CLINICAL REVIEW

Appropriate Use of Glycoprotein IIb/IIIa Blockade for Unstable Angina and Non–ST Segment Elevation Myocardial Infarction

Albert W. Chan, MD, MS, FRCP(C), and Sorin J. Brener, MD

Objective: To review the clinical trials of glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors for unstable angina or non–ST segment elevation myocardial infarction (MI) and to provide a practice guide for the use of these agents in this setting.

Methods: Clinical trials relating to GPIIb/IIIa antagonists and acute coronary syndromes were identified from a MEDLINE search of articles published between 1994 and 2001 and from presentations made during the official meetings of the American College of Cardiology, American Heart Association, and the European Heart Society in 1999 and 2000. Clinical trials related to ST segment elevation were excluded.

Results: Eleven clinical trials were identified, 7 relating to intravenous GPIIb/IIIa inhibitors and 4 relating to oral GPIIb/IIIa inhibition. When combined with aspirin and unfractionated heparin, eptifibatide and tirofiban improved clinical outcomes in patients with unstable angina or non–ST segment elevation MI, especially in the context of early revascularization. Abciximab was beneficial only as an adjunct to percutaneous coronary intervention. Oral chronic GPIIb/IIIa inhibition was associated with increased mortality in each of the clinical trials that were completed.

Conclusion: Barring the inherent differences in their structures and pharmacokinetics, both tirofiban and eptifibatide improve clinical outcomes of patients with unstable angina or non–ST segment elevation MI, especially in the context of early revascularization. Abciximab plays a pivotal role in percutaneous coronary intervention. Oral chronic GPIIb/IIIa inhibition was associated with increased mortality in each of the clinical trials that were completed.

Acute coronary syndromes refers to a spectrum of clinical presentations including unstable angina, non-Q wave myocardial infarction (MI), Q wave MI, and sudden ischemic death [1]. The presence of new ST segment elevation or left bundle branch block determines the eligibility of reperfusion therapy. In the absence of these findings, careful monitoring and appropriate use of pharmacotherapy will be required based on individual risk profile. Unstable angina and non–ST segment elevation MI have similar presentation, and the distinction between the 2 can only be made several hours later using serum markers for myocardial necrosis (ie, creatine kinase–MB, troponin T or I) [1]. Clinical features suggesting short-term high risk include age greater than 75 years, prolonged (>20 minutes) rest pain or recurrent ischemic pain, left ventricular dysfunction, pulmonary edema, transient electrocardiographic ST-T changes, and elevation of cardiac troponin T, troponin I, or creatine kinase–MB [2].

Pivotal to the pathogenesis of acute coronary syndromes is platelet activation and aggregation. Administration of aspirin plus unfractionated heparin or low-molecular-weight heparin has been established in the standard guideline as the initial management for acute coronary syndromes [2]. However, the antiplatelet effect of aspirin is rather modest. For intermediate and high-risk patients presenting with acute coronary syndromes, glycoprotein IIb/IIIa (GPIIb/IIIa) antagonists can provide additional therapeutic benefit.

Three classes of intravenous GPIIb/IIIa inhibitors have been tested in the clinical trials for the treatment of acute coronary syndromes: human-murine chimeric monoclonal antibody fragment (abciximab), synthetic peptide (eptifibatide), and synthetic non-peptide forms (tirofiban, lamifiban). All except for lamifiban are commercially available. While all GPIIb/IIIa inhibitors have a rapid onset of antiplatelet action, the biologic profiles of these agents are significantly different (Table I). In this article, we review the clinical trials related to the use of GPIIb/IIIa antagonists in patients with unstable angina and non–ST segment elevation MI.

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GLYCOPROTEIN IIb/IIIa BLOCKADE

Table 1. Biologic Properties of 4 Glycoprotein IIb/IIIa Antagonists

<table>
<thead>
<tr>
<th>Agent</th>
<th>Composition</th>
<th>Specificity to GPIIb/IIIa Receptors</th>
<th>Pharmacokinetics</th>
<th>Platelet Inhibition</th>
<th>Adjustment for Renal Insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abciximab (Reopro)</td>
<td>Fab fragment of the chimeric human-murine monoclonal antibody 7E3</td>
<td>Nonspecific to GPIIb/IIIa receptor; also binds to the vitronectin and Mac-1 receptors, the significance of which is unclear</td>
<td>T1/2 = 24-48 hours Protein binding: no Renal excretion: no</td>
<td>&gt; 90%</td>
<td>No</td>
</tr>
<tr>
<td>Eptifibatide (Integrilin)</td>
<td>Cyclic heptapeptide with 6 amino acids and 1 mercaptopropionyl residual</td>
<td>Specific</td>
<td>T1/2 = 2-4 hours Protein binding: 25% Renal excretion: 50%</td>
<td>&gt; 90%*</td>
<td>Yes</td>
</tr>
<tr>
<td>Tirofiban HCl (Aggrastat)</td>
<td>Non-peptide tyrosine derivative</td>
<td>Specific</td>
<td>T1/2 = 4-8 hours Protein binding: 65% Renal excretion: 65%</td>
<td>&gt; 90%</td>
<td>Reduce bolus and infusion rates by 50% if CrCl &lt; 30 mL/min</td>
</tr>
<tr>
<td>Lamifiban</td>
<td>Non-peptide tyrosine derivative</td>
<td>Specific</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

CrCl = creatine clearance.

