2B or not 2B?

ACS and the Role of IIb/IIIa Inhibitors.

Asad Mohmand
September 13, 2012
Overview

• Background
• GP IIb/IIIa Inhibitors
• Early and Contemporary Trials
• Review of the Guidelines
• Discussion


Mechanisms of Disease

A Platelets and inflammatory cells

- TXA2
- TPalpha
- TPbeta

B Platelets and red cells

- ADP
- P2Y1
- P2Y12

C Thrombin

- PAR1
- Rho GEFs
- Rho
- Ca2+

Adenylate cyclase

AA

COX

Fibrinogen

Glycoprotein Iib/IIa

von Willebrand factor

Platelet

Platelet

1cAMP

Ca2+

TP

ADP

P2Y

PGH2

TXA2

AA

PGH2

TXA2

PLA2

COX

PAR

Platelet

Glycoprotein Iib/IIa

von Willebrand factor

Platelet

NEJM 2007;357:2482-94
- Platelet-specific
- Calcium-dependent
- ~ 80,000 / platelet
- Bind adhesive proteins
- Mediate platelet aggregation
- Facilitate clot-retraction
- Glanzmann thrombasthenia
A Murine Monoclonal Antibody That Completely Blocks the Binding of Fibrinogen to Platelets Produces a Thrombasthenic-like State in Normal Platelets and Binds to Glycoproteins IIb and/or IIIa

Barry S. Coller, Ellinor I. Peerschke, Lesley E. Scudder, and Carole A. Sullivan, Departments of Medicine, Pathology and Microbiology, State University of New York at Stony Brook, Stony Brook, New York 11794

ABSTRACT To define better the role of the fibrinogen receptor in platelet physiology and to characterize it biochemically, a murine monoclonal antibody that completely blocks the binding of fibrinogen to the platelet surface was produced by the hybridoma technique with the aid of a functional screening assay. Purified F(ab)'2 fragments and/or intact antibody completely blocked aggregation induced by ADP, thrombin, or epinephrine and the binding of radiolabeled fibrinogen to platelets induced by ADP. The antibody did not block agglutination of formaldehyde-fixed platelets by ristocetin or shape change induced by either ADP or thrombin. ADP- and epinephrine-induced release of ATP was completely inhibited by the antibody, but inhibition of release induced by collagen and thrombin was dose dependent and partial. The antibody also dramatically inhibited platelet retention in glass-bead columns, platelet adhesion to glass, and clot retraction. Thus, the antibody induced a thrombasthenic-like state. Immunofluorescent studies confirmed the specificity of the antibody for normal platelets and megakaryocytes and suggested that there is a marked decrease in detectable antigen in thrombasthenic platelets. Radiolabeled antibody bound to an average of ~40,000 sites on normal platelets but it bound to <2,000 sites on the platelets of a patient with thrombasthenia. The antibody immunoprecipitated both glycoproteins IIb and IIIa, and both glycoproteins bound to an affinity column of the antibody. These studies indicate that there is probably a single a component site that is crucial to the binding of all fibrinogen molecules and that this site is most likely on the coprotein IIb/IIIa complex. It also suggests that thrombasthenic phenotype can be completely accounted for on the basis of the inhibition of fibrinogen binding to platelets.

INTRODUCTION

The interaction of fibrinogen with its platelet receptor occupies a central role in platelet physiology. Clinical evidence indicates that it is required to achieve values for the skin bleeding time, the adhesion of platelets to glass surfaces, and the aggregation of platelets induced by ADP, epinephrine, thrombin, or dextran acid metabolites (1-11). There is general agreement that patients with Glanzmann's thrombasthenia have a functional defect of their platelet fibrinogen receptors, as evidenced by the inability of the platelets to bind fibrinogen (12-15). As these patients are deficient in the membrane glycoprotein GPIIb/IIIa (16, 17) and as there is evidence that the glycoprotein complex together in association with fibrinogen (18), the GPIIb/IIIa complex has been tentatively identified as the fibrinogen receptor that persists, however, since it has been reported that thrombasthenic platelets have abnormality in the surface glycoproteins (18) and one group has suggested that thrombasthenic platelets do indeed have less fibrinogen, but are unable to expose the response to agonist activation (20).

