Cost and effectiveness of glycoprotein IIb/IIIa-receptor inhibitors in patients with acute myocardial infarction undergoing percutaneous coronary intervention

PATRICK L. MCCOLLAM, DAVID A. FOSTER, AND JEFFREY S. RIESMEYER

Several randomized clinical trials in patients with acute myocardial infarction (AMI) who underwent percutaneous coronary intervention (PCI) have examined different treatment strategies, including stenting and adjunctive drug therapy. The clinician seeks to understand the generalizability of the results of such studies to his or her practice setting. Anderson et al. recently published findings from a large registry that provided insight into practice patterns and outcomes for the AMI patient undergoing PCI. However, these data did not specifically include outcomes of treatment with glycoprotein (GP) IIb/IIIa-receptor inhibitors, which are commonly used.

In this study, we reviewed a large national hospital database to examine in-hospital mortality, complications, total hospital costs, and length of stay among AMI patients who did and did not receive a GP IIb/IIIa-receptor inhibitor during PCI. Risk adjustment was performed by logistic regression to account for differences in patient and institutional characteristics. Complications were evaluated as a composite of cardiac, noncardiac, procedural, and nonprocedural complications. Incremental costs and length of stay were analyzed by least-squares regression.

A total of 32,529 patients in 99 hospitals were included. Only abciximab had a significant benefit for risk-adjusted mortality (odds ratio [OR] = 0.74, 95% confidence interval [CI] = 0.59–0.92, p = 0.007) and shorter length of stay (0.21 day, 95% CI = 0.09–0.34 day, p = 0.0013) compared with the controls. Eptifibatide was associated with fewer complications (OR = 0.86, 95% CI = 0.75–0.98, p = 0.02), and tirofiban incurred the lowest incremental cost ($644, OR = $252–$1,036, p < 0.0001), but abciximab had the most favorable cost-effectiveness ratio ($14,515 per life-year gained).

Information from a large database supported the use of GP IIb/IIIa-receptor inhibitors in patients with AMI undergoing PCI. Treatment with abciximab was associated with favorable differences in survival, cost-effectiveness, and length of stay compared to treatment without a GP IIb/IIIa-receptor inhibitor.

Index terms: Abciximab; Angioplasty; Costs; Economics; Eptifibatide; Hospitals; Mortality; Myocardial infarction; Platelet aggregation inhibitors; Tirofiban

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Patients were included in the study if a diagnosis code for AMI and a primary procedure code for PCI were present. The outcomes of interest were in-hospital mortality, complications, total hospital costs, and length of stay. Cost-effectiveness (cost per life-year gained) was also calculated. Patients were grouped according to receipt of abciximab, eptifibatide, or tirofiban. After risk adjustment, each group was compared with a control group of patients who did not receive GP IIb/IIIa-receptor inhibitors. Data were collected for the period from January 1, 2000, to June 30, 2001.

Since this was a retrospective analysis, differences among treatment groups were possible because of nonrandomization. The analytical methods used attempted to account for these differences. Continuous data (incremental total hospital costs and length of stay) were estimated by least-squares regression to fit general linear models. Risk adjustment for binary outcomes (in-hospital mortality, complications) was performed by logistic regression with accepted methods. This model was constructed by using a larger Solucient database containing data on more than 17 million hospital discharges annually (including Medicare patients) from about 2500 U.S. hospitals. The models used database variables to account for differences in patient characteristics (age, sex, principal and secondary diagnoses and procedures [including stent use], clinical grouping, length of stay, discharge status) and differences in hospital characteristics (number of beds, U.S. Bureau of the Census division, teaching status, urban or rural setting). The risk-adjusted mortality index was calculated as the number of actual deaths divided by the number of expected deaths; the expected mortality rate was risk adjusted by using the model to predict the likelihood of death on the basis of the specific treatment group. A risk-adjusted complications index was calculated in the same manner (number of actual complications divided by number of expected complications). An odds ratio for an index of <1 would favor the treatment strategy. Exact 95% confidence intervals (CIs) were used to assess the significance of observed versus expected outcomes.

