A Comparison of Abciximab and Small-Molecule Glycoprotein IIb/IIIa Inhibitors in Patients Undergoing Primary Percutaneous Coronary Intervention
A Meta-Analysis of Contemporary Randomized Controlled Trials

Hitinder S. Gurm, MD; Umesh Tamhane, MD; Pascal Meier, MD; P. Michael Grossman, MD; Stanley Chetcuti, MD; Eric R. Bates, MD

Background—Current guidelines recommend abciximab as the preferred agent for patients undergoing primary percutaneous coronary intervention, yet small-molecule glycoprotein IIb/IIIa inhibitors are more commonly used in clinical practice. The objective of our meta-analysis was to evaluate for differences in clinical outcome between small-molecule glycoprotein IIb/IIIa inhibitors and abciximab in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention.

Methods and Results—Five randomized trials (n=2138 patients) comparing tirofiban or eptifibatide with abciximab as an adjunctive therapy to primary percutaneous coronary intervention were included in this meta-analysis. Summary odds ratios (ORs) for 30-day death, reinfarction, and major bleeding were calculated using random- and fixed-effect models. There were no differences in 30-day mortality (1.9% for small molecule versus 2.3% for abciximab; OR, 0.84; 95% CI, 0.46 to 1.55; \( P=0.58 \)), reinfarction (1.3% versus 1.2%; OR, 1.22; 95% CI, 0.51 to 2.91; \( P=0.69 \)), or major bleeding (1.7% versus 1.3%; OR, 1.21; 95% CI, 0.58 to 2.49; \( P=0.61 \)) between the 2 adjunctive strategies. Similarly, there was no significant difference in the incidence of death (3.9% versus 5%; OR, 0.77; 95% CI, 0.41 to 1.46; \( P=0.43 \)) or reinfarction on follow-up at 8 months between small-molecule glycoprotein IIb/IIIa inhibitors and abciximab.

Conclusion—In patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction, no difference in outcome could be identified in patients treated with small-molecule glycoprotein IIb/IIIa inhibitor or abciximab. (Circ Cardiovasc Intervent. 2009;2:230-236.)

Key Words: primary PCI ■ ST elevation MI ■ abciximab ■ tirofiban ■ eptifibatide

Primary percutaneous coronary intervention (PCI) is the preferred reperfusion strategy in ST-segment elevation myocardial infarction (STEMI).\(^1\) The optimal procedural anticoagulation strategy in patients undergoing primary PCI, however, remains to be defined. Although the current guidelines support the use of abciximab in patients undergoing primary PCI, a number of patients are treated with small-molecule glycoprotein (GP) IIb/IIIa agents or without GP IIb/IIIa inhibitors in “real-world” clinical practice for various reasons.\(^2\,^3\) The absolute magnitude of survival benefit demonstrated in association with abciximab is small and somewhat controversial.\(^4\,^5\) Further, eptifibatide or tirofiban—small-molecule agents that share some but not all pharmacological properties with abciximab—are significantly less expensive and more widely available in many hospitals. Observational data suggest similar outcomes in patients undergoing primary PCI who are treated with small-molecule GP IIb/IIIa inhibitors compared with those treated with abciximab.\(^2\,^7\,^8\)

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Small randomized trials evaluating predominantly angiographic end points have demonstrated no difference between small-molecule GP IIb/IIIa inhibitors and abciximab in patients undergoing primary PCI, although none of these trials were powered for clinical end points. We accordingly performed a meta-analysis of the randomized trials comparing abciximab with small-molecule GP IIb/IIIa inhibitors dosed per current recommendations in patients undergoing contemporary primary PCI.

Methods

We performed a computerized search to identify relevant articles from 2000 through October 30, 2008, in the MEDLINE, Embase, ISI Web of Knowledge, Current Contents, International Pharmaceutical Abstracts databases, and the Cochrane Central Register of Controlled Trials. We combined exploded medical subject headings and key-word searches for abciximab, tirofiban, eptifibatide, and primary PCI. Abstract lists from the 2008 scientific meetings of the American Heart Association were also searched.
A study was included if it randomized patients undergoing primary PCI for STEMI to abciximab or a small-molecule GP IIb/IIIa inhibitor in a randomized fashion and provided data on at least 1 outcome of interest over a follow-up period of at least 30 days. The end points of interest were death, reinfarction, and bleeding at 30 days.

