>Death</td>
<td>27 (4.1%)</td>
</tr>
<tr>
<td>Recurrent MI</td>
<td>15 (2.3%)</td>
</tr>
<tr>
<td>Urgent TVR</td>
<td>31 (4.7%)</td>
</tr>
<tr>
<td>Urgent PCI</td>
<td>28 (4.2%)</td>
</tr>
<tr>
<td>Urgent CABG</td>
<td>3 (0.5%)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>19 (2.9%)</td>
</tr>
<tr>
<td>Major CABG-related</td>
<td>8 (1.2%)</td>
</tr>
<tr>
<td>Major non-CABG-related</td>
<td>11 (1.7%)</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>29 (4.4%)</td>
</tr>
<tr>
<td>Minor CABG-related</td>
<td>10 (1.5%)</td>
</tr>
<tr>
<td>Minor non-CABG-related</td>
<td>19 (2.9%)</td>
</tr>
</tbody>
</table>

Early, pre-hospital initiation of high bolus tirofiban + infusion for up to 18h (vs provisional use of tirofiban in the cath lab), in addition to high-dose clopidogrel, does not increase bleeding.

*Ten Berg et al, JACC 2010*
Upstream vs. downstream use of GP IIB/IIA Inhibitors in primary PCI

Prehospital Abciximab in ST-Segment Elevation Myocardial Infarction
Results of the Randomized, Double-Blind MISTRAL Study

<table>
<thead>
<tr>
<th></th>
<th>Ambulance (n = 127)</th>
<th>Cath Lab (n = 129)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST-Segment Resolution &gt; 70% After PCI&lt;sup&gt;a&lt;/sup&gt;</td>
<td>70.3%</td>
<td>65.8%</td>
<td>0.49</td>
</tr>
<tr>
<td>TIMI 2/3 Flow Before PCI</td>
<td>46.8%</td>
<td>35.0%</td>
<td>0.08</td>
</tr>
<tr>
<td>Distal Embolization During PCI</td>
<td>8.1%</td>
<td>21.1%</td>
<td>0.008</td>
</tr>
</tbody>
</table>

<sup>a</sup> Primary endpoint

Early, pre-hospital bolus abciximab + 12h infusion post-pPCI (vs routine bolus abciximab in the cath lab pre-pPCI + 12h infusion post-pPCI) does not improve ST resolution or outcomes

Ohlmann et al, Circ Cardiovasc Interv 2012
In STEMI pts preloaded with 600 mg of clopidogrel, upstream use of abciximab before pPCI did not reduce infarct size and did not improve MACE

Mehilli et al, Circulation 2009
Outcomes in STEMI with GP IIb/IIa: importance of anticoagulation

HORIZONS AMI
Harmonizing Outcomes with Revascularization and Stents in AMI

3602 pts with STEMI with symptom onset ≤12 hours

Aspirin, thienopyridine

UFH + GP IIb/IIa inhibitor (abciximab or eptifibatide)

Bivalirudin monotherapy (± provisional GP IIb/IIa)

Emergent angiography, followed by triage to...

CABG – Primary PCI – Medical Rx

3006 pts eligible for stent randomization

Paclitaxel-eluting TAXUS stent

Bare metal EXPRESS stent

Clinical FU at 30 days, 6 months, 1 year, and then yearly through 5 years; angio FU at 13 months

Stone et al, NEJM 2008
In STEMI pts preloaded with 300 or 600 mg of clopidogrel, there is no clear benefit from upstream use of GP IIb/IIa inhibitor (abciximab bolus + 12h inf. or eptifibatide double bolus + 12-18h inf.) + UFH, compared to bivalirudin (with bail-out GP IIb/IIa inhibitor).

