A COST-EFFECTIVENESS MODEL COMPARING ALTERNATIVE MANAGEMENT STRATEGIES FOR THE USE OF GLYCOPROTEIN IIB/IIIA ANTAGONISTS IN NON-ST-ELEVATION ACUTE CORONARY SYNDROME

Stephen Palmer[a]
Mark Sculpher[a]
Zoe Philips[a]
Mike Robinson[b]
Laura Ginnelly[a]
Ameet Bakhai[c]
Chris Packham[d]
Keith Abrams[e]
Nicola Cooper[e]
Khaled Alfikah[f]
Marcus Flather[c]
David Gray[g]

a. Centre for Health Economics, University of York, York.
b. Nuffield Institute, University of Leeds, Leeds
c. Clinical Trials & Evaluation Unit, Royal Brompton and Harefield NHS Trust, London
d. Division of Public Health Sciences, University of Nottingham, Nottingham
e. Department of Epidemiology and Public Health, University of Leicester, Leicester
f. BHF Heart Research Centre at Leeds, Leeds General Infirmary, Leeds
g. Department of Cardiovascular Medicine, University Hospital, Queen's Medical Centre, Nottingham

Correspondence: Mark Sculpher, Centre for Health Economics, Heslington, York, YO10 5DD.
Email mjs23@york.ac.uk. Tel. 01904 433641

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Summary

Background. The glycoprotein IIb/IIIa antagonists (GPAs) represent a new class of drugs to prevent platelet aggregation in the acute treatment of non-ST-elevation acute coronary syndromes (ACS). Rapid reviews of GPAs for this indication have identified serious limitations in published cost-effectiveness analyses, including a dearth of cost-effectiveness estimates using life-years or quality-adjusted life-years (QALYs) as measures of effectiveness; a lack of UK-specific studies which reflect differences in patient selection and clinical practice in the UK compared to that in GPA trials, such as the lower rate of percutaneous coronary intervention (PCI); and an absence of studies comparing different strategies of how GPAs could be used in these patients. A model was developed to address these limitations in available cost-effectiveness studies.

Methods. The model is probabilistic and takes the perspective of the UK NHS, estimates health outcomes in terms of quality-adjusted life-years (QALYs) and has a lifetime time horizon. Four treatment strategies are evaluated: GPAs as part of initial medical management (Strategy 1); GPAs in patients with planned PCIs where GPAs are started once a decision to undertake PCI has been made (Strategy 2); GPAs as an adjunct to PCI where the agent is used at the time of PCI or is started up to 1 hour before the procedure (Strategy 3); and no use of GPAs (Strategy 4). A short-term model characterises the period up to 6 months following an episode of ACS. Baseline probabilities of death, non-fatal MI and revascularisation, as well as resource costs, are taken from PRAIS-UK, an observational cohort registry of 1046 patients admitted to 56 UK hospitals with acute coronary syndromes during 1998-9. To supplement one element of the PRAIS-UK data, a retrospective sample of ACS patients undergoing acute PCI in Leeds was identified. To model the effect of GPAs, these baseline event probabilities and costs are adapted using the relative risks associated with GPAs (compared to standard care) based on a systematic review of published randomised trials. If patients survive the 6 months following

ACS, their long-term costs and QALYs are estimated using a Markov model populated using probability and resource use data from two cohorts of the Nottingham Heart Attack Register. Patients in these cohorts had an initial working diagnosis of typical ischaemic pain / angina (rule out MI) on cardiac presentation together with patients who were suspected of having had an MI, but did not. Quality adjustment is undertaken assuming a single utility for all living patients based on data in ischaemic heart disease patients in the published literature. UK unit costs are used in the model at a 2000-2001-price base.

A series of sensitivity analyses have been undertaken to determine the robustness of the base-case model to a number of different scenarios including: alternative sources of baseline intervention and event data; variation in the assumptions used to derive the relative risks associated with GPAs; and finally the potential impact of considering additional comparators in addition to the four main strategies assessed in the base-case model.

Results. The base-case results of the overall model indicate that Strategy 2 is dominated by Strategy 3 as it is both more expensive and less effective. Strategy 3 can also be ruled out by extended dominance because the ICER of the next most effective strategy (Strategy 1) is lower than that of Strategy 3. The base-case ICER of Strategy 1 compared with Strategy 4 is £5,738 per QALY. For purposes of comparison, the base-case ICER for Strategy 3 relative to Strategy 4 is £25,811 per QALY. When reflecting uncertainty in mean costs and effects, if society is prepared to pay £10,000 for an additional QALY, the probability that Strategy 1 is cost effective is around 82%, increasing to 95% if the maximum willingness to pay is £50,000. The sensitivity analyses show that cost-effectiveness is most sensitive to the assumptions about the time horizon of the model, quality-adjustment, the costs of GPAs, and the sources of baseline event data. The inclusion of additional strategies, such as restricting the use of GPAs as part of initial medical management to high-risk patients and the use of clopidogrel as an alternative to the use of GPAs, potentially have a

significant impact on the optimal adoption decision. For the sensitivity analyses excluding the additional comparators, the ICERs for Strategy 1 range from £4,605 to £11,671 per QALY gained and, for Strategy 3 relative to Strategy 4 from £11,160 to £45,308 per QALY gained. When the use of GPAs in Strategy 1 is restricted to high-risk patients only, the ICER for this strategy relative to Strategy 4 is £3,966 and this targeted approach appears to be more cost-effective than the use of GPAs in the medical management of all ACS patients. When clopidogrel is included as a fifth alternative strategy in the model, clopidogrel is ruled out by extended dominance by Strategy 1. However, when the relative risks for Strategy 1 are adjusted using the results of a recently published patient level meta-analysis, clopidogrel is potentially the most cost-effective strategy.

Conclusions. The model presented here indicates that the most cost-effective use of GPAs in ACS is in the medical management of patients. The incremental cost per QALY gained of medical management is estimated at between £4,605 to £11,671. The strategy of using GPAs only as an adjunct to PCI was found to be economically inferior to medical management under all scenarios. If this latter strategy is compared to standard practice (without GPAs), the ICER ranges from £11,160 to £45,308 per QALY gained. These results appear particularly sensitive to the more restricted use of GPAs in the medical management of high-risk patients only and the inclusion of clopidogrel as an alternative to the use of GPAs. Further analysis of the cost-effectiveness of these additional strategies is required to confirm these results.

Introduction

The glycoprotein IIb/IIIa antagonists (GPAs) represent a new class of drugs to prevent platelet aggregation in the acute treatment of non-ST-elevation acute coronary syndromes (ACS). The initial[2,3] and updated[4] rapid reviews of GPAs for this indication for the National Institute for Clinical Excellence have identified serious limitations in published cost-effectiveness analyses. The first limitation is that the effectiveness data (and in most cases resource use data and costs), which typically underpin most of the analyses, are taken from randomised trials, which were undertaken wholly, or largely outside of the UK. This is particularly important with GPAs, because of the possibility that much of their effectiveness arises in conjunction with percutaneous coronary interventions (PCIs), the use of which is traditionally lower in the UK than in many developed countries.[5] Hence baseline clinical event rates, relative risk reductions, resource utilisation, costs and, therefore, cost-effectiveness may differ in the UK from that estimated in published studies.

A second problem is the short follow-up of the trials, typically no more than six months and often as little as 30 days. However, the use of GPAs to reduce the risk of mortality and non-fatal acute myocardial infarction in non-ST-elevation ACS will have important long-term implications for quality-adjusted survival and health service costs, and these 'downstream' consequences are not directly informed by the trials, although they need to be considered as part of the decision making process. A third limitation is that existing cost-effectiveness studies usually relate changes in costs, conditional on the use of GPAs, to differential outcomes which are not helpful to decision making, such as 'cardiac events avoided'. The use of condition-specific outcomes precludes comparison of the incremental cost-effectiveness of GPAs with independent programmes outside cardiology, which are competing for limited resources. The use of life-years or, preferably, quality-adjusted life-years as generic measures of health outcome is more appropriate for decisions about resource allocation. A fourth shortcoming of published economic

studies of GPAs in ACS is that none directly compares all the relevant alternative treatment strategies involving GPAs as used in the NHS. This reflects the design of the randomised trials in the field, but it is a further limitation on decision-making.

The long-term cost-effectiveness of GPAs, as used in the UK and in terms of generic health outcomes, has, therefore, not been fully addressed in published studies. This report details the results of a decision analytic model that has been developed to address this question.

2. Methods

2.1 The relationship between the model and systematic review

The decision analytic model builds on the trial-based evidence summarised in the accompanying systematic review of the effectiveness and cost-effectiveness of GPAs.[4] Although the review and modelling component share a common information base, it is important to recognise that the systematic review and the model have been specifically designed to serve separate, albeit complementary, functions. The principal objective of the review document is systematically to identify, summarise and critically appraise the results of all relevant studies. Due to various sources of between-study heterogeneity, no formal attempt is made in the review document formally to synthesise the results in relation to specific indications. While such an approach is entirely justified in the context of the review, it is equally important to recognise that, for the purposes of decision-making, this is a potentially significant limitation (particularly if individual studies give conflicting results). The model has been designed to overcome this limitation by addressing the specific issues faced by a decision-maker in assessing the potential cost-effectiveness of GPAs in ACS. The model is valuable as it can be used to address the relevance of the available evidence to a particular decision-making context (e.g. from the perspective of the NHS), in addition to providing an explicit judgement regarding the most cost-effective use of GPAs given the combined weight of evidence from all relevant studies.

2.2 Model overview

The model has been developed to estimate costs from the perspective of the UK NHS, and health outcomes in terms of life-years and quality-adjusted life-years (QALYs). For the main analysis, a lifetime time horizon has been used; that is, the model considers the costs and outcomes of a hypothetical cohort of patients with non-ST-elevation ACS over a period of 50 years. As a secondary analysis, cost and outcomes are also reported over a 5-year time horizon. The model is made up of two parts: a short-term element, which relates to a period of six months after a patient presents with non-ST-elevation ACS; and a long-term element which extrapolates a patient's lifetime costs and outcomes conditional on surviving the first six months after the acute episode.

The model is probabilistic in that input parameters are entered into the model as a probability distributions to reflect 2nd order uncertainty – that is, uncertainty in mean costs and outcomes, and in probabilities.[6] Monte Carlo simulation is used to propagate uncertainty in input parameters through the model in such a way that the results of the analysis can also be presented with their uncertainty. A 2000-2001 price base is used, and annual discount rates of 6% for costs and 2% for benefits are adopted based on UK guidance.[7]

2.3 Treatment strategies under comparison

Four treatment strategies have been identified as being relevant options for the use of GPAs in ACS:

Strategy 1: GPA as part of initial medical management. This envisages patients with ACS receiving an infusion of GPA as soon as their "high risk" nature has been established.

*Strategy 2: GPA in patients with planned percutaneous coronary interventions (PCIs)***.** GPA is started once a decision to undertake PCI (or angiography with a view to proceeding to PCI) has been made.

Strategy 3: GPA as adjunct to PCI. GPA is used at the time of PCI or is started up to 1 hour before the procedure.

Strategy 4: No use of GPA. With this strategy, patients are assumed to receive standard therapies (e.g. heparin (intravenous or subcutaneous), aspirin, nitrates and analgesia), without the use of GPA.

2.4 Short-term model

2.4.1 Model structure

The short-term model is structured as a decision tree as shown in Figure 1. For each strategy, the initial chance node (Node A) reflects uncertainty in whether a patient receives a PCI during the acute phase. For those who do not receive this 'acute PCI', there is uncertainty regarding whether they undergo a coronary artery bypass graft (CABG) instead during the acute period (Node J); and for those who do not undergo CABG, there is uncertainty regarding whether any revascularisation is undertaken during the initial 6-month period (Node M). For patients who receive an acute PCI, there is uncertainty regarding the need for repeat revascularisation (Node B), which might be a further PCI or CABG (Node C). For all patients, there is uncertainty regarding the final health-related outcomes of the short-term model over the initial 6-month period (Nodes D to G, H to I and O-T). Three mutually exclusive outcomes are modelled: non-fatal myocardial infarction (MI), death and ischaemic heart disease (IHD) without MI during the 6-month period.