Definitions and Outcome Measures

The end points of interest were death, reinfarction, and bleeding at 30 days. Medium-term mortality and reinfarction were also pooled. Death was defined as mortality from any cause. Target vessel revascularization (TVR) was defined as surgical or percutaneous revascularization of the infarct-related artery. Reinfarction and bleeding (major and minor) were defined slightly differently by each trial (Table 1). We used the study defined end points for the analysis.

In a secondary analysis, we evaluated procedural angiographic outcome (thrombolysis in myocardial infarction-3 flow and ST resolution). Data were collected independently by 2 reviewers (U.T. and P.M.) and disagreements were resolved by consensus. Baseline demographic, clinical, and angiographic outcomes were recorded for each arm, and demographic and clinical endpoints were included in the analysis. Given the small number of trials available, we did not exclude any trial based on study characteristics.

### Table 1. Baseline Characteristics of Studies Included in the Meta-Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent and dose</th>
<th>No. patients in each arm</th>
<th>Mean age, y</th>
<th>Diabetes, %</th>
<th>Prior MI, %</th>
<th>Anterior MI, %</th>
<th>Mean symptom to balloon time, min</th>
<th>Follow-up duration, d</th>
<th>Total No. patients</th>
<th>Primary outcome</th>
<th>Definition of major bleeding</th>
<th>Definition of minor bleeding</th>
<th>Definition of MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danzi et al, 2004</td>
<td>Tirofiban (bolus 25 µg/kg + 18-h infusion of 0.15 µg kg⁻¹ min⁻¹)</td>
<td>50</td>
<td>82</td>
<td>18</td>
<td>NA</td>
<td>42</td>
<td>214</td>
<td>30</td>
<td>100</td>
<td>Infarct-zone wall motion score index (IWMSI)</td>
<td>TIMI minor criteria</td>
<td>Symptoms consistent with acute MI &amp; ST-segment elevation in 2 contiguous leads or LBBB</td>
<td></td>
</tr>
<tr>
<td>Valgimigli et al, 2005</td>
<td>Tirofiban (bolus 0.25 mg/kg + 12-h infusion of 0.125 µg kg⁻¹ min⁻¹)</td>
<td>50</td>
<td>84</td>
<td>59</td>
<td>NA</td>
<td>32</td>
<td>200</td>
<td>30</td>
<td>175</td>
<td>Composite of death, MI, stroke, binary stenosis</td>
<td>TIMI major criteria</td>
<td>Chest pain &gt; 30 min and ST elevations ≥ 1 mm in 2 or more contiguous leads or New onset LBBB</td>
<td></td>
</tr>
<tr>
<td>EVA-AMI, 2007</td>
<td>Tirofiban (bolus 25 µg/kg + 18-h infusion of 0.125 µg kg⁻¹ min⁻¹)</td>
<td>87</td>
<td>77</td>
<td>16</td>
<td>NA</td>
<td>49</td>
<td>180</td>
<td>240</td>
<td>429</td>
<td>STR &gt; 70% at 60 min</td>
<td>NA</td>
<td>Chest pain &gt; 30 min and ST elevations ≥ 2 mm in precordial, ≥ 1 mm in limb lead</td>
<td></td>
</tr>
<tr>
<td>MULTISTRATEGY, 2008</td>
<td>Tirofiban (bolus 0.25 mg/kg + 12-h infusion of 0.125 µg kg⁻¹ min⁻¹)</td>
<td>88</td>
<td>69</td>
<td>12</td>
<td>13</td>
<td>41</td>
<td>180</td>
<td>240</td>
<td>744</td>
<td>STR ≥ 50% at 90 min MACE</td>
<td>TIMI major criteria</td>
<td>Chest pain &gt; 30 min and ST elevations ≥ 1 mm in 2 or more contiguous ECG leads or New onset LBBB</td>
<td></td>
</tr>
<tr>
<td>FATA, 2008</td>
<td>Tirofiban (bolus 0.25 mg/kg + 18-h infusion of 0.125 µg kg⁻¹ min⁻¹)</td>
<td>226</td>
<td>76.1</td>
<td>14.6</td>
<td>8.4</td>
<td>43.4</td>
<td>263</td>
<td>180</td>
<td>692</td>
<td>STR ≥ 70% at 90 min</td>
<td>Combination of TIMI and global use of strategies to open occluded coronary arteries (GUSTO) definitions</td>
<td>TIMI minor criteria</td>
<td>Chest pain &gt; 20 min and ST-segment elevation of at least 0.1 mV in 2 or more contiguous ECG leads</td>
</tr>
</tbody>
</table>
| MACE indicates major adverse cardiac events (death, MI, TVR); LBBB, left bundle-branch block; STR, ST-segment resolution; TIMI, Thrombolysis in Myocardial Infarction.

