Meta-Analysis of Randomized Controlled Trials Comparing Intracoronary and Intravenous Administration of Glycoprotein IIb/IIIa Inhibitors in Patients With ST-Elevation Myocardial Infarction

Yongshi Wang, MD,‡, Boting Wu, MD,♯, and Xianhong Shu, MD, PhD,∗

Glycoprotein IIb/IIIa receptor inhibitors (GPIs) have been widely adopted as an adjuvant regimen during primary percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction, but whether intracoronary administration of these potent antiplatelet agents conveys better efficacy and safety over the intravenous route has not been well addressed. A meta-analysis was performed by a systematic search of the published research for randomized controlled trials comparing intracoronary versus intravenous administration of GPIs in patients with ST-segment elevation myocardial infarction. Eight studies involving 686 patients in the intracoronary arm and 660 in the intravenous arm met the inclusion criteria. Postprocedural Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow (odds ratio [OR] 1.46, 95% confidence interval [CI] 1.08 to 1.98, p < 0.05) and myocardial reperfusion grade 2 or 3 (OR 1.78, 95% CI 1.29 to 2.46, p < 0.001) were markedly more often achieved in patients who received intracoronary boluses of GPIs than those receiving the intravenous strategy. Intracoronary administration resulted in a reduced incidence of mortality (OR 0.44, 95% CI 0.21 to 0.92, p < 0.05), target vessel revascularization (OR 0.53, 95% CI 0.29 to 0.99, p < 0.05), and the composite end point of major adverse cardiac events (OR 0.48, 95% CI 0.31 to 0.76, p < 0.005) at 30-day follow-up. No significant difference was found in terms of major or minor bleeding (OR 1.14, p = 0.71, and OR 0.86, p = 0.47 respectively). In conclusion, intracoronary administration of GPIs yielded favorable outcomes in postprocedural blood flow restoration and 30-day clinical prognosis in patients with ST-segment elevation myocardial infarction. The intracoronary use of GPIs can be recommended as a preferred regimen during primary percutaneous coronary intervention. © 2012 Elsevier Inc. All rights reserved. (Am J Cardiol 2012;109:1124–1130)

Glycoprotein IIb/IIIa receptor inhibitors (GPIs) are the most potent antiplatelet agents adopted as an adjuvant regimen during primary percutaneous coronary intervention (PCI) in patients with ST-segment elevation myocardial infarction (STEMI).1–4 On the basis of early success with intracoronary urokinase or heparin use5,6, the potential of localized administration of GPIs has been investigated with great interest.7,8 A systematic review by Hansen et al9 in 2010 argued that intracoronary abciximab reduced major adverse cardiac events (MACEs) in patients with acute coronary syndromes, but the results were not of adequate power, because of the varied clinical settings of the retrospective trials included as well as a limited number of randomized trials available in the analysis. With a thorough elaboration of angiographic and clinical outcomes, we aimed in this meta-analysis of randomized controlled trials to evaluate the efficacy and safety of intracoronary administration of GPIs in patients with STEMI, thus further optimizing the contemporary administration strategy of local antithrombotic approaches.

Methods

We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials for randomized clinical trials published from January 2000 to June 2011. The following key words were used: “intravenous,” “intracoronary,” “glycoprotein IIb/IIIa receptor inhibitor,” “abciximab,” “tirofiban,” “eptifibatide,” “primary PCI,” “myocardial infarction,” “randomized,” and “clinical trials.”

The inclusion criteria were as follows: (1) a diagnosis of STEMI, (2) a randomized trial that assigned patients to either intracoronary or intravenous GPIs before primary PCI, and (3) results reported and made available by the investigators. Regardless of the language or form of the publication, any studies that met these requirements were considered eligible for the meta-analysis. Two independent investigators searched and reviewed the reports and finally identified 8 randomized controlled trials comparing intracoronary with intravenous administration of GPIs in patients with STEMI who underwent primary PCI. The overall search procedure is shown in Figure 1.

The primary end points were postprocedural Thrombol-
The treatment effects were assessed by contacting the primary authors. Two independent investigators (Y.W. and B.W.) performed the study search, selection, abstraction, and appraisal. All outcomes of interest were abstracted on the basis of the protocol definitions of the trials included. We also collected baseline information, such as trial name, first author, year of publication, number of patients enrolled, and major clinical characteristics. Disagreements were resolved by consensus. In case of incomplete or unclear data, attempts were made to obtain clarification by contacting the primary authors. Quality of Reporting Meta-Analysis (QUOROM) guidelines were referred to in our meta-analysis.

