Management of non-ST-elevation acute coronary syndromes: how cost-effective are glycoprotein IIb/IIIA antagonists in the UK National Health Service


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 study evaluated four treatment strategies, three of which employed glycoprotein IIb/IIIa antagonists (GPAs), for patients presenting with non-ST-elevation acute coronary syndromes (NSTE-ACS).

In strategy 1, GPAs were given as part of the initial medical treatment. Patients with NSTE-ACS received an infusion of GPA as soon as their high-risk nature had been established.

In strategy 2, GPAs were given to patients with planned percutaneous coronary interventions (PCI). GPA was started once a decision to undertake PCI (or angiography with a view to proceeding to PCI) had been made.

In strategy 3, GPAs were given as an adjunct to the PCI procedure. A GPA was used at the time of PCI, or was started up to one hour before the procedure.

Strategy 4 was no use of GPAs. Patients were assumed to receive standard therapies (e.g. heparin, aspirin, nitrates and analgesia).

Type of intervention

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of patients presenting with NSTE-ACS in the UK, aged between 63 and 68 years.

Setting
The setting was secondary care. The economic study was conducted in York, Leeds, Nottingham and Leicester, UK.

Dates to which data relate
The effectiveness and resource use data were drawn from studies published between 1997 and 2003. The price year was 2000/01.

Source of effectiveness data
The effectiveness data were derived from a review of published studies.
Modelling

A decision tree analysis and state transition model, based on evidence from trials, were used to calculate the costs and benefits of the four strategies. A two-stage model, which comprised the "short term” and the "long term”, was constructed.

The short-term model was designed as a standard decision tree and modelled the cost and effects of the strategies over a 6-month period. For each strategy, a patient could receive a PCI, undergo a coronary artery bypass surgery (CABG), and undergo a revascularisation. The three final health outcomes were nonfatal myocardial infarction (MI), ischaemic heart disease (IHD) without MI during the 6-month period, and death.

The long-term model was designed as a four-state Markov process model. This sought to consider the costs and outcomes over a 5-year period of a patient who had finished the short-term model in one of two disease states: those who had experienced a nonfatal MI; and those who had not, but who remained alive (IHD). Patients entering the IHD state could experience a nonfatal MI, in which case they moved to the MI state for one year, after which they could move to the post-MI state or die. Patients experiencing any subsequent nonfatal MIs remained in the post-MI state. Monte Carlo simulation was used within the model so that the results of the analysis could reflect that all input parameters were probability distributions.

Outcomes assessed in the review

The main outcomes assessed within the short-term model were the transition probabilities, which included:

whether a patient received a PCI during the acute phase (Node A);

the probability of undergoing a CABG for those who did not receive a PCI;

the probability of revascularisation for those who did not undergo a CABG;

the probability regarding the need for revascularisation, which might be a further PCI or CABG for those who did receive an acute PCI; and

the probabilities of nonfatal MI, death and IHD without MI.

The main outcomes assessed in the long-term model were the annual transition probabilities, which included:

the probability of IHD patients remaining in the IHD state;

the probability of IHD patients experiencing a nonfatal MI, and the probability that they die; and

for those who have had a nonfatal MI, the probability of death or moving to the post-MI state.

Study designs and other criteria for inclusion in the review

Probabilities within the short-term model were derived from a systematic review of published randomised controlled trials, alongside the Prospective Registry of Acute Ischaemic Syndromes in the UK (PRAIS-UK) (Collinson et al. 2000, see ‘Other Publications of Related Interest’ below for bibliographic details) and an audit of all NSTE-ACS patients undergoing acute PCI at Leeds General Infirmary (Alfakih et al. 2003, see ‘Other Publications of Related Interest’ below for bibliographic details). Treatment effects associated with GPAs were derived from trials identified in a systematic review (Robinson et al. 2002, see 'Other Publications of Related Interest' below for bibliographic details), including all intravenous GPAs, regardless of whether or not a particular GPA would be expected to be used this way in practice. For strategy 3, only trials which included at least some patients with ACS or unstable angina were included in the model. Probabilities for transitions within the long-term model were derived from two cohorts from the Nottingham Heart Attack Register (NHAR), for which extensive additional follow-up had already been conducted.