*Median.
†In the studies with missing anterior MI rate, patients with left anterior descending artery as culprit artery were considered to have anterior MI.
‡The trial provided median values for patients that were randomized in a factorial design to bare metal or drug eluting stents. The mean value for the medians was provided.

College of Cardiology, the European Society of Cardiology, and the Transcatheter Cardiovascular Therapeutics and published review articles, editorials, and internet-based sources of information on trials of interest, including www.tctmd.com and www.theheart.org, were also reviewed.
were performed on an intention-to-treat basis. When the outcome did not occur in 1 or both groups, continuity correction was performed.\(^{11}\) We used fixed- and random-effect models to produce across-study odds ratios (ORs). Because both models yielded similar results, the fixed-effect models are preferentially reported. Cochran Q-test was used to assess heterogeneity. To assess the effect of individual studies on the summary estimate of effect, we did an influence analysis, in which the pooled estimates were recalculated omitting 1 study at a time.

We also calculated fail-safe N, ie, the number of studies required to nullify the significant differences in mortality between the 2 groups using the method of Rosenberg and Orwin.\(^{12,13}\) All analyses were performed using Comprehensive Meta-Analysis software (version 2.0, Biostat, Englewood, NJ).

### Results

A total of 268 citations published between January 2000 and October 2008 were screened. Studies comparing small-molecule GP IIb/IIIa receptor inhibitors with abciximab without randomization were excluded.\(^2,7,8\) One randomized trial was excluded, because it did not provide angiographic or mortality data.\(^{14}\) Our meta-analysis, thus, included 5 trials that randomized patients with STEMI to small-molecule GP IIb/IIIa receptor inhibitors versus abciximab. Of these, 4 trials comparing tirofiban with abciximab had been published in peer-reviewed journals.\(^{15–18}\) All these trials used the currently recommended higher loading dose (25 \(\mu\)g/kg) of tirofiban. One trial, EVA-AMI,\(^{19}\) which compared eptifibatide with abciximab, was presented at American Heart Association Scientific Sessions 2007, and the information was obtained from www.crtonline.org. A total of 2138 patients from 5 randomized, controlled trials constituted our final study population (Figure 1). The characteristics of included trials and study population are shown in Table 1. The raw clinical events in each arm across the trials are listed in Table 2. Summary ORs for death, TVR, reinfarction, and major and minor bleedings (all events at 30 days) generated using fixed- and random-effect models are shown in Table 3.

There was no difference in angiographic outcome between the 2 groups. Thrombolysis in myocardial infarction-3 flow was achieved in both groups in a large proportion of patients with no difference between the 2 groups (89% with small-molecule GP IIb/IIIa inhibitor versus 90% with abciximab; OR, 0.96; 95% CI, 0.72 to 1.27; \(P=0.77\)). Similarly no difference in ST resolution was noted between the 2 groups (72% with small-molecule GP IIb/IIIa inhibitor versus 71% with abciximab; OR, 1.04; 95% CI, 0.84 to 1.29; \(P=0.71\)).

### Clinical End Points

Data on 30-day mortality were available in 2138 patients (100%). Mortality in the trials ranged from 0% to 3.5% in the small-molecule arm and 0% to 3.5% in the abciximab arm. There were no differences in 30-day mortality between the 2 groups (1.9% for small molecule versus 2.3% for abciximab; OR, 0.84; 95% CI, 0.46 to 1.55; \(P=0.58\); Figure 2). None of the studies influenced the results, such that the results would

