Cost-effectiveness of platelet glycoprotein IIb/IIIa inhibition with eptifibatide in patients with non-ST-elevation acute coronary syndromes


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Eptifibatide (a bolus dose of 180 microg per kilogram of body weight, followed by an infusion of 1.3 microg per kilogram per minute, or a bolus dose of 180 microg per kilogram followed by an infusion of 2.0 microg per kilogram per minute), an intravenous glycoprotein (GP) IIb/IIIa platelet inhibitor, in addition to standard therapy in non-ST-elevation acute coronary syndromes.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis; cost-utility analysis.

Study population
Patients with acute coronary syndromes who did not have persistent ST-segment evaluation. Eligible patients met the following criteria: (1) ischemic chest discomfort of 10 minutes' or more duration within the previous 24 hours and (2) transient ST-segment elevation greater than 0.5 mm or transient or persistent ST-segment depression greater than 0.5 mm or T-wave inversion greater than 1 mm within 12 hours of symptoms or (3) elevated creatine kinase-MB fraction. Exclusion criteria included persistent ST-segment elevation greater than 1 mm, contraindications to anticoagulation, severe hypertension, or renal failure.

Setting
Hospital. The economic analysis was carried out in the USA.

Dates to which data relate
Effectiveness and resource use data corresponded to patients enrolled in the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) Trial between November 1995 and January 1997. To convert 6-month infarction-free survival data into life-expectancy estimates, the Duke Cardiovascular Disease Database with acute myocardial infarction (MI) or unstable angina between 1971 and 1994 was used. The price year was 1996.

Source of effectiveness data
The evidence for the final outcomes was based on a single study and a Duke University database.

Link between effectiveness and cost data
Costing was conducted prospectively on the sub-sample of trial patients' randomised in the United States (US PURSUIT patient sample).
Study sample
Power calculations were used to determine the sample size. A sample consisting of 9,382 patients in the two groups would provide the study with 80% power to detect a reduction of 20% (or an absolute difference of 1.7%) in the 30-day incidence of the composite end point, assuming an event rate of 8.5% in the placebo group. In total, 10,948 patients were randomly assigned to either the low-dose eptifibatide group (n=1,487), the high-dose eptifibatide group (n=4,722) with a median of 64 (range: 55-71) years of age or to the placebo group (n=4,739) with a median of 64 (range: 55-71) years of age. The number of US patients was 3,522 with a mean (SD) age of 62.2 (11.7) years versus 5,939 non-US patients with a mean (SD) age of 63.1 (10.8) years.

Study design
This was a double-blind randomised controlled trial, carried out in 726 centres in 28 countries. The duration of the follow-up was 30 days and 6 months after the index event. The study drug was discontinued before 72 hours in 8% of patients in the eptifibatide group versus 1% in the placebo group, (p<0.001). The need for coronary bypass surgery caused discontinuation of the study drug before 72 hours in 10.8% of the eptifibatide patients and 12.7% of the placebo patients. In reporting the bleeding complications, it was acknowledged that some data were missing (details of which were not given). PURSUIT was designed to reflect current practices in the care of patients with acute coronary syndrome, and protocol-specified care was minimal. A masked clinical events committee evaluated suspected infarctions. Investigators at the individual sites were also asked to determine whether an infarction had occurred. Because this study was the first large-scale study of higher doses of eptifibatide, it was specified in the protocol that the study would be stopped in the lower-dose group after the independent data safety and monitoring committee had conducted an interim review of safety data, provided the higher dose had an acceptable safety profile. After 3,218 patients had been randomly assigned to treatment groups, the committee recommended dropping the lower dose.

Analysis of effectiveness
The principle used in the analysis of effectiveness was intention to treat. The primary end point was a composite of death and nonfatal MI occurring up to 30 days after the index event. Bleeding complications were reported as the safety-related end-points. 6-month mortality rates were also reported. The cumulative event rate over time was estimated with the product-limit (Kaplan-Meier) method. The US patients were different from the non-US patients in terms of demographics (except for gender distribution), risk factors, prior cardiac history (except for history of congestive heart failure), and presenting findings (except for rest angina and T-wave inversion).