To define better the role of the fibrinogen receptor in platelet physiology and to characterize it biochemically, we have employed the hybridoma technique.
Plasma half-life: 10 – 30 min

Biological half-life: 12 – 24 hrs

Onset of action: Rapid

Offset of action: 12 – 36 hrs

Renal adjustment: Not required

FDA-approved use: PCI
Bolus*  
0.25 mcg/kg  

Infusion*  
0.125 mcg/kg/min (max 10 mcg/min)  

Duration  
12 hours  

> 80% IPA  
10 min – 6 hours (variable after 6 hrs)  

* Dosing established in the EPIC trial
### (eptifibatide) Injection INTEGRILIN

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma half-life</td>
<td>1 – 3 hrs</td>
</tr>
<tr>
<td>Biological half-life</td>
<td>2 – 4 hrs</td>
</tr>
<tr>
<td>Onset of action</td>
<td>Rapid</td>
</tr>
<tr>
<td>Offset of action</td>
<td>~50% 4hrs after stopping</td>
</tr>
<tr>
<td>Renal adjustment</td>
<td>Required (CI in HD)</td>
</tr>
<tr>
<td>FDA-approved use</td>
<td>PCI + ACS</td>
</tr>
<tr>
<td>PCI: Bolus x 2*</td>
<td>180 mcg/kg → 10 min → 180 mcg/kg</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Infusion**</td>
<td>2 mcg/kg/min</td>
</tr>
<tr>
<td>Duration</td>
<td>18 – 24 hrs.</td>
</tr>
<tr>
<td>ACS</td>
<td>180 mcg/kg → 2 mcg/kg/min** x 72 hrs.</td>
</tr>
</tbody>
</table>

* Dosing established in the PRIDE and ESPRIT studies
** If Cr-clearance < 50 mL/min, infuse at 1 mcg/kg/min
Thrombocytopenia

Absciximab:

- **Mild:** 4.2% vs. 1%  \( (p<0.001) \)
- **Severe:** 1% vs. 0.4%  \( (p=0.01) \)
- **Other Sx:** Fever, dyspnea, low BP, anaphylaxis
- **Risk Factors:** Prior exposure   Prior TIA
                 Female gender   Elevated Cr.
                 Age >65, Wt. <90k   PVD
- Delayed (5-8 days) thrombocytopenia is rare.
- Increased **risk** of death, bleeding and transfusions.
- Responds to **transfusion** of platelets.
Thrombocytopenia

Eptifibatide:

- Less common
- Natural or induced drug-depended antibodies?
- Short duration due to shorter half-life
- Drug can be dialysed due to high protein-binding
- **Treatment:** Discontinue eptifibatide
Abstract  Background. Platelets are believed to play a role in the ischemic complications of coronary angioplasty, such as abrupt closure of the coronary vessel during or soon after the procedure. Accordingly, we evaluated the effect of a chimeric monoclonal-antibody Fab fragment (c7E3 Fab) directed against the platelet glycoprotein IIb/IIIa receptor, in patients undergoing angioplasty who were at high risk for ischemic complications. This consists of the final common pathway for platelet aggregation.

Methods. In a prospective, randomized, double-blind trial, 2,094 patients treated at 56 centers received a bolus and an infusion of placebo, a bolus of c7E3 Fab and an infusion of placebo, or a bolus and an infusion of c7E3 Fab. They were scheduled to undergo coronary angioplasty or stent placement in high-risk clinical situations involving severe, unstable angina, evolving acute myocardial infarction, or high-risk coronary morphologic characteristics. The primary study end point consisted of any of the following: death, nonfatal myocardial infarction, unplanned repeat percutaneous coronary angioplasty, or unplanned repeat percutaneous coronary stent implantation. The numbers of end-point events were tabulated for 30 days after randomization.

Results. As compared with placebo, the c7E3 Fab bolus and infusion resulted in a 35 percent reduction in the rate of the primary end point (12.9 vs. 8.3 percent, P = 0.004), whereas a 10 percent reduction was observed (12.9 vs. 11.0 percent).
Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade

The EPISTENT Investigators*
Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-Ilb/Ilia blockade

The EPISTENT Investigators*
Randomised placebo-controlled trial of eptifibatide for complications of percutaneous coronary intervention