2.4.1 Baseline probabilities in the short-term model

The RCTs undertaken to evaluate the clinical effectiveness of the GPAs were mainly or wholly undertaken outside the UK.[4] In many respects, treatment patterns and resource use in the UK can be expected to differ from those in centres involved in the trials. For example, the rate of PCI in patients with ACS, and in IHD generally, is lower than in most developed countries.[5] One implication of these differences in UK practice is that the baseline event rates observed in the trials (i.e. in the control groups) are unlikely to provide reliable estimates for UK practice.

For this reason we have constructed baseline event rates, specific for UK practice, from an alternative data source – the Prospective Registry of Acute Ischaemic Syndromes in the UK (PRAIS-UK).[8] This is an observational cohort registry of 1046 patients admitted to 56 UK hospitals with ACS between 23 May 1998 and 3 February 1999. Patients were followed-up for 6 months after their index hospital admission. Patients were eligible if they were admitted to hospital with a primary clinical diagnosis of ACS without ST elevation on the admission ECG. The hospitals included in PRAIS-UK served 24% of the UK population. For the purposes of this study, patients who received GPA in PRAIS-UK (n=13; 1%) were excluded from the analysis.

The parameter estimates from PRAIS-UK relating to patients who received a PCI during the acute phase of their ACS were based on a relatively small number of patients (n=53). For this reason, an audit of unstable angina patients undergoing acute PCI at a large UK cardiac centre (Leeds) was undertaken. All acute PCIs (n=231) performed in the calendar year 2000 were identified from the angiography suite database. Case-notes were obtained from medical records. Data were abstracted using a standard *pro forma* by a specialist registrar in cardiology, including diagnosis (ST elevation MI or non-ST elevation acute coronary syndrome), use of GPA before or during the procedure, further revascularisation procedures (if any) during the subsequent 6 months, and outcome at 6 months if available. Those who had ST-elevation MI or

who had received a GPA were excluded from further consideration. When 6-month follow up data were not available from the case-notes, patients or their relatives were contacted by phone to ascertain this. Absolute numbers of Leeds patients in each baseline category were added to the equivalent numbers from PRAIS-UK and the totals entered into the model.

Table 1 details the combined probabilities taken from PRAIS-UK and the Leeds PCI audit that have been used to construct a UK-specific baseline. In other words, these probabilities relate to Strategy 4 above, or standard practice in the UK without GPAs. As well as the point estimates of the probabilities, the number of cases in the PRAIS-UK and Leeds datasets on which they are based are detailed, as the magnitude of these numbers determines the dispersion (uncertainty) in the probability distributions. Uncertainty in all distributions of probabilities is characterised as a beta distribution with the α parameter being the number of patients who experienced the event of interest in the relevant sub-sample, and β the number of patients who did not experience the event.

2.4.2 Baseline resource use and cost data

Within the short-term model, baseline resource use data (i.e. relating to Strategy 4) are taken from PRAIS-UK, and these data are detailed in Table 2. In part, resource use relates directly to the clinical events shown in Figure 1, specifically to revascularisation using PCI or CABG. In addition, mean length of in-patient hospital stay is taken from PRAIS-UK. This is entered separately into the model according to whether or not revascularisation was undertaken during the acute period and, if so, whether it was PCI or CABG. For patients who undergo (repeat or initial) revascularisation within the initial six months but outside of the acute period, length of stay data was not collected in PRAIS-UK. For PCI undertaken outside the acute period, a fully-allocated cost for the procedure has been applied from published estimates,[9] while for CABG it has been assumed that these parameters take on the same value as the length of stay observed

in the study for acute revascularisation. Uncertainty in the level of resource use has been incorporated by assigning distributions to each parameter. The probability of a particular resource use is characterised by a beta distribution, and length of stay data are characterised as lognormal distributions.

Three other areas of resource use are modelled explicitly within the baseline model: MI, complications associated with the use of GPAs and costs associated with death. For patients who experience a non-fatal MI during the 6-month period, resource use and cost is incorporated into the model based on costs estimated in NHS hospitals in England.[10] Only the GPA complication of gastrointestinal bleeding is incorporated into the model, and the baseline probability of this event (i.e. without GPAs) is taken from PRAIS-UK, and is detailed in Table 1. Although some trials suggest an excess risk of stroke in patients treated with GPAs,[4] the absolute additional risk is very small, so no allowance has been made for this cost. Costs associated with death are based on the likelihood of dying in hospital, and the associated length of hospital stay, as reported in the Nottingham Heart Attack Register (see Section 2.4.3 for details). All other costs in the short-term model (e.g. the costs of pharmaceuticals other than GPAs) are assumed to be equivalent in the various strategies.

All unit cost data used in the analysis to value resource use are shown in Table 3, together with the sources of those data. These unit costs are used, together with the resource use in Figure 1 and Table 2, to generate an overall mean cost (and standard deviation) of each of the pathways in Figure 1.

2.4.3 The effectiveness and costs of GPAs

The relative risks associated with GPAs are based on the trials identified as part of the update systematic review.[4] In the case of Strategy 1, relative risks come from all trials identified that

evaluate the effectiveness of GPAs in ACS. This includes three trials evaluating lamifiban. Although this drug is not licensed in the UK, it contributes to the weight of evidence on the effectiveness of GPAs. Only one trial relates directly to Strategy 2 – CAPTURE which evaluated abciximab. For Strategy 3, only trials which included at least some patients with ACS or unstable angina are included in the model. Table 4 summarises the trials included for each strategy, to estimate the relative risks of GPAs.

In the accompanying systematic review of the clinical effectiveness and cost-effectiveness of GPAs,[4] it was argued that heterogeneity between trials, with regard to drugs studied, types of patients enrolled, co-treatment strategies and outcome definitions, made any pooling of study results inappropriate. The results of individual trials were thus presented without any formal evaluation of the combined evidence in each of the separate indications. However, in the context of the decision model, the combined weight of evidence from all relevant trials provides a more useful aid to decision-making than the results from any individual trial. Accordingly, a random effects meta-analysis of the combined trial results relevant to each strategy was undertaken to provide an estimate of the overall effect of GPAs in relation to each of the proposed treatment strategies. A series of sensitivity analysis was undertaken to explore the potential impact of this assumption on the base-case results of the model (see Section 3.3 for more detail).

Having constructed a model with UK-specific data on baseline probabilities of clinical events, it is necessary to address the question of whether the relative risks associated with GPAs, which have been estimated in the trials, should be adjusted to reflect differences in UK practice. To inform this decision, meta-regression analysis was undertaken to establish whether, across published trials and taking each strategy separately, the relative risk in a trial was related to the absolute baseline risk in that study. No statistically significant association was found, which may

reflect the small number of trials in the analysis. For this reason, the relative risks from the trials have been incorporated into the model without adjustment, which is equivalent to assuming that relative risks are transportable across health care systems whilst the baseline risks in those studies are not.

The relative risks taken from the trials are shown in Table 4 for each of the three strategies. Separate relative risks from each trial are presented, together with pooled estimates from a random effects meta-analysis. Within the model, relative risks are incorporated as lognormal distributions to allow for uncertainty in the parameters. Three important assumptions were necessary in developing these estimates of treatment effect as detailed below:

(a) Trials relating to the three strategies used particular GPAs, which may not be used in routine practice in the UK.[4] For example, GUSTO IV used abciximab as medical management (Strategy 1), although this drug is not licensed for this purpose in the UK and is unlikely to be used in this way. However, in the base-case analysis, trials including all intravenous GPAs have been included in the meta-analysis to estimate treatment effects regardless of whether or not a particular GPA would be expected to be used in practice. In other words, the view is taken that the best estimate of the effectiveness of GPAs is obtained by including as many trials as possible in the meta-analysis, although it is recognised that there may be some differences between specific products.

(b) In order to estimate the pooled relative risks across trials for Strategies 1 and 3, a decision had to be made on the most appropriate comparator to be used in those trials reporting the results of more than one treatment arm (e.g. different doses or infusion times for GPAs). Wherever possible, these decisions were made on the basis of current NHS practice in consultation with clinical advisors. In those circumstances where a trial reported on the use of a drug for indications not currently licensed in the NHS (e.g. abciximab in Strategy 1), a decision was made based on which comparator would be most the most likely to be

implemented (e.g. the use of 24 hour infusion for abciximab was selected on the basis that the results of 48 hour infusion reported an increased risk, albeit insignificant, in several major endpoints including death).

(c) As indicated above, the time horizon of the short-term model is 6 months. However, not all trials reported their end-points over that long a period of follow-up. A number of studies simply reported end-points at 30 days follow-up. In the base-case analysis, in the absence of 6-month data, we have assumed that the relative risk reductions reported at 30 days also apply at 6 months. The use of an alternative assumption was explored whereby 30-day relative risks were extrapolated to six months assuming a constant hazard ratio. This produced very similar results to the assumption of constant relative risks, and the latter was used in the base-case analysis due to its relative simplicity.

The acquisition costs of the three licensed GPAs are shown in Table 3. These are based on undiscounted prices from the British National Formulary.[11] For Strategy 1, the total drug costs per patient are based on the average cost of eptifibatide and tirofiban, assuming a duration of infusion of 72 hours for eptifibatide and 48 hours for tirofiban for a 70kg person. We have assumed that part-vials cannot be used. The overall costs (including VAT) for the drugs in Strategy 1 are £534.74 for eptifibatide and £343.36 for tirofiban.

For Strategy 2, it is assumed that the majority of the period between the decision to undertake PCI and the procedure itself would involve the use of either eptifibatide or tirofiban. For the base-case analysis the relevant infusion period for Strategy 2 was considered to be 48 hours. As for strategy 1, the drug costs are based on an average of cost of eptifibatide and tirofiban. Using the same assumptions as for Strategy 1, the drug costs are £362.58 for eptifibatide and £343.36 for tirofiban (including VAT). In strategy 3 the drug costs are calculated on the basis of a 12-hour infusion of abciximab, totalling £987.00 per patient.

2.5 Long-term model

2.5.1 Rationale

Any assessment of the cost-effectiveness of GPAs, as part of the strategies being compared here, must allow for the long-term cost and outcome implications of the short-term effects of the drug. This 'extrapolation' is needed for two reasons. Firstly, many patients who are treated for ACS will continue to consume health service resources for their IHD for the remainder of their life, and the effectiveness of GPAs in the first 6 months may influence these costs. Secondly, in order to compare the cost-effectiveness of GPAs with other uses of health service resources (inside and outside cardiology), it is necessary to express the benefits of the drug in terms of a generic measure of health gain which can be compared across treatment areas. The most frequently used generic measure for this purpose is the quality-adjusted life-year (QALY). In order to provide a realistic estimate of the QALY impact of GPAs, the long-term implications for survival and health-related quality of life of the short-term (within 6 months) effects of the drugs need to be modelled.

The long-term (extrapolation) model estimates a future prognosis for patients who finish the short-term (six month) model in one of two disease states: those having experienced a non-fatal MI and those who have not but remain alive (IHD). That prognosis will include the possibility of patients experiencing further non-fatal MIs as well as dying for any reason. Hence, the extent to which the use of GPAs reduces the risk of death and non-fatal MI, relative to baseline, during the initial 6-month period will be translated into differences in long-term costs and QALYs on the basis of the long-term model.

2.5.2 Structure

The long-term model takes the form of a 4-state Markov process as illustrated in Figure 2. Depending on progress through the short-term model, patients enter the model either in the IHD state or the MI state. Patients entering the IHD state can experience a non-fatal MI, in which case

they move to the MI state for one year, after which they can die or move to the post-MI state. Patients experiencing any subsequent non-fatal MIs remain in the post-MI state, although the costs of such events are reflected in the model.

2.5.3 Transition probabilities

The transition probabilities used in the long-term model are shown in Table 5 and are based on a cycle length of one year. The annual probability of non-fatal MI and death is 1.8% and 7.5% respectively for IHD patients. The probability of death in the first year following non-fatal MI is 21%, and for subsequent years is 7.2%. These probabilities are assumed fixed with respect to time; in other words, the probabilities remain the same no matter how many cycles have elapsed. Further details justifying this assumption are provided below.

