Initial medical management of non-ST elevation acute coronary syndrome

Cost-effectiveness of alternative strategies for the initial medical management of non-ST elevation acute coronary syndrome: systematic review and decision-analytical modelling

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Executive summary

Health Technology Assessment 2005; Vol. 9: No. 27

Health Technology Assessment
NHS R&D HTA Programme

Executive summary

Background

This report describes the development of a decision model to evaluate the cost-effectiveness of glycoprotein IIb/IIIa antagonists (GPAs) in non-ST elevation acute coronary syndrome (ACS) and the systematic review that was undertaken to populate that model. A more general literature review has been published in a separate issue of *Health Technology Assessment* as an update report from an earlier Technology Assessment Review for the National Institute for Health and Clinical Excellence (NICE).

There are about 115,000 new cases per year of non-ST elevation ACS in England and Wales, and 5–14% of patients die within a year of diagnosis.

Objectives

The objectives of this study were:

- to identify and prioritise key areas of clinical uncertainty ('decision problems') regarding the medical management of non-ST elevation ACS in current UK practice
- to undertake a systematic review of relevant randomised controlled trials (RCTs) and previous economic evaluations
- to construct a decision-analytical model for the most important 'decision problem', and to populate this with the results of the systematic review and other relevant data
- to identify priorities for future research, by application of value of information techniques.

Methods

Potential areas of important uncertainty were identified by discussion with clinicians, and by identifying areas of disagreement in published clinical practice guidelines. Decision problems were prioritised on the basis of the extent of disagreement set out in guidelines and expressed by clinicians in a postal survey. This examined the intended management of a series of clinical vignettes and the level of uncertainty attached to each therapeutic decision.

A systematic literature review was limited to the most highly prioritised decision problems rather than including all medical treatments for non-ST elevation ACS. It focused on published RCTs and full economic evaluations. Standard methods, as recommended by the NHS Centre for Reviews and Dissemination, were used to carry out the review. All intravenous drugs within the broad class of agents prioritised for study were considered, whether or not they were currently licensed in the UK. The literature review included reports on high-risk subgroups of patients.

A two-part decision model was constructed that consisted of a short-term phase, during which the results of the systematic review could be directly applied, and a long-term phase that included relevant information from a UK observational study to extrapolate estimated costs and effects over a longer-term time horizon.

The short-term phase of the decision model covered the period up to 6 months after initial presentation. Baseline probabilities of death, non-fatal myocardial infarction (MI) and revascularisation during this period, as well as resource costs, were estimated from an observational cohort registry of 1046 patients admitted to 56 UK hospitals with ACS during 1998–9 (PRAIS-UK). To supplement these data, a retrospective sample of patients with ACS undergoing urgent percutaneous coronary intervention (PCI) at the Yorkshire Heart Centre in Leeds was identified and an audit of outcome at 6 months was undertaken.

To model the effect of GPAs during the short-term phase, baseline probabilities of death, non-fatal MI, revascularisation and major bleeding and costs from the UK data were adjusted using the relative risk reductions associated with each strategy derived from the systematic review.

Long-term costs and quality-adjusted life-years (QALYs) beyond 6 months were estimated using a Markov model populated with probability and resource use data from the 1992 and 1998 cohorts of the Nottingham Heart Attack Register. Patients in these cohorts had an initial working diagnosis of typical ischaemic pain/angina (but did not ▶

have ST-elevation acute MI) and had been followed up for 5 years and 21 months, respectively.

The model was probabilistic and took the perspective of the NHS as a whole. Standard discount rates for UK health economic evaluations were also applied. To examine the dependence of the results on baseline parameters, sensitivity analyses were undertaken using alternative data sources. Expected value of information analysis was carried out to estimate the expected value of perfect information associated with the decision problem. This provided an upper bound on the monetary value associated with additional research in the area.

Results

Discussions with clinicians produced a shortlist of seven current areas of clinical uncertainty (decision problems) in the drug treatment of patients with unstable angina. The agents concerned were clopidogrel, low molecular weight heparin, hirudin, and intravenous GPAs. Twelve published clinical guidelines for unstable angina or non-ST elevation ACS were identified, but few contained recommendations about the specified decision problems. The postal survey of clinicians showed that the greatest degree of disagreement existed for the use of small molecule GPAs, and the greatest degree of uncertainty existed for decisions relating to the use of abciximab (a large molecule GPA). Overall, decision problems concerning the GPA class of drugs were considered to be the highest priority for further study.

Searches for pre-existing systematic reviews identified a pair of reviews undertaken in 2000 as part of the NICE technology appraisal of GPAs. The two search strategies encompassed the literature considered necessary for the present study. Papers included in the present review were those that were relevant based on the previous reviews, plus results from update searches with a cut-off date of January 2001.

Papers describing the clinical efficacy of treatment were divided into three groups, each representing an alternative strategy. Strategy 1: use of GPAs as part of the initial medical management of all non-ST elevation ACS; strategy 2: use only in patients scheduled for early invasive management; and strategy 3: use as an adjunct to PCI for ACS patients at the time of the procedure or up to 1 hour beforehand.