The IMPACT-II Investigators*

Introduction

Abrupt closure of coronary arteries during percutaneous coronary intervention (PCI) and its related sequela, such as myocardial infarction, unplanned surgical or repeat percutaneous coronary procedure was started within 10–60 min of the end of the efficacy-response curve. Further investigation to understand the mechanism of this abrupt closure has led to the development of several agents, including eptifibatide (Integrilin, COR Therapeutics, South San Francisco, CA, USA) a cyclic heptapeptide, and a competitive inhibitor of platelet glycoprotein IIb/IIIa. It has been shown to be active ex vivo and in pilot studies during elective coronary intervention.** In this trial, a phase III investigation of a synthetic small-molecule inhibitor, our hypothesis was that eptifibatide would be effective in suppressing ischaemic complications related to PCI.
A randomised, blinded, trial of clopidogrel versus patients at risk of ischaemic events (CAPRIE)
Abciximab in Patients With Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention After Clopidogrel Pretreatment: The ISAR-REACT 2 Randomized Trial

Troponin >0.03 µg/L
Log-Rank P = .02

Troponin ≤0.03 µg/L
Log-Rank P = .98

JAMA. 2006;295:1531-1538
One-year clinical outcomes with abciximab vs. placebo in patients with non-ST-segment elevation acute coronary syndromes undergoing percutaneous coronary intervention after pre-treatment with clopidogrel: results of the ISAR-REACT 2 randomized trial

Aims
The aim of this study was to investigate whether the benefit of abciximab in patients with non-ST-segment elevation acute coronary syndromes (NSTEMI-ACS) undergoing percutaneous coronary intervention (PCI) after pre-treatment with 600mg clopidogrel is sustained at 1 year.

Hypothesis and results
We performed 1-year follow-up of 3020 high-risk patients with NSTEMI-ACS undergoing urgent PCI, who were randomized to abciximab or placebo after pre-treatment with 600mg clopidogrel in the ISAR-REACT 2 trial. The composite outcome was death, myocardial infarction, or target vessel revascularization at 1 year was the primary outcome analysis. At 1 year, the primary outcome was reached in 23.0% of patients randomized to clopidogrel vs. 24.2% of patients randomized to clopidogrel (relative risk 0.92, 85% confidence interval 0.81-1.05, P<0.05). The combined incidence of death or myocardial infarction was 14.6% in patients randomized to clopidogrel vs. 15.3% in patients randomized to placebo (HR 0.95, 95% CI 0.89-1.02, P=0.26).

Conclusion
In high-risk patients with NSTEMI-ACS undergoing PCI after pre-treatment with 600mg clopidogrel, abciximab occurred less frequently with clopidogrel and the early benefit was maintained at 1 year after administration.

Keywords
Abciximab • Acute coronary syndromes • Clopidogrel • Percutaneous coronary intervention

Survival free of MI

Survival
IIb/IIIa in NSTEMI

30-day Death or MI – No Early PCI

Eur Heart J, Vol. 23, issue 18, September 2002
IIb/IIIa in NSTEMI

30-day Death or MI – *Early* PCI

![Graph showing 30-day death or MI results for Placebo and 2b3a Inhibitor in PURSUIT, PRISM PLUS, PARAGON B, and CAPTURE trials.](image)

*P-values highlighted: p=0.01, P<0.05, p=NS, p=0.03.*

*Eur Heart J, Vol. 23, issue 18, September 2002*
Bivalirudin for Patients with Acute Coronary Syndromes

- 13819 patients
- NSTE-ACS
- Three Tx groups:
  1. Bival
  2. Bival + IIb/IIIa
  3. Hep/LMWH + IIb/IIIa
- Death + MI + TVR
- Major Bleeding
- NACE
ACUITY

Bivalirudin for Patients with Acute Coronary Syndromes

- 13819 patients
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Bivalirudin for Patients with Acute Coronary Syndromes

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  3. Hep/LMWH + IIb/IIa
- Death + MI + TVR
- Major Bleeding
- NACE
Routine Upstream Initiation vs Deferred Selective Use of Glycoprotein IIb/IIIa Inhibitors in Acute Coronary Syndromes
The ACUITY Timing Trial

Composite Ischemia (Time-to-Event)

Major Bleeding

Net Clinical Outcomes

JAMA. 2007;297:591-602
EARLY ACS
NEJM 2009. 360;21

9492 High Risk NSTEMI

86 Excluded

9406 Intention-to-treat

4722 early eptifibatide
8 Had incomplete 30-day follow-up data
2 Were lost to follow-up
4 Withdrew consent
2 Had early 30-day visit