Sources searched to identify primary studies

NHS Economic Evaluation Database (NHS EED)
Criteria used to ensure the validity of primary studies
No criteria were used to ensure the validity of the primary studies.

Methods used to judge relevance and validity, and for extracting data
No methods were used to judge the relevance and the validity of the extracted data.

Number of primary studies included
Four primary studies were included in the review.

Methods of combining primary studies
Within the short-term model, data from relevant trials were synthesised using a random-effects meta-analysis to generate a pooled relative risk for strategies 1 to 3. Within the long-term model, the transition probabilities were calculated from the two cohort studies using survival analysis techniques. For each transition, an annual hazard and the variance of the hazard was calculated by assuming an exponential survival distribution (i.e. fixed hazard). The hazard rates were then converted into annual transition probabilities (with variance).

Investigation of differences between primary studies
The authors did not investigate possible differences between the primary studies.

Results of the review
For the short-term model:

Node A, the probability of acute PCI was 0.05;
Node B, the probability of repeat revascularisation was 0.048;
Node C, the probability of repeat revascularisation (PCI) was 1.00;
Node D, the probability of death following Node C was 0.00;
Node E, the probability of MI following Node C was 0.13;
Node F, the probability of death following revascularisation (CABG) was 0.00;
Node G, the probability of MI following revascularisation (CABG) was 0.00;
Node H, the probability of death following acute PCI but no repeat revascularisation was 0.03;
Node I, the probability of MI following acute PCI but no repeat revascularisation was 0.03;
Node J, the probability of CABG following no acute PCI was 0.05;
Node K, the probability of death following Node J was 0.05;
Node L, the probability of MI following Node J was 0.07;
Node M, the probability of 6-month revascularisation following no acute PCI and no CABG was 0.05;
Node N, the probability of 6-month revascularisation (PCI) was 0.48;
Node O, the probability of death following node N was 0.09;
Node P, the probability of MI following Node N was 0.10;
Node Q, the probability of death following 6-month revascularisation (CABG) was 0.00;
Node R, the probability of MI following 6-month revascularisation (CABG) was 0.16;
Node S, the probability of death following no acute PCI and no revascularisation was 0.08; and
Node T, the probability of MI following no acute PCI and no revascularisation was 0.05.

In the long-term model, the mean annual probabilities were:

- for IHD patients remaining in state IHD, 0.9049 (95% confidence interval, CI: 0.8896 - 0.9186);
- for IHD patients experiencing nonfatal MI, 0.0186 (95% CI: 0.0133 - 0.0254);
- for IHD patients dying, 0.0765 (95% CI: 0.063 - 0.0904);
- for dying in the first 12 months following a nonfatal MI, 0.21 (95% CI: 0.1529 - 0.2822);
- for remaining in post-MI state for the first year following a nonfatal MI, 0.79 (95% CI: 0.7177 - 0.8471);
- for remaining in post-MI state for following years after a nonfatal MI, 0.9266 (95% CI: 0.9024 - 0.9466);
- for dying in subsequent years following a nonfatal MI, 0.0734 (95% CI: 0.0534 - 0.976).

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

The benefit measure was the quality-adjusted life-years (QALYs). The authors acknowledged the lack of sources to provide utility estimates for the different health states in the model. Therefore, they assumed that the health states of all those alive were valued, on average, at the same quality weight regardless of the health status they were in. The utility estimates were derived from a published study. No further information was provided. The health benefits were discounted at an annual rate of 2%.