Effectiveness results
The effectiveness results were as follows:

As compared with the placebo group, the eptifibatide group had a 1.5% absolute reduction in the incidence of the primary end point (14.2% in the eptifibatide group versus 15.7% in the placebo group, (p=0.04)).

In the US cohort, the 6-month death or MI rate was 15.2% in the eptifibatide group and 18.9% in the placebo group (p=0.004).

The corresponding 6-month mortality rates were 4.99% in the eptifibatide group and 5.48% in the placebo group (p=0.52).

The benefit of the study drug was fully established by 96 hours and was maintained without attenuation or amplification through 30 days.

The point estimate of the treatment effect consistently favoured eptifibatide in all major subgroups except women (odds ratio for women: 1.10; 95% CI: 0.91-1.34).

The observed treatment effect varied among geographical regions, with the greatest benefit observed among North American patients. Among both men and women in North America, there was a benefit associated with treatment with
The use of eptifibatide was associated with increased bleeding and a more frequent need for transfusions, although there was no increase in the incidence of strokes or intracranial haemorrhage.

**Clinical conclusions**

Inhibition of platelet aggregation with eptifibatide reduced the incidence of the composite end point of death or nonfatal MI in patients with acute coronary syndromes who did not have persistent ST-segment elevation.

**Measure of benefits used in the economic analysis**

Life expectancy and quality-adjusted life-years were the main health benefit measures. To obtain an individual covariate-specific lifetime survival prediction for each patient, 4 models were developed and then linked together (2 survival Cox proportional hazards regression models to model the initial 6-month survival in the PURSUIT population adjusting for covariates and survival projection beyond 6 months employing the Duke database; and 2 MI models to estimate the long-term survival effect of nonfatal end-point MI and to estimate the probability of a 30-day end-point MI adjusting for covariates by using a logistic regression model). The individual predicted survival estimates were then averaged over all patients for both treatment groups to produce a mean predicted survival estimate for each treatment group. The incremental life expectancy due to eptifibatide was finally computed using differences between the area under each survival curve. The utility values were measured at 6 months for the US patients who completed a time trade-off interview (n= 1,978).

**Direct costs**

Costs were not discounted due to the 6-month time frame of the cost analysis. Some quantities were reported separately from the costs. Cost items were reported separately. Power calculations were performed for the cost analysis (it was planned to collect cost data on 1,000 or more patients per treatment group to have at least 80% power to detect a $1,000 or greater cost difference between the study groups for the index hospitalisation). Cost analysis was deemed to be based on the intention-to-treat principle based on the cost results for the total US cohort (measured costs plus imputed costs). Cost analysis covered the index hospitalisation (hospital and physician costs) and cumulative 6-months costs due to cardiac catheterisation, percutaneous intervention, coronary bypass surgery, length of hospital stay, and study drug. The perspective adopted in the cost analysis was stated to be that of society. Physician fees were assigned based on the Medicare Fee Schedule. The hospital costs were based on hospital bills from 2,464 (70%) US patients selected randomly from the final 3,522 US patients. 99% of collectable bills were obtained for the 4,562 baseline and follow-up hospitalisations. Hospital charges were converted to costs using the department-specific correction factors contained in each hospital's annual Medicare Cost Report. Available resource data from the clinical case-report form were used to develop 2 linear-regression imputation models based on the patients who had complete billing data in order to impute hospital costs for the 1,055 US patients without hospital billing data. The average wholesale price of the study drug and the actual weight-based dose administered to each patient was used to estimate the costs of eptifibatide therapy. The price year was 1996. Inpatient consultations were not recorded, and follow-up outpatient care (other than cardiac catheterisation) was not assessed. The base-case analysis assumed no incremental cost difference between the study groups after 6 months.