4714 available for follow-up

4684 delayed eptifibatide
20 Had incomplete 30-day follow-up data
9 Were lost to follow-up
10 Withdrew consent
1 Had early 30-day visit

4664 available for follow-up
• No difference in primary composite endpoint

• No difference in secondary endpoint (death or MI)

• More TIMI major bleeding with early IIb/IIIa (p = 0.02)

• More transfusions (8.6 vs. 6.7%, p = 0.001)
guidelines
<table>
<thead>
<tr>
<th>Year</th>
<th>Non-invasive</th>
<th>Early Invasive</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>Continued ischemia OR High-risk features</td>
<td>All patients</td>
</tr>
<tr>
<td>2002</td>
<td>High-risk features Abciximab</td>
<td>All patients with Hep + ASA Hep + ASA + clopidogrel</td>
</tr>
<tr>
<td>2007</td>
<td>Unchanged</td>
<td>GPI or clopidogrel load GPI + clopidogrel</td>
</tr>
<tr>
<td>2011</td>
<td>Ischemic discomfort with DAPT DAPT + eptifibatide or tirofiban Abciximab</td>
<td>Upstream GPI or clopidogrel Clopidogrel + GPI Omit if Bival + 300mg clopid.</td>
</tr>
<tr>
<td>2012</td>
<td>Changes made to P2Y12 agents</td>
<td>Changes made to P2Y12</td>
</tr>
</tbody>
</table>
• **Abciximab** most widely studied IIb/IIIa inhibitor

• Improved perfusion, recovery of LVEF \(^1\)

• Reduction in long-term **mortality** & 30-day **reinfarction** \(^2\)

• 59% decrease in **MACE** with primary PCI (stenting) \(^2\)

• Abciximab was superior to ticlopidine

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2. ADIMRAL study. JAMA 2005 Apr 13; 293 (14): 1759-65
Is abciximab beneficial after adequate preloading with clopidogrel?

- Primary PCI for STEMI
- 800 patients randomized
- 600mg clopidogrel
- Upstream abciximab vs. placebo
- Infarct size on SPECT
- Ischemic composite higher with abciximab at 30 days (3.8% vs. 5%)

Interventional Cardiology

Abciximab in Patients With Acute ST-Segment–Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention After Clopidogrel Loading
A Randomized Double-Blind Trial

Julinda Mehilli, MD; Adnan Kastrati, MD; Stefanie Schulz, MD; Stefan Früngel; Stephan G. Nekolla, PhD; Werner Moshage, MD; Franz Dotzer, MD; Kurt Huber, MD; Jürgen Pache, MD; Josef Dirschinger, MD; Melchior Seyfarth, MD; Stefan Martinoff, MD; Markus Schweiger, MD; Albert Schöning, MD; for the Bavarian Reperfusion Alternatives Evaluation-3 (BRAVE-3) Study Investigators

Background—The glycoprotein IIb/IIIa receptor inhibitor abciximab has improved the efficacy of primary percutaneous coronary interventions in patients with acute myocardial infarction. However, it is not known whether abciximab remains beneficial after adequate clopidogrel loading in patients with acute ST-segment–elevation myocardial infarction.

Methods and Results—A total of 800 patients with acute ST-segment–elevation myocardial infarction within 24 hours from symptom onset, all treated with 600 mg clopidogrel, were randomly assigned in a double-blind fashion to receive either abciximab (n=401) or placebo (n=399) in the intensive care unit before being sent to the catheterization laboratory. The primary end point, infarct size measured by single-photon emission computed tomography with technetium-99m sestamibi before hospital discharge, was 15.7±17.2% (mean±SD) of the left ventricle in the abciximab group and 16.6±18.6% of the left ventricle in the placebo group (P=0.47). At 30 days, the composite of death, recurrent myocardial infarction, stroke, or urgent revascularization of the infarct-related artery was observed in 20 patients in the abciximab group (5.0%) and 15 patients in the placebo group (3.8%) (relative risk, 1.3; 95% CI, 0.7 to 2.6; P=0.40). Major bleeding complications were observed in 7 patients in each group (1.8%).

