Cost-Effectiveness of Platelet Glycoprotein IIb/IIIa Inhibition With Eptifibatide in Patients With Non–ST-Elevation Acute Coronary Syndromes

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Background—In the PURSUIT trial, eptifibatide significantly reduced the 30-day incidence of death and myocardial infarction relative to placebo in 9461 patients with an acute coronary syndrome (unstable angina or non–Q-wave myocardial infarction).

Methods and Results—We conducted a 2-part prospective economic substudy of the 3522 US patients enrolled in PURSUIT: (1) an empirical intention-to-treat comparison of medical costs (hospital plus physician) up to 6 months after hospitalization and (2) a lifetime cost-effectiveness analysis. The base-case cost-effectiveness ratio was expressed as the 1996 US dollars required to add 1 life-year with eptifibatide therapy. The 2 treatment arms had equivalent resource consumption and medical costs (exclusive of the cost of the eptifibatide regimen) during the index (enrollment) hospitalization ($P = 0.78$) and up to 6 months afterward ($P = 0.60$). The average wholesale price of the eptifibatide regimen was $1217, but a typical hospital discounted price was $1014. The estimated life expectancy from randomization in the US patients was 15.96 years for eptifibatide and 15.85 years for placebo, an incremental difference of 0.111. The incremental cost-effectiveness ratio for eptifibatide therapy in US PURSUIT patients was $16,491 per year of life saved. This result was robust through a wide range of sensitivity analyses. The cost-utility ratio for eptifibatide (using time trade-off defined utilities) was $19,693 per added quality-adjusted life-year.

Conclusions—Based on the results observed in the US PURSUIT patients, the routine addition of eptifibatide to standard care for non–ST-elevation acute coronary syndrome patients is economically attractive by conventional standards. 

Key Words: coronary disease ■ cost-benefit analysis ■ glycoproteins ■ eptifibatide

Recently, the US Food and Drug Administration approved 2 new intravenous antiplatelet agents for clinical use in acute coronary syndromes. Both agents block the final common pathway for platelet aggregation, which involves the platelet surface membrane glycoprotein (GP) IIb/IIIa receptor, thereby providing much more complete inhibition of platelet aggregation than is achieved with aspirin. This more aggressive antiplatelet effect offers the potential to further reduce ischemic events in acute coronary syndrome patients.

Eptifibatide (Integrilin) is the GP IIb/IIIa receptor antagonist that has been studied in the largest number of acute coronary syndrome patients. The PURSUIT (Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy) trial randomized 10,948 patients with acute coronary syndrome and found a statistically significant 1.5% absolute reduction in the 30-day incidence of death or myocardial infarction (MI) with eptifibatide relative to placebo. As part of the prospective PURSUIT research efforts, we conducted an economic analysis of the US PURSUIT results.

Methods

Patient Population

Between November 1995 and January 1997, 10,948 patients with acute coronary syndrome were enrolled in PURSUIT at 726 hospitals in 28 countries. Eligible patients met the following criteria: (1) ischemic chest discomfort of ≥10 minutes’ duration within the previous 24 hours and (2) transient ST-segment elevation >0.5 mm or transient or persistent ST-segment depression >0.5 mm or T-wave inversion ≥1 mm within 12 hours of symptoms or (3) an elevated creatine kinase–MB fraction. Exclusion criteria included persistent ST-segment elevation >1 mm, contraindications to anticoagulation, severe hypertension, or renal failure.
Overview of Major Clinical Outcomes in PURSUIT