Stone et al, NEJM 2008
GP IIb/IIIa Inhibitors use in STEMI

ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiplatelet therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin oral or i.v. (if unable to swallow) is recommended</td>
<td>I</td>
<td>B</td>
<td>133, 134</td>
</tr>
<tr>
<td>An ADP-receptor blocker is recommended in addition to aspirin. Options are:</td>
<td>I</td>
<td>A</td>
<td>135, 136</td>
</tr>
<tr>
<td>• Prasugrel in clopidogrel-naive patients, if no history of prior stroke/TIA, age &lt;75 years.</td>
<td>I</td>
<td>B</td>
<td>109</td>
</tr>
<tr>
<td>• Ticagrelor</td>
<td>I</td>
<td>B</td>
<td>110</td>
</tr>
<tr>
<td>• Clopidogrel, preferably when prasugrel or ticagrelor are either not available or contraindicated.</td>
<td>I</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>GP IIb/IIIa inhibitors should be considered for bailout therapy if there is angiographic evidence of massive thrombus, slow or no-reflow or a thrombotic complication.</td>
<td>IIa</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>Routine use of a GP IIb/IIIa inhibitor as an adjunct to primary PCI performed with unfractionated heparin may be considered in patients without contraindications.</td>
<td>IIb</td>
<td>B</td>
<td>137–141</td>
</tr>
<tr>
<td><strong>Upstream use of a GP IIb/IIIa inhibitor (vs. in-lab use) may be considered in high-risk patients undergoing transfer for primary PCI.</strong></td>
<td>IIb</td>
<td>B</td>
<td>127, 128, 137, 142</td>
</tr>
<tr>
<td>Options for GP IIb/IIIa inhibitors are (with LoE for each agent):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Abciximab</td>
<td>A</td>
<td></td>
<td>137</td>
</tr>
<tr>
<td>• Eptifibatide (with double bolus)</td>
<td>B</td>
<td></td>
<td>138, 139</td>
</tr>
<tr>
<td>• Tirofiban (with a high bolus dose)</td>
<td>B</td>
<td></td>
<td>140, 141</td>
</tr>
</tbody>
</table>
GP IIb/IIIa Inhibitors use in STEMI

2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction

<table>
<thead>
<tr>
<th>IV GP IIb/IIIa receptor antagonists in conjunction with UFH or bivalirudin in selected patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abciximab: 0.25-mg/kg IV bolus, then 0.125 mcg/kg/min (maximum 10 mcg/min)</td>
</tr>
<tr>
<td>Tirofiban: (high-bolus dose): 25-mcg/kg IV bolus, then 0.15 mcg/kg/min</td>
</tr>
<tr>
<td>In patients with CrCl &lt;30 mL/min, reduce infusion by 50%</td>
</tr>
<tr>
<td>Eptifibatide: (double bolus): 180-mcg/kg IV bolus, then 2 mcg/kg/min; a second 180-mcg/kg bolus is administered 10 min after the first bolus</td>
</tr>
<tr>
<td>In patients with CrCl &lt;50 mL/min, reduce infusion by 50%</td>
</tr>
<tr>
<td>Avoid in patients on hemodialysis</td>
</tr>
<tr>
<td>Pre-catheterization laboratory administration of IV GP IIb/IIIa receptor antagonist</td>
</tr>
<tr>
<td>Intracoronary abciximab 0.25-mg/kg bolus</td>
</tr>
</tbody>
</table>
GP IIB/IIA Inhibitors in PCI for NSTE-ACS
In NSTE-ACS pts undergoing PCI after pretreatment with 600 mg of clopidogrel, abciximab (bolus during cath + 12h infusion) improves outcomes. The benefit appears to be confined to patients presenting with an elevated troponin level. 

*Kastrati et al: JAMA 2006*
Upstream vs. downstream use of GP IIb/IIa Inhibitors in NSTE-ACS

ACUITY Study Design: First Randomization

Moderate- to high-risk patients with UA or NSTEMI undergoing an invasive strategy (N = 13,819)

- Aspirin in all
- Clopidogrel dosing and timing per local practice

UFH or enox + GP IIb/IIIa n=4603

Bivalirudin + GP IIb/IIIa n=4604

Bivalirudin alone n=4,612

Angiography within 72 h

- Medical management
- PCI
- CABG

Stone et al: Am Heart J 2004
Moderate- to high-risk patients with UA or NSTEMI undergoing an invasive strategy (N = 13,819)

ACUITY Study Design: Second Randomization

- UFH or Enoxaparin
  - Routine upstream GPI in all pts (2294)
  - GPI started in CCL for PCI only (2309)
- Bivalirudin
  - Routine upstream GPI in all pts (2311)
  - GPI started in CCL for PCI only (2293)

vs

- Routine upstream GPI in all pts n=4603
- Deferred GPI for PCI only N=4604

Primary analysis

Secondary analysis

Stone et al: Am Heart J 2004

Moderate-to high-risk ACS

Aspirin in all; Clopidogrel dosing and timing per local practice
Upstream vs. downstream use of GP IIB/IIA Inhibitors in NSTE-ACS

ACUITY Study

GP IIb/IIIa inhibitors were used in 55.7% of patients for 13.1 h in the deferred selective strategy and in 98.3% of patients for 18.3 h (pre-treatment median 4 h) in the routine upstream strategy. 64% of patients received thienopyridines before angiography /PCI.