*135 µg/kg bolus and 0.5 µg/kg/min infusion.
†180 µg/kg bolus and 2.0 µg/kg/min infusion.

Methods

Reports published between 1994 and January 2001 relating to GPIIb/IIIa inhibition for acute coronary syndromes were identified on MEDLINE using the keywords glycoprotein IIb/IIIa antagonists, unstable angina, myocardial infarction, and human. Randomized, double-blinded, placebo-controlled trials that enrolled more than 500 patients were included in the review. Reports of the primary studies, as well as those of the subsequent sub-analyses, were retrieved. Relevant abstracts and late-breaking trials presented at the annual scientific sessions of the American College of Cardiology, American Heart Association, and the European Society of Cardiology in the years 1999 and 2000 were also reviewed. Studies that were related to ST segment elevation MI were excluded from analysis.

Results

A total of 11 major randomized trials were identified [3–13]. Seven trials were related to intravenous GPIIb/IIIa antagonists and 4 were related to oral therapy, enrolling a total of 31,402 and 35,294 patients respectively. Five of the intravenous GPIIb/IIIa antagonist trials (collectively known as the 5 Ps) led to the U.S. Food and Drug Administration approval of eptifibatide and tirofiban for initial medical management of acute coronary syndromes. These trials are the Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary syndrome Events in a Global Organization Network A and B (PARAGON A and B) [3,4], the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) [5], the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) [6], and the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) [7]. The use of abciximab as an adjunctive therapy for acute coronary syndromes patients scheduled for urgent percutaneous coronary intervention was examined in the c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) trial [9]. The Global Use of Strategies To open Occluded coronary arteries (GUSTO) IV trial, which aimed to study abciximab as a primary medical regimen for acute coronary syndromes, was recently completed [8].

Efficacy of the Synthetic Molecules in Acute Coronary Syndromes: The 5 P Trials

Five randomized trials evaluated the role of these highly specific GPIIb/IIIa receptor blockers for initial medical management of unstable angina or non-ST segment elevation MI (Tables 2 and 3, Figure 1). Except for PURSUIT, cardiac catheterization and percutaneous coronary intervention were discouraged until 48 to 72 hours after randomization. PARAGON A was a dose-finding study that randomized 2282 patients to 5 regimens: high- and low-dose lamifiban, with or without heparin, and heparin alone [3]. At 30 days, there was no difference in death or MI among the 5 groups. However, at 6-month follow-up, patients assigned to the low-dose lamifiban with or without heparin did better than the placebo group (death or MI, 13.7% versus 17.9%, P = 0.027), but high-dose lamifiban subgroup did not (16.4% versus 17.9%, P = not significant) (Table 3). Postulated mechanisms
Table 2. Overview of Trials Evaluating Glycoprotein IIb/IIIa Inhibitors in Acute Coronary Syndromes

