The Role of Risk Stratification in the Decision to Provide Upstream Versus Selective Glycoprotein IIb/IIIa Inhibitors for Acute Coronary Syndromes
A Cost-Effectiveness Analysis
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OBJECTIVES
We endeavored to determine under what conditions a strategy of upstream use of small molecule platelet glycoprotein (GP) IIb/IIIa inhibitors for all acute coronary syndromes (ACS) patients is cost effective compared to that of selective use of abciximab in only those patients requiring percutaneous coronary intervention (PCI).

BACKGROUND
Small molecule GP IIb/IIIa inhibitors have shown benefit in ACS, but abciximab, the more expensive GP IIb/IIIa inhibitor, may be more effective during PCI. However, abciximab does not have proven efficacy in medical management. No prior study has attempted to balance these competing benefits.

METHODS
A decision analysis was performed to examine two strategies: 1) treat all ACS patients upstream with a small molecule GP IIb/IIIa inhibitor and continue through medical management and PCI, if performed; or 2) wait, and selectively use abciximab only in patients who ultimately undergo PCI. Applicable randomized controlled trial data were used for the principal analysis.

RESULTS
The strategy of upstream use of a small molecule GP IIb/IIIa inhibitor was superior to selective use, and economically acceptable, with a cost-effectiveness ratio of $18,000 per year of life gained. The superiority of the upstream use strategy persisted over the majority of sensitivity analyses. When stratified by risk according to Thrombolysis in Myocardial Infarction risk score, a strategy of upstream use was only cost effective in those patients with moderate or high risk.

CONCLUSIONS
Upstream use of small molecule GP IIb/IIIa inhibition in ACS patients with moderate or high risk for cardiovascular events is a cost-effective approach that should be considered in this subset of patients. (J Am Coll Cardiol 2005;47:529–37) © 2006 by the American College of Cardiology Foundation

Randomized trials of patients with acute coronary syndromes (ACS) have demonstrated a significant reduction in myocardial infarction (MI) and death with the use of the small molecule platelet glycoprotein (GP) IIb/IIIa receptor inhibitors, tirofiban and eptifibatide (1–4). In contrast, the alternative GP IIb/IIIa inhibitor, abciximab, was not beneficial when administered to a predominantly medically managed ACS population (5). However, during percutaneous coronary intervention (PCI) abciximab was superior to the small molecule GP IIb/IIIa inhibitor, tirofiban (6). These findings suggest that small molecule GP IIb/IIIa inhibitors may provide some benefit during medical management of ACS, but may not be as effective during PCI as abciximab, a drug that is more costly and provides no benefit during medical management.

No randomized controlled trial has addressed the key question that clinicians must answer when a patient with ACS presents for care; namely, whether a strategy of upstream use of a small molecule platelet GP IIb/IIIa inhibitor, with continuation of the drug in those patients undergoing PCI, or a strategy of selective use of abciximab in only those patients undergoing PCI, is the optimal therapeutic option. In addition, validated measures of risk, such as the Thrombolysis In Myocardial Infarction (TIMI) risk score (7), have not been applied to upstream versus selective GP IIb/IIIa inhibition (8–10).

Decision analysis allows clinicians to compare the possible outcomes of different therapeutic strategies, particularly in the face of uncertainty, when no appropriate randomized clinical trial is available (11). The purpose of this study was to use decision analysis and primary data from randomized controlled trials to determine whether one strategy is superior to the other, to calculate the cost-effectiveness of that strategy, and to assess the value of the TIMI risk score in choosing the most cost-effective strategy.

METHODS
Decision tree. We performed a decision analysis (DATA version 4.0, TreeAge Software Inc., Williamstown, Massa-
and MI with small molecule GP IIb/IIIa inhibitors in patients who do not undergo PCI were derived from the pooled ORs of death and MI versus placebo for the five major randomized trials comparing small molecule GP IIb/IIIa inhibitors versus placebo in a predominantly medically managed population. A total of 24% of these patients underwent PCI (13). However, because the exclusion of a subgroup of patients based on their subsequent care could bias our estimates (14), we did not exclude those receiving PCI from the pooled estimate.