These data are based on two cohorts from the Nottingham Heart Attack Register (NHAR). The NHAR was initially set up in 1973 to audit the development of a new paramedic service in Nottingham. It has since been developed extensively, and now collects some 175 data points on each patient covering pre-hospital and in-hospital events, admission and discharge data, risk factor profiles and follow-up plans.[12,13] The medical notes of all patients admitted with any symptoms suggestive of a heart attack to either hospital in Nottingham are reviewed (approximately 15,000 per annum), and those in whom tests were done to confirm or refute this presumed diagnosis are entered onto the database (approximately 9000 per annum).

The two cohorts used in this analysis were from 1992 and 1998. The subgroup of patients employed were those classified on the NHAR as having an initial working diagnosis, made by the admitting clinician, of either typical ischaemic pain / angina on cardiac presentation (rule out MI), or patients who were suspected of having had an MI, but did not. Diagnostic coding was based on enzyme and ECG findings during the index admission. The 1992 cohort included 979

patients and had five years follow-up data for survival. Subsequent MIs between 1992 and 1997 in these patients were identified though the hospitals PAS systems, by searching for discharge codes of MI (ICD9=410). The 1998 cohort included 300 patients who were followed-up prospectively over a 21-month period for all hospital-based activity and survival. Subsequent MIs in this cohort were identified according to ECG and enzyme changes.

Transition probabilities have been calculated from the NHAR data using survival analysis techniques. These methods allowed for both censoring and differential follow-up between the two NHAR cohorts. The equality of the survivor functions (for death and MI) of the two separate cohorts was first tested using the log-rank statistic to determine whether there were any significant differences between the cohorts. No significant differences were found, and hence data from the two cohorts were pooled. From the data, 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 converted into annual transition probabilies (plus variance) using standard techniques.[14] The uncertainty associated with each transition probability was characterised by a log-normal distribution.[15] Due to the nature of the Markov model, it was only possible to consider the use of time dependent transition probabilities for transitions from the IHD state because, unlike other states, the time at which patients enter that state was know. Transitions from IHD, to death and MI, were modelled using a Weibull distribution formally to test the constant hazard assumption. The results demonstrated that the exponential model could not be rejected statistically and provided further justification for assuming a constant hazard in all transistions.

2.5.4 Costs in the long-term model

Costs have been incorporated into the Markov model by attaching a mean annual cost to the IHD, non-fatal MI and post-MI states. In addition, a cost is added when a patient dies. These state and transition costs relate to hospital resource use only, and are based on data collected

as part of the 1998 cohort of the NHAR. Within the register, all hospital activity was recorded for each patient, including tests and interventions undergone. This included hospital in-patient stays (cardiac and non-cardiac) and associated length of stay, day case and out-patient visits. Hospital in-patient stays, which included time on CCU, were recorded, although the amount of time spent in CCU was not. For the purpose of this analysis, we have assumed that patients spent half of their stay in CCU and half on a general cardiac ward. PCI, CABG and angiography rates were also included in the costings.

Average annual health state costs were calculated by aggregating the resources consumed by each patient in the 1998 NHAR cohort according to whether they would have fallen into the three non-dead states in the model: IHD, MI or Post MI. The resource use and costs used in the long-term model are detailed in Table 6. As for the short-term model, the uncertainty in resource use in the long-term model is characterised by beta distributions (to refect the proportion of patients utilising a particular resource item) and log-normal distributions (to reflect the intensity of use).

2.5.5 Quality-adjustment

In order to estimate QALYs, it is necessary to quality-adjust the period of time the average patient is alive within the model using an appropriate utility or preference score. Ideally, utility data are required which differentiate between the health status of patients in the IHD, MI and Post-MI states of the long-term model. A number of data sources exist providing estimates of utilities associated with IHD and MI. These include baseline utilities (based on responses to the EQ-5D) from patients randomised into trials evaluating alternative forms of management for stable angina[16] and direct utility assessments as part of trials looking at thrombolytic therapies.[17] However, none of these sources provides separate estimates of the three non-dead states in the long-term model based on consistent valuation methods. In the base-case analysis, it has been assumed that the health states of all patients who are alive are valued, on average, at the same utility regardless of which of health

state they are in. For the base-case analysis, this is assumed to be 0.8 with a standard deviation of 0.09, which was synthesised from available estimates using Bayesian methods for a re-analysis of the cost-effectiveness of alternative thrombolytic therapies using data from the GUSTO trial.[18]

2.5 Analytical methods

The overall model is run for a period of 50 cycles (equivalent to 50 years), after which the vast majority of patients will have died in the model. Therefore, the mean life-years and QALYs per patient can be calculated for each strategy, as well as the mean lifetime costs. The age of the patients in the model is not incoporated as an explicit parameter, so the age to which the analysis relates will reflect that of the patients in the cohorts used to populate the model. In PRAIS-UK, the mean age of patients was 66 years; in the NHAR the mean age of the two cohorts was 68 years. In the trials of GPAs in ACS, the mean age of patients at baseline ranges between 63 and 65 years.[4]

Similarly, the model does not formally include the results of any particular sub-groups of patients, and therefore reflects the balance of baseline features in the trials, PRAIS-UK and the NHAR. These data sources include a mix of patients with and without high-risk features such as positive troponins and ST depression, and the model's results relate to the average effects across all sub-groups.

The results of the model will be presented in two ways. Firstly, mean lifetime costs and QALYs of the four strategies will be presented and their cost-effectiveness compared, estimating incremental cost-effectiveness ratios as appropriate, using standard decision rules.[19] The advantage of entering input parameters as uncertain variables is that this uncertainty can be propogated through the model and reflected in model outputs. To present the uncertainty in the cost-effectiveness of the alternative strategies, cost-effectiveness acceptability curves (CEACs) are used.[20,21] These show

the probability that each strategy is more cost-effective than the other three using alternative values for the maximum value the health service is willing to pay for an additional QALY in these patients.

The model has been developed in Excel with the Crystal Ball 'add-on'. The Monte-carlo simulation was run for 10,000 iterations. The model is run several times, once for a base-case analysis and then for a number of alternative sensitivity analyses. The random number seed was kept constant in all sensitivity analyses. The sensitivity analyses have been divided into three main sections to assess the robustness of the results of the base-case model to the use of alternative assumptions in the following areas:

(1) variation in the sources of data used to populate the base-case model;

(2) variation in the baseline event rates using non-UK specific sources of data

(3) the inclusion of additional strategies to those considered in the base-case model.

Table 7 summarises the key assumptions used in the base-case analysis and how these have been varied in the sensitivity analyses.

3. Results

3.1 Results of the short-term model

Table 8 details the results of the short-term model. Despite the relative risks of death and non-fatal MI being the lowest for Strategy 3, Strategy 1 yields the lowest probability of leaving the short term model in either the non-fatal MI or death health state. This is because the relative risks associated with Strategy 3 are applied to a relatively small baseline event risk. Strategy 2 has a higher probability of death than the baseline. This reflects the increased, albeit small, relative risk of death associated with Strategy 2. Strategy 1 is the most expensive option, costing an average of £2,526 per patient as opposed to Strategies 2 and 3, which cost around £2,130. This is because the drug

costs are incurred by all patients, and not only those receiving PCI during the acute period. The average GPA costs for Strategies 1-3 were £439, £353 and £989 respectively.

3.2 Base-case results of the long-term model

Table 9 presents the analysis of the incremental cost-effectiveness ratio (ICER) for the base-case analysis. The ICER examines the additional costs that one strategy incurrs over another and compares this with the additional benefits. When more than two programmes are being compared the ICERs are calculated using the following process:[19]

i) The strategies are ranked in terms of cost (from the least expensive to the most costly).

ii) If a strategy is more expensive and less effective than the previous strategy, then this strategy is said to be dominanted and is excluded from the calculation of the ICERs.

iii) The ICERs are calculated for each successive alternative, from the cheapest to the most costly. If the ICER for a given strategy is higher than that of the next more effective strategy, then this strategy is ruled out on the basis of extended dominance.

iv) Finally, the ICERs are recalculated excluding any strategies that are ruled out using the notions of dominance and extended dominance.

Applying this process to the base-case results, Strategy 2 is dominated by Strategy 3 as it is both more expensive and less effective. Strategy 3 can also be ruled out by extended dominance because the ICER of the next most effective strategy (Strategy 1) is lower than that of Strategy 3. This process is illustrated graphically in Figure 3 by plotting the mean costs and QALYs of each strategy. The ICER is given by the slope of the line joining any two strategies. Strategies 1 and 4 can be joined by a line with a lower slope (and hence lower ICER) than the line connecting Strategies 3 and 4. The options under consideration in the base-case analysis of the ICER are, therefore, Strategies 1 and 4. The ICER of Strategy 1 compared with Strategy 4 is £5,738 per

QALY. Hence the results of the base-case analysis indicate that Strategy 1 is the optimal decision provided that the decision-maker is prepared to pay at least this amount per additional QALY.

Although Strategy 3 is ruled out by extended dominance, the ICER of this strategy in relation to Strategy 4 has been included for comparative purposes. The potential relevance of this comparison is covered in the discussion section below. In the base-case analysis, the ICER for Strategy 3 is £25,811 per QALY.

While the results of the ICER can be used to determine the optimal decision based on a comparison of mean costs and QALYs, they do not incorporate the uncertainty surrounding this decision. Figure 3 presents the base-case results in the form of cost-effectiveneness acceptibity curves (CEACs) for each strategy. These curves detail the probability that each strategy is cost-effective (1 – error probability) over a range of potential maximum values that the health service is prepared to pay for an additional QALY (selected values are presented in the final three columns of Table 9). The results of the CEACs incorporate the uncertainty within the model in relation to both the estimates of mean costs and QALYs, and in the maximum willingness to pay for an additional QALY. The CEACs demonstrate that the probability that Strategy 1 is cost-effective increases as the maximum willingness to pay increases: if society is prepared to pay £10,000 for an additional QALY, the probability that Strategy 1 is cost effective is around 82%, increasing to 95% if the maximum willingness to pay is £50,000. Consequently, the results from the base-case analysis demonstrate that if the health service is prepared to pay over £5,738 per QALY then Strategy 1 is always the optimal decision.

3.3 Results of the sensitivity analyses to explore the impact of alternative assumptions relating to the sources of data used in the base-case model

Table 10 details the results of each individual sensitivity analysis undertaken to assess the robustness to the base-case model results to variation in the sources of data used to populate the base-case model. None of the sensitivity analyses on parameters used to model the four GPA strategies results in a change of the relative ordering of the strategies in terms of mean costs and QALYs. In addition, in each of the analyses, Strategy 2 is always dominated, and Strategy 3 is always ruled out because of extended dominance. Consequently, the calculation of the ICER in Table 10 is always based on a comparison of Strategy 1 with Strategy 4. Although Strategy 3 is ruled out by extended dominance, the ICER of Strategy 3 in relation to Strategy 4 is once again presented for comparative purposes.

Reducing the time horizon of the model to 5 years results in an almost two-fold increase in the ICER for Strategy 1 to £11,671, and reduces the probability that this strategy is cost-effective from 82% to 35% at a maximum WTP of £10,000 per QALY. This analysis clearly demonstrates the benefit of including the longer-term impact of costs and outcome in the base-case analysis.

The sensitivity analysis on the trials included in the pooled estimates of relative risks of GPAs has little effect on the ICER for Strategy 1. The exclusion of those trials which did not report results up to the time-frame of the short-term model (6 months) had the most significant impact, increasing the ICER to £8,915 per QALY. This increase is primarily driven by the less favourable risk reduction associated with death (0.89; 95% CI 0.63 –1.25) in comparison to the base-case analysis (0.84; 95% CI = 0.71 – 0.98). The impact of only including the pooled results of the trials evaluating eptifibatide and tirofiban (considered to be the most likely treatments to be offerered in the context of Strategy 1 in the NHS) increased the ICER marginally to £5,824 per QALY.