PURSUIT was designed to reflect current practices in the care of patients with acute coronary syndrome, and protocol-specified care was minimal. The primary study end point, a composite of death or nonfatal (re)infarction at 30 days, occurred in 15.7% of the placebo patients and 14.2% of the eptifibatide patients, a 1.5% absolute reduction ($P=0.042$). In the US patients, the primary study end point occurred in 15.4% of placebo and 11.9% of eptifibatide patients at 30 days ($P=0.002$). The benefit of study drug was fully established by 96 hours and was maintained without attenuation or amplification through 30 days. The use of investigator-reported infarctions as part of the primary end point rather than the Clinical Events Committee adjudicated events yielded a 30-day event rate in the overall trial of 10.0% for placebo versus 8.1% for eptifibatide ($P=0.001$). In the US subset, the corresponding figures were 9.4% for placebo and 7.1% for eptifibatide ($P=0.012$). Bleeding was more common in the eptifibatide arm: major bleeding (TIMI criteria) occurred in 10.6% versus 9.1% of placebo patients ($P=0.02$). Neither strokes nor intracranial hemorrhage rates increased with eptifibatide, and most of the excess bleeding was mild.

Overview of PURSUIT US Economic Substudy

As part of the PURSUIT research effort, we conducted a prospective economic substudy of trial patients randomized in the United States. This substudy had 2 major components: an intention-to-treat analysis of empirical resource use and costs and a cost-effectiveness analysis. All costs were expressed in 1996 US dollars. The perspective of the analyses was societal, although some societal costs (eg, nonmedical costs, outpatient care, and productivity costs) were omitted.

Descriptive and Intention-to-Treat Analyses

We measured medical resource use and costs starting with the index (enrollment) hospitalization and extending through the 6-month follow-up period. To have at least 80% power to detect a ≥$1000 cost difference between the best eptifibatide arm and placebo for the index hospitalization, we planned to collect costs data on ≈1000 patients per treatment group. Of the final 3522-patient US enrollment, we collected hospital bills related to 2464 (70%) selected at random. For the 4562 baseline and follow-up hospitalizations that these patients had, we obtained >99% of collectable bills. In the analysis, hospital charges were converted to costs by use of the department-specific correction factors contained in each hospital’s annual Medicare Cost Report. Physician fees were assigned from the 1996 Medicare Fee Schedule for the following activities: daily examination/evaluation (intensive care unit [ICU] and non-ICU), cardiac catheterization, coronary angioplasty, and coronary bypass surgery. Inpatient consultations were not recorded, and follow-up outpatient care (other than cardiac catheterization) was not assessed.

Because eptifibatide was provided without cost, we used the average wholesale price of the drug and the actual weight-based dose administered to each patient to estimate the cost of eptifibatide therapy. If only some of a vial of the drug was used, the remainder was assumed to be wasted. Because many hospitals obtain pharmaceuticals at a discounted cost, we also used the cost of eptifibatide at Duke Hospital to provide a second estimate of drug cost.

To impute hospital costs for the 1055 US patients without hospital billing data, including patients at centers such as Veterans Administration hospitals that do not produce bills and patients who were not in the random subset selected for bill collection, we used the available resource data from the clinical case-report form to develop 2 linear-regression imputation models (baseline [$R^2=0.80$] and follow-up [$R^2=0.83$]) on the patients who had complete billing data. For the primary US intention-to-treat cost comparisons, the total US cohort (measured costs plus imputed costs) was used. Similar results (not presented) were obtained when only patients with complete billing data were used.

Descriptive statistics are presented as percentages for discrete variables and means ± SDs for continuous variables. Treatment groups were compared by intention to treat for index hospitalization costs (hospital plus physician costs) and for cumulative 6-month costs. Statistical testing was performed with either the Wilcoxon rank sum test (for continuous variables) or the $\chi^2$ test (for discrete variables).

Cost-Effectiveness Analysis

Base-Case Overview

For the base-case analysis, we estimated the cost-effectiveness ratio as the additional lifetime costs required to add 1 extra life-year with eptifibatide therapy plus standard care versus standard care alone. The analysis was based on 6-month survival and infarction-free survival among the 3522 US PURSUIT patients enrolled in the study, along with their resource use and cost data. Life expectancy was estimated with long-term follow-up data from the Duke Cardiovascular Disease Database on PURSUIT-eligible patients. Discounting was performed at 3%.

