National economic impact of tirofiban for unstable angina and myocardial infarction without ST elevation; example from the United Kingdom

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
The use of tirofiban, a short-acting glycoprotein IIb/IIIa inhibitor, given in addition to heparin for the prevention of adverse outcomes in patients with acute coronary syndromes (ACS).

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised heparin-treated patients who had experienced ACS without ST elevation on the admission electrocardiogram. In addition, three specific high-risk sub-groups were considered:

(1) age 60 years or older with the presence of an abnormal electrocardiogram;

(2) ST depression or any bundle branch block on admission;

(3) ST depression or bundle branch block on the admission electrocardiogram, or acute myocardial infarction (MI) diagnosed at admission on the basis of initial cardiac enzymes.

Setting
The setting was secondary care. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness evidence came from two studies published in 1990 and 2000. The resource use data were derived from a cost database (1994) and data from the previous studies. The price year was 1999.

Source of effectiveness data
The effectiveness data were derived from a completed study and a national registry.

Outcomes assessed in the review
The health outcomes estimated from the published studies were:

the adverse event risk reduction of MI and refractory angina or ischaemia (RFA), estimated through the relative risk (RR) and the 95% confidence interval (CI);
the primary composite end point of death from any cause, new MI, refractory angina or readmission for unstable angina within 7 days; and
the calculated numbers of events avoided in the registry and in the UK.

Study designs and other criteria for inclusion in the review
The effectiveness evidence came from the Prospective Registry of Acute Ischaemic Syndromes in the UK (PRAIS-UK) and the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS). The PRAIS-UK is a multi-centre registry that was used to provide the event rates. The PRISM-PLUS was a double-blind randomised trial that was used to estimate tirofiban adverse outcomes. A formal systematic review of the literature was not undertaken.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
The validity of the data was ensured by the use of a randomised trial. However, the authors noted that the use of an observational registry represented a more limited source of data.

Methods used to judge relevance and validity, and for extracting data
Not stated.

Number of primary studies included
Two primary studies were used.

Methods of combining primary studies
A mathematical formula was provided. This showed how the estimates coming from the two studies were combined to achieve the final event rate.

Investigation of differences between primary studies
The authors investigated the differences between the primary studies by comparing the two groups of patients in terms of their baseline characteristics, such as demographics and clinical data.

Results of the review
The RR with tirofiban, relative to heparin alone, was 2.1 (95% CI: 1.3 - 3.5) for MI and 1.2 (95% CI: 0.9 - 1.7) for RFA.

From the trial, the primary composite end point of death from any cause, new MI, refractory angina or readmission for unstable angina within 7 days, occurred in 12.9% of patients treated with tirofiban and 17.9% of those treated with heparin alone (risk ratio 0.68, 95% CI: 0.53 - 0.88; P=0.004).

The risk ratio in the whole cohort of patients considered in the analysis was 0.465 (95% CI: 0.2393 - 0.8084) for MI and 0.830 (95% CI: 0.564 - 1.1922) for RFA.

The corresponding figures for the sub-groups were:

for MI, 0.439 (95% CI: 0.1738 - 0.9035) in sub-group 1, 0.408 (95% CI: 0.1481 - 0.8838) in sub-group 2, and 0.363
(95% CI: 0.1468 - 0.7168) in sub-group 3; and

for RFA, 0.814 (95% CI: 0.5224 - 1.2262) in sub-group 1, 0.886 (95% CI: 0.5669 - 1.3394) in sub-group 2, and 0.855 (95% CI: 0.5555 - 1.2734) in sub-group 3.

The calculated numbers of events avoided were 18 episodes of MI and 5 episodes of RFA in the PRAIS-UK, and 1,918 cases of MI and 499 cases of RFA per annum in the UK in the whole sample of patients. Details of all three sub-groups were also reported.

**Measure of benefits used in the economic analysis**
The summary benefit measure was the proportion of events observed with and without tirofiban. It was derived from the clinical data derived from the published study. No discount rate was applied.

**Direct costs**
Discounting was irrelevant since the time horizon of the study was 6 months. The unit costs were only reported separately from the quantities of resources used for tirofiban. The health services included in the economic evaluation were treatment with tirofiban and ACS (e.g. MI and RFA). The cost/resource boundary adopted in the study was that of the hospital trusts.

The costs were estimated using data coming from the CHKS (Clinical Accountability, Service Planning and Evaluation (CASPE) and Healthcare Knowledge Systems Company) national comparative database, which referred to 120 UK hospitals and contained more than 7 million patient records for each year. The main cost drivers were identified through a multivariate regression analysis. Only patients who matched PRAIS-UK inclusion criteria were selected from the cost database. This left a sample of 44,502 individuals. Two series of unit cost estimates were used depending on whether the patient was discharged after the first admission (series 1) or whether the patient was transferred to another hospital or was readmitted during the 6-month follow-up (series 2). Tirofiban use was derived using data from the PRISM-PLUS study. The price year was 1999.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
The indirect costs were not included in the economic analysis, which was consistent with the perspective adopted.