Data were processed according to the intention-to-treat principle. Dichotomous variables are expressed as odds ratios (ORs) and 95% confidence intervals (CI). We assessed heterogeneity among studies using Cochran's test and computing the I2 statistic. We examined publication bias by constructing Begg's funnel plots and Egger's plots.

The pooled OR was calculated with the Mantel-Haenszel method for fixed effects and the DerSimonian and Laird method for random effects. Finally, sensitivity analyses were performed by excluding each study one at a time to assess the contribution of each individual study to the overall treatment effect. Statistical analyses were performed using the RevMan version 5 (The Cochrane Collaboration, Oxford, United Kingdom) and Stata version 9.0 (StataCorp LP).

Table 1: Baseline characteristics of included trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Mean Age (years)</th>
<th>Men</th>
<th>DM</th>
<th>SH</th>
<th>Previous MI</th>
<th>LAD Culprit Artery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bellandi et al10</td>
<td>IC 22, IV 23</td>
<td>62, 61</td>
<td>IC 17 (77%), IV 18 (78%)</td>
<td>IC 4 (18%), IV 7 (30%)</td>
<td>IC 10 (46%), IV 8 (35%)</td>
<td>IC 0, IV 0</td>
<td>IC 10 (46%), IV 10 (44%)</td>
</tr>
<tr>
<td>Yang et al11</td>
<td>IC 28, IV 26</td>
<td>60, 57</td>
<td>IC 26 (93%), IV 17 (65%)</td>
<td>IC 5 (18%), IV 6 (23%)</td>
<td>IC 13 (46%), IV 13 (50%)</td>
<td>IC 2 (7%), IV 1 (4%)</td>
<td>IC NA, NA</td>
</tr>
<tr>
<td>LIPSIAbciximab-STEMI12</td>
<td>IC 77, IV 77</td>
<td>64, 66</td>
<td>IC 63 (82%), IV 59 (77%)</td>
<td>IC 24 (31%), IV 22 (29%)</td>
<td>IC 54 (70%), IV 57 (74%)</td>
<td>IC 8 (10%), IV 7 (9%)</td>
<td>IC NA, NA</td>
</tr>
<tr>
<td>Domínguez-Rodríguez et al13</td>
<td>IC 25, IV 25</td>
<td>66, 70</td>
<td>IC 18 (72%), IV 20 (80%)</td>
<td>IC 13 (52%), IV 15 (60%)</td>
<td>IC 14 (56%), IV 13 (52%)</td>
<td>IC NA, NA</td>
<td>IC 14 (56%), IV 16 (64%)</td>
</tr>
<tr>
<td>CICERO14</td>
<td>IC 271, 263</td>
<td>64, 64</td>
<td>IC 208 (77%), IV 187 (71%)</td>
<td>IC 36 (13%), IV 29 (11%)</td>
<td>IC 119 (44%), IV 129 (49%)</td>
<td>IC 32 (12%), IV 23 (9%)</td>
<td>IC 121 (45%), IV 124 (47%)</td>
</tr>
<tr>
<td>EASY-MI15</td>
<td>IC 53, 52</td>
<td>59, 59</td>
<td>IC 41 (77%), IV 43 (83%)</td>
<td>IC 4 (8%), IV 5 (10%)</td>
<td>IC 23 (43%), IV 23 (44%)</td>
<td>IC 6 (11%), IV 9 (17%)</td>
<td>IC 22 (42%), IV 21 (40%)</td>
</tr>
<tr>
<td>Iversen et al16</td>
<td>IC 185, 170</td>
<td>62, 62</td>
<td>IC 151 (82%), IV 135 (80%)</td>
<td>IC 26 (14%), IV 18 (11%)</td>
<td>IC 73 (40%), IV 68 (40%)</td>
<td>IC NA, NA</td>
<td>IC 88 (48%), IV 86 (51%)</td>
</tr>
<tr>
<td>Kirmu et al17</td>
<td>IC 25, 24</td>
<td>57, 56</td>
<td>IC 23 (92%), IV 21 (88%)</td>
<td>IC 3 (12%), IV 5 (21%)</td>
<td>IC 5 (20%), IV 8 (33%)</td>
<td>IC NA, NA</td>
<td>IC 15 (60%), IV 15 (63%)</td>
</tr>
</tbody>
</table>

CICERO = Comparison of Intracoronary Versus Intravenous Abciximab Administration During Emergency Reperfusion of ST-Segment Elevation Myocardial Infarction; DM = diabetes mellitus; EASY-MI = Early Discharge After Transradial Stenting of Coronary Arteries in Acute Myocardial Infarction; IC = intracoronary; IV = intravenous; LAD = left anterior descending coronary artery; LIPSIAbciximab-STEMI = Leipzig Immediate Percutaneous Coronary Intervention Abciximab i.v. Versus i.c. in ST-Elevation Myocardial Infarction; MI = myocardial infarction; NA = not applicable; SH = systemic hypertension.
significant heterogeneity was found among trials (chi-square 1.46, 95% CI 1.08 to 1.98, p = 0.26; chi-square = 0.84, p = 0.84, I^2 = 0%) and MACEs (OR 0.66, 95% CI 0.36 to 1.22, p = 0.19; chi-square = 2.74, p = 0.26, I^2 = 26.9%).