Major Assumptions

Our cost-effectiveness analysis made 3 important assumptions in designing the base-case scenario. First, we assumed that the best available estimate of the effectiveness of eptifibatide for the United States was provided by the empirical results observed in the US PURSUIT cohort. Second, we assumed that the Clinical Events Committee’s adjudicated primary end point (death plus nonfatal MI) was the most reliable clinical efficacy end point to use in our life-expectancy extrapolations. Finally, in estimating the adverse prognostic impact of an end-point nonfatal MI beyond the 6-month PURSUIT follow-up, we assumed that we did not need to account for infant death.

Lifetime Costs

Because there were no empirical data on costs after 6 months and because there was no evidence of higher incremental costs in the eptifibatide arm between hospital discharge and 6 months (exclusive of drug costs), the base-case analysis assumed no incremental cost difference between the treatment groups after 6 months.

Life-Expectancy Modeling

PURSUIT was designed to detect a significant difference in the primary end point but not a mortality benefit from treatment with eptifibatide. Because the prevention of nonfatal MI is an important therapeutic goal with presumptive long-term survival effects beyond those measured empirically in PURSUIT, we developed a method to extrapolate the composite primary end point into life expectancy for each treatment cohort. This was done in 2 parts: estimation of lifetime survival from 6-month PURSUIT survival data and estimation of the additional lifetime prognostic effects of PURSUIT nonfatal end-point MIs.

The basic life-expectancy projection, exclusive of the MI effect, is composed of 2 primary components: (1) the observed 6-month survival and (2) the lifetime survival projection beyond the 6-month study follow-up period. However, 2 supplementary models were required to incorporate the effect of a nonfatal MI on subsequent survival. Thus, a total of 4 models (2 survival models and 2 MI models) were used to extrapolate life expectancy for the PURSUIT study population.

Model 1: Initial Observed 6-Month Follow-Up Period

The observed 6-month survival in the PURSUIT population was modeled with the Cox proportional hazards regression model. We chose to model the initial 6 months rather than use the observed survival data to ensure that overall differences in life expectancy were based on treatment-effect differences only and not on any covariate imbalances that may have existed between the 6-month survivors in each treatment group. This survival model was stratified on the basis of treatment and was adjusted for age, history of MI, and history of diabetes. The 6-month predicted survival estimates from this model were essentially identical to those observed for US eptifibatide patients (observed survival 0.9501; predicted survival 0.9501) and for US placebo patients (observed survival 0.9452; predicted survival 0.9454).
Model 2: Survival Projection Beyond 6 Months
For projected survival beyond 6 months, we used the Cox proportional hazards regression model with left-truncated and right-censored data to model the hazard of death as a function of age, conditional on surviving the initial 6-month period, and adjusted for additional prognostic factors through covariates. This model was developed with 8169 patients from the Duke database with acute MI or unstable angina who presented for cardiac catheterization between 1971 and 1994 and then survived 6 months. There were a total of 887 deaths among these patients during follow-up. The model “adjusts” for age as the metric over which the hazard is computed and treats additional prognostic factors available in both the Duke and PURSUIT databases (sex, history of cerebrovascular disease, history of MI, history of hypertension, history of diabetes, history of smoking, and year of presentation) as covariates. The hazard relationship, which under proportional hazards is well estimated through the age range represented in our data, is used for prediction on a patient-by-patient basis. By estimating the hazard over the age metric (rather than over the traditional time metric), we produced data-based survival predictions through a much longer time period owing to the broad representation of ages in our database. Thus, the need for parametric extrapolation of the data was eliminated.

Model 3: Modeling the Effect of Nonfatal End-Point MIs
To estimate the long-term survival effect of a nonfatal end-point MI, we modeled the independent effect of an MI occurring within the first 30 days in our Duke population. There were 3234 such MI events available in the Duke data. MI in the Duke database is defined by the presence of a consistent clinical presentation with either diagnostic ST-segment elevation or elevated serum cardiac markers. We chose the effect of any acute MI occurring within this time frame to represent the base case. Such a model provides the increased relative risk in the mortality rate attributable to an MI. The base-case hazard ratio assigned to a nonfatal MI was 1.33.