### Table 2. Clinical Events in Each Arm Across the Trials in the Meta-Analysis

<table>
<thead>
<tr>
<th>Study/Author</th>
<th>Small Molecule Death</th>
<th>Abciximab Death</th>
<th>Small Molecule Reinfarction</th>
<th>Abciximab Reinfarction</th>
<th>Small Molecule TVR</th>
<th>Abciximab TVR</th>
<th>Small Molecule Major Bleeding</th>
<th>Abciximab Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danzi et al, 2004</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Valgimigli et al, 2005</td>
<td>2 (2.3)</td>
<td>3 (3.4)</td>
<td>1 (1.1)</td>
<td>3 (3.4)</td>
<td>1 (1.1)</td>
<td>3 (3.4)</td>
<td>1 (1.1)</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td>EVA-AMI, 2007</td>
<td>8 (3.5)</td>
<td>7 (3.5)</td>
<td>0 (0)</td>
<td>3 (1.5)</td>
<td>6 (2.7)</td>
<td>8 (4)</td>
<td>4 (1.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>MULTISTRATEGY, 2008</td>
<td>4 (1.1)</td>
<td>9 (2.4)</td>
<td>10 (2.7)</td>
<td>5 (1.3)</td>
<td>8 (2.2)</td>
<td>6 (1.6)</td>
<td>9 (2.4)</td>
<td>6 (1.6)</td>
</tr>
<tr>
<td>FATA, 2008</td>
<td>7 (2)</td>
<td>5 (1.5)</td>
<td>2 (0.6)</td>
<td>1 (0.3)</td>
<td>3 (0.9)</td>
<td>0 (0)</td>
<td>5 (1.4)</td>
<td>6 (1.8)</td>
</tr>
</tbody>
</table>

NA indicates not applicable.
have changed significantly; the influence analysis omitting 1 study at a time consistently showed no difference in survival of patients treated with either strategy (data not shown).

TVR and Reinfarction

Data on 30-day TVR were available in 2038 patients (95%). The incidence of TVR ranged from the 0.9% to 2.7% in the small-molecule arm and 0% to 4% in the abciximab arm. Overall, TVR occurred in 18 patients (1.7%) in the small-molecule GP IIb/IIIa receptor inhibitors group and 17 patients (1.7%) in the abciximab group. There was no significant difference in the likelihood of TVR in patients treated with small molecules as compared with those treated with abciximab (OR, 0.95; 95% CI, 0.47 to 1.91; P = 0.89).

Data on 30-day reinfarction were available in 2038 patients (95%). The incidence of reinfarction ranged from 0% to 2.7% in the small-molecule arm and 0.3% to 3.4% in the abciximab arm. There were no significant differences in the incidence of 30-day reinfarction between the 2 groups (1.3% for small molecule versus 1.2% for abciximab; OR, 1.22; 95% CI, 0.51 to 2.91; P = 0.69).

Safety End Points

Data on major bleeding were available in 2138 patients (100%). Major bleeding in the trials ranged from 0% to 2.4% in the small-molecule arm and 0% to 2.3% in the abciximab arm. In the pooled estimate, major bleeding occurred in 19 patients (1.7%) in the small-molecule GP IIb/IIIa receptor inhibitors group and 14 patients (1.3%) in the abciximab group. There were no significant differences in the incidence of 30-day reinfarction between the 2 groups (1.3% for small molecule versus 1.2% for abciximab; OR, 1.22; 95% CI, 0.51 to 2.91; P = 0.69).

Publication Bias

There was no evidence of publication bias for any of the end points studied (Figure 4, funnel plot for mortality). The Eggers test of intercept suggested no evidence for publication bias for mortality (1-tailed P = 0.35) or any of the other end points. The classic fail-safe number was not relevant, because there was no difference in any of the end points between the 2 agents. Calculations of Orwin’s fail-safe N suggested that 9 studies favoring abciximab with a mean OR of 2 would be needed to bring the combined OR > 1.5.
Discussion

Our data suggest that the use of tirofiban or eptifibatide is associated with a clinical outcome similar to that associated with the more widely evaluated agent abciximab in patients undergoing primary PCI. No difference in outcome of patients treated with the 2 classes of drugs could be identified in the early or medium-term outcome with respect to mortality, reinfarction, or bleeding.

Mechanical reperfusion is currently the pre-eminent reperfusion therapy for acute STEMI. Although stent-based PCI has been established as the standard for primary PCI, the optimal pharmacological regimen for these patients is only now being scrutinized. In contrast to studies of fibrinolytic agents, most placebo-controlled trials evaluating GP IIb/IIIa inhibitors in primary PCI for acute STEMI have been small and underpowered to demonstrate a survival benefit. Within this small body of data, most studies have evaluated the role of abciximab. The clinical support for the use of abciximab is derived from a meta-analysis performed by De Luca et al., in which the use of abciximab was associated with a significant reduction in 30-day mortality, reinfarction, and long-term mortality without an increase in bleeding events. A trend toward reduction in early and late mortality with abciximab was also observed by Montalescot et al. in a patient-level meta-analysis of patients undergoing stenting for primary PCI. The key finding of their analysis was that the use of abciximab was associated with a 37% reduction in the composite hazard of death or reinfarction at 3 years (HR, 0.63; 95% CI, 0.45 to 0.88; \( P = 0.008 \)).