Major bleeding rates were based on pooled estimates of bleeding rates in randomized controlled ACS trials (13). Bleeding after CABG was estimated using the published subanalyses of these trials (12,15,16).

**Outcomes.** The primary outcome measure was the incremental cost-effectiveness ratio (ICER), measured as the difference in cost of the two strategies divided by the difference in life expectancy (both discounted at a rate of 3% per year; life expectancy values and life years that are described throughout the Results section reflect such discounting). The secondary end point was difference in major bleeding rate.

**COSTS.** Estimates were obtained for 30-day, 6-month, and lifetime costs, with lifetime cost used to calculate the ICER. The cost assigned to each 10-mg vial of abciximab was $450, with an assumption of a mean of three vials used per patient (i.e., $1,350) (17–20). The cost ($1,060) assigned to upstream small molecule GP IIb/IIIa inhibitor was based on the mean cost of drug in the Treat angina with Aggrastat and determine Cost of Therapy with Invasive or Conservative Strategy (TACTICS) trial (median duration of therapy = 48 h in the invasive arm) (21).

The 30-day and 6-month costs of procedures and hospital stay were derived by adjustment of costs reported for the invasive arm of the TACTICS trial and for the Evaluation in PTCA to Improve Long-term Outcome with abciximab GP IIb/IIIa blockade (EPILOG) trial (18,21). These costs include the costs of MI, bleeding, and of increased length of stay. All costs were further adjusted to 2002 dollars. Costs after six months (for the lifetime cost estimate) were derived from projections for a typical 60-year-old MI patient from the Cholesterol And Recurrent Events (CARE) trial population (17,22).

**EFFECTIVENESS.** Effectiveness was measured in terms of additional life expectancy. Life expectancies were modeled for four main outcomes in the decision tree: survivors who did not require PCI or CABG; survivors who required PCI or CABG and did not have a subsequent nonfatal MI; survivors who had a subsequent nonfatal MI; and those who died within 30 days (life expectancy = 0). Life expectancy for patients with ACS who did not require PCI or CABG was derived from vital statistics data (23). Life expectancy for those with ACS who had a nonfatal MI was derived from modeling from Kaplan-Meier estimates in patients with creatine kinase elevation after PCI; life expectancy for those who underwent PCI without nonfatal MI was simi-
larly derived from patients without creatine kinase elevation (24). The mean age in the cohorts used to derive life expectancy values was 61 years, and 76% of patients were men. Life expectancy for survivors who did not require PCI or CABG was 17.592 years; for survivors who required PCI or CABG and did not have a nonfatal MI was 15.535 years; for all survivors who had a subsequent nonfatal MI was 13.524 years. Life expectancy estimates matched closely the estimates used in other cost-effectiveness analyses of GP IIb/IIIa inhibitors, including those derived from the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PUR-SUIT) trial and Duke database (25,26). Effects of the treatments on the patients’ quality of life were examined separately in a sensitivity analysis (27).

Assessment of the role of risk stratification. Baseline patient risk was assessed by published risk for death and MI according to TIMI risk score at six weeks (9) and categorized as low, intermediate, and high risk (7). These analyses provided the cost-effectiveness of upstream use of GP IIb/IIIa inhibition in low-, intermediate-, and high-risk score patients.

Sensitivity analyses. Sensitivity analyses were performed for important clinical questions. Stability of the model’s predictions was assessed by varying all parameters in the tree across a
### Table 1. Probability of Outcomes Used in the Decision Model

<table>
<thead>
<tr>
<th>Factor</th>
<th>Base Case Probability or Relative Risk</th>
<th>Range</th>
<th>References Base Case</th>
<th>Additional References for Range or 95% CI Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI</td>
<td>0.4</td>
<td>0.2–0.8</td>
<td>TACTICS, invasive arm (12)</td>
<td>GUSTO IV, FRISC II, RITA 3, PRISM PLUS, PURSUIT (1,3,5,40,41)</td>
</tr>
<tr>
<td>CABG</td>
<td>0.15</td>
<td>0.11–0.35</td>
<td>PRISM, PRISM PLUS, PURSUIT, TACTICS, RITA 3, GUSTO IV (1–3,5,12,41)</td>
<td>FRISC II (40)</td>
</tr>
</tbody>
</table>