Model 4: Estimating the Probability of an End-Point MI
We used logistic regression to develop a model to predict the probability of a 30-day end-point MI to incorporate the patient- and treatment-specific risk associated with an end-point MI into our lifetime projections. This model adjusted for age, sex, and treatment.

Integration of Models
Using the above models, we predicted lifetime survival for each individual PURSUIT patient as a function of (1) their covariates, (2) their probability of surviving the first 6 months, (3) their treatment- and covariate-specific likelihood of experiencing an end-point MI, and (4) their probability of surviving beyond 6 months, conditional on surviving the initial 6-month study period, incorporating the effect of a nonfatal end-point MI on lifetime survival. When the laws of conditional probability were applied, these 4 models were linked together to obtain an individual covariate-specific lifetime survival prediction for each patient. The individual predicted survival estimates were then averaged over all the patients for both treatment groups to produce a mean predicted survival estimate for each treatment group. To obtain mean life expectancy for each treatment group, the estimated mean survival curves were integrated over a lifetime. Finally, differences between the area under each survival curve were computed to obtain the incremental life expectancy due to eptifibatide. The survival curve for the eptifibatide arm is shown in the Figure.

Sensitivity Analyses
Extensive sensitivity analyses were conducted on the main starting parameters in the base-case model. We varied the prognostic effects of nonfatal MIs, the definition of MI used in the primary end point, and the size of the absolute 30-day treatment benefit used to generate life-expectancy estimates. Costs were varied according to the 95% confidence limits around the cumulative 6-month cost difference observed in the US cohort. Cost utility ratios were calculated with the utility values measured at 6 months for the US patients who completed a time trade-off interview (n=1978). These patients were asked to trade 10 years in their current health against less time in excellent health. Alternative discount rates for the base case of 0%, 5%, and 7% were calculated.

Results

Baseline Characteristics
The baseline characteristics of the entire PURSUIT cohort have been reported previously. The US cohort had a mean age of 62 years, with 65% male enrollment (Table 1). ST-segment depression was present on the qualifying ECG in 39%, transient ST-segment elevation in 16%, and T-wave inversion in 50% of patients. Compared with the non-US PURSUIT cohort, the US patients were a year younger, 7 kg heavier, and more likely to be current smokers and to have

Table 1. Baseline Characteristics of US Patients and Non-US Patients Enrolled in PURSUIT

<table>
<thead>
<tr>
<th></th>
<th>US (n=3522)</th>
<th>Non-US (n=5939)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>62.2±11.7</td>
<td>63.1±10.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>Male, %</td>
<td>65</td>
<td>64</td>
<td>0.40</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>83.4±18.1</td>
<td>76.8±13.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Risk factors, %</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Current smoker</td>
<td>31</td>
<td>27</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>62</td>
<td>51</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>45</td>
<td>40</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>27</td>
<td>21</td>
<td>0.001</td>
</tr>
<tr>
<td>Prior cardiac history, %</td>
<td>34</td>
<td>32</td>
<td>0.015</td>
</tr>
<tr>
<td>Prior MI</td>
<td>11</td>
<td>11</td>
<td>0.20</td>
</tr>
<tr>
<td>History of CHF</td>
<td>21</td>
<td>8</td>
<td>0.001</td>
</tr>
<tr>
<td>Prior PTCA</td>
<td>20</td>
<td>7</td>
<td>0.001</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>52</td>
<td>53</td>
<td>0.33</td>
</tr>
<tr>
<td>Presenting findings, %</td>
<td>39</td>
<td>57</td>
<td>0.001</td>
</tr>
<tr>
<td>Rest angina (&lt;6 wk)</td>
<td>16</td>
<td>12</td>
<td>0.001</td>
</tr>
<tr>
<td>ST depression</td>
<td>50</td>
<td>51</td>
<td>0.16</td>
</tr>
<tr>
<td>ST elevation (transient)</td>
<td>14</td>
<td>4</td>
<td>0.001</td>
</tr>
</tbody>
</table>

CHF indicates congestive heart failure.
TABLE 2. Index Hospitalization Resource Consumption and Costs

