Eptifibatide Is Noninferior to Abciximab in Primary Percutaneous Coronary Intervention

Results From the SCAAR (Swedish Coronary Angiography and Angioplasty Registry)

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Objectives

The aim of this study was to test the noninferiority of eptifibatide relative to abciximab in patients with ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI).

Background

Glycoprotein IIb/IIIa inhibitors are recommended by international guidelines in patients with acute coronary syndromes undergoing PCI. Abciximab is recommended with a higher level of evidence than eptifibatide in patients with STEMI. No large, prospective, randomized trial comparing abciximab and eptifibatide has been published.

Methods

All (n = 11,479) STEMI patients in Sweden who underwent primary PCI and received either eptifibatide or abciximab from 2004 to 2007 were derived from the SCAAR (Swedish Coronary Angiography and Angioplasty Registry). The primary end point was death or myocardial infarction (MI) during 1-year follow-up, with adjustment for baseline differences with a multivariate logistic regression analysis including propensity score. The pre-specified noninferiority margin was set to 1.29.

Results

The combined end point occurred in 353 of 2,355 patients (15.0%) treated with eptifibatide and in 1,432 of 9,124 patients (15.7%) treated with abciximab. The unadjusted odds ratio (OR) for eptifibatide versus abciximab was 0.95 (95% confidence interval [CI]: 0.84 to 1.08). Multivariate adjustment (n = 11,317) confirmed noninferiority, with an OR of 0.94 (95% CI: 0.82 to 1.09). The adjusted secondary end points of death and MI separately also showed noninferiority, with ORs of 0.99 (95% CI: 0.82 to 1.19) and 0.88 (95% CI: 0.73 to 1.05), respectively.

Conclusions

This large registry study suggests that eptifibatide is noninferior to abciximab in patients with STEMI undergoing primary PCI with respect to death or MI during 1 year, thereby supporting the use of either drug in clinical practice. (J Am Coll Cardiol 2010;56:470–5) © 2010 by the American College of Cardiology Foundation

Glycoprotein (GP) IIb/IIIa inhibitors potently inhibit platelet aggregation and reduce the incidence of ischemic events in patients undergoing percutaneous coronary interventions (PCIs), especially in patients with acute coronary syndromes (ACS) (1–4). Abciximab is recommended with a high level of evidence in both the European and American guidelines as adjunctive treatment during PCI for high-risk patients with ACS, including primary PCI in patients with ST-segment elevation myocardial infarction (STEMI) (5–8). Eptifibatide and tirofiban have less scientific documentation but are approved for adjunctive medical therapy during PCI in stable coronary disease, as well as in patients with ACS (2,4,7,8). Eptifibatide is not recommended for primary PCI by the European guidelines (5) and receives a lower level of evidence compared with abciximab in the latest updated American College of Cardiology/American Heart Association STEMI guidelines (6,9).

In 2004, 2 large Swedish university hospitals changed their GP IIb/IIIa inhibitor therapy from abciximab to
Eptifibatide on all indications to reduce pharmacological costs. An additional 7 hospitals (of 27 hospitals performing PCI) have been using both abciximab and eptifibatide (10). The present study was designed to test a pre-specified hypothesis that eptifibatide is noninferior to abciximab with respect to death or myocardial infarction (MI) during 1 year in patients with STEMI undergoing primary PCI.

Methods

Subjects and study design. The patient population was derived from SCAAR (Swedish Coronary Angiography and Angioplasty Registry), a registry with complete coverage of all hospitals performing coronary angiography and interventions in Sweden. The registry is supported by Swedish Health Authorities and is independent of commercial funding (10).

Between January 2004 and December 2007, a total of 15,542 procedures were performed in 15,120 patients with STEMI as primary PCI. In this retrospective observational study, only patients with primary PCI receiving adjunctive therapy with either eptifibatide or abciximab were included (n = 11,479) (10). Each patient was followed for 1 year and was included in the study only once. In hospitals using both eptifibatide and abciximab, the selection of the GP IIb/IIIa inhibitor was at the operator’s discretion. Patients receiving tirofiban (n = 463) were excluded as well as patients undergoing rescue PCI. Patients treated with adjunctive fondaparinux (n = 15) or bivalirudin (n = 63) were not excluded. All episodes of PCI-related bleeding during the hospital stay were to be reported in the SCAAR registry (10), but this assessment was not a part of the primary objective of the study.

The long-term follow-up was derived by merging the SCAAR database with the Swedish Cause of Death Register and the Swedish National Patient Register regarding reinfarction after hospital discharge (International Classification of Diseases-10th Revision codes I21 and I22). The study was approved by the local ethics committee at Uppsala University. The study complied with the Declaration of Helsinki.