The effect of using life-years gained as an outcome measure (equivalent to assuming utility of 1 for the IHD and non-fatal MI states) results in a reduction of the ICER to £4,605, while reducing the

utility weight for these states from 0.8 in the base case to 0.65 increased the ratio to £7,005 per QALY. The effect of changing the base-case assumption of the same utility associated with the IHD and MI states (by applying a decrement of 0.05 to the utility of the MI and post MI states) reduces the base-case ICER by only £8 to £5,730.

The results of the base-case model were based on the baseline risks derived by combining two separarate data sources (PRAIS-UK and the Leeds PCI audit). Separate sensitivity analysis using the individual results of the separate data sources had minimal impact on the ICER of Strategy 1.

To expore the impact of the assumptions used to derive the pooled estimates of relative risk for Strategy 1, a separate sensitivity analysis was underaken using the results of a recently published patient-level meta-analysis of all major randomised clinical trials in patients who were not routinely scheduled to undergo early coronary revascularisation (incorporating the majority of trials used in Strategy 1).[22] Access to the patient level data enabled the authors' to estimate the pooled relative risks for all patients randomised to any GPA treatment (n=18,297) versus control (n=13,105) at 30 days. By including all treatment arms (e.g. both 24 and 48 hour infusion for abciximab), rather than the treatment arms which were deemed most likely to be applied within the context of the NHS, the resulting relative risks are potentially a more conservative estimate than those applied within the base-case model (e.g. the pooled odds ratio for death and non-fatal MI were 0.91 [95% CI = 0.81-1.03] and 0.92 [95% CI=0.85-1] respectively, as opposed to the base-case estimates of relative risks of 0.84 [95% CI = 0.71-0.98] and 0.94 [95% CI=0.87-1.02]). Applying these estimates to Strategy 1 increased the ICER to £10,343, although Strategies 2 and 3 were still ruled out by dominance and extended dominance, respectively.

Although the sensitivity analysis indicates that the ICER of Strategy 1 is relatively robust to changes in the assumptions of the base-case model, the ICER of Strategy 3 in relation to Strategy 4 is more

sensitive, although Strategy 3 is always subject to extended dominance relative to Strategy 1. The impact of reducing the GPA costs associated with Strategy 3, by assuming an average cost of eptifibatide and tirofiban (as opposed to abciximab), reduces the ICER to just over £17,000 in comparison to £25,811 in the base-case analysis. This sensitivity analysis assumes that the relative risk reductions for these two small-molecule GPAs is equivalent to the pooled relative risk reductions for all Strategy 3 trials (including abciximab). However, a separate analysis which combines the average cost of eptifibatide and tirofiban with the pooled results of only those trials relating to these small molecule drugs reduced the ICER to £19,786 per QALY. While these results indicate that the ICER of Strategy 3 is sensitive to the selection of trials, it is important to treat these results with extreme caution. In particular, a direct comparison of the relative cost-effectiveness of small versus large molecule GPAs for Strategy 3 should not be made on the basis of the data presented here. The results presented are used to illustrate the sensitivity of the results of Strategy 3 to the assumptions made in the base-case analysis. The exclusion of head to head trials from the model precludes a direct comparison of the cost-effectiveness of alternative drugs. Consequently, the differences noted in the sensitivity analysis may actually reflect important clinical differences in the characteristics of patients enrolled in the trials, rather than actual differences in the cost-effectiveness of alternative drugs.

Given the potential heterogeneity of patients enrolled in the PCI trials, a separate sensitivity analysis was undertaken to explore the potential impact of the use of GPA in a subgroup of patients with unstable angina. Due to a lack of available data in this specific subgroup, these relative risk adjustments were only possible for Strategy 3. Using the base-case GPA costs for Strategy 3 (abciximab), but applying relative risk data from the subgroup analysis of unstable angina patients within EPIC (E. Topol, personal communication) leads to a more favourable ICER (£13,364). Despite the increase in relative risk associated with adverse events reported in the EPIC study, the

results are more favourable due to the considerable reduction in the risk of non-fatal MI and death reported in this subgroup analysis.

The sensitivity analyses reported above for Strategy 3 are the best-case scenarios for this strategy. The remaining sensitivity analyses reported in Table 10 indicate the the ICER for Strategy 3 is increased to £38,350 when only trials reporting at 6 months are included, and £45,308 when the time horizon for the model is constrained to 5 years.

3.4 Sensitivity analyses using alternative sources of baseline data

Since PRAIS-UK was undertaken in 1998-99, some aspects of the management of these patients – other than the use of GPAs - may have changed, such as a greater use of PCI during the acute period. Although one of the previous sensitivity analyses modelled an increased rate of PCI by simply increasing the proportion of patients receiving an acute PCI, this analysis did not take into account possible alterations to the case-mix of patients undergoing PCI (and hence to the baseline event data for outcomes such as death, non-fatal MI etc). To address these limitations, the model has been re-run using baseline event data from the recently published patient-level meta-analysis undertaken by Boersma et al.

In addition to the potential uncertainty in relation to the baseline data, two further sensitivity analyses have been undertaken to examine the robustness of the relative risk estimates applied in Strategy 1. In the base-case model the same relative risk estimates are applied to all patients undergoing medical management, regardless of any subsequent interventions (e.g. acute PCI/no acute PCI) or pre-specified indicators of high risk (e.g. age, diabetes, ST depression or positive baseline troponin levels). However, the recent meta-analysis undertaken by Boersma et al provides evidence to suggest that the treatment effect of GPAs as part of initial medical management may differ depending on these factors. Although these estimates of relative risks

do not represent strictly randomised comparisons, they may be considered broadly indicative of the potential differential in the effectiveness of GPAs, as part of medical management, across various subgroups.

3.4.1 Methods used to derive new baseline event rates

New baseline event probabilities were derived from the control group data of the Boersma et al patient level meta-analysis. Since the meta-analysis only reported event rates at 30 days, an extrapolation was required in order to apply these data to our short-term decision model since the model requires event rates at 6 months. Details of the assumptions used are provided below.

In the meta-analysis, patients were categorised to the acute PCI, acute CABG and no acute intervention pathways depending on whether patients had undergone an intervention within 5 days of randomisation. Using this data the rate of PCI increases from 5% in the baseline model to approximately 15% using the new data (the rate of acute CABG increased only marginally from 4.5% to 4.9%).

The 30-day death and non-fatal MI event data reported in the Boersma paper were extrapolated from 30-days to 6 months, using the predicted hazard of these events estimated from the Strategy 1 trials reporting at both time intervals. The probabilities of death and non-fatal MI at 6 months, conditional on surviving to 30-days without an event, were derived from the Strategy 1 trial data. These conditional probabilities were then applied to the relevant numbers of patients in the acute PCI/acute CABG/no acute intervention groups to determine the expected number of events between 30-days and 6 months. These data were then combined with the 30-day data to calculate the total expected number of events between baseline and 6 months. Uncertainty in these event rates was reflected in the assigned beta distributions.

Table 11 summarises the baseline event rates for death and NFMI using the alternative data sources for the 3 patient groups considered in the short-term model. Both the 30-day event data reported in the Boersma paper and the extrapolated event data at 6 months have been provided to illustrate the impact of the assumptions used in the extrapolation on each of the relevant events. The effect of changing the source of baseline event data appears to have the largest impact on the event rates reported in the acute PCI group: the rate of death increases from 3.3%, using the UK specific baseline data, to 5.62% using the meta-analysis. Similarly the rate of NFMI rises from 3.6% to 19.27%. In both data sources the death rate in the acute PCI group at 6 months is lower than in patients who do not undergo acute revascularisation (although this differential is reduced using the new baseline data). However, the rate of NFMI is now higher in the acute PCI group using the new baseline data (19.27% vs. 13.43% compared to 3.6% vs. 4.7%).

3.4.2 Results of sensitivity analyses using alternative sources of baseline data

Two separate sensitivity analysis have been undertaken using the new baseline event data. The first analysis applies the same relative risks as in the base case from the main report. The second analysis applies the relative risks reported in the Boersma paper to Strategy 1 and uses separate relative risks for those patients undergoing/not undergoing acute PCI (i.e. PCI within 5 days). Table 12 provides details of the relative risks used in the two separate analyses for Strategy 1.

None of the two additional sensitivity analyses using the revised baseline event data results in a change of the relative ordering of the strategies in terms of mean costs and QALYs. As before, in each of the analyses, Strategy 2 is dominated, and Strategy 3 is ruled out because of extended dominance. Consequently, the calculation of the ICER in Table 13 is based on a comparison of Strategy 1 with Strategy 4. Although Strategy 3 is ruled out by extended dominance, the ICER of Strategy 3 in relation to Strategy 4 continues to be presented for

comparative purposes. The results of each of the sensitivity analyses are described in further detail below.

The impact of changing the baseline event rates, but not the relative risks, reduces the ICER of Strategy 1 from £5,738 to £5,753. The slight increase in uncertainty surrounding this decision is reflected in the lower probability the Strategy 1 is cost-effective in comparison to the base-case estimates.

Although the revised baseline event rates have minimal impact on the ICER of Strategy 1 and do not appear to alter the optimal adoption decision, they do have a significant impact on the comparison between Strategies 3 and 4. The ICER of Strategy 3 relative to Strategy 4 falls from £25,811 in the base-case model to £11,160 using the revised baseline event data. However, Strategy 3 is still ruled out by Strategy 1 on the basis of extended dominance.

The impact of changing both the baseline event rates and using separate relative risks for acute PCI/no acute PCI for Strategy 1 has a much greater impact on the results. The ICER for Strategy 1 increases from £5,667 to £9,609. There is also greater uncertainty associated with the optimal decision. Since the revised assumptions for this sensitivity analysis only alter the relative risks applied to Strategy 1, the ICER for Strategy 3 in comparison with Strategy 4 remains the same. However, as in the previous sensitivity analysis, Strategy 3 is still ruled out by Strategy 1 by extended dominance.

3.5 Results of the sensitivity analyses including alternative strategies to those considered in the base-case model

3.5.1 The use of GPAs as part of initial medical management in high-risk ACS patients only

An additional subgroup analysis in Boersma reported on the rate of death and non-fatal myocardial according to baseline cardiac troponin concentration. The results from Boersma demonstrated a significant differential treatment effect between patients with positive and negative troponins. The use of GPAs in patients with positive troponins was associated with a 15% reduction in the relative risk of death or non-fatal myocardial infarction compared with placebo; in patients with negative troponins there was no associated risk reduction. This subgroup analysis indicates that GPAs as part of initial medical management are potentially only effective in high-risk patients. Approximately 45% of those patients with data on baseline cardiac troponin had levels of troponin T or I $\geq$ 0.1 μg/L (positive troponin).

The results from the troponin subgroup analysis indicate that an alternative strategy based on the medical management of ACS patients should be considered in conjunction with the four existing strategies. In this alternative strategy only patients identified at *high-risk* are given GPAs as part of initial medical management. Due to limitations in the reporting of subsequent interventions according to baseline troponin levels it was not possible to populate the short-term decision model using the event data reported in Boersma. Similarly due to the lack of available baseline troponin data reported in PRAIS-UK (troponin levels were only assessed in 4.6% of patients) it was not practical to use PRAIS-UK baseline event data according to troponin status and then apply the relevant relative risks reported in Boersma. Given these restrictions, it was decided that the most appropriate method would be to use other non-troponin based markers of high-risk to define a high and low-risk population using data from PRAIS-UK. The relative risks reported in Boersma based on positive troponin status are then applied to the high-risk subgroup defined according to age, diabetes and ST-depression. No GPA administration, and no relative risk reductions are applied to low-risk Strategy 1 patients, including those undergoing PCI.

Using data from PRAIS-UK, high-risk status was determined by the presence of at least one of the following characteristics: age ≥70, ST-depression or diabetes. Using these risk markers approximately 58% of patients were identified as being at high risk.