Selective use abciximab during PCI only

- No PCI, no drug, bleed
  - Probability: 0.01
  - Range: 0.01–0.03
  - References: Boersma et al. (placebo arm) (13)
  - Additional References: GUSTO IV ACS (placebo arm) (5)
- No PCI, no drug, MI
  - Probability: 0.081
  - Range: 0.039–0.135
  - References: Boersma et al. (placebo arm) (13)
- No PCI, no drug, death
  - Probability: 0.037
  - Range: 0.029–0.051
  - References: Boersma et al. (placebo arm) (13)

CABG, bleed
- Probability: 0.93
- Range: PURSUIT (placebo group) (1)

CABG, MI
- Probability: 0.21
- Range: 0.06–0.28
- References: Boersma et al. (placebo arm) (13)

CABG, death
- Probability: 0.045
- Range: 0.045–0.058
- References: Boersma et al. (placebo arm) (13)

PCI with abciximab, bleed
- Probability: 2.05
- Range: 1.03–4.09
- References: CAPTURE (4)

PCI with abciximab, MI
- Probability: 0.48
- Range: 0.30–0.78
- References: CAPTURE (4)

PCI with abciximab, death
- Probability: 0.75
- Range: 0.27–2.09
- References: CAPTURE (4)

Upstream use small molecule GP IIb/IIIa inhibitor in all ACS patients

- No PCI, small molecule, bleed
  - Probability: 1.4
  - Range: 1.3–2.07
  - References: Boersma et al. (small molecule analysis) (13)
- No PCI, small molecule, MI
  - Probability: 0.88
  - Range: 0.47–0.95
  - References: Boersma et al. (small molecule analysis) (13)
- No PCI, small molecule, death
  - Probability: 0.88
  - Range: 0.41–0.95
  - References: Boersma et al. (small molecule analysis) (13)

CABG, bleed
- Probability: 1.0 (vs. CABG no GPIIb/IIIa inhibitor MI)
- Range: 0.65–3.01
- References: PURSUIT (1)

CABG, MI
- Probability: 0.58
- Range: 0.2–0.8
- References: PURSUIT (1)

CABG, death
- Probability: 1.0 (vs. CABG no GPIIb/IIIa inhibitor death)
- Range: 0.49–2.5
- References: Empiric

PCI, small molecule, bleed
- Probability: 1.0 (vs. PCI bleed abciximab)
- Range: 0.8–2.7
- References: TARGET (6)

PCI, small molecule, MI
- Probability: 1.5 (vs. PCI MI abciximab)
- Range: 0.9–2.5
- References: TARGET ACS cohort (44)

ACS = acute coronary syndromes; CABG = coronary artery bypass grafting; CAPTURE = C7E3 Anti Platelet Therapy in Unstable REfractory angina trial; CI = confidence interval; EPIC = Evaluation of c7E3 for Prevention of Ischemic Complications trial; FRISC II = Fragmin and Fast Revascularization during Instability in Coronary Artery disease trial; GP = glycoprotein; GUSTO IV = Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries IV trial; MI = myocardial infarction; PCI = percutaneous coronary intervention; PRISM PLUS = Platelet Receptor Inhibition in ischemic Syndrome Management in Patients Limited by Unstable Signs and symptoms trial; PURSUIT = Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy trial; RITA 3 = Randomized Intervention Trial of unstable Angina; RR = relative risk; TACTICS = Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy; TARGET = Do Tirofiban and Reo-Pro Give Similar Efficacy Outcome Trial.
range defined either by clinical plausibility or by the variables’ 95% confidence intervals observed in the randomized trials.

RESULTS

Probabilities. The probability of death or MI at 30 days was 11.9% in the upstream strategy and 12.1% in the selective abciximab strategy. The probability of major bleeding was 10.2% with upstream use and 9.7% in the selective abciximab strategy. The rates of non-CABG-related major bleeding were 3.6% and 3.0%, with upstream and selective abciximab use, respectively.