**Currency**
UK pounds sterling (€).

**Sensitivity analysis**
A sensitivity analysis was carried out by adding the cost attributable to major bleeding, which was quantified as a repeat percutaneous coronary intervention. However, major bleeding was not identified as a relevant predictor of the total costs. An absolute increased risk of bleeding of 0.7% was used.

**Estimated benefits used in the economic analysis**
The proportion of MI cases was 4.1% without tirofiban and 1.9% with tirofiban. The proportion of RFA cases was 3.4% without tirofiban and 2.8% with tirofiban. The proportion of deaths due to other events (which sums up to 100% when added to the previous rates) was 95.2% without tirofiban and 65.3% with tirofiban.
Cost results
The mean cost per patient was 2,436 without tirofiban and 2,819 with tirofiban.

Considering the whole group of PRAIS-UK patients, the total costs would be 1,958,544 without tirofiban and 2,266,476 with tirofiban. The reported costs showed a 15.7% increase with the use of tirofiban.

The projected costs of care over 6 months for the 87,339 ACS patients in the UK is approximately 213 million. The use of tirofiban would increase the budget by about 33 million (19 million in sub-group 1, 13 million in sub-group 2 and 12 million in sub-group 3).

Synthesis of costs and benefits
The cost per event avoided was 13,388 in the whole group, 10,856 in sub-group 1, 10,571 in sub-group 2 and 5,953 in sub-group 3. When the costs due to major bleeding were included, the cost per event avoided (whole group) was 13,773 (+2.9%).

Authors' conclusions
The use of tirofiban as an adjunct to heparin led to improved clinical outcomes in patients with acute coronary syndromes (ACS), at modest proportional increases in costs. The study identified those sub-groups of patients at high risk who may receive the greatest benefits from the treatment.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator was clear. The strategy of heparin alone was selected since the aim of the study was to evaluate the active value of tirofiban. You should decide whether heparin alone represents a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness used data from two published sources (a randomised clinical trial and a national registry). A systematic review of the literature was not carried out and the primary studies were identified selectively. The authors reported extensive details of the studies, in particular, patient characteristics, dates of recruitment, eligibility criteria and methods used. It was therefore possible to assess the validity of the sources used, which was high in the case of the randomised trial. The authors explained the approach used to combine the primary estimates, and a detailed comparison of the patient samples was carried out. These factors enhance the internal validity of the analysis. Given that the authors were selective in their choice of effectiveness evidence, it is likely that there is a plethora of suitable studies that should have been included to ensure the validity of the results obtained.

Validity of estimate of measure of benefit
The summary benefit measure was specific to the disease and the intervention under evaluation. As such, it is comparable only with the benefits of similar interventions, which reduces the transferability of the results. The use of a more comparable measure, such as (quality-adjusted) life-years, would have been more appropriate. However, the authors stated that long-term mortality and quality of life data were not available from the sources used to provide the effectiveness evidence.

Validity of estimate of costs
The authors explicitly stated the perspective adopted in the study. It appears that all the relevant categories of costs have been included. Patient costs and indirect costs were not considered in the analysis and the authors did not discuss the implications of these exclusions. The data on unit costs and resource use were only presented separately for tirofiban use. Other details of the analysis were not reported, thus making the replication of the economic analysis difficult. The source of the cost data was reported. The price year was given, thus enhancing reflation exercises in other settings. The cost data were not treated stochastically and variations in the costs were not explored. Consequently, the cost estimates
were specific to the study setting.

Other issues
The authors made several comparisons of their findings with those from other studies that evaluated other treatments for patients with ACS. A common result was that the cost-effectiveness ratios decreased in high-risk patients. However, the issue of the generalisability of the study results was not addressed and extensive sensitivity analyses were not carried out. Consequently, the external validity of the analysis was low. The authors discussed the limitations due to the fact that clinical and economic data were derived from different sources, which differed in terms of the patient samples involved. However, the authors stated that conservative values were selected in order to achieve conservative estimates of the cost-effectiveness ratios.

Implications of the study
The study results suggested that when appropriate risk stratification is considered, then clinically and economically effective treatments may be identified (e.g. tirofiban) for ACS. This conclusion represents a recommendation for decision-makers to make appropriate use of glycoprotein IIa/IIIb for patients who are most likely to benefit from this treatment.

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Bibliographic details

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Other publications of related interest


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MeSH
Aged; Angina, Unstable /drug therapy /economics /epidemiology; Anticoagulants /adverse effects /therapeutic use; Cardiac Catheterization; Coronary Angiography; Coronary Disease /drug therapy /economics /epidemiology; Electrocardiography /economics; Female; Great Britain /epidemiology; Hemorrhage /chemically induced /economics /epidemiology; Heparin /adverse effects /therapeutic use; Humans; Male; Middle Aged; Myocardial Infarction /drug therapy /economics /epidemiology; Patient Admission; Platelet Aggregation Inhibitors /adverse effects /economics /therapeutic use; Platelet Glycoprotein GPIIb-IIIa Complex /adverse effects /economics /therapeutic use; Predictive Value of Tests; Prospective Studies; Risk Factors; Sensitivity and Specificity; Syndrome; Treatment Outcome; Tyrosine /adverse effects /analogs & derivatives /economics /therapeutic use