The inclusion of an alternative medical management strategy, in which the use of GPAs and the relevant relative risks are applied to high-risk patients only, has a significant impact on the results from the base-case model. The results presented in Table 14 indicate that this alternative strategy applied to high-risk patients is potentially more cost-effective than either the use of GPAs in the medical management of all ACS patients or the use of GPAs alongside PCI in ACS. The ICER for this new strategy (Strategy 1 – high risk patients only) is £3,966. In this revised model, Strategies 2 and 3 are still ruled out by dominance and extended dominance respectively. Although the average QALY is higher using GPAs in all ACS patients (Strategy 1 - all patients), there is only a small additional QALY benefit for use in all patients compared to use in high-risk patients alone; the cost per additional QALY for this additional benefit is £91,000.

Despite these findings care should be exercised in the interpretation of these results. Due to limitations in the reporting of baseline data, it was not possible to provide a consistent basis for the definition of high-risk. Consequently the relative risk reductions reported in troponin positive patients reported in Boersma may not accurately represent the actual relative risk differences in the high-risk group defined according to age, diabetes and ST-depression from PRAIS.

3.5.2 Clopidogrel

The recent publication of the results of the CURE trial suggests that the antiplatelet agent clopidogrel has beneficial effects in patients with ACS without ST elevation. Although the cost-effectiveness of clopidogrel has not been assessed in relation to conventional care, the overall cost of £348.98 based on the regimen used in the CURE trial (300mg immediately, followed by 75 mg once daily and a mean duration of treatment of 9 months) indicates that this agent may be a cost-

effective alternative to the use of GPAs. To explore the potential cost-effectiveness of this agent in comparison to the strategies considered in the base-case model, clopidogrel was included as a fifth alternative strategy in the sensitivity analysis based on the results from the CURE trial.[1]
The relative risks applied in the model based on the CURE trial were as follows: all-cause death (0.92, 95% CI=0.79 - 1.05); NFMI (0.77, 95% CI=0.67 - 0.89); all revascularisation (0.92, 95% CI=0.85 - 0.98) and major bleeding (1.38, 95% CI=1.13 - 1.67).

Using the same assumptions applied in the base-case model, clopidogrel is ruled out through extended dominance by Strategy 1. However, when the more conservative relative risk estimates derived from the patient-level meta-analysis[22] are applied to Strategy 1, clopidogrel now appears to be the optimal strategy, ruling out Strategies 1 and 2 by dominance and Strategy 3 by extended dominance. The resulting ICER for clopidogrel in comparison to Strategy 4 is £6,978.

The results of the base-case model appear highly sensitive to the inclusion of clopidogrel as a fifth alternative strategy. However, since the trials assessing the use of clopidogrel were not identified as part of the overall systematic review, these results should be interpreted with some caution.

4. Discussion

4.1 Summary of results

The results here suggest that Strategy 1 – the use of GPAs as part of initial medical management – is the most cost-effective use of these agents in ACS patients. This finding is robust to the uncertainty in the sources of data used in the base-case model and in the baseline event data used to populate the short-term model. The maximum cost per QALY/life-year gained emerging from the analysis is £11,671 compared to Strategy 4 (standard therapy without GPAs). Strategies 2 and 3 are subject to dominance and extended dominance, respectively, in the base-case and sensitivity analyses.

The results do appear to be potentially sensitive to the inclusion of additional comparators not considered in the base-case model. The inclusion of an alternative medical management strategy, in which the use of GPAs and the relevant relative risks are only applied to high-risk patients, suggests that this strategy is potentially the most cost-effective strategy. Although the use of GPAs in all ACS patients is a more effective strategy, the small incremental gain in outcome achieved by administering GPAs in low-risk patients does not appear to provide good value for money. Despite the potential importance of this finding, the limitations in the reporting of baseline data meant that it was not possible to provide a consistent basis for the definition of high-risk using available data sources. Consequently it is difficult to either assess the reliability of this analysis or to identify the most appropriate markers of "high-risk". However, the importance of this analysis indicates that further analysis of a strategy of more restricted use of GPAs in the medical management of ACS patients is required. Finally, the sensitivity of the results to the inclusion of clopidogrel as an alternative to the use of GPAs indicates that further research is required to examine the relative cost-effectiveness of this agent in a more systematic manner than was achieved in this analysis which has focussed on different strategies related to the use of GPAs.

The results of the decision model should not be seen as contradictory to the findings of the systematic review.[22] Although the systematic review has highlighted the uncertainty in the effectiveness of GPAs in the medical management ACS (caused in part by the conflicting results of some of the trials, in particular GUSTO IV), no attempt was made formally to synthesise either the effectiveness or cost-effectiveness data from the studies. In such a scenario, it is difficult to make an overall assessment of the potential cost-effectiveness of this strategy without consideration of both the combined weight of evidence from the trials and the applicability of the results in the context of current UK practice. The results of the decision model clearly demonstrate that when these additional factors are considered, the use of GPAs as medical management appears to be the most cost-effective strategy, despite the uncertainty in effectiveness reported across individual trials.

In terms of effectiveness, these results are supported by the patient-level meta analysis of the effectiveness of GPAs referred to above.[22] The results of this analysis support the conclusion that GPAs reduce the incidence of death and myocardial infarction in this group of patients. The model presented in this report provides significant additional information in relation to the likely cost-effectiveness of implementing this strategy in the context of the NHS.

4.2 Comparison with the results of other studies

There have been few attempts to assess the cost-effectiveness of GPAs in ACS in a UK context. In part, this has been due to the fact that the trials of these agents have mainly been undertaken on non-UK patients, so absolute treatment effects and resource use from these trials may not generalise to the UK. The only study identified in the review[4] of economic studies of GPAs in the medical management of ACS, which estimated cost per life-year gained in UK patients, was contained in the Schering Plough submission to the earlier rapid review in 2000.[23] That study estimated the cost-effectiveness of eptifibatide using resource use data from both UK patients (n=429) and all Western European (n=3697) patients in the multi-national PURSUIT trial, and reported both separately. Unit costs were taken from UK sources. The effectiveness of eptifibatide was based on all Western European patients: a 0.37% risk difference for survival and a 1.01% risk difference for MI-free survival at 6 months favouring eptifibatide. Using the modelling approach and life expectancy data detailed in a US paper by Mark *et al* using similar methods,[24] life-years gained were estimated. Using cost data from UK patients, the cost-effectiveness analysis showed that treatment with eptifibatide was dominant. When all Western European PURSUIT patients were used to calculate cost, the ICER varied from £8,179 to £11,079 per additional life-year depending on the discount rate used for survival.

The study presented here differs from the Schering Plough analysis in a number of important ways, including the fact that the model reported here includes a set of UK-specific baseline event rates

and uses relative risks from all available trials rather than just PURSUIT. However, the incremental cost-effectiveness ratios for Strategy 1 here are similar to those in the Schering Plough submission: £4,605 to £10,343 based on a lifetime analysis here compared to £8,179 to £11,079 in the submission. No other economic evaluation of GPAs in medical management of ACS identified in the review presented costs per life-year or QALY gained for a UK setting.

The earlier and updated systematic reviews identified a number of economic studies evaluating the cost-effectiveness of GPAs alongside PCI.[3,4] These studies included data from several trials which randomised a range of types of patient. Again, few of these economic studies presented costs per life-year or QALY gained, nor did they apply their results directly to UK practice. The analysis which was closest to achieving these characteristics was the cost-effectiveness of abciximab alongside PCI as part of Eli Lilly's submission to the 2000 review undertaken by NICE.[25] The analysis used absolute reductions in the rate of clinical events observed in EPIC, EPILOG and EPISTENT at 30 days and 1 year and valued these using UK unit costs. To estimate the impact of therapy on life-years gained, it was assumed that those patients in the trial surviving the first year would live for a further 15 years. No differential costs were assumed as part of this longer-term extrapolation. QALYs were estimated assuming a quality-adjustment factor of 0.8 for all living patients. These assumptions generated estimates of cost per life-year gained for abciximab of £3,554 for EPISTENT, £6,247 for EPILOG and £12,421 for EPIC. The authors argued that cost-effectiveness results based on EPISTENT and EPILOG are the most relevant to UK practice, and sensitivity analyses revealed that the maximum cost per life-year for EPILOG was £13,191 and £11,196 for EPISTENT (assuming a lower reduction in mortality for both trials). Cost per QALY estimates ranged between £6,941 and £9,053 for EPILOG and £3,949 and £5,151 for EPISTENT, although this range did not include the full sensitivity analysis which generated the range of cost per life-year estimates.

The Eli Lilly submission did not include a medical management comparator similar to Strategy 1 here, and it did not share the focus of this paper on ACS patients. However, the comparisons presented in the submission can be considered broadly equivalent to those between Strategies 3 and 4 in the model presented here. The ICERs estimated here for Strategy 3 (relative to Strategy 4) with abciximab range from £11,160 to £45,308 per QALY gained, with the lower value based on relative risks from a sub-group analysis of unstable angina patients in the EPIC trial, and the higher value based on constraining the extrapolation model to 5 years as opposed to 50 years in the baseline. Therefore, the cost-effectiveness ratios presented here are generally higher than those in the Eli Lilly analysis, which is likely to be due to the fact that the analysis reported here used absolute baseline event probabilities from UK sources rather than the control groups of the trials.

4.3 Limitations of the model

The model presented here has some potential limitations. The first is that ACS includes a range of patients with important different characteristics, which are likely to affect prognosis. For example, the medical management trials, which provide the relative risks for Strategy 1 of the model, include patients with a variety of ages, with and without ST depression and with and without troponin positivity. The trials evaluating GPAs alongside PCI include an even greater range of patients, as most do not just focus on ACS patients, and some include patients with stable angina having elective procedures or patients having primary PCI following an acute MI. The relative risks used here to model Strategy 3 were taken from trials that included any patients with unstable angina, but it is recognised that the resulting pooled estimates of relative risk will reflect considerable heterogeneity. The only trial giving results in a sub-group of unstable angina patients (the EPIC trial) generates the lowest cost per QALY for Strategy 3 (£13,364), although it is still subject to extended dominance when Strategy 1 is included.

A second limitation of the model relates to the data used to estimate transition probabilities and resource use for the long-term extrapolation model. As for PRAIS-UK, the NHAR was identified as the best source of data on the resource use and long-term prognosis of patients who had survived a period of 6 months after ACS with or without a non-fatal MI. However, the maximum follow-up for these patients (based on the 1992 cohort) was only 5 years. Despite these assumptions, the average life expectancy of 9.65 years predicted by the extrapolation model does not appear unreasonable when compared to the UK life table data for the life expectancy of 66 year olds (14.73 years for males and 17.93 years for females) based on data for the years 1998-2000.

In addition to these specific limitations of the observational cohort data, there remains the more general issue of whether the results of the trials are generalisable to the observational data used in the model. Both cohorts were carefully selected to minimise this potential problem (on the basis that they represent the best sources of information relating to the management of ACS patients in UK). However, the different selection processes used in both the trials and observational cohorts inevitably means that the results should be treated with some caution.

A further limitation of the model concerns the choice of outcome measures applied in the short-term model that are subsequently used to define the disease states for the extrapolation exercise. The outcomes of interest in the model are confined to death, non-fatal MI and IHD. However, the results of the systematic review of trials of medical management indicate that the use of GPAs has an additional benefit in reducing recurrent ischaemia in patients with IHD. It has not been possible formally to incorporate this additional benefit for the following reasons: (i) both the definition and the actual reporting of recurrent ischaemia is inconsistent in Strategy 1 trials; (ii) there is no information on recurrent ischaemia in relation to Strategy 3 trials due to the inclusion of non-ACS patients; and (iii) it is not possible to reflect the potentially different long-term prognosis, quality of life and costs from the observational cohort data in patients with and

without recurrent ischaemia. If the use of GPAs has a significant impact on the rates of recurrent ischaemia, then the cost-effectiveness estimates presented here will be conservative estimates if there are important long-term differences between patients with IHD who experience recurrent ischaemia and those who do not.

The final limitation of the model concerns the recent evidence of the effectiveness of clopidogrel from the CURE trial.[1] The current baseline used in the model for Strategy 4 asumes that the appropriate comparator for the use of GPAs is the use of standard therapies (e.g. heparin (intravenous or subcutaneous), aspirin, nitrates and analgesia). If the use of clopidogrel (plus standard therapy) compared to standard therapy alone, is shown to be cost-effective, then the current baseline comparator used in the model may be inappropriate. Although the potenital implications of the use of clopigogrel have been explored in the sensitivity analysis, it is clear that further consideration using a more systematic approach to data collection is required.