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>n</th>
<th>Treatment</th>
<th>Patient Profile</th>
<th>Dose Regimen</th>
<th>Primary Endpoints</th>
<th>PCI Performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPTURE</td>
<td>1997</td>
<td>1266</td>
<td>Abciximab versus placebo</td>
<td>Refractory UA (within 48 hours with ST-T changes, and angiographic lesion suitable for PCI)</td>
<td>1. Abciximab 0.25 mg/kg bolus + 10 µg/min × 18–24 hours before PTCA and continue for 1 hour after PTCA 2. Placebo</td>
<td>Death/MI urgent revascularization at 30 days</td>
<td>All</td>
</tr>
<tr>
<td>GUSTO-IV</td>
<td>2000</td>
<td>7800</td>
<td>Abciximab versus placebo*</td>
<td>Symptoms of angina with troponin T elevation or ST-T changes</td>
<td>1. Abciximab bolus + 48-hour infusion 2. Abciximab bolus + 24-hour infusion 3. Placebo</td>
<td>Death/MI at 30 days</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>PURSUIT</td>
<td>1998</td>
<td>10,948</td>
<td>Eptifibatide versus placebo†</td>
<td>UA within 24 hours, with CKMB elevation or ST-T changes</td>
<td>1. Eptifibatide 180 µg/kg bolus + 2.0 µg/kg/min × 72 hours 2. Eptifibatide 180 µg/kg bolus + 1.3 µg/kg/min × 72 hours 3. Placebo</td>
<td>Death/MI at 30 days</td>
<td>24%</td>
</tr>
<tr>
<td>PRISM</td>
<td>1998</td>
<td>3232</td>
<td>Tirofiban versus placebo†</td>
<td>UA/NQMI within 24 hours, with new ST-T changes elevated CKMB or history of CAD</td>
<td>1. Tirofiban 0.6 µg/kg/min × 30 min + 0.15 µg/kg/min infusion × 47.5 hours 2. Placebo</td>
<td>Death/MI refractory ischemia at 48 hours</td>
<td>21%</td>
</tr>
<tr>
<td>PRISM-PLUS</td>
<td>1998</td>
<td>1915</td>
<td>Tirofiban (high-dose) versus tirofiban (low-dose) + heparin versus heparin</td>
<td>UA/NQMI within 12 hours and new ischemic ST-T changes</td>
<td>1. Tirofiban 0.6 µg/kg/min × 30 min + 0.15 µg/kg/min infusion × 48 hours + placebo heparin × 48 hours 2. Tirofiban 0.4 µg/kg/min × 30 min + 0.1 µg/kg/min infusion × 48 hours + heparin × 48 hours 3. Heparin alone</td>
<td>Death/MI refractory ischemia within 7 days</td>
<td>31%</td>
</tr>
<tr>
<td>PARAGON-A</td>
<td>1998</td>
<td>2282</td>
<td>5 arms: High-dose lamifibain (± heparin) versus low-dose lamifibain (± heparin) versus heparin</td>
<td>UA within 12 hours with ST-T changes</td>
<td>1. Lamifiban 750 µg bolus + 5.0 µg/min infusion (± heparin) × 3–5 days 2. Lamifiban 300 µg bolus + 1.0 mg/min infusion (± heparin) × 3–5 days 3. Heparin alone</td>
<td>Death/MI at 30 days</td>
<td>14%</td>
</tr>
<tr>
<td>PARAGON-B</td>
<td>2000</td>
<td>5225</td>
<td>Lamifibian versus placebo†</td>
<td>UA within 12 hours with ST-T changes or elevated CKMB (or troponin T)</td>
<td>1. Lamifiban 500 mg bolus + 1.0, 1.5, or 2.0 mg/min infusion (based on SCr) × 72 hours 2. Placebo</td>
<td>Death/MI recurrent ischemia at 30 days</td>
<td>27%</td>
</tr>
</tbody>
</table>

CAD = coronary artery disease; CKMB = creatine kinase-MB; MI = myocardial infarction; NQMI = non-Q wave myocardial infarction; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty; SCr = serum creatine; UA = unstable angina.

*Low-molecular-weight heparin substudy was performed in a fraction of patients in each group. Unfractionated heparin was given to the rest of the patients.

†All patients in both treatment and control groups received aspirin, unfractionated heparin bolus, and infusion.
Table 3. Incidence of Death or Nonfatal MI at 6 Months in GPIIb/IIIa Acute Coronary Syndrome Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>GPIIb/IIIa Inhibitor</th>
<th>n</th>
<th>GPIIb/IIIa Inhibitor</th>
<th>Control</th>
<th>Risk Reduction, %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PURSUIT [7]</td>
<td>Eptifibatide</td>
<td>9461</td>
<td></td>
<td>17.8</td>
<td>19.0</td>
<td>6.3</td>
</tr>
<tr>
<td>PRISM-PLUS [6]*</td>
<td>Tirofiban</td>
<td>1570</td>
<td></td>
<td>12.3</td>
<td>15.3</td>
<td>19.6</td>
</tr>
<tr>
<td>PARAGON-A [3]</td>
<td>Lamifiban</td>
<td>2282</td>
<td></td>
<td>16.4</td>
<td>17.9</td>
<td>8.4</td>
</tr>
<tr>
<td>PARAGON-B [4]</td>
<td>Lamifiban</td>
<td>5225</td>
<td></td>
<td>14.9</td>
<td>15.9</td>
<td>6.3</td>
</tr>
</tbody>
</table>

MI = myocardial infarction; NS = not significant.

*Tirofiban/heparin versus heparin alone.

Figure 1. Results of the clinical trials examining the use of glycoprotein IIb/IIIa antagonists as medical therapy for patients presenting with unstable angina or non-ST segment elevation MI at 30 days. NS = not significant. *48-hour abciximab versus placebo; †High-dose eptifibatide versus placebo; ‡Tirofiban/heparin versus heparin alone.
included paradoxical platelet activation with high-dose lamifiban and possible “passivation” of the plaque at low-dose.

Consequently, PARAGON-B was designed to confirm the benefit with low-dose lamifiban observed in PARAGON-A (Table 2) [4]. In this study, lamifiban was dosed according to patients’ creatinine clearance. The 30-day primary composite endpoint of death, MI, or recurrent ischemia was not different between the 2 groups (Figure 1). Marked benefit of lamifiban, however, was observed among 1160 patients who had elevated troponin T during hospitalization (30-day death or MI, 11% and 19% for lamifiban and placebo; \( P = 0.018 \)), and in those who underwent early percutaneous revascularization during lamifiban infusion (11.6% versus 18.5%, \( P < 0.05 \)). Nevertheless, since lamifiban did not achieve significant treatment effect in 2 clinical trials, it is not currently approved for clinical use.