An all-inclusive composite of over 40 variables (cardiac, noncardiac, procedural, and nonprocedural) was used for the complications index in order to align with an institutional perspective. Pertinent cardiac complications are listed in the appendix. Death was not included in the complications index, since it was analyzed separately. Both the risk-adjusted mortality index and the risk-adjusted complications index are standard reporting indices used by Solucient for institutional benchmarking. This concept of “grade cards” is widely used by federal and state government agencies for disease-specific and institutional comparisons on a local level.

An incremental cost-effectiveness ratio (ICER), expressed as the cost per life-year gained, was calculated as the cost of therapy with GP IIb/IIIa-receptor inhibitors minus the cost of therapy without GP IIb/IIIa-receptor inhibitors divided by the corresponding difference in effectiveness (in this case, risk-adjusted mortality). Wage-adjusted incremental costs (including pharmacy costs) were used in this analysis. For these calculations, we assumed that survival at discharge implied an additional life expectancy of 14 years, which was discounted at 3% per year to yield 11.6 discounted years.

The model's discrimination was its ability to correctly differentiate the patients who had a given outcome from those who did not. The C-statistic, an overall measure of model discrimination, was calculated for both risk-adjusted indices (C-statistic is analogous to r² for linear regression). The value of the C-statistic may range from 0.5 (no predictive ability) to 1 (perfect predictive ability). This statistic is widely reported in these types of studies.

Data were obtained from the UB-92 forms, general ledger operating expenses, and charge-description master obtained by Solucient. All results refer to the in-hospital time period. All analyses were performed by the Clinical Informatics Research group at Solucient by using SAS version 8.1 (SAS Institute Inc., Cary, NC). Comparisons were made on a pairwise basis for each GP IIb/IIIa-receptor inhibitor group versus the control group.

The final sample consisted of 32,529 patients from 99 hospitals across the United States. The sample size among therapies was unbalanced, since the sample reflected clinical practice patterns rather than randomization. The models demonstrated excellent discrimination, as measured by the C-statistic. The C-statistic for the risk-adjusted mortality index was >0.916 for all three GP IIb/IIIa-receptor models. Similarly, for the risk-adjusted complications index, the C-statistic was >0.789 for all three models.

Table 1 presents patient demographics, health characteristics, and
hospital characteristics. The typical patient was a man over 60 years of age who had received at least one coronary stent. Heart failure was present in over 15% of patients, and over 20% had diabetes. Many patients had been admitted via the emergency room. Overall, the predominant payer was Medicare (41–49%), followed by health maintenance organizations (18–24%). The largest numbers of hospitals were in the North Central and South regions, a majority had more than 300 beds, and approximately 20% were teaching hospitals.

The main outcome results are shown in Table 2 and Figure 1. The overall unadjusted inpatient mortality rate was 3.5%. Both the risk-adjusted mortality index and the risk-adjusted complications index indicated several significant differences between GP IIb/IIIa-receptor recipients and the control group. The point estimate and 95% CI for the risk-adjusted mortality index indicated a favorable treatment effect for abciximab ($p = 0.007$). A neutral treatment effect was found for both eptifibatide and tirofiban ($p = 0.23$ and 0.93, respectively).

The risk-adjusted complications index was neutral for abciximab and tirofiban and lower for eptifibatide compared with the controls. Again, this index was a composite endpoint (cardiac, noncardiac, procedural, and nonprocedural complications) and did not include death. In this analysis, complications were not weighted for severity.