Routine upstream use of GP IIB/IIA inh. in moderate/high risk NSTE-ACS pts undergoing an early invasive strategy does not improve outcomes and increases bleeding.

Upstream vs. downstream use of GP IIb/IIa Inhibitors in NSTE-ACS

Early-ACS Trial

2 of 3 high-risk criteria:
1. Age ≥ 60 years
2. + CKMB or TnT/I
3. ST ↓ or transient ST ↑
   (Or age 50-59, history CVD and + CKMB or TnT/I)

High-risk NSTE ACS

n = 10,500 (9500)

Early, routine eptifibatide (180/2/180)

Placebo / provisional eptifibatide pre-PCI

Randomize within 12 hours of presentation

Invasive strategy: 12 to 96 hours after randomization

1° Endpoint: 96-hr Death/MI/Urgent Revasc/Thrombotic bailout

2° Endpoint: 30-d Death/MI

Fade in safety endpoints at 120 hours (bleeding (GUSTO and TIMI scales), transfusions, stroke, non-hemorrhagic SAEs)

Giugliano et al: NEJM 2009
- In patients with high-risk NSTE-ACS, the use of eptifibatide 12 hours or more before angiography was not superior to the provisional use of eptifibatide after angiography.
- Similar findings in important subgroups (diabetics, trop +)

Giugliano et al: NEJM 2009
In patients with high-risk NSTE-ACS, the use of eptifibatide 12 hours or more before angiography (compared to the provisional use of eptifibatide after angiography) is associated with an increased risk of non–life-threatening bleeding and need for transfusion.

_Giugliano et al: NEJM 2009_
Upstream vs. downstream use of GP IIB/IIA Inhibitors in NSTE-ACS

Meta-analysis of 12 randomized trials conducted between 1996 and 2009

<table>
<thead>
<tr>
<th>Effect of Upstream GPIs</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-Day Death</td>
<td>0.93</td>
<td>0.83-1.05</td>
</tr>
<tr>
<td>30-Day MI</td>
<td>0.91</td>
<td>0.84-0.97</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>1.23</td>
<td>1.02-1.48</td>
</tr>
</tbody>
</table>

**Conclusion:** Among NSTE ACS patients, upstream GPI use decreases MI risk but increases major bleeding, with no effect on mortality. Selected periprocedural GPI use in high-risk patients undergoing PCI may be optimal.

*Tricoci et al: Circ Cardiovasc Qual Outcomes 2011*
ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

<table>
<thead>
<tr>
<th>Recommendations for GP IIb/IIIa receptor inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendations</strong></td>
</tr>
<tr>
<td>The choice of combination of oral antiplatelet agents, a GP IIb/IIIa receptor inhibitor, and anticoagulants should be made in relation to the risk of ischaemic and bleeding events.</td>
</tr>
<tr>
<td>Among patients who are already treated with DAPT, the addition of a GP IIb/IIIa receptor inhibitor for high-risk PCI (elevated troponin, visible thrombus) is recommended if the risk of bleeding is low.</td>
</tr>
<tr>
<td>Eptifibatide or tirofiban added to aspirin should be considered prior to angiography in high-risk patients not preloaded with P2Y12 inhibitors.</td>
</tr>
</tbody>
</table>

In high-risk patients, eptifibatide or tirofiban may be considered prior to early angiography in addition to DAPT, if there is ongoing ischaemia and the risk of bleeding is low.

GP IIb/IIIa receptor inhibitors are not recommended routinely before angiography in an invasive treatment strategy.

GP IIb/IIIa receptor inhibitors are not recommended for patients on DAPT who are treated conservatively.
GP IIb/IIIa Inhibitors use in ACS

What biases the evaluation of early vs. late GPI treatment in trials?

Type, dose and timing of oral antiplatelet treatment
- 300 vs. 600 mg loading dose of clopidogrel
- Clopidogrel vs. ticagrelor / prasugrel

Type of anticoagulant
- UFH vs. bivalirudin

Definition of early/late GPI use
- Early: prehospital vs. just before angio, bolus vs bolus + infusion
- Late: provisional GPI vs routine GPI
In patients with ACS treated with PCI, prasugrel reduces the risk of CV events regardless of whether or not a GP IIb/IIIa inhibitor is used.