Costs, life expectancy, quality-adjusted life years (QALY), and cost-effectiveness. Despite the higher drug cost of abciximab ($1,350 per patient for abciximab vs. $1,060 for small molecule), an upstream strategy of small molecule GP IIb/IIIa inhibition for all ACS patients was more costly than selective abciximab use, with an incremental lifetime cost of $720 per patient (Table 2) because, in large part, of the higher proportion of patients receiving a GP IIb/IIIa inhibitor in the upstream strategy.

The average life expectancy was 15.68 years with the upstream strategy, compared with 15.64 years for selective abciximab. This yielded a gain of 4,000 years of life per 100,000 patients treated with the strategy of upstream small molecule GP IIb/IIIa inhibition.

Thus, the use of upstream small molecule GP IIb/IIIa inhibitors resulted in an ICER of $18,000 per year of life gained (Table 2). Quality adjustment to years of life gained yielded an average life expectancy of 14.80 QALYs with upstream use versus 14.76 with selective use of abciximab. This yielded a cost-effectiveness ratio of $18,000 per QALY gained.

The role of risk stratification. Increasing patient baseline risk for adverse events amplified the benefits of the upstream use strategy. Patients with low TIMI risk scores (0 to 2) had a gain of only 1,000 years of life per 100,000 patients treated with upstream use, with an ICER of $58,300 per year of life gained (Fig. 2). In contrast, patients with moderate or higher TIMI risk scores (3 to 4 and 5 to 7) had more years of life saved with an upstream GP IIb/IIIa inhibitor strategy, resulting in economically favorable cost-effectiveness ratios ($24,730 and $14,444 per year of life gained, in moderate and high TIMI risk score patients, respectively, Fig. 2).

Further sensitivity analyses of high-risk patients revealed an extremely favorable cost-effectiveness ratio ($1,276 per year of life gained) for the upstream GP IIb/IIIa strategy if the probability of PCI was increased to 80%. However, the upstream use strategy became less cost effective if the probability of CABG was also extremely high. For instance, if the probability of CABG was 30% and the probability of

Table 2. Costs, Effectiveness, and Incremental Cost-Effectiveness Ratio for Upstream Use Strategy Compared With Selective Use Strategy

<table>
<thead>
<tr>
<th></th>
<th>Selective Use Abciximab During PCI Only</th>
<th>Upstream Use Small Molecule GPIIb/IIIa Inhibitor in All ACS Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day cost per patient</td>
<td>$17,631</td>
<td>$18,210</td>
</tr>
<tr>
<td>6-month cost per patient</td>
<td>$23,463</td>
<td>$24,092</td>
</tr>
<tr>
<td>Lifetime cost per patient*</td>
<td>$81,124</td>
<td>$81,844</td>
</tr>
<tr>
<td>Incremental lifetime cost per patient</td>
<td>—</td>
<td>$720</td>
</tr>
<tr>
<td>Incremental lifetime cost per 100,000 patients*</td>
<td>—</td>
<td>$72,000,000</td>
</tr>
<tr>
<td>Years of life per 100,000 patients</td>
<td>1,564,000</td>
<td>1,568,000</td>
</tr>
<tr>
<td>Incremental years of life gained per 100,000 patients</td>
<td>—</td>
<td>4,000</td>
</tr>
<tr>
<td>Incremental cost per year of life gained</td>
<td>—</td>
<td>$18,000</td>
</tr>
</tbody>
</table>

*Used for calculation of incremental cost-effectiveness ratio.

ACS = acute coronary syndromes; GP = glycoprotein; PCI = percutaneous coronary intervention.

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Cost effectiveness of upstream glycoprotein IIb/IIIa use according to Thrombolysis In Myocardial Infarction (TIMI) risk score of patient.
PCI was 50%, upstream GP IIb/IIIa use had a borderline favorable cost-effectiveness ratio of $55,571.

Additional sensitivity analyses. The superior effectiveness of upstream use of GP IIb/IIIa inhibition persisted in most cases when applying a wide range of plausible probabilities in reduction of death and MI for both strategies during sensitivity analyses (Table 3). The assumption that small molecule GP IIb/IIIa inhibitors and abciximab have equal efficacy during PCI resulted in further effectiveness of an upstream use strategy (5,000 years of life gained per 100,000 patients treated).