The use of tirofiban for acute coronary syndromes was studied in the PRISM and PRISM-PLUS trials [5,6]. Patients’ risk profiles differed in the 2 studies: ST segment changes were present in more than 90% of patients enrolled in PRISM-PLUS but in only 39% of patients in PRISM. In addition, tirofiban infusion was continued after percutaneous coronary intervention in PRISM-PLUS but was limited to 48 hours in PRISM, prior to angiography. In the PRISM trial, tirofiban demonstrated efficacy at 48 hours by lowering the primary composite endpoint of death, MI, or refractory ischemia by 33% (\( P = 0.01 \)), and more marked benefit was observed in patients with electrocardiographic ischemia (ST segment depression or T wave inversion) at initial presentation. Moreover, mortality benefit was observed in the tirofiban group at 30 days (2.3% versus 3.6%, \( P = 0.02 \)). Although the choice of subsequent treatment strategies (medical therapy, percutaneous coronary intervention, or coronary artery bypass graft [CABG]) was not randomized, a reduced rate of death, MI, or refractory ischemia was observed with early percutaneous coronary intervention (21.6% versus 27.3%, \( P < 0.05 \)) but not with medical therapy (10.0% versus 11.7%, \( P = \text{not significant} \)). No evidence of rebound phenomenon was observed after cessation of tirofiban infusion.

PRISM-PLUS initially randomized acute coronary syndromes patients into 3 arms (Table 2). The tirofiban-alone arm was stopped prematurely after a 4.6% mortality rate was noted in that group at 7 days compared with 1.1% in the control group. The duration of infusion averaged about 3 days (71.3 ± 20 hours) and was continued for an additional 15.4 ± 8 hours in patients who underwent percutaneous coronary intervention. Reduction of death, MI, or refractory ischemia was observed with tirofiban/heparin therapy as early as 48 hours (5.7% versus 7.8%, \( P = 0.08 \)), and at 7 days (12.9% versus 17.9%, \( P = 0.004 \)), 30 days (18.5% versus 22.3%, \( P = 0.03 \)) (Figure 1) and 6 months (27.7% versus 32.1%, \( P = 0.02 \)) (Table 3) when compared with heparin alone. The benefit resulted mainly from the reduction in recurrent MI. Early divergence of the endpoints suggested the benefit of the drug was independent of subsequent revascularization therapy. Among 475 patients who subsequently underwent percutaneous coronary intervention, death, MI, or refractory ischemia was observed in 8.8% of the tirofiban group and 15.3% of the control group (risk ratio, 0.55; 95% confidence interval, 0.32 to 0.94). For patients who were managed with medical therapy alone, clinical outcome was slightly better with tirofiban/heparin combination therapy, although the difference did not reach statistical significance (composite endpoint at 30 days, 14.8% versus 16.8%; risk ratio, 0.87; 95% confidence interval, 0.60 to 1.25).

The PURSUIT trial was the largest of the GPIIb/IIIa–acute coronary syndrome trials [7]. The initial study protocol included 3 treatment arms: high-dose eptifibatide, low-dose eptifibatide, or placebo (Table 2). After demonstrating the safety in the high-dose eptifibatide arm, the low-dose treatment arm was discontinued according to the protocol. No restriction on the timing of revascularization was imposed. Reduction of death or MI was consistently observed in favor of eptifibatide at 96 hours (7.6% versus 9.1%, \( P = 0.01 \)), 7 days (10.1% versus 11.6%, \( P = 0.02 \)), and 30 days (14.2% versus 15.7%, \( P = 0.04 \)). Percutaneous coronary intervention appeared to provide additional benefits to eptifibatide, since a greater reduction of the composite endpoint at 30 days was observed (11.6% versus 16.7%, \( P = 0.01 \)). Patients who did not undergo revascularization procedures had a non-statistically significant reduction of the composite endpoint (14.5% versus 15.6%, \( P = 0.23 \)), a finding similar to PARAGON B, PRISM, and PRISM-PLUS trials (Figure 2).

In conclusion, there was a marked clinical benefit of the synthetic GPIIb/IIIa antagonists (eptifibatide, tirofiban, and lamifiban) in high-risk patients presenting with unstable angina or non-ST segment elevation MI. Clinical benefits were most evident when GPIIb/IIIa antagonists were given to patients with ST segment changes (as in PRISM and PRISM-PLUS) or troponin elevation (PARAGON, PRISM-PLUS) and to those who were considered for percutaneous coronary intervention during drug infusion phase (PRISM, PRISM-PLUS, PURSUIT, PARAGON B) (Figure 2).