Tirofiban and eptifibatide, small-molecule GPs, belong to the same family of antiplatelet agents as abciximab. When studies concerning small-molecule GPs were excluded, angiographic advantages and favored clinical out-

### Results

A total of 8 randomized controlled trials comparing intracoronary with intravenous administration of GPs in patients with STEMI were enrolled in our meta-analysis.  

The baseline characteristics of the included trials are listed in Table 1. Of 1,346 patients involved, 686 were randomized to the intracoronary group and 660 to the intravenous group. Detailed information about dosage regimens of GPs is listed in Table 2. Intracoronary boluses of GPs were delivered just after restoration of antegrade flow to allow high GP concentration in the target region. Intravenous GPs were administered before or during PCI. Patient selection criteria and trial designs were similar among all studies. However, blinded visual assessment of angiographic parameters was performed in 7 of 8 trials.

All patients were pretreated with dual-antiplatelet therapy (loading doses of aspirin 300 to 600 mg and clopidogrel 300 to 600 mg) followed by maintenance doses of aspirin 75 to 100 mg/day and clopidogrel 75 mg/day for ≥6 months, except for those in the trial by Bellandi et al, who were treated with intravenous aspirin 500 mg followed by clopididine 250 mg twice daily for 4 weeks and aspirin 100 mg/day indefinitely.

Final TIMI grade 3 flow was achieved in 86.9% and 82.2% of the patients in the intracoronary group and intravenous groups, respectively. By the fixed-effects model, we found that patients benefited more from intracoronary bolus in terms of procedural success rate (TIMI grade 3 flow; OR 1.46, 95% CI 1.08 to 1.98, p < 0.05; Figure 2). No significant heterogeneity was found among trials (chi-square = 7.38, p = 0.39, I^2 = 5.1%). Myocardial reperfusion in the PCI-targeting area was assessed by myocardial blush grade or TIMI myocardial perfusion grade as the 2 methods were currently preferred to confirm tissue-level myocardial perfusion after primary PCI. Incidence of myocardial blush grade 2 or 3 or TIMI myocardial perfusion grade 2 or 3 was higher in the intracoronary group than in the intravenous group (OR 1.78, 95% CI 1.29 to 2.46, p < 0.001; chi-squares = 7.32, p = 0.12, I^2 = 45.3%; Figure 2). Excluding 1 study at a time did not have any relevant influence on the overall results of the analyses.

Compared with intravenous bolus of GP, intracoronary bolus proved to be effective in reducing 30-day mortality (OR 0.44, 95% CI 0.21 to 0.92, p < 0.05; chi-square = 2.53, p = 0.12, I^2 = 0%; Figure 3) and target vessel revascularization (OR 0.53, 95% CI 0.29 to 0.99, p < 0.05; chi-square = 2.05, p = 0.36, I^2 = 2.4%) in patients with STEMI by the fixed-effect model. In addition, a trend toward a decrease in reinfarction at 30-day follow-up in the intracoronary group was observed, but not of statistical significance (OR 0.52, 95% CI 0.23 to 1.19, p = 0.12; chi-square = 0.71, p = 0.87, I^2 = 0%). The composite end point of mortality, reinfarction, and target vessel revascularization was significantly reduced in the intracoronary group (OR 0.48, 95% CI 0.31 to 0.76, p < 0.005; chi-square = 5.11, p = 0.16, I^2 = 41.3%; Figure 3). When I study by Iversen et al focusing on comparing MACEs between intracoronary and intravenous administration was removed, there was still a trend favoring intracoronary over intravenous bolus in reducing 30-day mortality (OR 0.61, 95% CI 0.26 to 1.45, p = 0.26; chi-square = 0.84, p = 0.84, I^2 = 0%) and MACEs (OR 0.66, 95% CI 0.36 to 1.22, p = 0.19; chi-square = 2.74, p = 0.26, I^2 = 26.9%).

College Station, Texas). Statistical significance was defined as a 2-sided p value < 0.05.