Adjusted incremental total hospital costs (including drug costs) and length of stay also indicated several significant differences between GP IIb/IIIa-receptor recipients and the control group (Table 2). All treatment groups had significantly higher total costs than the control group. On a rank-order basis, tirofiban had the lowest adjusted incremental cost, eptifibatide was intermediate, and abciximab was highest. The ICER

<table>
<thead>
<tr>
<th>Item</th>
<th>Controls (n = 6,920)</th>
<th>Abciximab (n = 11,816)</th>
<th>Eptifibatide (n = 10,093)</th>
<th>Tirofiban (n = 3,700)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male pts. (%)</td>
<td>63.0</td>
<td>69.1</td>
<td>67.1</td>
<td>68.7</td>
</tr>
<tr>
<td>Mean age of pts. (yr)</td>
<td>64.4</td>
<td>61.6</td>
<td>62.3</td>
<td>62.6</td>
</tr>
<tr>
<td>Payer type (% pts.)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicare</td>
<td>49.1</td>
<td>41.2</td>
<td>44.6</td>
<td>46.3</td>
</tr>
<tr>
<td>Medicaid</td>
<td>2.3</td>
<td>3.1</td>
<td>2.4</td>
<td>2.7</td>
</tr>
<tr>
<td>Blue Cross</td>
<td>9.6</td>
<td>11.2</td>
<td>9.9</td>
<td>10.9</td>
</tr>
<tr>
<td>Health maintenance organization</td>
<td>22.1</td>
<td>22.9</td>
<td>24.5</td>
<td>18.5</td>
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<tr>
<td>Emergency-room admission (% pts.)</td>
<td>35.7</td>
<td>45.2</td>
<td>38.3</td>
<td>45.9</td>
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<tr>
<td>Stent use (% pts.)</td>
<td>85.7</td>
<td>91.6</td>
<td>90.6</td>
<td>89.8</td>
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<tr>
<td>Teaching hospital (% pts.)</td>
<td>22.2</td>
<td>21.9</td>
<td>19.0</td>
<td>22.7</td>
</tr>
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<td>36</td>
<td>33</td>
<td>23</td>
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<tr>
<td>Northeast</td>
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<td>2</td>
<td>1</td>
<td>2</td>
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<tr>
<td>South</td>
<td>51</td>
<td>47</td>
<td>45</td>
<td>35</td>
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<tr>
<td>West</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>No. beds</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200–299</td>
<td>30</td>
<td>29</td>
<td>27</td>
<td>21</td>
</tr>
<tr>
<td>300–499</td>
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<tr>
<td>≥500</td>
<td>22</td>
<td>19</td>
<td>17</td>
<td>12</td>
</tr>
</tbody>
</table>

Figure 1. Cost and effectiveness of adjunctive therapy with various glycoprotein (GP) IIb/IIIa-receptor inhibitors in patients with acute myocardial infarction undergoing percutaneous coronary intervention. Quadrant A = lower cost and greater effectiveness, quadrant B = higher cost and greater effectiveness, quadrant C = higher cost and lower effectiveness, and quadrant D = lower cost and lower effectiveness. Data points represent the point estimate and 95% confidence interval for each drug group compared with the control group (no GP IIb/IIIa-receptor inhibitors). Only abciximab’s effect was statistically significant.
was calculated for comparison with the control group. Abciximab's ICER was $14,515 per life-year gained on the basis of the point estimate from the risk-adjusted mortality index and incremental cost. Neither eptifibatide nor tirofiban had a significant effect on mortality (the effectiveness measure used in the calculation). However, on the basis of the point estimates from the risk-adjusted mortality index, eptifibatide's ICER was $21,731 and tirofiban's $163,286 per life-year gained.

When cost versus effectiveness is plotted (as suggested by Mark), the values for abciximab are entirely within the quadrant of higher cost and greater effectiveness, while the values for both eptifibatide and tirofiban enter the quadrant of higher cost and lower effectiveness (Figure 1).

Abciximab recipients had a significantly shorter length of stay (0.21 day shorter) than the control group ($p = 0.0013$) (Table 2). In other words, for every 100 patients treated with abciximab, 21 days of hospitalization would be saved. Neither tirofiban nor eptifibatide significantly affected length of stay.