**Efficacy of Abciximab in Acute Coronary Syndromes**

The c7E3 Fab Antiplatelet Therapy in Unstable Refractory angina (CAPTURE) trial was designed primarily to examine the clinical efficacy of abciximab in acute coronary syndrome patients undergoing percutaneous coronary intervention [9]. A total of 1266 patients were randomized to either abciximab for 18 to 24 hours before and for 1 hour after percutaneous coronary intervention or placebo. Reduction in MI with abciximab was observed both during the medical stabilization phase (0.6% versus 2.1% in placebo, \( P = 0.029 \)) and
within the first 24 hours after percutaneous coronary intervention (2.6% versus 5.5%, \( P = 0.009 \)). At 30 days, the abciximab group had a 29% reduction in the composite endpoint of death, MI, or urgent intervention compared with placebo (11.3% versus 15.9%, \( P = 0.012 \)) [9]. Further examination of the trial showed that the marked benefit of abciximab occurred in patients who had elevated troponin T levels at the time of presentation (6-month event rate, 9.5% and 23.9% for abciximab and placebo, \( P = 0.002 \)), but not in those who had normal levels (9.4% versus 7.5%, \( P = 0.47 \)), suggesting that abciximab reduced the risk of patients with elevated troponin T to that of patients with normal troponin T [14]. These findings highlight the important role of troponin T in the risk stratification of acute coronary syndromes and the clinical benefit of abciximab in the presence of thrombus reflected by elevated troponin T levels. In a pooled analysis of the CAPTURE (abciximab), PURSUIT (eptifibatide), and PRISM-PLUS (tirofiban) trials, GPIIb/IIIa blockade resulted in a significant reduction of death or MI during medical treatment (2.5% versus 3.8%; risk reduction, 34%; \( P < 0.001 \)), and percutaneous coronary intervention further reduced the event rate by 41% within the first 48 hours after the procedure (4.9% versus 8.0%, \( P < 0.001 \)) [15].

The consistent benefits of eptifibatide and tirofiban seen in the acute coronary syndromes trials prompted a study of abciximab as medical therapy for acute coronary syndromes. The main difference between GUSTO IV and the 5 P trials was that early catheterization was prohibited in GUSTO IV unless severe refractory ischemia occurred. In fact, less than 5% patients underwent percutaneous coronary intervention within 3 days after enrollment. The trial randomized 7800 patients who were believed to have acute coronary syndromes based on anginal symptom, plus elevation of troponin T or ischemic electrocardiographic changes. The study randomized patients to 3 arms: abciximab bolus plus 48-hour infusion, abciximab bolus plus 24-hour infusion, or placebo (Table 2). Aspirin and unfractionated heparin were given to all patients. At 30 days, the composite endpoint of death/MI was not different across the 3 treatment arms (48-hour abciximab, 9.1%; 24-hour abciximab, 8.2%; placebo, 8.0%; \( P = \) not significant). Paradoxically, a trend of increased death/MI with high-dose abciximab was present. The marked benefit demonstrated consistently in the troponin-positive patients in the other GPIIb/IIIa inhibitor–acute coronary syndrome trials was not observed among those patients given abciximab (death/MI at 30 days: 11.7% for 48-hour abciximab, 10.2% for 24-hour abciximab, and 9.7% for placebo). When the results of all GPIIb/IIIa antagonist–acute coronary syndromes trials are pooled, GPIIb/IIIa inhibition still confers a significant 9% reduction in death or MI at 30 days (\( P = 0.04 \)) [16].

Postulated explanations for the negative results from this trial include enrollment of a relatively low-risk population, identified by positive troponin alone without electrocardiographic manifestations of ischemia, uncertainty regarding appropriate dosing, and the possibility of untoward “toxic”
effect with prolonged platelet inhibition with abciximab. The difference in efficacy of abciximab in GUSTO IV and in CAPTURE trial underscore the complementary role of percutaneous coronary intervention during GPIIb/IIa inhibitor administration—a finding that has been noted when comparing the patients who were treated with percutaneous coronary intervention or medical therapy in the 5 P trials (Figure 2).

Choice of GPIIb/IIa Inhibitor in Candidates for Percutaneous Coronary Intervention

Two recently completed studies further complicated the choice of GPIIb/IIa antagonists in acute coronary syndrome patients who are candidates for percutaneous coronary intervention. The first was the Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS-TIMI 18) trial, which demonstrated the superiority of an early invasive strategy over a conservative strategy (6-month death, MI, or rehospitalization for acute coronary syndromes, 10.4% versus 15.9%; P = 0.025) [17]. Tirofiban was given to all patients in this study. Patients who were troponin-positive had even more significant reduction in the primary endpoint with early aggressive therapy (14% versus 24%; risk reduction, 42%). The second trial was the Do Tirofiban and ReoPro Give similar Efficacy Trial (TARGET). This trial concluded that abciximab administration during elective or urgent percutaneous coronary intervention resulted in 26% less incidence of death/MI/refractory angina at 30 days compared with tirofiban [18]. Among the acute coronary syndromes subgroup, the benefit of abciximab was even more substantial (6.3% versus 9.3%; risk reduction, 32%).