Conclusion—Upstream administration of abciximab is not associated with a reduction in infarct size in patients presenting with acute myocardial infarction within 24 hours of symptom onset and receiving 600 mg clopidogrel. (Circulation. 2009;119:1933-1940)
<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of patients</th>
<th>Agent used</th>
<th>Primary endpoint (%; GP IIb/IIIa vs placebo)</th>
<th>TIMI bleeding (%; GP IIb/IIIa vs placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADMIRAL</td>
<td>300</td>
<td>Abciximab</td>
<td>Death, reinfarction and TVR at 30 days: 6 vs 14.6; <em>p</em> = 0.01</td>
<td>Major: 0.7 vs 0; <em>p</em> = NS</td>
</tr>
<tr>
<td>CADILLAC</td>
<td>1046</td>
<td>Abciximab</td>
<td>Death, reinfarction, stroke and ischaemia-driven TVR at 30 days: 4.8 vs 8.3; <em>p</em> = 0.02</td>
<td>Major: 0.4 vs 0.6; <em>p</em> = NS</td>
</tr>
<tr>
<td>PTCA</td>
<td></td>
<td></td>
<td></td>
<td>Moderate: 2.3 vs 2.5; <em>p</em> = NS (GUSTO)</td>
</tr>
<tr>
<td>CADILLAC</td>
<td>1036</td>
<td>Abciximab</td>
<td>Death, reinfarction, stroke and ischaemia-driven TVR at 30 days: 4.4 vs 5.7; <em>p</em> = NS</td>
<td>Major: 0.8 vs 0.2; <em>p</em> = NS</td>
</tr>
<tr>
<td>Stent</td>
<td></td>
<td></td>
<td></td>
<td>Moderate: 4.3 vs 2.5; <em>p</em> = NS (GUSTO)</td>
</tr>
<tr>
<td>BRAVE3</td>
<td>800</td>
<td>Abciximab</td>
<td>Death, MI, stroke, urgent TVR at 30 days: 5 vs 3.8; <em>p</em> = 0.04</td>
<td>Major: 1.8 vs 1.8; <em>p</em> = NS</td>
</tr>
<tr>
<td>ACE</td>
<td>400</td>
<td>Abciximab</td>
<td>Death, reinfarction, target vessel revascularization and stroke at 1 mo were lower with abciximab (4.5 vs 10.5, <em>p</em> = 0.023). Improved survival and reinfarction rates at 1 y. No difference in mortality at 1 mo or 6 mo</td>
<td>No differences in haemorrhagic complications requiring blood transfusion or vascular repair between the groups; 3.5 vs 3.0; <em>p</em> = 0.778</td>
</tr>
</tbody>
</table>
### STEMI Guidelines

<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><strong>Class IIa</strong></td>
<td><strong>Class I</strong></td>
</tr>
<tr>
<td>Abciximab</td>
<td>Without stenting</td>
</tr>
<tr>
<td><strong>Class IIb</strong></td>
<td><strong>Class Ila</strong></td>
</tr>
<tr>
<td>Tirofiban, eptifibatide</td>
<td>With stenting</td>
</tr>
<tr>
<td>Class IIb</td>
<td><strong>Class IIb</strong></td>
</tr>
<tr>
<td>Abciximab with half-dose lytic for patients age &lt; 75 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Class III</strong></td>
</tr>
</tbody>
</table>
### STEMI Guidelines

#### 2004/2005/2007 Recommendations: 2004 STEMI Guideline Section 6.3.1.6.8.2.3; Also 2005 PCI Guideline Section 6.2.2

#### Class IIa

1. It is reasonable to start treatment with abciximab as early as possible before primary PCI (with or without stenting) in patients with STEMI. (Level of Evidence: B)

#### Class IIb

1. Treatment with tirofiban or eptifibatide may be considered before primary PCI (with or without stenting) in patients with STEMI. (Level of Evidence: C)

### 2009 Joint STEMI/PCI Focused Update Recommendations

#### Comments

- **COR for eptifibatide and tirofiban changed to IIa**

#### Class IIa

1. It is reasonable to start treatment with glycoprotein IIb/IIIa receptor antagonists (abciximab\(^{8,11}\) [Level of Evidence: A], tirofiban\(^{11,14}\) [Level of Evidence: B]) or eptifibatide\(^{8,13}\) [Level of Evidence: B]) at the time of primary PCI (with or without stenting) in selected patients with STEMI.