5. Conclusions

The model presented here indicates that the most cost-effective use of GPAs in ACS is the medical management of patients. The incremental cost per QALY gained of medical management is estimated at between £4,605 to £11,671. The strategy of using GPAs only as an adjunct to PCI was found to be economically inferior to medical management under all scenarios. If this strategy is compared to standard practice (without GPAs), ICERs range between £11,160 to £45,308 per QALY gained when the cost of abciximab is used.

Table 1. Baseline probabilities used in the short-term model taken from PRAIS-UK and Leeds audit. Node labels relate to the decision tree in Figure 1.

Node	Description	Probability	Parameters of the beta distribution	
			α	β
A	Acute PCI	0.05	53	980
B	Repeat revasc.	0.048	8	157
C	Repeat revasc. PCI	1.00	-	-
D	Death (revasc. PCI)	0.00	0.01	7.99
E	MI (revasc. PCI)	0.13	1	7
F	Death (revasc. CABG)	0.00	-	-
G	MI (revasc. CABG)	0.00	-	-
H	Death (no repeat revasc.)	0.03	5	152
I	MI (no repeat revasc.)	0.03	5	147
J	CABG	0.05	47	933
K	Death (CABG)	0.11	5	42
L	MI (CABG)	0.07	3	39
M	6 month revasc	0.05	48	885
N	6 month revasc PCI	0.48	23	25
O	Death (6 month revasc. PCI)	0.09	2	21
P	MI (6-month revasc. PCI)	0.10	2	19
Q	Death (6-month revasc. CABG)	0.00	0.01	24.99
R	MI (6-month revasc. CABG)	0.16	4	21
S	Death (no revasc.)	0.08	68	817
T	MI (no revasc.)	0.05	40	777
	Baseline risk of gastrointestinal bleeding:			
	(i) Undergoing PCI in acute period	0.00	0.01	52.99
	(ii) Undergoing CABG in acute period	0.02	1	46
	(iii) No initial revasc.	0.01	12	921

Table 2. Resource use associated with the short-term model taken from PRAIS-UK

Item of resource use	**Probability**	**Parameters of the beta distribution**	
		α	β
Angiography when:			
(i) Undergoing PCI in acute period	0.96	51	2
(ii) Undergoing CABG in acute period	0.81	38	9
(iii) No initial revascularisation	0.21	193	740
CCU stay when:			
(i) Undergoing PCI in acute period	0.38	20	33
(ii) Undergoing CABG in acute period	0.61	28	18
(iii) No initial revascularisation	0.41	375	543
	Mean value	**Standard deviation**	
Length of in-patient stay			
(i) Undergoing PCI in acute period	10.30	8.04	
(ii) Undergoing CABG in acute period	15.28	12.32	
(iii) No initial revascularisation	5.45	4.78	
Length of CCU stay			
(i) Undergoing PCI in acute period	3.70	4.12	
(ii) Undergoing CABG in acute period	4.71	6.61	
(iii) No initial revascularisation	2.11	1.95	

Table 3. Unit costs used in the analysis

Unit cost	Unit	Base-case value	Source
PCI	Procedure	£1,410.04	[9]
CABG	Procedure	£4,902.22	[9]
Repeat PCI	Per diem	£2,976	[9]
Angiogram	Procedure	£748.25	[9]
Cardiac ward	Day	£157.47	[9]
Non cardiac ward	Day	£244.00	[9]
CCU	Day	£459.04	[9]
Outpatient	Visit	£59.70	[9]
Cardiac day case	Visit	£108.58	[9]
Non cardiac day case	Visit	£182.00	[9]
Guidewire	Item	£61.75	[9]
Stent	Item	£599.01	[9]
Guiding catheter	Item	£37.05	[9]
Blood	Unit	£85.00	Specific NHS trust
Full blood count	Item	£4.00	Specific NHS trust
Endoscopy	Item	£246.00	[26]
Tirofiban	12.5mg vial	£146.11 (+VAT)	[11]
Eptifibatide	20mg vial	£15.54 (+ VAT)	[11]
Eptifibatide	75mg vial	£48.84 (+ VAT)	[11]
Abciximab	10mg vial	£280.00 (+VAT)	[11]
Omeprazole	28 tab pack 10mg	£18.91	[11]
Clopidogrel	28 tab pack 75mg	£35.31	[11]

Table 4. Relative risks from the trials used in the model[a]

Trial	Options (n)	Relative risks (95% confidence intervals)					
		Non-fatal MI	**Death**	**Revasc**[b]	**PCI**[b]	**CABG**[b]	**GI Bleed**
Strategy 1	GUSTO IV Abciximab[c] (7800)	1.10 (0.88, 1.38)	0.87 (0.65, 1.14)	0.94 (0.87, 1.02)	0.92 (0.82, 1.03)	0.98 (0.84, 1.14)	2.29 (0.94, 5.56)
	PARAGON A Lamifiban (2282)	0.72 (0.43, 1.22)	0.72 (0.43, 1.22)	NR	0.75 (0.55, 1.01)	0.92 (0.64, 1.32)	0.67 (0.14, 3.30)
	PARAGON B Lamifiban[c] (5225)	0.90 (0.76, 1.06)	0.87 (0.64, 1.18)	NR	1.04 (0.95, 1.13)	1.00 (0.88, 1.14)	1.46 (0.86, 2.47)
	PRISM Tirofiban[c] (3232)	0.96 (0.66, 1.40)	0.64 (0.42, 0.96)	NR	0.99 (0.87, 1.13)	1.10 (0.95, 1.28)	1.00 (0.32, 3.09)
	PRISM PLUS Tirofiban (1915)	0.96 (0.66, 1.40)	0.79 (0.58, 1.07)	NR	1.04 (0.90, 1.21)	1.01 (0.85, 1.21)	1.33 (0.79, 2.25)
	PURSUIT Eptifibatide[c] (9461)	0.93 (0.84, 1.04)	0.94 (0.48, 1.87)	NR	0.94 (0.87, 1.01)	0.97 (0.88, 1.07)	1.15 (1.02, 1.30)
	Theroux et al Lamifiban[c] (365)	0.20 (0.01, 3.37)	0.60 (0.07, 4.99)	NR	NR	NR	18.00 (2.23, 145.14)
Pooled[d]		**0.94 (0.87, 1.02)**	**0.81 (0.70, 0.93)**	**0.94 (0.87, 1.02)**	**0.97 (0.91, 1.03)**	**1.00 (0.94, 1.06)**	**1.37 (1.00, 1.87)**

Strategy 2	CAPTURE Abciximab (1265)	0.70 (0.48, 1.03)	1.22 (0.61, 2.46)	1.02 (0.84, 1.24)	1.04 (0.84, 1.29)	0.76 (0.49, 1.17)	2.02 (1.02, 4.00)
Pooled[d]		**0.70 (0.48, 1.03)**	**1.22 (0.61, 2.46)**	**1.02 (0.84, 1.24)**	**1.04 (0.84, 1.29)**	**0.76 (0.49, 1.17)**	**2.02 (1.02, 4.00)**
Strategy 3	Chen Abciximab[c] (42)	0.13 (0.01, 2.38)	NR	NR	NR	NR	0.3 (0.01, 7.07)
	EPIC Abciximab (2099)	0.74 (0.52, 1.07)	0.90 (0.51, 1.59)	0.77 (0.65, 0.92)	0.69 (0.55, 0.87)	0.85 (0.62, 1.16)	2.12 (1.52, 2.95)
	EPILOG Abciximab (2792)	0.51 (0.36, 0.71)	0.63 (0.29, 1.38)	0.98 (0.81, 1.18)	NR	NR	0.66 (0.37, 1.17)
	EPISTENT Abciximab (2399)	0.50 (0.35, 0.72)	0.41 (0.13, 1.29)	0.86 (0.66, 1.33)	0.81 (0.59, 1.13)	0.94 (0.59, 1.48)	1.57 (0.74, 3.34)
	ERASER Abciximab (225)	0.74 (0.29, 1.87)	0.19 (0.01, 3.88)	0.86 (0.39, 1.90)	0.86 (0.39, 1.90)	NR	0.95 (0.06,14.85)
	ESPRIT Eptifibatide (2064)	0.68 (0.51, 0.90)	0.56 (0.24, 1.34)	NR	0.85 (0.61, 1.18)	1.05 (0.63, 1.75)	NR
	Galassi Abciximab[c] (106)	0.39 (0.08, 1.90)	0.32 (0.01, 7.71)	NR	NR	NR	NR
	Harrington Eptifibatide[c] (73)	0.18 (0.02, 1.83)	NR	NR	0.18 (0.02, 1.83)	0.12 (0.01, 2.86)	1.82 (0.09,36.26)
	IMPACT II Eptifibatide[c]	0.86	0.73	NR	NR	NR	1.11

	(4010)	(0.66, 1.12)	(0.34, 1.58)				(0.79, 1.56)
	RESTORE Tirofiban (2141)	0.83 (0.60, 1.13)	1.27 (0.65, 2.48)	NR	0.92 (0.76, 1.11)	0.81 (0.58, 1.13)	1.42 (0.96, 2.11)
Pooled[d]		**0.67 (0.57, 0.79)**	**0.77 (0.57, 1.05)**	**0.87 (0.76, 0.98)**	**0.82 (0.73, 0.93)**	**0.87 (0.72, 1.05)**	**1.29 (0.92, 1.91)**

a. See update rapid review[4] for more details on systematic review strategy

b. Repeat revascularisation rate for Strategies 2 and 3

c. Trials, which only report at 30 days follow-up. For the base-case analysis, it has been assumed that the 30-day relative risks remain the same at 6 months

d. Based on random effects meta-analysis

NR – Not reported

Table 5. Annual transition probabilities used in the long-term model (95% confidence intervals)

From state:	To state:			
	IHD	**Non-fatal MI**	**Post-MI**	**Dead**
IHD	0.9049 (0.8896, 0.9186)	0.0186 (0.0133, 0.0254)	-	0.0765 (0.0643, 0.0904)
Non-fatal MI	-	-	0.7900 (0.7177, 0.8471)	0.2100 (0.1529, 0.2822)
Post-MI	-	-	0.9266 (0.9024, 0.9466)	0.0734 (0.0534, 0.0976)
Dead	-	-	-	1 -

Table 6. Resource use and costs for the long-term model based on data from the Nottingham Heart Attack Register

	IHD*			MI**			Post MI***		
	Number of patients	**Average total LOS/number of visits**	**SD**	**Number of patients**	**Average total LOS/number of visits**	**SD**	**Number of patients**	**Average total LOS/number of visits**	**SD**
Hospital stays									
Cardiac									
Day case	1								
Non CCU	76	8.87	9.58	5	10.80	7.82	5	5.95	6.05
Inc. CCU	17	6.82	6.82	10	8.80	6.44	1	2.00	-
Outpatient visit	115	3.44	2.50	21	3.43	3.06	8	2.88	1.73
Non cardiac									
Day case	1								
Non CCU	67	10.39	17.81	7	12.00	13.60	3	7.00	7.94
Inc. CCU									
Outpatient visit	138	4.86	4.91	15	3.27	3.45	9	2.33	1.32
Interventions									
Angiography	20			5					
PTCA	2			3					
CABG	7			1					
Average Health State cost (SD)[a]	£1,421 (£944)			£3,966 (£1,722)			£1,587 (1,091)		

* 252 patients, 113,222 patient days follow-up. ** 27 patients, 7,248 patient days follow-up. *** 15 patients, 2993 patient days follow-up.

a based on the Monte Carlo simulation.