The outcome of the 3 trials (GUSTO IV, TARGET, and TACTICS-TIMI 18) provided more questions than answers regarding choice of GPIIb/IIa inhibitor in the management of acute coronary syndromes. The question of which agent should be given and when it should be started has recently been debated. Based on the results of these trials, together with PRISM and PRISM-PLUS, medium- or high-risk acute coronary syndrome patients should be started on tirofiban while being triaged for early catheterization within 48 hours, followed by revascularization by either percutaneous coronary intervention or CABG. If angiography procedures can be arranged within the first few hours of admission, GPIIb/IIa inhibitor administration could probably be postponed and abciximab should be started in the catheterization laboratory once percutaneous coronary intervention is undertaken, based on the superior results of abciximab compared to tirofiban in TARGET. Another issue, which has never been studied in clinical trials, is whether tirofiban or eptifibatide started before patient arrival to the catheterization laboratory could or should be switched to abciximab at the time of percutaneous coronary intervention. We believe that although rebound phenomenon has not been seen after discontinuation of eptifibatide or tirofiban infusion, the risk of bleeding related to switching from one GPIIb/IIa inhibitor to another is uncertain and this practice is currently not recommended without appropriate trials addressing this issue.

Combination of Low-Molecular-Weight Heparin and GPIIb/IIa Inhibitors

While unfractionated heparin inhibits thrombin formation by binding to antithrombin III, low-molecular-weight heparin such as enoxaparin or dalteparin may be more effective in blocking the coagulation cascade by inhibiting factor Xa in addition to its antithrombin activity. Low-molecular-weight heparin binds less avidly to plasma and tissue proteins and thus has higher bioavailability and a more predictable therapeutic effect. Large clinical trials have demonstrated its superior efficacy in the setting of unstable angina and non-ST segment elevation MI compared to unfractionated heparin [19–21]. The National Investigators Collaborating on Enoxaparin (NICE)-3 was an observational study demonstrating the feasibility of combining enoxaparin and GPIIb/IIIa inhibitors for acute coronary syndrome patients who subsequently underwent percutaneous coronary intervention [22]. The GUSTO IV dalteparin substudy showed the safety, and a trend toward improved efficacy, for the combination of dalteparin and abciximab for medical management of acute coronary syndromes patients [23]. Furthermore, the NICE-4 trial demonstrated the safety of enoxaparin and abciximab combination therapy in the percutaneous coronary intervention setting [24, 25]. The Antithrombotic Combination Using Tirofiban and Enoxaparin (ACUTE)-II trial, which randomized 525 acute coronary syndromes patients to tirofiban/enoxaparin or tirofiban/unfractionated heparin, showed no significant difference in the primary endpoint of bleeding and a trend toward reduced cardiac events with enoxaparin at 30 days [26].

Since increasingly more acute coronary syndrome patients are started on the combination of low-molecular-weight heparin and GPIIb/IIIa inhibitors during initial hospitalization, current research is focused on the dose regimen and the choices of low-molecular weight heparin and GPIIb/IIIa inhibitor to facilitate a smooth transition and continuation of anticoagulation therapy from medical stabilization to revascularization for acute coronary syndrome patients [27].

Safety of GPIIb/IIIa Blockade

Bleeding. A trend towards increased bleeding and a greater need for blood transfusion is observed in the active treatment
arms across all the GPIIb/IIIa trials (Table 4). Fortunately, the incidence was only modestly increased, and bleeding mostly occurred at the femoral access sites of the patients who underwent cardiac catheterization. Considering the trade-off in terms of reduction of the risk of death or MI, the increased risk of bleeding was acceptable.

For patients who need to undergo emergency or urgent CABG surgery, considerable concern about postoperative bleeding caused by GPIIb/IIIa inhibitor infusion has been raised. Insight regarding the effect of GPIIb/IIIa inhibition on the safety of CABG was gained from the PURSUIT trial [28]. In this trial, 1558 patients (14.2% of the total population) required emergency or urgent CABG surgery, of which 866 patients (56%) received eptifibatide for a median of 71.8 hours prior to CABG (interquartile range, 36 to 72 hours). Time of drug discontinuation to CABG in the eptifibatide group was 66.5 hours (median; interquartile range, 18 to 184 hours), which was similar to the control group (median, 57.8 hours; P = 0.2). The subsequent risks of major (eptifibatide, 58.2%; placebo, 56.6%) or minor (eptifibatide, 23.5%; placebo, 23.6%) bleeding were not different between the 2 groups. Only 1 intracranial hemorrhage occurred in the study population. Patients who received eptifibatide had 16% less postoperative death or MI at 6-month follow-up. An additional 20% reduction in postoperative death or MI was evident when eptifibatide was given within 24 hours prior to CABG. The rapid reversibility (2 to 4 hours) of eptifibatide explains the absence of increased bleeding after CABG compared with placebo.

Analysis of the EPIC patients who required emergency or urgent CABG (56 patients [2.8%), with 46 patients undergoing surgery within 24 hours) indicated that the more prolonged biologic half-life of abciximab was a concern for this group of patients [29]. Comparing abciximab with placebo, the mortality rate was higher (23.5% versus 8.0% in placebo) as was blood product requirement (76.5% versus 64.0% for packed red blood cells and 76.5% versus 56.0% for platelets). Weight-adjusted heparin doses were used in the subsequent EPILOG and EPISTENT trials. Among 42 patients who underwent emergency CABG (abciximab was discontinued within 6 hours of operation in 50% to 60% of patients), there were no significant differences in 30-day clinical outcome (death or MI, 32% and 45% for abciximab and placebo; P = not significant), need of surgical exploration (12% and 3% for abciximab and placebo, P = 0.21), or packed red blood cell transfusion (57% and 50% for abciximab and placebo, P = not significant) between the comparison groups [30].