The use of the same, small molecule GP IIb/IIIa inhibitor selectively or upstream resulted in 5,000 years of life saved per 100,000 patients treated with upstream versus selective use; there was also a higher incremental lifetime cost of $848 for upstream use. Thus, the ICER was $16,960 per year of life gained.

If the probability of ACS patients undergoing PCI was 65% or greater, selective use of abciximab was more effective than upstream use of small molecule GP IIb/IIIa inhibitors (Fig. 3). If the probability of PCI was greater than 60%, upstream use of small molecule GP IIb/IIIa inhibitors was

### Table 3. Incremental Cost-Effectiveness Ratios in Sensitivity Analyses

<table>
<thead>
<tr>
<th>Subject of Sensitivity Analysis</th>
<th>Principal Analysis Estimate</th>
<th>Estimates Used for Sensitivity Analyses</th>
<th>Years of Life With Upstream Small Molecule Use*</th>
<th>Years of Life With Selective Abciximab Use*</th>
<th>Years of Life Gained With Upstream Use*</th>
<th>Cost Effectiveness of Upstream Use (Dollars per Year Life Gained)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal simulation</td>
<td>0.40</td>
<td>(threshold 0.63)</td>
<td>1,568,000</td>
<td>1,564,000</td>
<td>4,000</td>
<td>18,000</td>
</tr>
<tr>
<td>PCI rate</td>
<td>0.2</td>
<td>1,603,000</td>
<td>1,596,000</td>
<td>7,000</td>
<td>18,000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.8</td>
<td>1,498,000</td>
<td>1,501,000</td>
<td>-3,000</td>
<td>8,000</td>
<td></td>
</tr>
<tr>
<td>CABG rate</td>
<td>0.15</td>
<td>1.577,000</td>
<td>1.573,000</td>
<td>4,000</td>
<td>18,000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.11</td>
<td>1.522,000</td>
<td>1.520,000</td>
<td>2,000</td>
<td>18,000</td>
<td></td>
</tr>
<tr>
<td>No PCI, MI</td>
<td>0.081</td>
<td>1.577,000</td>
<td>1.574,000</td>
<td>3,000</td>
<td>18,000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.039</td>
<td>1.556,000</td>
<td>1.552,000</td>
<td>4,000</td>
<td>18,000</td>
<td></td>
</tr>
<tr>
<td>No PCI, death</td>
<td>0.037</td>
<td>1.577,000</td>
<td>1.575,000</td>
<td>2,000</td>
<td>18,000</td>
<td></td>
</tr>
<tr>
<td>CABG, MI</td>
<td>0.21</td>
<td>1.572,000</td>
<td>1.569,000</td>
<td>3,000</td>
<td>18,000</td>
<td></td>
</tr>
<tr>
<td>CABG, death</td>
<td>0.045</td>
<td>1.568,000</td>
<td>1.564,000</td>
<td>4,000</td>
<td>18,000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.058</td>
<td>1.565,000</td>
<td>1.561,000</td>
<td>4,000</td>
<td>18,000</td>
<td></td>
</tr>
<tr>
<td>PCI with abciximab, MI</td>
<td>RR 0.48</td>
<td>1.570,000</td>
<td>1.565,000</td>
<td>5,000</td>
<td>14,400</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.30</td>
<td>1.565,000</td>
<td>1.563,000</td>
<td>2,000</td>
<td>18,000</td>
<td></td>
</tr>
<tr>
<td>PCI with abciximab, death</td>
<td>RR 0.75</td>
<td>1.579,000</td>
<td>1.575,000</td>
<td>4,000</td>
<td>18,000</td>
<td></td>
</tr>
<tr>
<td>No PCI, MI with upstream small molecule in all ACS patients</td>
<td>RR 0.88</td>
<td>1.574,000</td>
<td>1.564,000</td>
<td>10,000</td>
<td>18,000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.47</td>
<td>1.566,000</td>
<td>1.564,000</td>
<td>2,000</td>
<td>18,000</td>
<td></td>
</tr>
<tr>
<td>No PCI, death with upstream small molecule in all ACS patients</td>
<td>RR 0.88</td>
<td>1.582,000</td>
<td>1.564,000</td>
<td>18,000</td>
<td>4,000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.41</td>
<td>1.565,000</td>
<td>1.564,000</td>
<td>1,000</td>
<td>72,000</td>
<td></td>
</tr>
<tr>
<td>PCI, MI with upstream small molecule in all ACS patients†</td>
<td>RR 1.5</td>
<td>1.569,000</td>
<td>1.564,000</td>
<td>5,000</td>
<td>14,400</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>1.565,000</td>
<td>1.564,000</td>
<td>1,000</td>
<td>72,000</td>
<td></td>
</tr>
<tr>
<td>PCI, death with upstream small molecule in all ACS patients†</td>
<td>RR 1.0</td>
<td>(threshold RR 1.2 LE = 1,565,000)</td>
<td>1.568,000</td>
<td>4,000</td>
<td>18,000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>1.544,000</td>
<td>1.564,000</td>
<td>-20,000</td>
<td>—</td>
<td></td>
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<tr>
<td>Life expectancy discount rate</td>
<td>3%</td>
<td>1%</td>
<td>1,961,800</td>
<td>4,300</td>
<td>16,700</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5%</td>
<td>1,289,000</td>
<td>1,286,000</td>
<td>3,000</td>
<td>24,000</td>
<td></td>
</tr>
</tbody>
</table>