#### Class IIb

1. The usefulness of glycoprotein IIb/IIIa receptor antagonists (as part of a preparatory pharmacological strategy for patients with STEMI before their arrival in the cardiac catheterization laboratory for angiography and PCI) is uncertain.\(^{8,12}\) (Level of Evidence: B)

### Upstream use deemed “uncertain”
ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation

The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC)

Authors/Task Force Members: Ph. Gabriel Steg (Chairperson) (France)*, Stefan K. James (Chairperson) (Sweden)*, Dan Atar (Norway), Luigi P. Badano (Italy), Carla Blomstrom Lundqvist (Sweden), Michael A. Borger (Germany), Carlo Di Mario (United Kingdom), Kenneth Dickstein (Norway), Gregory Ducrocq (France), Francisco Fernandez-Aviles (Spain), Anthony H. Gershlick (United Kingdom), Pantaleo Giannuzzi (Italy), Sigrun Halvorsen (Norway), Kurt Huber (Austria), Peter Juni (Switzerland), Adnan Kastrati (Germany), Juhani Knuuti (Finland), Mattie J. Lenzen (Netherlands), Kenneth W. Mahaffey (USA), Marco Valgimigli (Italy), Arnoud van't Hof (Netherlands), Petr Widimsky (Czech Republic), Doron Zahger (Israel)

ESC Committee for Practice Guidelines (CPG): Jeroen J. Bax (Chairman) (Netherlands), Holmert Baumgartner (Germany), Claudio Cecconi (Italy), Veronica Dean (France), Christi Deaton (UK), Robert Fagard (Belgium), Christian Funck-Brentano (France), David Hasdai (Israel), Arno Hoes (Netherlands), Paulus Kirchhof (Germany UK), Juhani Knuuti (Finland), Philippe Kohl (Belgium), Theresa McDonagh (UK), Cyril Moulin (France), Bogdan A. Popenescu (Romania), Željko Reiner (Croatia), Udo Sechtem (Germany), Per Anton Sirnes (Norway), Michal Tendler (Poland), Adam Tomicki (Poland), Alex Yahavian (France), Stephan Windecker (Switzerland).

Document Reviewers: David Hasdai (CPG Review Coordinator) (Israel), Felicity Astin (UK), Karin Æstrom-Olsson (Sweden), Andrzej Budaj (Poland), Peter Cremersken (Denmark), Jean-Philippe Collet (France), Keith A. Fox (UK), Ahmet Fuat (UK), Oliviya Gustiene (Lithuania), Christian W. Hamm (Germany), Petr Kaia (Czech Republic), Patrizio Lanciotti (Belgium), Aldo Pietro Maggioni (Italy), Béla Merkely (Hungary), Franz-Josef Neumann (Germany), Massimo R. Piepoli (Italy), Frans Van der Werf (Belgium), Freek Verheugt (Netherlands), Lars Wallentin (Sweden)
**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.

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.

Upstream use of a GP IIb/IIIa inhibitor (vs. in-lab use) may be considered in high-risk patients undergoing transfer for primary PCI.

Options for GP IIb/IIIa inhibitors are (with LoE for each agent):

- **Abciximab**
- **Eptifibatide (with double bolus)**
- **Tirofiban (with a high bolus dose)**

In very high-risk patients in whom cessation of antiplatelet therapy before surgery seems to carry a high risk (e.g. within the first weeks after stent implantation), it has been suggested to switch, before surgery, to a short half-life and reversible antiplatelet agent, e.g. the GP IIb/IIIa receptor inhibitors tirofiban or eptifibatide,[182] but there is no clinical evidence to support this approach based solely on pharmacokinetic or pharmacodynamic studies. In the future, the use of cangrelor, an i.v. reversible ADP receptor antagonist, may permit platelet inhibition to be maintained up to surgery in patients discontinuing oral antiplatelet therapy.[183]
TIMI 3 Flow

Reperfusion

30d Mortality

MACE

Am J Cardiol 2012;109: 1124 ~1130
Underutilization of clopidogrel and glycoprotein IIb/IIIa inhibitors in non-ST-elevation acute coronary syndrome patients: The Canadian Global Registry of Acute Coronary Events (GRACE) experience.
Early Use of Glycoprotein IIb/IIIa Inhibitors in Non-ST-Elevation Acute Myocardial Infarction
Observations From the National Registry of Myocardial Infarction 4
Summary

• The most potent inhibitors of platelet aggregation
• Decrease ischemic endpoints
• Guidelines are quite clear about use
• Underutilized
• Modified regimens? IC route?
• Limited data on TRA and newer P2Y12 agents
• Bleeding remains major limiting factor