The use of a GP IIb/IIIa inhibitor increases bleeding (HR~1.6), but does not accentuate the relative risk of bleeding with prasugrel as compared with clopidogrel.

- The use of a GP IIb/IIIa inhibitor increases bleeding (HR~1.6), but does not accentuate the relative risk of bleeding with prasugrel as compared with clopidogrel.

O’Donoghue et al, JACC 2009

Hoschholzer et al, Circulation 2011
GP IIb/IIIa Inhibitors use in ACS in the era of intense antithrombotic treatment

Pooled analysis of ACUITY and ISAR-REACT4 Trials

In clopidogrel pretreated NSTE-ACS pts treated with PCI, UFH + GP IIb/IIa inh. is associated with similar ischemic events but more bleeding compared to bivalirudin.

Ndrepepa et al, Cir Cardiovasc Interv 2012
GP IIb/IIIa Inhibitors use in ACS in the era of intense antithrombotic treatment

In STEMI, prasugrel + a bolus only of GP IIb/IIIa inhibitor, obviates the need of post-bolus infusion and almost completely abolishes residual variability of platelet aggregation

Valgimigli et al, JACC Cardiovasc Interv 2012
GP IIb/IIIa Inhibitors use in ACS

Conclusions

- In the era of potent DAPT (particularly when prasugrel or ticagrelor is used), the role of routine (upstream or downstream) use of GP IIb/IIIa inhibitors in ACS patients undergoing PCI is not definitive.

- In STEMI, use of GP IIb/IIIa inhibitors as bailout therapy in the event of angiographic evidence of large thrombus, slow or no-reflow and other thrombotic complications is reasonable (but not yet proven in a randomized trial).

- In STEMI, routine upstream use of GP IIb/IIIa inhibitors is not recommended. Upstream use may be beneficial in high-risk pts not adequately preloaded with P2Y$_{12}$ receptor inhibitors who will not take bivalirudin during pPCI.

- In NSTE-ACS, “upstream” PCI (early invasive strategy) is perhaps more important than upstream GP IIb/IIIa inhibitors.
Ticagrelor vs. Prasugrel in ACS Patients with High On-Clopidogrel Platelet Reactivity Following PCI

44 pts randomized to ticagrelor (90 mg twice daily) or prasugrel (10 mg once daily) for 15 days, then crossed over for another 15 days; reactivity assessed by VerifyNow P2Y12 assay.

- Overall, ticagrelor reduced platelet reactivity to 32.9 PRU vs. 101.3 PRU with prasugrel (\( P < 0.001 \))
- No patient on ticagrelor and only 1 patient on prasugrel failed to fall below the efficacy threshold of 235 PRU
- No patient in either group experienced major adverse cardiovascular or bleeding events

Implications: In ACS pts with high on-clopidogrel platelet reactivity after PCI, ticagrelor produces more profound platelet inhibition than prasugrel.

REPLACE – 2 Trial Design

Trial design
Bivalirudin
0.75 mg/kg bolus
1.75 mg/kg/h procedure
Provisional abciximab or eptifibatide

Endpoints
30-day
• Death
• MI
• Revascularization
• Hemorrhage

Economics
1-year mortality

1:1 randomization

6000 PCI Patients
Urgent or elective PCI

Aspirin
Plavix
PCI

Bivalirudin
0.75 mg/kg bolus
1.75 mg/kg/h procedure
Provisional abciximab or eptifibatide

Heparin
65 U/kg

Abciximab or Eptifibatide
REPLACE - 2

Primary Endpoint

- Heparin + GP 2b/3a (n=3008)
- Bivalirudin (n=2994)

%:
- Composite: 10% (Heparin) vs 9.2% (Bivalirudin), p=0.324
- Death: 0.4% (Heparin) vs 0.2% (Bivalirudin), p=0.255
- MI: 6.2% (Heparin) vs 7% (Bivalirudin), p=0.43
- Urg TVR: 1.4% (Heparin) vs 1.2% (Bivalirudin), p=0.435
- Major Bleed: 4.1% (Heparin) vs 2.4% (Bivalirudin), p<0.001
REPLACE - 2

Outcomes

- CK-MB
- Q MI
- Minor Bleed
- Transfuse
- Thrombocytopenia

Heparin + GP 2b/3a
Bivalirudin

p=ns
p<0.001
p=ns
p=ns
p=ns