**Direct costs**

The resources measured within the short-term model were derived from the PRAIS-UK. They included the probability of the use of angiography, the probability of coronary care unit (CCU) stay, the length of inpatient stay and the length of CCU stay. The resources measured within the long-term model included length of hospital stay (cardiac, non cardiac) and the use of angiography, PCI and CABG. The costs measured within the short-term model were for PCI, repeat PCI, CABG, angiogram, endoscopy, full blood count, unit of blood, ward stay (CCU, cardiac and non-cardiac wards), outpatient visit, day case, medication (e.g. tirofiban, eptifibatide, abciximab and omeprazole) and equipment (e.g. guidewire, stent and guiding catheter). These data sought to reflect the cost of revascularisation (PCI or CABG), MI, complications associated with GPA use and the costs associated with death. The costs were derived from previous studies and from data provided by the specific NHS trust. The acquisition costs of the three licensed GPAs were based on undiscounted prices from the British National Formulary. The authors acknowledged that no cost allowance was made for the suggested risk of stroke in patients treated with GPAs. Further, all other costs were assumed to be equivalent in the various strategies.

In the long-term model, the mean annual cost of IHD state, nonfatal MI state and post-MI state were calculated. These were based on data collected as part of the 1998 cohort of the NHAR.

The quantities and the costs were analysed separately. The price year was 2000-01. All future costs were discounted at
an annual rate of 6%, based on UK government guidelines.

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

**Indirect Costs**
The indirect costs were not calculated.

**Currency**
UK pounds sterling (L).  

**Sensitivity analysis**
A series of one-way sensitivity analyses were conducted to explore the strength of the conclusions of the model to changes in assumptions and data sources. Also, to look at the cost-effectiveness in particular patient sub-groups (high-risk patients). The authors referred the reader to a report which provides full details of these analyses (Palmer et al. 2002, see ‘Other Publications of Related Interest’ below for bibliographic details).

**Estimated benefits used in the economic analysis**
The lifetime QALYs were:

- 7.7875 with strategy 1,
- 7.6839 with strategy 2,
- 7.6910 with strategy 3, and
- 7.6883 with strategy 4.

**Cost results**
From the short-term model, the expected cost per patient was:

- 2,526 (95% CI: 1,730 - 4,347) with strategy 1,
- 2,132 (95% CI: 1,332 - 3,950) with strategy 2,
- 2,158 (95% CI: 1,356 - 3,979) with strategy 3, and
- 2,107 (95% CI: 1,309 - 3,926) with strategy 4.

This was based on a follow-up of 6 months. Some of the costs of adverse effects were considered in the costing, although the authors acknowledged that the suggested increased risk of stroke through the use of GPAs was not considered.

The mean lifetime cost was:

- 12,688 with strategy 1,
- 12,207 with strategy 2,
- 12,188 with strategy 3, and
12,119 with strategy 4.

This was based on a follow-up of 50 years.

**Synthesis of costs and benefits**
The incremental cost-effectiveness ratios (ICERs) were calculated. Strategy 2 was dominated by strategy 3 as it was both more expensive and less effective. Strategy 3 was ruled out by extended dominance because the ICER of strategy 1 was lower than strategy 3. The ICER of strategy 3 compared with strategy 4 was 25,811 per QALY gained. The ICER of strategy 1 compared with strategy 4 was 5,738 per QALY gained. Cost-effectiveness acceptability curves indicated that the probability that strategy 1 was cost-effective increased as the maximum willingness to pay for health outcomes increased. If society was prepared to pay 10,000 for an additional QALY, the probability that strategy 1 was cost-effective was around 0.82, increasing to 0.95 if the maximum willingness to pay was 50,000.

The findings remained robust after most of the sensitivity analyses, including the use of life-years gained as an outcome measure and the use of non-UK specific baseline event data. The inclusion of a fifth strategy had a significant impact on the results. This strategy was the use of GPAs as part of initial medical treatment, but only in a high-risk sub-group of NSTE-ACS patients. Strategy 5 had a cost per QALY gained of 3,966 compared with strategy 4. Strategies 2 and 3 remained dominated. The cost per additional QALY for using GPAs in all patients, rather than just those at high-risk, was 56,180.