*Represents years of life per 100,000 patients; †Represents relative risk versus PCI with abciximab.

ACS = acute coronary syndromes; CABG = coronary artery bypass grafting; LE = life expectancy; MI = myocardial infarction; PCI = percutaneous coronary intervention; RR = relative risk.
not cost effective (ICER of $100,000 or greater). When the effect of GP IIb/IIIa inhibitors in medically managed patients was varied from an OR of 0.47 to 1.0 (to examine ORs from other published subanalyses), an upstream strategy was still superior (Table 2). This also held true when ORs were simultaneously varied for death and MI in two-way sensitivity analyses. The OR death or MI with small molecule versus placebo would need to be 0.97 for the two strategies to break even.

Sensitivity analyses in which the costs of abciximab and small molecule GP IIb/IIIa inhibitors were equal yielded a higher incremental cost of upstream use of $848, and a cost-effectiveness ratio of $21,200.

In sensitivity analyses of bleeding, rates were 5.0% in upstream use versus 4.0% in selective use of abciximab at the lower limit of the 95% confidence interval of CABG-related bleeding. Bleeding rates were 14.0% with a strategy of upstream use versus 13.0% with selective use of abciximab when CABG-related bleeding was at the upper limit of the 95% confidence interval.

**DISCUSSION**

The use of upstream GP IIb/IIIa inhibition versus selective use in only those patients undergoing PCI is a key question that clinicians face when caring for the ACS patient. It has been argued that a randomized clinical trial examining this question is needed, but no such trial has been completed yet (28). In the absence of a specific randomized trial, a decision analysis may provide formal insight into what conditions may make one strategy potentially more beneficial than another. Through an analysis that utilized randomized trial data, we found that upstream use of small molecule GP IIb/IIIa inhibitors in ACS patients is superior to selective use of abciximab. The ICER of $18,000 per year of life gained per patient with upstream use is economically attractive compared with other widely accepted cardiovascular treatments (21,29–31).

Importantly, though, when using TIMI risk score as a measure of a patient’s baseline risk for adverse outcome, the benefits of upstream GP IIb/IIIa inhibition were marginal, and thus no longer cost effective, in those patients with the lowest risk. In contrast, patients with moderate or high risk showed benefit and favorable cost effectiveness with upstream GP IIb/IIIa inhibition. These findings support the American College of Cardiology and American Heart Association recommendation to manage ACS patients with upstream GP IIb/IIIa inhibition based on level of risk (32).

There has been considerable controversy about the extent of reduction in death or MI with GP IIb/IIIa inhibitors during medical management. Both the post-randomization categorization of patients into “medically managed” versus “PCI” subgroups, and the use of meta-analysis have been
criticized (14,33–35). By developing a decision tree where the effects of GP IIb/IIIa inhibition in medical management may be more precisely examined, we could estimate that as long as upstream therapy reduced risk of death or MI by more than 3%, this strategy was superior.