**Statistical analysis of costs**

The Wilcoxon rank sum test appears to have been used to compare costs between the study groups. A bootstrap 95% confidence interval (CI) around the observed US cumulative 6-month cost difference (excluding drug costs) was calculated. 2 linear-regression imputation models were developed to impute hospital costs for the 1,055 US patients without hospital billing data.

**Indirect Costs**

Not included.
Currency
US dollars ($).

Sensitivity analysis
Extensive one-way sensitivity analyses were conducted on the main starting parameters in the base-case model.

Estimated benefits used in the economic analysis
Using the empirical US PURSUIT primary end-point results, the authors projected a life expectancy from the time of randomisation 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 (i.e., 11.1 additional life-years per 100 patients treated with eptifibatide). 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). The incremental survival in the eptifibatide group was weighted by the observed 6-month utility weight. The actual quality-adjusted life-years values were not reported. The discount rate applied in the base-case analysis was 3% for the life expectancy and 0% for the quality-adjusted life-years.

Cost results
The cumulative 6-months medical costs (exclusive of the cost of the eptifibatide therapy) in the US PURSUIT cohort were $18,456 for the eptifibatide group versus $18,828 for the placebo group (p=0.78). The average (SD) wholesale price for the bolus-and-infusion regimen of eptifibatide, based on actual drugs administered, was $1,217 ($574).

Synthesis of costs and benefits
The incremental cost-effectiveness ratio for eptifibatide versus placebo was $16,491 per year of life saved. This result was robust through a wide range of sensitivity analyses. The incremental cost-utility ratio (when weighted by the observed 6-month utility weight) was $19,693 and $23,449 when the rating scale weights were used.

Authors’ 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.

CRD COMMENTARY - Selection of comparators
The authors chose placebo as a comparator for the intervention drug. This allowed the active value of the treatment to be evaluated.

Validity of estimate of measure of effectiveness
The effectiveness results are likely to be internally valid given the double blind randomised nature of the study design, the power calculations performed, and intention-to-treat basis of the analysis conducted. The US patients were significantly different from the non-US patients in terms of most baseline characteristics. The study sample appears to have been representative of the study population.

Validity of estimate of measure of benefit
The estimation of benefits was modelled and utility values were obtained from interviews with a subgroup of the patients. The instruments used to derive measures of health benefits (Cox proportional hazards regression model, logistic regression model, and time trade-off technique), appear to be appropriate.

Validity of estimate of costs
Some quantities were reported separately from the costs and adequate details of methods of cost estimation were given. The price year was specified. The application of cost-to-charge ratios may have enhanced the internal and external validity of the cost results. The authors stated that a societal perspective was adopted, however some important cost elements (such as non-medical costs and opportunity costs) were omitted from the analysis. The effects of alternative procedures on indirect costs were not addressed. Statistical analyses were performed on resource use and cost data.

Other issues
The authors’ conclusions appear to be justified given the randomised nature of the study design and the extensive sensitivity analyses performed. The issue of generalisability to other settings or countries appears to have been addressed in the sensitivity analysis. Some comparisons were made with other studies. It was reported that because the US cohort had the largest absolute benefit with eptifibatide and because a higher proportion of US patients underwent early revascularisation, the study results are most relevant to similar cohorts of acute coronary syndrome patients. It was also reported that the apparent geographical variation in the benefit of the study drugs was not primarily because of different revascularisation rates (multivariate analysis, oral communication), and difference in the percentage of percutaneous revascularisation (as shown in the original study. Other, unmeasured aspects of patient selection or care may be responsible. It was acknowledged that this study was not powered to detect a significant difference in life expectancy (which required a larger sample); a within-trial cost-effectiveness ratio was not calculated since the authors felt that the 6-month empirical follow-up was insignificant to give an interpretable result.

Implications of the study
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 of how much money society should spend on health care.

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