In summary, the mortality index favored abciximab use, the complications index favored eptifibatide, total costs were lowest for tirofiban, incremental cost-effectiveness analysis favored abciximab, and length of stay was shortest for abciximab.

**Discussion**

We believe this is the largest naturalistic study of GP IIb/IIIa-receptor inhibitors in AMI patients undergoing PCI to date. The results show that abciximab had a favorable treatment effect on risk-adjusted mortality during the study period, while the small-molecule agents had a neutral treatment effect. The cost-effectiveness analysis demonstrated the most favorable ICER for abciximab, even though its incremental total costs were highest.

We chose in-hospital mortality as the primary clinical endpoint, since our data did not allow precise measurement of a composite endpoint, such as death plus myocardial infarction plus revascularization of involved vessels. The fit of the risk-adjustment models appeared to be quite good, with high C-statistic values that matched or exceeded those in other studies of this type.

**Why was a survival advantage seen in abciximab recipients?** Survival in AMI is related to myocardial salvage and improved left ventricular function. Several studies have shown that abciximab may have dethrombotic effects and may improve Thrombolysis in Myocardial Infarc-

tion grade-3 blood flow and microvascular perfusion. The cause of improved microvascular flow may be more potent platelet inhibition or perhaps antiinflammatory effects not mediated by GP IIb/IIIa-receptors. These factors may explain the significant reduction in mortality observed with abciximab. These same effects have not been demonstrated with the small-molecule agents.

Complications, as defined in this study, were neutral to less in the treated patients. Although the complications index was favorable in eptifibatide recipients, this apparently did not translate into a shorter length of stay. Alternatively, while abciximab had a neutral effect on complications, recipients had shorter stays.

Higher in-hospital total costs for GP IIb/IIIa-receptor therapy were not unexpected; data from the EPISTENT and ESPRIT studies also suggested this. However, cost-effectiveness analysis indicated that abciximab was the most cost-effective therapy. In fact, some would argue that one should calculate only the ICER for abciximab, since it was the only agent to show a statistically significant difference in the effectiveness measure (risk-adjusted mortality) compared with the control group. Further examination of these cost data by using previously published econometric methods is warranted.

It is important to note the consistency in the length-of-stay findings. Length of stay is an often used and easily measurable hospital benchmark. The current results continue to support previous research using sample-selection-model analyses. Shortening the length of stay without incurring more complications may be important in improving efficiency in busy interventional settings.

This study has the limitations of any retrospective observational study. Nevertheless, well-done observational studies can provide valuable contributions to the medical literature. We observed actual clinical

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**Table 2. Main Outcome Results for Glycoprotein IIb/IIIa-Receptor Inhibitors versus Control**

<table>
<thead>
<tr>
<th>Drug Group</th>
<th>Risk-Adjusted Mortality Index</th>
<th>Risk-Adjusted Complications Index</th>
<th>Incremental Hospital Cost, $ (95% CI)</th>
<th>Length of Stay, Days (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abciximab (n = 11,816)</td>
<td>0.74 (0.59 to 0.92)</td>
<td>0.92 (0.81 to 1.03)</td>
<td>1,807 (1,529 to 2,085)</td>
<td>–0.21 (–0.09 to –0.34)</td>
</tr>
<tr>
<td>Eptifibatide (n = 10,093)</td>
<td>0.87 (0.68 to 1.10)</td>
<td>0.86 (0.75 to 0.98)</td>
<td>1,147 (849 to 1,445)</td>
<td>–0.006 (–0.22 to 0.14)</td>
</tr>
<tr>
<td>Tirofiban (n = 3,700)</td>
<td>0.99 (0.73 to 1.34)</td>
<td>0.94 (0.79 to 1.12)</td>
<td>644 (252 to 1,036)</td>
<td>–0.04 (–0.14 to 0.12)</td>
</tr>
</tbody>
</table>

*Control patients received no glycoprotein IIb/IIIa-receptor inhibitors.