Renal insufficiency. Eptifibatide and tirofiban are cleared by renal excretion, while abciximab is cleared by the reticuloendothelial system. Patients with renal insufficiency were not well-represented in the clinical trials. Patients with a serum creatinine value greater than 2.0 to 2.5 mg/dL were excluded from PURSUIT, PRISM, and PRISM-PLUS. The dosage of tirofiban should be half of the normal in the presence of renal insufficiency. A reduced dose of eptifibatide (135 µg/kg bolus + 0.5 µg/kg/min) was given to patients with serum creatinine levels between 2 and 4 mg/dL in the percutaneous coronary intervention setting [31], but this dose regimen has not been tried in medical management for acute coronary syndromes in which the infusion period is usually much longer. Both tirofiban and eptifibatide are dialyzable, but this modality is rarely required because of their relatively short half-lives. Abciximab is not currently recommended for patients on dialysis.

Thrombocytopenia. Across all the GPIIb/IIIa inhibitor trials, thrombocytopenia occurred slightly more often in the active

**Table 4. Safety Profile of Glycoprotein IIb/IIIa Antagonists for Acute Coronary Syndromes in the Clinical Trials**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trial</th>
<th>Major Bleeding, %*</th>
<th>Blood Transfusion, %</th>
<th>Thrombocytopenia, %†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Treatment</td>
<td>Control</td>
<td>Treatment</td>
</tr>
<tr>
<td>Abciximab</td>
<td>CAPTURE [9]</td>
<td>3.8</td>
<td>19</td>
<td>7.1</td>
</tr>
<tr>
<td></td>
<td>GUSTO IV [8]</td>
<td>1.0</td>
<td>0.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Eptifibatide</td>
<td>PURSUIT [7]</td>
<td>11.6</td>
<td>9.2</td>
<td>N/A</td>
</tr>
<tr>
<td>Tirofiban</td>
<td>PRISM [5]</td>
<td>0.4</td>
<td>0.4</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>PRISM-PLUS [6]</td>
<td>4</td>
<td>3</td>
<td>4.0</td>
</tr>
<tr>
<td>Lamifiban</td>
<td>PARAGON-A [3]</td>
<td>2.4</td>
<td>0.8</td>
<td>8.7</td>
</tr>
<tr>
<td></td>
<td>PARAGON-B [4]</td>
<td>1.3</td>
<td>0.9</td>
<td>N/A</td>
</tr>
</tbody>
</table>

N/A = not available

*Defined by > 5.0 g/dL decrease in the blood hemoglobin level, the need for transfusion of ≥ 2 units of blood, the need for corrective surgery, the occurrence of an intracranial or retroperitoneal hemorrhage, or a combination of these events.

†Defined by a decrease in platelet count to ≤ 90,000/mm³.
Unstable angina, non-ST segment elevation MI

Medical stabilization with aspirin, UFH or LMWH, β blocker, ± statins, nitrates

Medium- or high-risk profile: age > 75, rest angina, pulmonary edema, CKMB or troponin elevation, transient ST-T changes, LV dysfunction

PRESENT

Catheterization within 4-48 hours

Tirofiban or eptifibatide bolus and infusion

Cardiac catheterization

PCI, continue tirofiban or eptifibatide infusion for 12-18 hours

CABG; stop tirofiban or eptifibatide at least 4-6 hours prior to surgery

ABSENT

Further risk stratification with noninvasive studies

Catheterization ≤ 4 hours

Medical therapy

PCI indicated: start abciximab in the lab, followed by 12-hour infusion post-PCI

CABG

Figure 3. Proposed critical pathway for the management of unstable angina or non-ST segment elevation MI based on contemporary clinical trials. CABG = coronary artery bypass graft; CKMB = creatine kinase-MB; LMWH = low-molecular-weight heparin; LV = left ventricular; MI = myocardial infarction; PCI = percutaneous coronary intervention; UFH = unfractionated heparin.

arm (Table 4). The incidence of severe thrombocytopenia (< 50,000 platelets/mm³) was 0.2% in eptifibatide-treated patients (PURSUIT) and 0.4% to 0.5% in tirofiban-treated patients (PRISM, PRISM-PLUS). Although these figures were higher than those in the control groups (0.1% to 0.2%), the absolute number of patients was still small. Abciximab, however, was associated with a higher incidence of thrombocytopenia (0.9% to 1.8% in EPIC, EPILOG, and CAPTURE), and the association increased with the dosage of heparin [32].