### Table 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial Design (GPI Administration)</th>
<th>Inclusion Criteria</th>
<th>Primary End Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bellandi et al</td>
<td>IC abciximab bolus (0.25 mg/kg) with a subsequent 12-hour abciximab infusion (0.125 µg/kg/min) vs IV</td>
<td>STEMI &lt;6 hours</td>
<td>LVEF, TIMI flow, MBG</td>
</tr>
<tr>
<td>Yang et al</td>
<td>IC tirofiban bolus (10 µg/kg) with a subsequent 36-hour tirofiban infusion (0.15 µg/kg/min) vs IV</td>
<td>STEMI &lt;12 hours</td>
<td>TIMI flow, TMPG, MACEs</td>
</tr>
<tr>
<td>LIPSI Abciximab-STEMI</td>
<td>IC abciximab bolus (0.25 mg/kg) with a subsequent 12-hour abciximab infusion (0.125 µg/kg/min) vs IV</td>
<td>STEMI &lt;12 hours</td>
<td>Microvascular obstruction extent, infarct size,</td>
</tr>
<tr>
<td>Dominguez-Rodriguez et al</td>
<td>IC abciximab bolus (0.25 mg/kg) with a subsequent 12-hour abciximab infusion (0.125 µg/kg/min) vs IV</td>
<td>STEMI &lt;6 hours</td>
<td>TIMI flow</td>
</tr>
<tr>
<td>CICERO</td>
<td>IC abciximab bolus only (0.25 mg/kg) vs IV abciximab bolus (0.25 mg/kg) plus infusion (12 hours at 0.125 µg/kg/min) vs IV</td>
<td>STEMI or new</td>
<td>Complete ST-segment resolution</td>
</tr>
<tr>
<td>EASY-MI</td>
<td>IC abciximab bolus (0.25 mg/kg) plus infusion (12 hours at 0.125 µg/kg/min) or fixed-dose bolus only (the sum of bolus and infusion amount) vs IV</td>
<td>STEMI or new</td>
<td>Platelet aggregation inhibition 10 minutes after bolus</td>
</tr>
<tr>
<td>Iversen et al</td>
<td>IC abciximab bolus (0.25 mg/kg) with a subsequent 12-hour abciximab infusion (0.125 µg/kg/min) vs IV</td>
<td>STEMI &lt;12 hours</td>
<td>MACEs</td>
</tr>
<tr>
<td>Karma et al</td>
<td>IC tirofiban bolus only (25 µg/kg) vs IV tirofiban bolus (25 µg/kg) plus infusion (18 hours at 0.15 µg/kg/min)</td>
<td>STEMI or new</td>
<td>Microvascular resistance, coronary flow reserve</td>
</tr>
</tbody>
</table>
comes of intracoronary abciximab administration persisted (all p values <0.05). However, 2 randomized controlled trials concerning tirofiban were not of adequate power to detect the differences between intracoronary and intravenous bolus of small-molecule GPIs in patients with STEMI.

We found no significant difference between intracoronary and intravenous GPIs bolus in terms of major bleeding (OR 1.14, 95% CI 0.58 to 2.24, p = 0.71; chi-square = 1.73, p = 0.63, I² = 0%) and minor bleeding (OR 0.86, 95% CI 0.57 to 1.30, p = 0.47; chi-square = 1.92, p = 0.75, I² = 0%). No individual study remarkably affected the overall effect of the analyses.

We performed Begg’s and Egger’s tests for funnel-plot asymmetry. No evidence of publication bias with respect to any of the study end points (final TIMI grade 3 flow: Begg’s test z = 0.37, p = 0.71, Egger’s test t = 0.69, p = 0.52; final myocardial reperfusion grade 2 or 3: Begg’s test z = -0.24, p = 1.00, Egger’s test t = 0.43, p = 0.70; 30-day mortality: Begg’s test z = 0.24, p = 0.81, Egger’s test t = -0.33, p = 0.76; 30-day MACEs: Begg’s test z = 0.34, p = 0.73, Egger’s test t = -0.65, p = 0.58; and major bleeding complications: Begg’s test z = 0.34, p = 0.73, Egger’s test t = 0.64, p = 0.59).