Statistical analysis. The primary hypothesis was that eptifibatide would be noninferior to abciximab with respect to the primary end point of death or MI at 1 year. The pre-specified non-inferiority margin was set to 1.29, preserving 50% of the estimated effect by abciximab by the point estimate of the odds ratio (OR) of abciximab versus placebo in patients with STEMI (11,12). The pre-specified secondary end points were death and MI separately during 1 year of follow-up.

Logistic regression with drug as a predictor was used to obtain the estimates of ORs and 95% confidence intervals (CIs). To compensate for pre-treatment differences, we added propensity score (13) as a predictor in a multivariate logistic regression. The individual propensity scores, defined as the conditional probability of obtaining eptifibatide, based on all variables in Tables 1 and 2, were estimated using multivariate logistic regression. Age was dichotomized (≤65 years vs. >65 years) before entering the model. Fondaparinux and bivalirudin were not used as individual factors in the propensity score analysis.

Results

A total of 11,479 patients with STEMI underwent primary PCI with adjunctive therapy of either eptifibatide (n = 2,355) or abciximab (n = 9,124). Baseline characteristics are presented in Table 1, and ongoing or periprocedural medications are listed in Table 2.

Table 1  Clinical Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (n = 11,479)</th>
<th>Abciximab (n = 9,124)</th>
<th>Eptifibatide (n = 2,355)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>11,479</td>
<td>65 (57–74)</td>
<td>65 (57–74)</td>
</tr>
<tr>
<td>Women</td>
<td>11,479</td>
<td>28.1% (2,568)</td>
<td>27.0% (636)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11,479</td>
<td>17.7% (1,616)</td>
<td>16.3% (385)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11,479</td>
<td>34.6% (3,157)</td>
<td>33.6% (791)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>11,478</td>
<td>18.1% (3,157)</td>
<td>16.5% (389)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>11,479</td>
<td>3.3% (300)</td>
<td>2.9% (69)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>11,476</td>
<td>29.5% (2,688)</td>
<td>27.7% (652)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>11,479</td>
<td>14.9% (1,355)</td>
<td>14.8% (349)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>11,465</td>
<td>8.6% (782)</td>
<td>9.0% (211)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>11,475</td>
<td>2.7% (242)</td>
<td>3.0% (71)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>11,479</td>
<td>5.0% (458)</td>
<td>4.1% (97)</td>
</tr>
<tr>
<td>Previous renal failure</td>
<td>11,479</td>
<td>1.0% (88)</td>
<td>1.2% (28)</td>
</tr>
<tr>
<td>Previous major bleeding</td>
<td>11,479</td>
<td>3.2% (291)</td>
<td>2.6% (62)</td>
</tr>
</tbody>
</table>

Data are expressed as median (25th–75th percentile) or percent (frequency). CABG = coronary artery bypass grafting; n = number of patients with nonmissing values; PCI = percutaneous coronary intervention.
During the follow-up period, a total of 908 patients died, of whom 179 (7.6%) were in the eptifibatide group and 729 (8.0%) were among the abciximab-treated patients. The total number of MIs was 1,016, of which 197 (8.4%) occurred in the eptifibatide group and 819 (9.0%) in the abciximab group. The combined end point of death or MI during 1 year occurred in 353 patients (15.0%) treated with eptifibatide and 1,432 patients (15.7%) treated with abciximab. The unadjusted OR for eptifibatide versus abciximab was 0.95 (95% CI: 0.84 to 1.08) (Fig. 1). Multivariate adjustment (n = 11,317) using logistic regression with propensity score adjusting for all variables in Tables 1 and 2 also showed noninferiority for eptifibatide versus abciximab, with an OR of 0.94 (95% CI: 0.82 to 1.09) (Fig. 2).

The unadjusted OR for death during 1 year was 0.95 (95% CI: 0.80 to 1.12), and in a multivariate logistic regression including propensity scores, the OR was 0.99 (95% CI: 0.82 to 1.19) on the basis of 11,317 subjects (Fig. 3). The unadjusted OR for MI alone during 1 year of follow-up was 0.93 (95% CI: 0.79 to 1.05; n = 11,317) (Fig. 4).

As a secondary safety end point, a total of 318 episodes of in-hospital PCI-related bleeding in hospital were recorded, of which 75 (3.2%) were in the eptifibatide cohort and 243 (2.7%) in the abciximab cohort. The unadjusted OR was 1.20 (95% CI: 0.92 to 1.56).