Table 7. Details of key elements of the base-case analysis and how these are varied in the sensitivity analysis

(1) VARIATION IN THE SOURCES OF DATA USED TO POPULATE THE BASE-CASE MODEL		
Elements	*Position in base-case analysis*	*Variation in sensitivity analysis*
Time horizon of model	50 cycles (50 years)	5 cycles (5 years)
Trials included in pooled estimates of relative risks of GPAs	All trials relevant to particular strategy, including those only reporting 30 day relative risks (which are assumed also to apply at 6 months)	a) Only those trials which report outcomes at 6 months b) Focus on those trials evaluating drugs most likely to be used for given strategy: (i) Strategy 1 risk reductions based on pooled results of eptifibatide and tirofiban trials (excluding lamifiban and abciximab trials); (ii) Strategy 2 same as base-case; (iii) Strategy 3 based on abciximab trials only (excluding tirofiban and eptifibatide trials). c) Base-case but cost Strategy 3 as mean of tirofiban and eptifibatide for 12 hour infusion d) Base-case except: (i) Strategy 1 risk reductions based on pooled results of eptifibatide and tirofiban trials (excluding lamifiban and abciximab trials); ii) Strategy 3 based on pooled

		results of eptifibatide and tirofiban (excluding abciximab trials), cost as mean of tirofiban and eptifibatide for 12 hour infusion. e) Base- case but relative risk data for strategy 3 based on EPIC subgroup analysis of unstable angina patients.
Utilities used to calculate QALYs	Assumption of mean utility of 0.8 (95% CI 0.6 – 0.94) for all non-death states in the long-term model based on data from GUSTO trial (ref).	a) Assumption of fixed utility of 1.0 for all non-death states (i.e. life-years analysis) b) Assumption of mean utility of 0.649 (SD 0.28) for all non-death states based on EQ-5D utility data from study of patients with angina (ref). c) Base-case assumption for IHD state but a 0.05 utility decrement for the Non-fatal MI and Post-MI states.
Rate of PCI during acute phase	Rate as reported in PRAIS (5%)	Increase PCI rate to 10%
Source of baseline data	Combined PRAIS and Leeds Audit data	a) PRAIS data only. b) Leeds audit data on parameters collected during the audit, otherwise use PRAIS. c) Baseline data derived from patient level meta analysis
Relative risk data used in strategy 1	Pooled relative risks reported in trials	Relative risks taken from patient level meta

		analysis[22] for strategy 1. Base-case for strategies 2-4.
Clopidogrel	No considered	a) Add clopidogrel as a fifth strategy in the model using published relative risk estimates.[1] b) Add clopidogrel as a fifth option plus use relative risk data from patient level meta analysis[22] in Strategy 1.
(2) VARIATION IN THE SOURCES OF BASELINE EVENT DATA		
Elements	*Position in base-case analysis*	*Variation in sensitivity analysis*
Baseline Event Data	UK – specific data derived from PRAIS-UK and Leeds cohort	a) New baseline event data derived from control group data reported in Boersma. Same relative risks applied as in base-case model. b) Baseline event data derived as above. Separate relative risks applied to strategy 1 to patient undergoing/not undergoing acute-PCI from patient-level meta analysis.
(3) VARIATION IN THE CHOICE OF COMPARATORS		
Elements	*Position in base-case analysis*	*Variation in sensitivity analysis*
Medical management of high-risk patients only	Not considered	a) Add medical management of high-risk patients only as a fifth strategy in the model.
Clopidogrel	Not considered	a) Add clopidogrel as a fifth strategy in the model

		using published relative risk estimates.[1] b) Add clopidogrel as a fifth option plus use relative risk data from patient level meta analysis[22] in Strategy 1.

Table 8. Results of the short-term model: probabilities (95% CI)[a] of leaving short-term model in one of three health states and expected costs for each strategy (95% CI)[a]

Health state	Strategy 1	Strategy 2	Strategy 3	Strategy 4
IHD	0.8907 (0.8680, 0.9110)	0.8766 (0.8558, 0.8958)	0.8775 (0.8569, 0.8965)	0.8766 (0.8559, 0.8958)
Non-fatal MI	0.0623 (0.0459, 0.0819)	0.0747 (0.0593, 0.0915)	0.0739 (0.0587, 0.0904)	0.0741 (0.0590, 0.0907)
Dead	0.0470 (0.0349, 0.0611)	0.0488 (0.0366, 0.0628)	0.0487 (0.0365, 0.0626)	0.0493 (0.0371, 0.0633)
Expected cost per patient	£2,526 (£1,730, £4,347)	£2,132 (£1,332, £3,950)	£2,158 (£1,356, 3,979)	£2,107 (£1,309, £3,926)

a. Based on mean and 2½ and 97½ percentiles from the Monte Carlo simulation

Table 9. Base-case estimates of mean lifetime costs and QALYs for the four strategies, together with incremental analysis

Strategy	Cost	QALY	ICER	Probability cost effective for maximum WTP[a]:		
				£10,000	£30,000	£50,000
1	£12,688	7.7875	£5,738	81.67	94.15	95.19
2	£12,207	7.6839	D	0.48	0.6	0.53
3	£12,188	7.6910	ED (£25,811)[b]	1.03	2.77	3.01
4	£12,119	7.6883		16.82	2.48	1.27

a. The probability that each strategy is more cost-effective than the others conditional on different maximum willingness to pay for an additional QALY

b. ICER Strategy 3 versus Strategy 4

D = Dominated, ED = Option ruled out by extended dominance

Table 10. Results of the sensitivity analyses using summarised in Table 7

Element	Sensitivity Analysis	Strategy	Cost	QALY	ICER	Probability cost effective for maximum WTP[a]:		
						£10,000	£30,000	£50,000
Time horizon of the model	5 cycles	1	£7,272	3.2654	£11,671	35.41	89.24	93.51
		2	£6,838	3.2217	D	0.36	0.78	0.73
		3	£6,840	3.2247	ED (£45,308)[b]	0.07	2.18	2.89
		4	£6,781	3.2234		64.16	7.80	2.87
Trials included in pooled estimates of relative risks of GPAs	a) only trials reporting outcomes at 6 months	1	£12,626	7.7452	£8,915	55.36	66.68	68.5
		2	£12,207	7.6839	D	1.43	3.84	4.53
		3	£12,195	7.6903	ED (£38,350)[b]	1.15	10.6	14.75
		4	£12,119	7.6883		42.06	18.88	12.22
	b) focus on drugs most likely to be used	1	£12,673	7.7837	£5,824	69.47	79.68	81.27
		2	£12,206	7.6839	D	0.95	1.96	2.14
		3	£12,184	7.6912	ED (£22,986)[b]	2.45	10.57	12.27
		4	£12,118	7.6883		27.13	7.79	4.32
	c) cost of Strategy 3 changed to average of eptifibatide/tirofiban	1	£12,688	7.7875	£5,738	81.51	94.12	95.13
		2	£12,207	7.6839	D	0.44	0.49	0.50
		3	£12,165	7.6910	ED (£17,137)[b]	3.74	3.61	3.40
		4	£12,119	7.6883		14.31	1.78	0.97

Trials included in pooled estimates of relative risks of GPAs	d) pooled results of eptifibatide and tirofiban trials for Strategies 1 and 3	1	£12,673	7.7837	£5,824	69.32	79.61	81.11
		2	£12,206	7.6839	D	0.87	1.56	1.73
		3	£12,189	7.6919	ED (£19,786)[b]	5.64	12.26	13.30
		4	£12,118	7.6883		24.17	6.57	3.86
	e) Strategy 3 = EPIC subgroup analysis of unstable angina patients	1	£12,688	7.7875	£5,738	80.90	93.49	94.41
		2	£12,207	7.6839	D	0.32	0.15	0.12
		3	£12,226	7.6963	ED (13,364)[b]	6.35	5.11	4.81
		4	£12,119	7.6883		12.43	1.25	0.66
Utilities used to calculate QALYs	a) life-year analysis	1	£12,688	9.7173	£4,605	87.67	94.86	95.51
		2	£12,207	9.5882	D	0.48	0.57	0.51
		3	£12,188	9.5971	ED (£20,497)[b]	1.51	2.83	3.15
		4	£12,119	9.5937		10.34	1.74	0.83
	b) utilities reduced to 0.649 for all non-dead states	1	£12,808	5.6383	£7,005	59.89	90.28	93.2
		2	£12,324	5.5635	D	0.51	0.49	0.45
		3	£12,307	5.5687	ED (£36,616)[b]	0.97	2.49	2.75
		4	£12,237	5.5668		38.63	6.74	3.60
	c) Utility decrement of 5% on MI/Post MI states	1	£12,688	7.6968	£5,730	81.97	94.39	95.36
		2	£12,207	7.5934	D	0.49	0.57	0.51
		3	£12,188	7.6005	ED (£23,230)[b]	1.16	2.93	3.07
		4	£12,119	7.5975		16.38	2.11	1.06

Rate of PCI during ACS phase	Increase to 10%	1	£12,778	7.7881	£5,838	81.19	93.90	94.97
		2	£12,329	7.6837	D	0.90	0.81	0.83
		3	£12,340	7.6979	ED (£22,511)[b]	1.21	3.13	3.10
		4	£12,219	7.6925		16.7	2.16	1.10
Source of baseline data	a) PRAIS only	1	£12,717	7.7891	£5,756	81.34	93.83	95.10
		2	£12,238	7.6878	D	0.59	0.42	0.41
		3	£12,215	7.6923	ED (£36,444)[b]	1.60	2.04	2.23
		4	£12,149	7.6905		16.47	3.71	2.26
	b) Leeds PCI audit (including PRAIS data on all non-acute PCI parameters)	1	£12,851	7.7709	£5,746	81.74	94.34	95.38
		2	£12,367	7.6662	D	0.66	0.52	0.55
		3	£12,350	7.6745	ED (£22,322)[b]	1.33	3.03	3.08
		4	£12,279	7.6713		16.27	2.11	0.99
Relative risk data for Strategy 1	Patient level meta-analysis for Strategy 1	1	£12,649	7.7395	£10,343	47.4	79.09	83.24
		2	£12,208	7.6839	D	1.58	2.14	2.01
		3	£12,189	7.6910	(£25,807)[b]	3.11	9.49	10.27
		4	£12,120	7.6883		47.91	9.28	4.48

a. The probability that each strategy is more cost-effective than the others conditional on different maximum willingness to pay for an additional QALY

b. ICER Strategy 3 versus Strategy 4

Table 11: Comparison of baseline event rates between UK-specific sources used in the base-case model and non-UK specific sources derived from Boersma

Revasc Group	Event	Base Case Model – 6 month event rates (from PRAIS & Leeds)	Boersma – 30 day event rates	Boersma – 6 months event rates (extrapolated from 30 day rates)
Acute PCI	Death NFMI	3.3% 3.6%	1.99% 12.77%	5.62% 19.27%
Acute CABG	Death NFMI	10.6% 6.4%	4.54% 22.46%	8.14% 28.79%
No Acute Revasc	Death NFMI	7.1% 4.7%	3.97% 6.77%	7.53% 13.43%

Table 12: Relative risk reductions used in sensitivity analysis for Strategy 1

Revasc Group	Event	Baseline Relative Risks	Separate RR for acute PCI/no acute PCI
Acute PCI	Death NFMI	0.84 (0.71 – 0.98) 0.94 (0.87 – 1.02)	0.83 (0.53 – 1.29) 0.80 (0.65 – 0.95)
Acute CABG	Death NFMI	0.84 (0.71 – 0.98) 0.94 (0.87 – 1.02)	0.91 (0.81 – 1.04) 0.95 (0.86 – 1.03)
No Acute Revasc	Death NFMI	0.84 (0.71 – 0.98) 0.94 (0.87 – 1.02)	0.91 (0.81 – 1.04) 0.95 (0.86 – 1.03)

Table 13: Results of sensitivity analyses using alternative sources of baseline data

Element	Sensitivity Analysis	Strategy	Cost	QALY	ICER	Probability cost effective for maximum WTP:		
						£10,000	£30,000	£50,000
Alternative baseline intervention and event data	(a) Same RR as applied in base-case model	1	£14,235	7.7921	£5,753	78.97	91.71	93.08
		2	£13,787	7.6728	D	2.56	1.43	1.23
		3	£13,844	7.7101	ED (£11,160)	6.82	4.88	4.35
		4	£13,678	7.6952		11.65	1.98	1.34
	(b) Strategy 1 RR based on patient-level meta analysis: Differential RR applied to acute PCI/no acute	1	£14,174	7.7468	£9,609	45.30	70.03	73.92
		2	£13,787	7.6728	D	6.45	4.8	4.22
		3	£13,844	7.7101	ED (£11,160)	18.51	16.92	15.77
		4	£13,678	7.6952		29.74	8.25	6.09