<table>
<thead>
<tr>
<th></th>
<th>Eptifibatide (n=1754)</th>
<th>Placebo (n=1765)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical resource consumption, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac catheterization</td>
<td>85</td>
<td>85</td>
</tr>
<tr>
<td>Percutaneous intervention</td>
<td>35</td>
<td>36</td>
</tr>
<tr>
<td>Coronary bypass surgery</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Length of stay, d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td>3.7±3.8</td>
<td>3.7±4.0</td>
</tr>
<tr>
<td>Total</td>
<td>6.5±5.2</td>
<td>6.5±5.4</td>
</tr>
<tr>
<td>Medical costs,* $</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital costs</td>
<td>12 420±9194</td>
<td>12 617±10 019</td>
</tr>
<tr>
<td>Physician costs</td>
<td>2309±1793</td>
<td>2340±1890</td>
</tr>
<tr>
<td>Total costs*</td>
<td>14 729±10 825</td>
<td>14 957±11 744</td>
</tr>
</tbody>
</table>

Three patients were excluded because of incomplete economic data. All P values >0.10.

Costs of eptifibatide therapy not included.

TABLE 3. Follow-Up Medical Resources and Costs

<table>
<thead>
<tr>
<th></th>
<th>Eptifibatide (n=1754)</th>
<th>Placebo (n=1765)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up resource consumption, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac catheterization</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Percutaneous intervention</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Coronary bypass surgery</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Length of stay, d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td>0.6±2.3</td>
<td>0.6±2.4</td>
</tr>
<tr>
<td>Total</td>
<td>2.2±6.2</td>
<td>2.3±6.3</td>
</tr>
<tr>
<td>Follow-up medical (hospital + physician costs, $)</td>
<td>3727±8878</td>
<td>3871±9430</td>
</tr>
<tr>
<td>Cumulative 6-mo medical costs,* $</td>
<td>18 456±13 886</td>
<td>18 828±15 185</td>
</tr>
</tbody>
</table>

Three patients were excluded because of incomplete economic data. All P values >0.10.

Costs of eptifibatide therapy not included.

patients in the eptifibatide group and $3871 for those given placebo (P=0.60). Thus, the cumulative 6-month costs observed in the PURSUIT US cohort were $18 456 for the eptifibatide arm and $18 828 for the placebo arm (P=0.78).

Cost-Effectiveness Analysis: Base Case

Costs
At the end of the 6-month follow-up for PURSUIT, there was a $372 cost advantage for eptifibatide (exclusive of the drug cost). Because this difference was not statistically distinguishable from a $0 cost difference, we chose not to count this in calculating the incremental lifetime treatment costs for eptifibatide. The Red Book average wholesale price for the bolus-and-infusion regimen of eptifibatide based on actual drug administered was $1217±574.

Life Expectancy
In the US cohort, the 6-month death or MI rate was 15.2% in the eptifibatide arm and 18.9% in the placebo arm (P=0.004). The corresponding 6-month mortality rates were 4.99% and 5.48%, respectively (P=0.52). Using the empirical US PURSUIT primary end-point results, we projected a life expectancy from the time of randomization in PURSUIT of 15.96 years for patients treated with eptifibatide and 15.85 years for patients receiving placebo, yielding an undiscounted incremental life expectancy of 0.111 (ie, 11.1 additional life-years per 100 patients treated with eptifibatide).

Cost-Effectiveness
With an incremental life expectancy of 0.111 years of life per patient, an incremental cost of $1217 per patient, and a discount rate of 3%, the incremental cost-effectiveness ratio for eptifibatide versus placebo was $16 491 per year of life saved.

Cost-Effectiveness Analysis: Sensitivity Analyses

Major Assumptions
Each of the 3 major assumptions that defined key parameters of the base-case analysis was subjected to sensitivity analysis. The magnitude of reduction in the combined incidence of death or nonfatal MI with eptifibatide was larger in the US cohort than in the overall PURSUIT Trial. When the more conservative effectiveness produced by eptifibatide in the overall PURSUIT cohort was substituted in the base-case analysis (with other factors remaining unchanged), the cost-effectiveness ratio increased to $33 619.