Our analysis enabled us to examine additional important questions that have not been formally tested as of yet in clinical trials. For one, it has been suggested that at proper doses of tirofiban, or with the use of epifibatide, the small molecule class of GP IIb/IIIa inhibitors may be equally effective as abciximab during PCI (36–38). Our analysis suggests superiority of an upstream use strategy if one assumes all GP IIb/IIIa inhibitors have equal efficacy during PCI, but that small molecules have greater efficacy than abciximab during medical management. Second, it is not known whether the use of upstream epifibatide for all ACS patients is superior to using epifibatide selectively in only PCI patients. We found that a strategy of upstream use of epifibatide was superior to selective epifibatide, and still had a favorable ICER.

The results of this analysis may also help to guide under which clinical conditions one particular therapy is more appropriate. For instance, patients who are highly (65% or greater) likely to undergo PCI may benefit from a selective abciximab strategy. However, there are few cases in which a clinician is certain that the patient will undergo percutaneous revascularization. Contemporary trials of ACS have shown that a relatively small proportion (<64%) of patients with ACS will subsequently undergo PCI, even with aggressive revascularization strategies (12,39). In addition, if one assumes an equivalent effect of small molecules and abciximab during PCI, then the upstream use strategy remains superior, even if PCI rates are very high.

The major strength of the decision model in this study is that each comparison was based directly on randomized controlled trial data (1–6,12,13,40–44). However, there are also limitations to our analysis. First, despite using randomized trial data, we may not be able to fully account for variable patient presentation. Randomized trials may not represent the full spectrum of ACS patients; those patients at high risk for adverse outcomes may have been excluded. However, increasing patient risk of death or MI in sensitivity analyses further improved the cost-effectiveness of a strategy of upstream use. Second, our study was not designed to examine the potential benefits of novel antiplatelet therapies including clopidigrel, which may reduce the baseline risk of the ACS patient and/or the risk of MI and death during PCI (45). Sensitivity analyses may provide a rough estimate of the effects of clopidigrel. For instance, if clopidigrel reduces further the overall risk for death and MI in the ACS patient by 30%, upstream GP IIb/IIIa inhibition still has a favorable ICER of $26,500 per year of life gained. However, the effect of clopidigrel in reducing potential efficacy of GP IIb/IIIa inhibitors is not known and therefore could not be studied in our analysis. Third, we did not directly take into account the timing of PCI. Markedly earlier PCI in both strategies may diminish the benefit of upstream use (39), but no randomized trial has simultaneously compared GP IIb/IIIa inhibition versus placebo and early PCI versus late PCI. Fourth, RRs from the Chimeric 7E3 Antiplatelet Therapy in Unstable Angina REfractory to Standard Treatment (CAPTURE) trial were used to estimate the effect of abciximab during PCI, but, in that trial, abciximab was administered for a period before PCI, unlike in the present model. Finally, our cost analysis did not account for the incremental costs of drug-eluting stent use, which would increase overall costs of both strategies, but should not change the incremental cost of upstream use. Indirect and long-term costs may not be fully incorporated. Further, cost and utilization data are limited to that from randomized trials, and this is a potentially significant limitation to all cost-effectiveness analyses performed using randomized trials.

A systematic approach to the appropriate selection of therapy becomes increasingly important when multiple therapeutic options, each with individually proven benefits and incremental costs, are available. This analysis quantifies under what conditions a strategy of upstream small molecule use is superior to selective use of abciximab, and confirms the importance of risk stratification in guiding therapy. It further suggests that the upstream use of small molecule GP IIb/IIIa inhibitors is a superior, cost-effective strategy that should be considered for those moderate and high-risk patients presenting with ACS.

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REFERENCES

8. Sabatine MS, Morrow DA, Giugliano RP, et al. Implications of upstream glycoprotein IIb/IIIa inhibition and coronary artery stenting in the invasive management of unstable angina/non ST elevation myocardial infarction: a comparison of the Thrombolysis in Myo-


34. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in early treatment of unstable angina: aspirin, clopidogrel, glycoprotein IIb/IIIa antagonists, or all three? Heart 2002;88:11–4.