Discussion

On the issue of antithrombotic therapy in cardiovascular diseases, there is a long-existing puzzle concerning how the optimal pharmacologic effect can be achieved. When handling a clotted coronary vessel with diminished forward blood flow, especially in the setting of STEMI, which is typically caused by occlusive thrombosis after the rupture of an atherosclerotic plaque, conventional PCI is often accompanied by unique complications such as distal microembolization and subsequent microvascular dysfunction. In the recent practical guidelines for the management of patients

Figure 2. Forest plot for (A) postprocedural TIMI grade 3 flow and (B) myocardial reperfusion grade 2 or 3, intracoronary (IC) versus intravenous (IV) administration of GPIs. CICERO = Comparison of Intracoronary Versus Intravenous Abciximab Administration During Emergency Reperfusion of ST-Segment Elevation Myocardial Infarction; EASY-MI = Early Discharge After Transradial Stenting of Coronary Arteries in Acute Myocardial Infarction; LIPSIAbciximab-STEMI = Leipzig Immediate Percutaneous Coronary Intervention Abciximab i.v. Versus i.c. in ST-Elevation Myocardial Infarction.
with STEMI, intravenous GPIs followed by oral dual-antiplatelet therapy was recommended as a class IIa (at the time of primary PCI) or IIb (before primary angiography and PCI) indication.\(^{18,19}\) It remained unsettled whether systemic administration of antithrombotic agents was the optimal strategy. The present meta-analysis of all currently available randomized controlled trials demonstrates that intracoronary administration of GPIs yielded favorable outcomes in postprocedural blood flow restoration and 30-day clinical prognosis in patients with STEMI.

The major advantage of intracoronary administration of antithrombotic agents during PCI is achieving a higher local concentration, resulting in a higher procedural success rate, demonstrated by TIMI grade 3 flow, and better tissue-level reperfusion status, indicated by a myocardial blush grade or a TIMI myocardial perfusion grade of 2 or 3 compared to intravenous delivery. The pharmacologic mechanism of GPIs has been summarized, and the most intriguing point is that they demonstrate a thrombolytic effect on freshly formed thrombi at high local concentrations, which constitutes the rationale for their intracoronary use.\(^{20,21}\) Depending on the imbalance between inflow and washout at the culprit vessel, the concentration of GPI at the site of thrombus after an intracoronary bolus may be up to 280-fold higher than after intravenous administration.\(^{22,23}\) Therefore, it is quite logical to consider that an intracoronary bolus can yield better receptor occupancy and additional thrombolytic effects as well. And the reperfusion data achieved in the intracoronary arm clearly elaborated the rationale for the use of intracoronary boluses of GPIs during primary PCI in patients with STEMI.

It is believed that impaired TIMI flow or myocardial reperfusion strongly correlates with increased mortality.\(^{24-27}\) The angiographic benefits of intracoronary bolus led further to favorable clinical outcomes, as indicated by a reduction in 30-day MACEs. After the intracoronary bolus
administration of GPIs, 30-day mortality and target vessel revascularization rates were significantly reduced, and there was a trend toward favorable outcomes in the case of reinfarction. The proposed mechanism underlying the lower occurrence of target vessel restenosis might be the adequate local antithrombotic and anti-inflammatory effects arising from the use of an intracoronary bolus. Moreover, our findings are highly consistent with those from a retrospective study in 2003 by Wöhrl et al. except for the high overall incidence of 30-day MACEs up to 12.9% after coronary angioplasty. As shown in Figure 3, among 6 trials that provided data concerning MACEs, 2 reported no adverse events in the 2 treatment arms, while 3 of all 8 trials reported no deaths. It might be the low incidence of adverse cardiac events and the limited number of patients included in each prospective, randomized trial that explain why the supposed advantages of intracoronary bolus on the clinical end points was not detected. Unfortunately, the beneficial effects of intracoronary bolus on myocardial salvage and left ventricular function could not be proved because of inadequate power due to unavailable data from most of the included trials.

In our meta-analysis, the safety end point of intracoronary bolus did not differ significantly from intravenous bolus. On the current basis of more cautious dosing of antithrombotic agents, closer attention to sheath management, and a higher success rate with the transradial approach, incidences of bleeding were quite low, and the patient population of our meta-analysis might not have been large enough to detect differences between the treatment arms.

Several limitations to this meta-analysis should be acknowledged. Although no statistical heterogeneity was found in our analysis, the dosing regimen at the operators’ discretion resulted in heterogeneity between protocols. Relevant reviews, editorials, correspondence, Internet-based resources of information on clinical trials, as well as abstracts from scientific meetings of the American College of Cardiology, the American Heart Association, the European Society of Cardiology, and others, were also reviewed to avoid publication bias. Limited studies on the intracoronary bolus–only strategy made it difficult to evaluate whether the postprocedural continuous intravenous infusion was necessary. Lack of raw and individual data from the included trials prohibited exploring the relation of the treatment and a higher success rate with the transradial approach, incidences of bleeding were quite low, and the patient population of our meta-analysis might not have been large enough to detect differences between the treatment arms.

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