**Authors’ conclusions**
The most cost-effective use of glycoprotein IIb/IIIa antagonists (GPAs) in non-ST-elevation acute coronary syndromes (NSTE-ACS) in the National Health Service was likely to be the medical treatment of patients with an incremental cost per quality-adjusted life-year (QALY) gained of between 4,605 and 10,343. Focusing this use of GPAs on those at particularly high risk is likely to represent the most cost-effective use of resources.

**CRD COMMENTARY - Selection of comparators**
The choice of the comparator was clear. The readers should consider whether this reflects current practice in their own setting.

**Validity of estimate of measure of effectiveness**
A systematic review of the literature does not appear to have been undertaken. Although this is common practice with models, in the current study it appears that the studies have been selected from the literature according to convenience or the authors’ preferences. Therefore, the effectiveness estimates derived may not be the best available. The authors acknowledged the limitations associated with using these data sources. The measure of effectiveness was based on cohort studies in which the data collected were specific to the UK. This reflected the aim of the study, since much of the trial evidence on GPAs came from outside of the UK. One systematic review provided the evidence on the treatment effects associated with GPAs. The study designs, other inclusion criteria for the review, and the methods of combining the studies were reported. However, possible differences between the primary studies were not investigated. The estimates were investigated by sensitivity analysis, although the authors did not justify the ranges selected on the basis of the literature.

The authors reported several limitations. For example, the evidence of effectiveness was derived from studies that evaluated particular GPAs which may not be used in routine UK practice. Another limitation was that the effectiveness data were derived from trials that included a range of patients with different characteristics which are likely to affect prognosis. The authors also commented that the different selection processes used in the trials and cohorts that provided the data need to be recognised when interpreting the results. Finally, the data source for the long-term model was based on a cohort with a maximum follow-up of 5 years.

**Validity of estimate of measure of benefit**
The measure of health benefit (QALYs) was derived from a state transition model. The life-years were derived from a study that followed two cohorts of patients, using survival analysis techniques. The utility values were derived from the literature. The authors explored the uncertainty in utility values using a beta distribution. The benefits were discounted at a rate of 2%, based on government guidance.

Validity of estimate of costs
All the categories of costs relevant to a health service perspective appear to have been included in the analysis. The unit costs were presented separately from the quantities of resources used, which will allow the study to be replicated in other contexts. The authors limited their analysis to the direct costs. The resource quantities were derived from published sources, while the unit costs were derived from published sources and expert opinion. A thorough sensitivity analysis was conducted to assess the robustness of the results when the estimated costs were modified. The authors discounted the costs at a rate of 6%, based on government guidance, which was appropriate. The date to which the prices referred was reported, which aids future reflation exercises.

Other issues
The authors made appropriate comparisons of their findings with those from other studies, although the number of studies referred to was restricted because of the limited data on the cost-effectiveness of the different strategies, particularly within the UK. The issue of generalisability to other settings was addressed. The study investigated the impact of GPAs for the treatment of NSTE_ACS and this was reflected in the authors' conclusions.

The authors reported a number of further limitations to their study, some of which have been highlighted already. These related to the assumptions adopted and the data sources used. In the sensitivity analyses, limitations in the reporting of the data meant that it was not possible to provide a consistent basis for the definition of "high risk". It was therefore difficult to assess the reliability of the sensitivity analysis and to identify the most appropriate markers of "high risk".

Implications of the study
The authors did not report any implications following their study.

Source of funding
Funded by the UK NHS Health Technology Assessment Programme.

Bibliographic details

PubMedID
15823630

DOI
10.1016/j.ijcard.2004.08.042

Other publications of related interest

http://www.nice.org.uk/Docref.asp?id=32030


**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Coronary Disease /drug therapy; Cost-Benefit Analysis; Drug Costs; Great Britain; Humans; Models, Econometric; Myocardial Infarction /drug therapy; Platelet Aggregation Inhibitors /economics /therapeutic use; Platelet Glycoprotein GPIIb-IIIa Complex /antagonists & inhibitors; Quality-Adjusted Life Years; Risk; State Medicine /economics

**AccessionNumber**

22005000821

**Date bibliographic record published**

31/05/2006

**Date abstract record published**

31/05/2006