Eight trials were identified for strategy 1, one for strategy 2 and 10 for strategy 3. Trials varied considerably in size, inclusion criteria and results. In addition, 18 papers were identified that reported results in high-risk subgroups of the main trials, but there was insufficient information to construct reliable relative risk reductions (RRRs) for specific subgroups suitable for inclusion in the model. Approaches to individual investigators yielded little additional information.

Results before sensitivity analysis suggested that strategy 1 (use of GPAs as part of the initial medical management of all non-ST elevation ACS) was the optimal choice, with an incremental cost-effectiveness ratio (ICER) of £5738 per QALY compared with no use of GPAs. Strategy 2 was both more expensive and less effective than no use of GPAs. Strategy 3 was cost-effective compared with no use of GPAs, but was inferior to strategy 1. Stochastic analysis showed that if the health service is willing to pay £10,000 per additional QALY, the probability that strategy 1 was cost-effective was around 82%, increasing to 95% at a threshold of £50,000 per QALY. The conclusion that strategy 1 was the optimal approach was robust to all the sensitivity analyses undertaken, including variations on the time horizon of the model, quality adjustment, the costs of GPAs, the inclusion of clopidogrel as an alternative to the use of GPAs, and the calculation of baseline event rates from a recent patient level meta-analysis of trial data. For the sensitivity analyses that excluded the use of clopidogrel, the ICERs for strategy 1 ranged from £4605 to £10,343 per QALY gained.

The only sensitivity analysis in which strategy 1 was not the optimal approach was a two-way analysis, both changing the treatment without GPAs to include routine clopidogrel and applying the RRRs for GPAs reported in a recently published meta-analysis using patient-level data. In this analysis, treatment with clopidogrel instead of GPAs was the most cost-effective option. It was not possible to model the use of GPAs in combination with clopidogrel.

A sensitivity analysis including an additional strategy of using GPAs as part of initial medical management only in patients at particularly high risk (as defined by age, ST depression or diabetes) showed this additional strategy was yet more cost-effective than strategy 1 in the base case, with an ICER of £3996 per QALY compared with no treatment with GPA. ▶

Value of information analysis suggested that there was considerable merit in additional research to reduce the level of uncertainty in the optimal decision. At a threshold of £10,000 per QALY, the maximum potential value of such research in the base case was calculated as £12.7 million per annum for the UK as a whole. Taking account of the greater uncertainty in the sensitivity analyses including clopidogrel, this figure was increased to approximately £50 million.

Conclusions

Initial consideration of a number of new drug treatments for non-ST elevation ACS concluded that the most important uncertainties surrounded the use of GPAs. The systematic review and decision model clearly demonstrated that use of GPAs in all patients as part of initial medical management was more cost-effective than selective use associated with intervention, or no use at all. The best estimate of the magnitude of this benefit was an increase in quality-adjusted survival of about 35 days per patient at an additional cost of £570 per patient. This suggests the use of GPAs in all non-ST elevation ACS patients as part of their initial medical management. Sensitivity analysis showed that virtually all of the benefit could be realised by treating only high-risk patients, defined as those aged over 70 years, with diabetes, or with ST depression or positive cardiac troponins.

This conclusion conforms in general terms with current guidelines from the specialist association (British Cardiac Society) and from NICE, which recommend use of GPAs as part of initial medical management in high-risk patients, although these guidelines also recommend use in all patients undergoing PCI, which was not supported by the model. Current practice in the NHS (as at May 2002) is likely to use an even higher threshold for GPAs, with clopidogrel being used instead as part of initial medical treatment, and GPAs predominantly used as adjunctive to PCI. This approach most closely resembles strategy 3 of the model. Although this was shown to be cost-effective compared with no use of GPAs, with an ICER of £25,000 per QALY in the base case, it was inferior to strategy 1, use of GPAs as part of the initial medical management of all non-ST elevation ACS.

Further clarification of the optimum role of GPAs in the UK NHS depends on the availability of further high-quality observational and trial data. Value of information analysis derived from the model suggests that a relatively large investment in such research may be worthwhile. This should be focused on:

- the identification of the characteristics of patients who benefit most from GPAs as part of medical management
- the comparison of GPAs with clopidogrel as an adjunct to standard care
- follow-up cohort studies of the costs and outcomes of high-risk non-ST elevation ACS over several years, building on such studies as the Nottingham Heart Attack Register
- exploring how clinicians' actual decisions combine a normative evidence-based decision model with their own personal behavioural perspective.

Publication

Robinson M, Palmer S, Sculpher M, Philips Z, Ginnelly L, Bowens A, *et al*. Cost-effectiveness of alternative strategies for the initial medical management of non-ST elevation acute coronary syndrome: systematic review and decision-analytical modelling. *Health Technol Assess* 2005;**9**(27).

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NHS R&D HTA Programme

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The HTA Programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, service-users groups and professional bodies such as Royal Colleges and NHS Trusts.

Research suggestions are carefully considered by panels of independent experts (including service users) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or conducting a trial to produce new evidence where none currently exists.

Additionally, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme is able to commission bespoke reports, principally for NICE, but also for other policy customers, such as a National Clinical Director. TARs bring together evidence on key aspects of the use of specific technologies and usually have to be completed within a short time period.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this monograph was commissioned by the HTA Programme as project number 98/29/04. The contractual start date was in December 2004. The draft report began editorial review in June 2002 and was accepted for publication in September 2004. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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ISSN 1366-5278

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Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.