**Discussion**

This large registry study demonstrates that patients with STEMI undergoing primary PCI with either eptifibatide or abciximab as adjunctive therapy experienced the combined end point of death or MI during 1-year follow-up at comparable rates (15.0% vs. 15.7%). The pre-specified noninferiority margin for eptifibatide versus abciximab was also met in a multivariate regression analysis adjusting for differences in baseline characteristics and cointerventions including a propensity score. Adjusted ORs for the individual end points of death and MI also indicated noninferiority.

Abciximab has been shown to reduce the composite end point of death, ischemia-driven revascularization, reinfarction, and stroke at 6 months after PCI in patients with ACS (1). In patients with STEMI, the addition of abciximab has,
in a meta-analysis, proven a significant reduction of the composite end point of death and MI from 19.0% to 12.9% at 1 year, with a remaining positive effect for abciximab after 3 years of follow-up (11). Abciximab is therefore recommended with a high level of evidence in both the European and American guidelines for patients with ACS, including primary PCI in STEMI (5–9).

Eptifibatide has shown a significant reduction in ischemic end points in stable coronary disease as well as in death and nonfatal MI within 30 days in patients with ACS (2). However, a small study (n = 400) investigating upstream eptifibatide treatment versus placebo in patients with STEMI showed no reduction in the combined end point of death, reinfarction, or recurrent severe ischemia at 30 days (14). In the latest European guidelines for the treatment of non–ST-segment elevation ACS, eptifibatide has received a Class IIa recommendation (7), but because of the weaker scientific evidence for the treatment of patients with STEMI, eptifibatide is not a generally recommended treatment during primary PCI (5,6,9).

Direct comparative studies between the two different GP IIb/IIIa inhibitors are sparse, and a large prospective comparison between eptifibatide and abciximab with clinical outcomes has not yet been performed. A retrospective registry study in which 3,541 primary PCI-treated patients with STEMI received adjunctive GP IIb/IIIa inhibitors demonstrated no difference in the in-hospital outcome of death or recurrent MI (15). In the EVA-AMI (Eptifibatide Versus Abciximab in Primary PCI for Acute Myocardial Infarction) trial, 429 patients with STEMI were randomized to either abciximab (n = 203) or eptifibatide (n = 226), with the primary end point of ST-segment resolution 1 h after the intervention. Although designed to show noninferiority between eptifibatide and abciximab, in fact eptifibatide showed superiority regarding the primary end point (16). The EVA-AMI trial was later included in a meta-analysis of 6 randomized trials comparing abciximab (n = 1,082) with small-molecule GP IIb/IIIa inhibitors (eptifibatide [n = 226] or tirofiban [n = 889]), showing no significant differences in the primary end point of 30-day mortality or reinfarction (17). Compared with the EVA-AMI study, our study enrolled a much larger number of patients with STEMI and provided a longer follow-up of hard end points, including mortality.

Patients undergoing coronary interventions today have to a higher extent been pretreated with oral dual-antiplatelet therapy than in previously published studies evaluating GP IIb/IIIa inhibitors (2,18). One might hypothesize that this important difference could affect the outcome and render less ischemic events compared with the prior GP IIb/IIIa studies performed before clopidogrel was available. With current high rates of clopidogrel treatment and future clinical use of more potent P2Y12 inhibitors such as prasug-
rel (19) and ticagrelor (20), the role of the GP IIb/IIIa inhibitors may be more difficult to assess.

**Study limitations.** Inherent limitations to a nonrandomized registry study need to be addressed. Despite appropriate statistical adjustments, unknown confounders may have affected the results. To limit a potential doctor's selection bias, we compared the 2 solely eptifibatide-using hospitals with 2 similar abciximab-using hospitals. This evaluation showed similar background characteristics as well as results for these 2 cohorts.

During the study period, both anticoagulant and oral antiplatelet treatment have partly changed. The lack of information about the clopidogrel loading doses and the duration of clopidogrel treatment makes it impossible to relate the timing of events with discontinuation of dual-antiplatelet therapy.

A trend for higher bleeding rates in the eptifibatide cohort was seen, but report rates are likely to differ between hospitals, and unknown biases are likely not accounted for. The bleeding assessment was not a part of the primary end point, and no firm conclusion is thus drawn from this result.

**Conclusions**

This large-scale registry study suggests that eptifibatide is noninferior to abciximab in patients undergoing primary PCI regarding the composite end point of death or MI during a 1-year follow-up period after propensity score multivariate adjustments. In the absence of large head-to-head prospective randomized comparisons of hard end points between these 2 commonly used GP IIb/IIIa inhibitors, our study supports the clinical use of either drug in patients with STEMI undergoing primary PCI.

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**REFERENCES**


Key Words: eptifibatide ■ abciximab ■ ST-segment elevation myocardial infarction ■ death ■ myocardial infarction.