Thrombocytopenia during readministration of abciximab, an immunologic phenomenon related to IgG antibodies, was reported to be 2.4% to 4.0% in observational registries [33,34], and the incidence increased with proximity to the previous administration. Efficacy of abciximab did not change during readministration. Our current recommendation is to check platelet count at 2 to 4 hours after beginning the abciximab infusion and repeat in 12 to 24 hours, regardless of a history of prior use. Neither eptifibatide nor tirofiban have been
reported to cause immunologic reaction, but it is prudent to check platelet count 6 to 24 hours after therapy initiation.

**Oral GPIIb/IIa Blockade for Acute Coronary Syndromes**

In view of the remarkable benefit of intravenous GPIIb/IIa agents in acute coronary syndromes and percutaneous coronary intervention, it was hypothesized that moderate chronic inhibition of platelet aggregation with oral agents may further reduce major adverse coronary events. Three different oral agents were tested in 4 trials among 35,294 patients [10–13,35]. Despite the diversity of the patient population and inherent differences in the pharmacokinetics of the drugs, each of the 4 trials strikingly demonstrated lower efficacy (higher mortality) and safety after 30 days of intake (Table 5). All except for the first SYMPHONY trial were terminated prematurely due to increased mortality observed during interim analyses. However, the incidence of MI and urgent revascularization were not different between the comparison groups in any of these trials. The disparity between the increased mortality and neutral effect on MI or revascularization (attributable to a prothrombotic effect) suggests untoward mechanism(s) unrelated to a prothrombotic effect, such as (1) inadequate platelet inhibition (only 30% to 50% platelet inhibition could be achieved by oral therapy) and partial activation of platelet [36,37]; (2) proinflammatory response as a result of release of CD-40 ligand and activation of P-selectin [37,38]; and (3) induction of myocytic apoptosis, resulting in arrhythmias [39,40]. The disappointing results from these trials call for a reexamination of the role of oral GPIIb/IIa inhibitors in acute coronary syndromes.

**Economic Considerations**

In view of the efficacy of GPIIb/IIa inhibitors for acute coronary syndromes patients demonstrated in CAPTURE, PURSUIT, PRISM, and PRISM-PLUS trials, economic consideration has been the major issue with respect to the choice of agents. The cost savings derived from the reduction of ischemic events may offset the cost of acquisition of these agents. The incremental cost-effectiveness ratio of abciximab for patients undergoing percutaneous coronary intervention for acute coronary syndromes was estimated to be $4000 to $7000 per life-year saved [41]. For eptifibatide, this ratio was $16,491 per year of life saved based on U.S. PURSUIT patients [42]. These data are not comparable since many of the eptifibatide patients in PURSUIT did not undergo percutaneous coronary intervention. However, the reasonable cost-effectiveness ratios suggest that empirical use of GPIIb/IIa inhibitors for unstable angina or non–ST segment elevation MI patients is attractive compared with some other conventional therapies ($19,000 for hypertension, $26,000 for CABG, $32,000 for tissue plasminogen activator in patients with acute MI, and $35,000 for hemodialysis) [43].

**Conclusion**

The current standard of therapy for unstable angina or non–ST segment elevation MI should include tirofiban or eptifibatide administration, beginning soon after hospitalization. Since most of the benefits shown in the clinical trials were derived from the complementary usage of percutaneous coronary intervention and intravenous GPIIb/IIa antagonists, all but low-risk patients should undergo early cardiac catheterization for further risk stratification and possible revascularization while receiving GPIIb/IIa inhibitor infusion (Figure 3). Abciximab should be reserved for patients who are taken immediately to the catheterization laboratory and have not been treated with other agents. There is currently no role for oral GPIIb/IIa inhibition for acute coronary syndromes until the pathophysiologic mechanisms responsible for increased mortality are further elucidated. The combination of low-molecular-weight heparin and GPIIb/IIa inhibitor is currently being investigated in phase III clinical trials.

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**Table 5. Summary of the Trials of Oral Glycoprotein IIb/IIa Inhibitors for Acute Coronary Syndromes**

<table>
<thead>
<tr>
<th>Trial</th>
<th>GPIIb/IIa Inhibitor</th>
<th>n</th>
<th>Mortality, %*</th>
<th>MI, %*</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPUSTIMI 16</td>
<td>Orobofiban [12]</td>
<td>10,288</td>
<td>2.0</td>
<td>1.4</td>
</tr>
<tr>
<td>SYMPHONY</td>
<td>Sibrafiban [10]</td>
<td>9169</td>
<td>2.0</td>
<td>1.8</td>
</tr>
<tr>
<td>2nd SYMPHONY</td>
<td>Sibrafiban [11]†</td>
<td>6637</td>
<td>2.1</td>
<td>1.3</td>
</tr>
<tr>
<td>BRAVO</td>
<td>Lotrafiban [13]</td>
<td>9200</td>
<td>2.7</td>
<td>2.0</td>
</tr>
</tbody>
</table>

MI = myocardial infarction; N/A = not available.
*Endpoints at 30 days and beyond.
†Low-dose sibrafiban + aspirin versus high-dose sibrafiban alone versus aspirin alone.
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### References