In the only large-scale randomized trial evaluating the relative efficacy of tirofiban and abciximab for PCI, there seemed to be a reduction in ischemic events in patients treated with abciximab that was predominantly seen in patients with acute coronary syndromes. The dose of tirofiban used in this trial was lower than the currently recommended dose and the lack of equivalent platelet inhibition with the 2 regimens has been invoked as the reason for the better outcome with abciximab. Patients with acute STEMI were excluded from the trial and until the completion of the trials discussed in the current meta-analysis, there were no randomized data comparing the efficacy of different GP IIb/IIIa inhibitors in primary PCI. All the trials included in our meta-analysis used the currently recommended higher dose of small-molecule GP IIb/IIIa inhibitors and this may explain the observed lack of difference in clinical outcomes between abciximab and small-molecule GP IIb/IIIa inhibitors in our study.

Our data are, thus, important for many reasons. Our results corroborate the earlier observational data demonstrating no major difference in survival of patients treated with abciximab or small-molecule agents. Second, the incidence of bleeding events in these trials was low and not influenced by the specific agent used. Based on contemporary 30-day outcome of patients undergoing primary PCI, a trial powered for mortality would need to enroll >10,000 patients to...
demonstrate superiority of 1 agent over another. Given the lack of major differences in observational data, cost of large trials and market realities, and the results of this meta-analysis, such a trial is unlikely to be performed.

Limitations

Our meta-analysis is subject to the limitations inherent to all meta-analyses, which include publication bias (although tested nonsignificant in our study) and the difficulties in comparing the results because of the different study populations, study designs, and reporting methods as well as the absence of individual patient data, which prohibits adjustment for confounding factors.25 Further, we did not have data on long-term outcome. Previous observational studies have detected differences in long term but not in short-term outcome of patients treated with GP IIb/IIIa inhibitors versus those treated with heparin only.26 It is possible that the enhanced microcirculatory improvement achieved with these drugs impacts long-term survival. Our study cannot detect differences in long-term outcome, because these data were not available. Further, we combined data from 4 trials of tirofiban with 1 trial of eptifibatide. Although there was no statistical heterogeneity in our analysis, there are no direct comparative data to support (or refute) clinical equivalence of the 2 agents. The summary ORs for intermediate-term outcome are limited because these calculations ignore time to event, and hazard ratios cannot be calculated in the absence of patient-level data.

Finally, the event rates in this meta-analysis are very low suggesting enrollment of low-risk patients and a possible Type II error cannot be excluded. These rates are comparable with the rates reported in the abciximab group in the meta-analysis of De Luca et al (30-day mortality 2.4%) suggesting similarity of patients enrolled and are thus likely extant.

Conclusions

Among patients undergoing contemporary primary PCI, there was no difference in the clinical outcome of patients treated with small-molecule GP IIb/IIIa inhibitors or abciximab. Our findings provide further support for the widespread current use of small-molecule GP IIb/IIIa inhibitors in patients undergoing primary PCI.

Acknowledgments

We are grateful to Ms Dawn Ambs for help with formatting and submission of this manuscript.

Disclosures

None.

References


CLINICAL PERSPECTIVE

Although current guidelines support the use of abciximab in patients undergoing primary percutaneous coronary intervention, small-molecule glycoprotein IIb/IIIa inhibitors are more commonly used in contemporary clinical practice. Small, randomized trials evaluating predominantly angiographic end points have demonstrated no difference between small-molecule glycoprotein IIb/IIIa inhibitors and abciximab in patients undergoing primary percutaneous coronary intervention, although none of these trials were powered for clinical end points. We report a systematic evaluation of clinical outcomes of studies comparing small-molecule glycoprotein IIb/IIIa inhibitors with abciximab in patients undergoing primary percutaneous coronary intervention. Our meta-analysis included 2138 patients from 5 randomized controlled trials. There were no differences in 30-day mortality (odds ratio, 0.84; P=0.58), reinfarction (odds ratio, 1.22; P=0.69), or major bleeding (odds ratio, 1.21; P=0.61) between the 2 adjunctive strategies. Similarly, there was no significant difference in the incidence of death (odds ratio, 0.77; P=0.43) or reinfarction on intermediate-term follow-up. Our findings provide further support for the widespread current use of small-molecule glycoprotein IIb/IIIa inhibitors in patients undergoing primary percutaneous coronary intervention.
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Circ Cardiovasc Interv. 2009;2:230-236; originally published online April 21, 2009; doi: 10.1161/CIRCINTERVENTIONS.108.847996

Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-7640. Online ISSN: 1941-7632

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