The second major assumption was that the Clinical Events Committee’s adjudicated primary end point was the most reliable estimate of the effectiveness of eptifibatide. When the base-case analysis was recalculated with investigator-defined MIs included in the primary end point (with other parameters unchanged), the cost-effectiveness ratio increased to $20 839. The use of both of the above changes in base-case analysis (ie, investigator-defined end-point MIs and the outcomes of the overall PURSUIT cohort) yielded a cost-effectiveness ratio of $31 942 per added life-year.

The third major assumption was that we did not need to account for end-point MI size. When incremental life expectancy was calculated from the observed 6-month difference in
survival in US PURSUIT patients, with nonfatal end-point MIs assumed to exert no long-term prognostic effects beyond the 6-month follow-up, the incremental cost-effectiveness ratio rose to $34,771. If the long-term prognostic weight given to end-point nonfatal MIs is adjusted to give greater weight to large MIs (ie, creatine kinase–MB ≥5 times the upper limit of normal) and no prognostic weight to smaller MIs, the incremental undiscounted life expectancy is essentially unchanged from the base case at 0.124 life-years, yielding a cost-effectiveness ratio of $15,308 per added life-year. If long-term prognostic weight is given only to the largest end-point MIs (ie, creatine kinase–MB ≥10 times the upper limit of normal), the corresponding cost-effectiveness ratio is $18,986.

**Discount Rate**

With a discount rate of 5%, the cost-effectiveness ratio increased to $20,768 per year of life saved. The corresponding ratios with 0% and 7% discount rates were $10,954 and $25,460 per life-year saved, respectively.

**Incremental Costs**

When the price of eptifibatide at Duke Hospital was substituted for the average wholesale price of the drug, the result was an incremental cost of $1014 and a cost-effectiveness ratio of $13,740 per year of life saved. A bootstrap 95% CI around the observed US cumulative 6-month cost difference (excluding drug costs) was −$13,999 to $652. The addition of these costs to the cost of the eptifibatide regimen yielded corresponding cost-effectiveness ratios ranging from dominance (better outcomes and lower net costs) to $25,325 per life-year added.

**Cost Utility Analysis**

At 6 months, the US eptifibatide patients reported a mean time trade-off value of 0.84, whereas the placebo patients reported a value of 0.83 (P = 0.45). The corresponding rating scale (0 to 100) measures were 69.5 and 70.3 (P = 0.19).

Weighting of the increased survival in the eptifibatide group by the observed 6-month utility weight yielded a cost utility ratio of $19,693 per quality-adjusted life-year added. When the rating scale weights were used as more conservative utility substitutes, a cost per quality-adjusted life-year of $23,449 resulted.

**Discussion**

We provide the first detailed economic analysis of an intravenous GP IIb/IIIa platelet inhibitor in non–ST-elevation acute coronary syndromes. Although the threshold for defining when a therapy does not provide enough medical benefit relative to its incremental costs is controversial, many agree that a cost-effectiveness ratio of <$50,000 per life-year added is economically attractive, whereas a ratio of ≥$100,000 per life-year added is too high. On the basis of extensive empirical data, our study shows that the cost per life-year added with eptifibatide therapy in the PURSUIT trial falls in the economically attractive range over a wide spectrum of starting parameters and assumptions.

Our base-case analysis used empirical data from US PURSUIT patients to estimate incremental lifetime effective-ness and costs. Because the US cohort had the largest absolute benefit with eptifibatide and because a higher proportion of US patients underwent early revascularization, our results are most relevant to similar cohorts of acute coronary syndrome patients. However, 2 points are worth noting. First, the benefit of eptifibatide over placebo at 30 days in the United States alone was statistically significant. The benefit in Canada and Western Europe was more modest in magnitude, whereas in Latin America and Eastern Europe, small adverse effects on the primary end point were noted for eptifibatide. The reason for this apparent geographic variation remains unclear, but multivariate analyses have shown that it is not primarily a function of different revascularization rates (R.A.H., oral communication, 1999). Other, unmeasured aspects of patient selection or care may be responsible. Second, the larger benefit of eptifibatide in the US patients was not a result of the greater number of patients who underwent percutaneous revascularization. As reported previously, the absolute benefit for eptifibatide in patients who underwent intervention within 72 hours of randomization was 3.8% before the procedure, 2.8% at 96 hours, and 2.2% at 30 days. Thus, the benefit of eptifibatide was actually attenuated after percutaneous revascularization rather than amplified by it.