*(CI) = confidence interval.

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*Significantly different from value for control group ($p = 0.0007$).

$p < 0.0001$.

$p = 0.0013$.

$p = 0.02$. 

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practice, but patient randomization did not occur. Only in-hospital data were recorded in this database, so long-term follow-up was not possible. While many hospitals across the United States were included, they too were not randomly selected. To make the sample more homogeneous, only patients who underwent PCI were included; thus, these results may not apply to noninterventional medical therapy of AMI.

While the models were quite robust, as measured by the C-statistic, the models can account only for recorded variables in the risk-adjusted indices. Because of potential coding biases, complications are probably the weakest outcome measure. Complications were not weighted for severity, so a same-stay emergency by-pass surgery is not differentiated from a minor complication in the results. This is an area for further study within the data.

The CADILLAC trial found an overall in-hospital death rate of 1.5% and a death rate of 1.9% at 30 days. In contrast, other recent trials in AMI patients who received stents found 30-day death rates ranging from 2.6% to 5%. In our study, the overall in-hospital mortality rate was 3.5%, which is quite consistent with rates indicated by other large databases. For the American College of Cardiology–National Cardiovascular Data Registry the rate was 5.2%; for the National Registry of Myocardial Infarction the rate was 3.5–5%, depending on treatment strategy; and for the Healthcare Cost and Utilization Project the rate was 2.7%. Thus, CADILLAC in-hospital mortality rates appear to be in the low range of the clinical trial data, and the clinical trial data rates appear to be lower than registry data. Our results may simply reflect differences between samples of “all comers” and patients highly selected for clinical trials.

Understanding the outcomes and costs of new therapies is increasingly important in today’s health care environment. This large database provides additional insight into the contemporary use of GP IIb/IIIa-receptor inhibitors in patients undergoing PCI and provides some answers to questions about outcomes and costs. The results support the use of GP IIb/IIIa-receptor inhibitors in AMI patients in the setting of usual care. The point estimate and 95% CI for abciximab suggested a favorable treatment effect on risk-adjusted inpatient mortality. This translated into the most favorable cost-effectiveness results for abciximab, even though these patients did have the highest incremental costs. While subject to the difficulties inherent to coding in the medical record, the risk-adjusted complications index appeared similar for abciximab and tirofiban and was favorable for eptifibatide. Finally, the data support earlier findings of a consistently shorter length of stay for abciximab recipients.

Conclusion

Information from a large database supported the use of GP IIb/IIIa-receptor inhibitors in patients with AMI undergoing PCI. Treatment with abciximab was associated with favorable differences in survival, cost-effectiveness, and length of stay compared to treatment without a GP IIb/IIIa-receptor inhibitor.

References

21. Pennsylvania Health Care Cost Contain-
22. Disruption of operative wound.

Appendix—Selected medical and surgical cardiovascular complications

1. Gastrointestinal complications after procedure.
2. Postoperative septicemia, abscess, and wound infection.
3. Complications involving cardiac devices.
4. Complications involving vascular and hemodialysis devices.
5. Complications involving other and unspecified devices, implants, and grafts.
6. Other surgical complications.
7. Miscellaneous complications.
8. Cardiorespiratory arrest, shock, or failure.
9. Postoperative complications related to nervous system.
11. Postoperative cardiac abnormalities except AMI.
12. Procedure-related perforation or laceration.
14. Hemorrhage, hematoma, or seroma complicating a procedure.
15. Postprocedure complications of other body systems.
17. Complications related to blood products.
18. Complications related to drugs affecting cardiac rhythm regulation.
19. Complications related to cardiotoxic glycosides (e.g., digoxin) and drugs of similar action.
20. Complications related to other drugs affecting the cardiovascular system.
21. Percutaneous transluminal coronary angioplasty followed by coronary artery bypass grafting during the same hospitalization.
22. Disruption of operative wound.