**The Prognostic Importance of Preventing Nonfatal MIs**

Like all current large-scale trials of new therapies for acute non–ST-elevation coronary syndromes, PURSUIT was not designed to detect a mortality difference. A recent overview of ≥33,000 acute coronary syndrome patients randomized in trials of GP IIb/IIIa inhibitors showed that prevention of infarction was the primary benefit evident from these agents at up to 6 months of follow-up. The central tenet of the PURSUIT and other GP IIb/IIIa trials, therefore, is that preventing a nonfatal MI is a worthwhile clinical accomplishment with important prognostic benefits. The absence of a statistically significant mortality difference, however, poses unique challenges to a cost-effectiveness analysis. Specifically, to convert 6-month infarction-free survival data into life-expectancy estimates, the quantitative effect that a nonfatal MI (with survival to 6 months) has on life expectancy must be established. Because no modern clinical trial has a sufficiently long follow-up to answer this question empirically, we used the extensive follow-up experience in the Duke Cardiovascular Disease Database to estimate this effect. These analyses showed that an acute MI was associated with a long-term hazard ratio of between 0.33 and 0.75, depending on how the MI was defined. A 33% increase in long-term hazard for MI survivors translates into an ≈2-year reduction in life expectancy. Thus, the prevention of a nonfatal MI in a cohort with a life expectancy of ≈16 years has only one eighth the prognostic value of preventing a death. Even with this conservative weighting of MIs relative to death, our analyses showed that the relationship of incremental life expectancy to incremental costs of eptifibatide in PURSUIT made it “cost-effective” or economically attractive.

Because some of the end-point MIs in PURSUIT were diagnosed by the Clinical Events Committee but not the
clinician who cared for the patient, and because these MIs tended to be smaller, with little discernible short-term effect on left ventricular function, we considered that our base-case incremental life-expectancy calculations might be too optimistic. Substitution of the investigator-defined MIs in the base-case analysis raised the cost-effectiveness ratio very modestly to $20,839. Hence, the elimination of “enzyme bump” MIs from the primary end point did not materially alter our results.

The other dimension of end-point MIs to be considered is size. In the present study, crediting all nonfatal end-point MIs with an intermediate long-term prognostic weight was quantitatively equivalent to giving larger MIs a bigger prognostic weight and smaller MIs no prognostic weight. The conclusions of our analysis, therefore, were not sensitive to differential prognostic weighting of end-point MIs on the basis of size. The GISSI (Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto miocardico) investigators recently demonstrated in the GISSI-1 database that infarct size is important for short-term (eg, 30 day) prognosis but not for long-term (eg, 5 to 10 years) prognosis.

Study Limitations

Several caveats should be considered in the interpretation of our study. First, our study was not powered to detect a significant difference in life expectancy. A statistical comparison of life expectancy would require a significantly larger sample than even the entire PURSUIT cohort. Second, we did not calculate a within-trial cost-effectiveness ratio because we felt that the 6-month empirical follow-up was insufficient to give an interpretable result. Finally, the finding that a therapy is economically attractive does not guarantee that it will be adopted. Cost-effectiveness helps to define the most efficient ways to produce health benefits within a given healthcare budget. It does not address the more fundamental policy question of how much money society should spend on health care.

Conclusions

Based on the results of the PURSUIT trial in US patients, the routine addition of eptifibatide to the usual care for non–ST-elevation acute coronary syndrome patients is economically attractive by conventional standards.

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References

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