Table 14: Sensitivity analysis including an alternative medical management strategy based on the use of GPAs in high-risk patients only

Strategy	Cost	QALY	ICER	Probability cost effective for maximum WTP		
				£10,000	£30,000	£50,000
1 - all patients	£12,738	7.7776	£91,000	38.36	47.15	48.29
1 - high risk patients only	£12,556	7.7756	£3,966	55.14	51.46	50.67
2	£12,257	7.6759	D	0.18	0.1	0.11
3	£12,234	7.6803	ED (£36,667)	0.60	0.44	0.45
4	£12,168	7.6785		5.72	0.85	0.48

Table 15: Results of sensitivity analysis including clopidogrel

Element	Sensitivity Analysis	Strategy	Cost	QALY	ICER	Probability cost effective for maximum WTP[a]:		
						£10,000	£30,000	£50,000
Clopidogrel	a) Add clopidogrel as a fifth option	1	£12,723	7.7862	£5,750	61.04	71.27	72.32
		5 (Clop)	£12,526	7.7405	ED (£6,978) [b]	30.85	27.32	26.67
		2	£12,244	7.6825	D	0.12	0.12	0.13
		3	£12,223	7.6896	ED (£26,296)[c]	0.29	0.48	0.56
		4	£12,152	7.6869		7.7	0.81	0.32
	b) Add clopidogrel as a fifth option plus use patient level meta analysis for RR for Strategy 1	1	£12,684	7.7438	D	26.76	42.19	44.25
		5 (Clop)	£12,526	7.7457	£6,978	52.04	52.87	52.27
		2	£12,244	7.6879	D	0.44	0.34	0.41
		3	£12,223	7.6946	ED (£26,296) [c]	0.86	1.95	1.84
		4	£12,152	7.6923		19.9	2.65	1.23

a. The probability that each strategy is more cost-effective than the others conditional on different maximum willingness to pay for an additional QALY

b. ICER Clopidogrel versus strategy 4.

c. ICER Strategy 3 versus Strategy 4

Figure 1. Structure of the short-term model

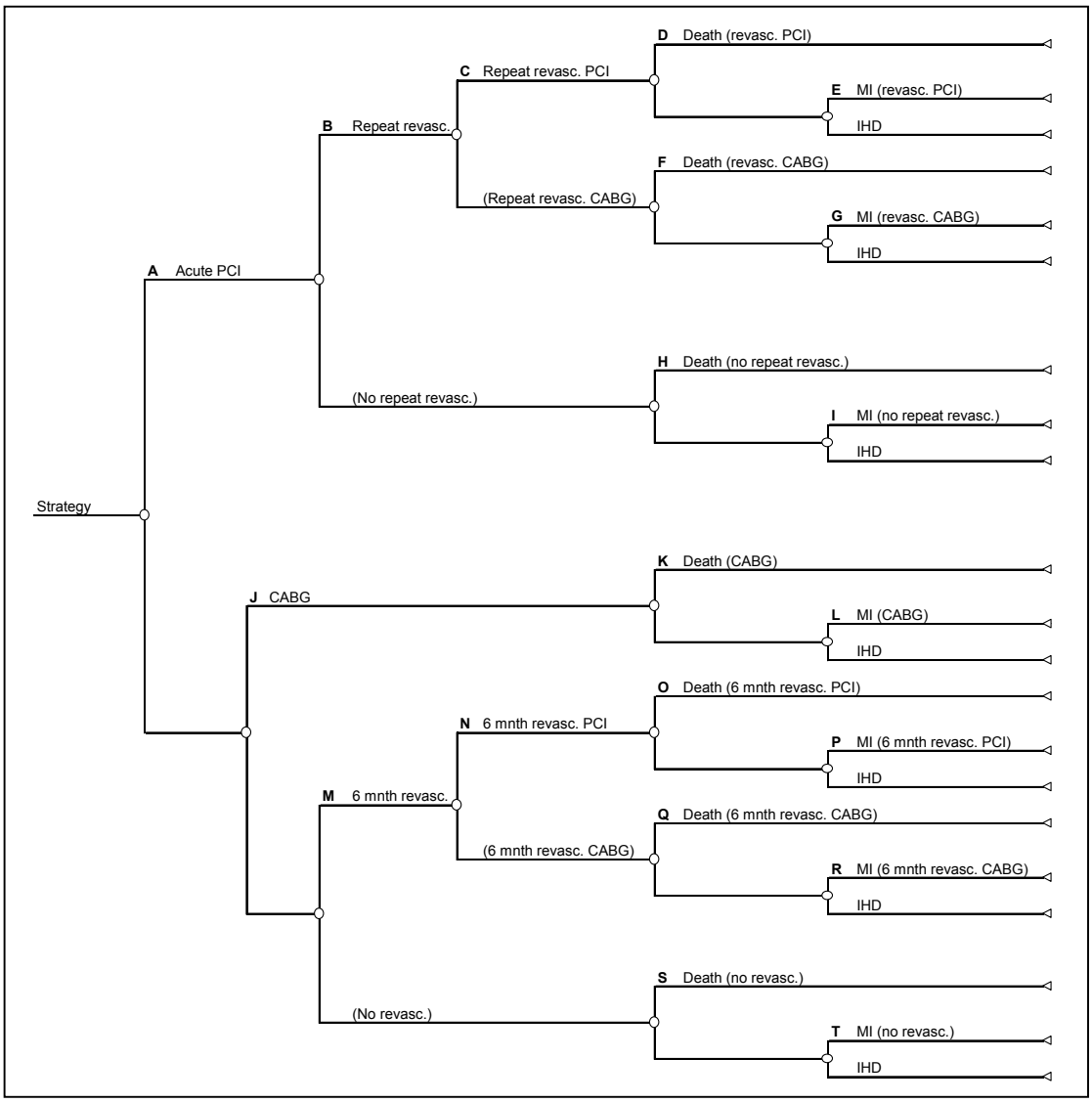


Figure 2. Structure of the long-term model

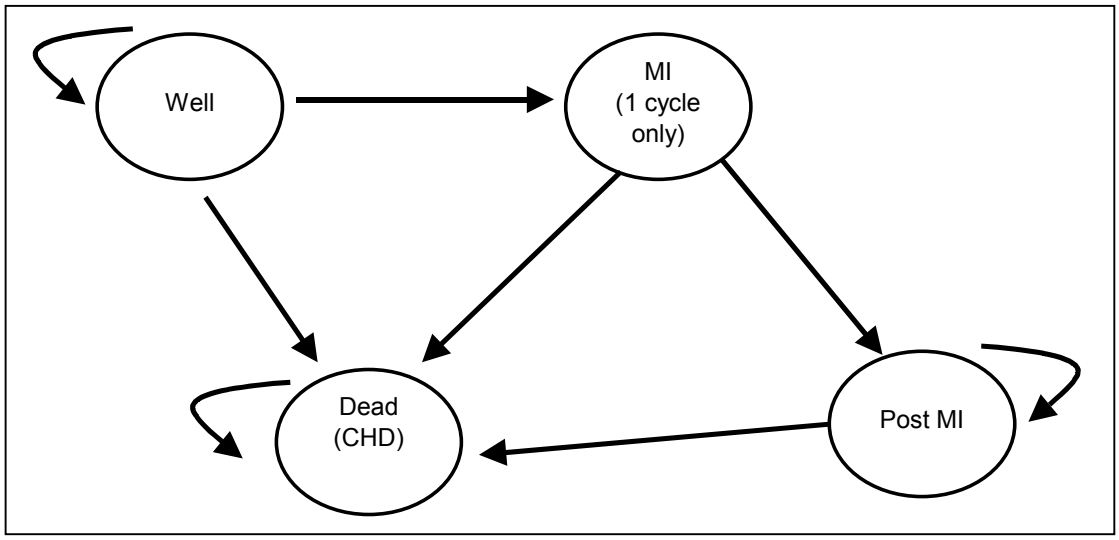


Figure 3: Graphical representation of the mean costs and outcomes of the 4 strategies

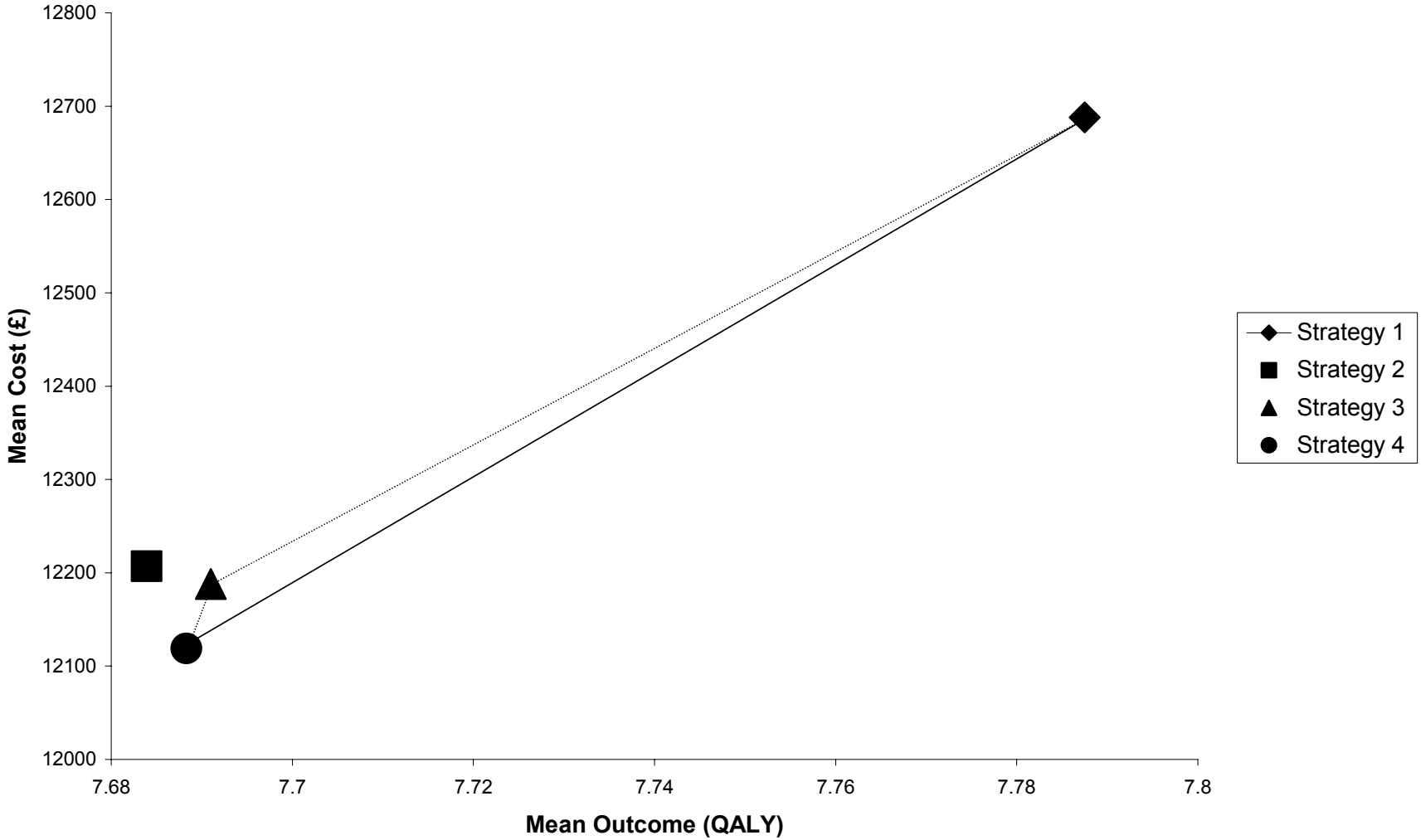
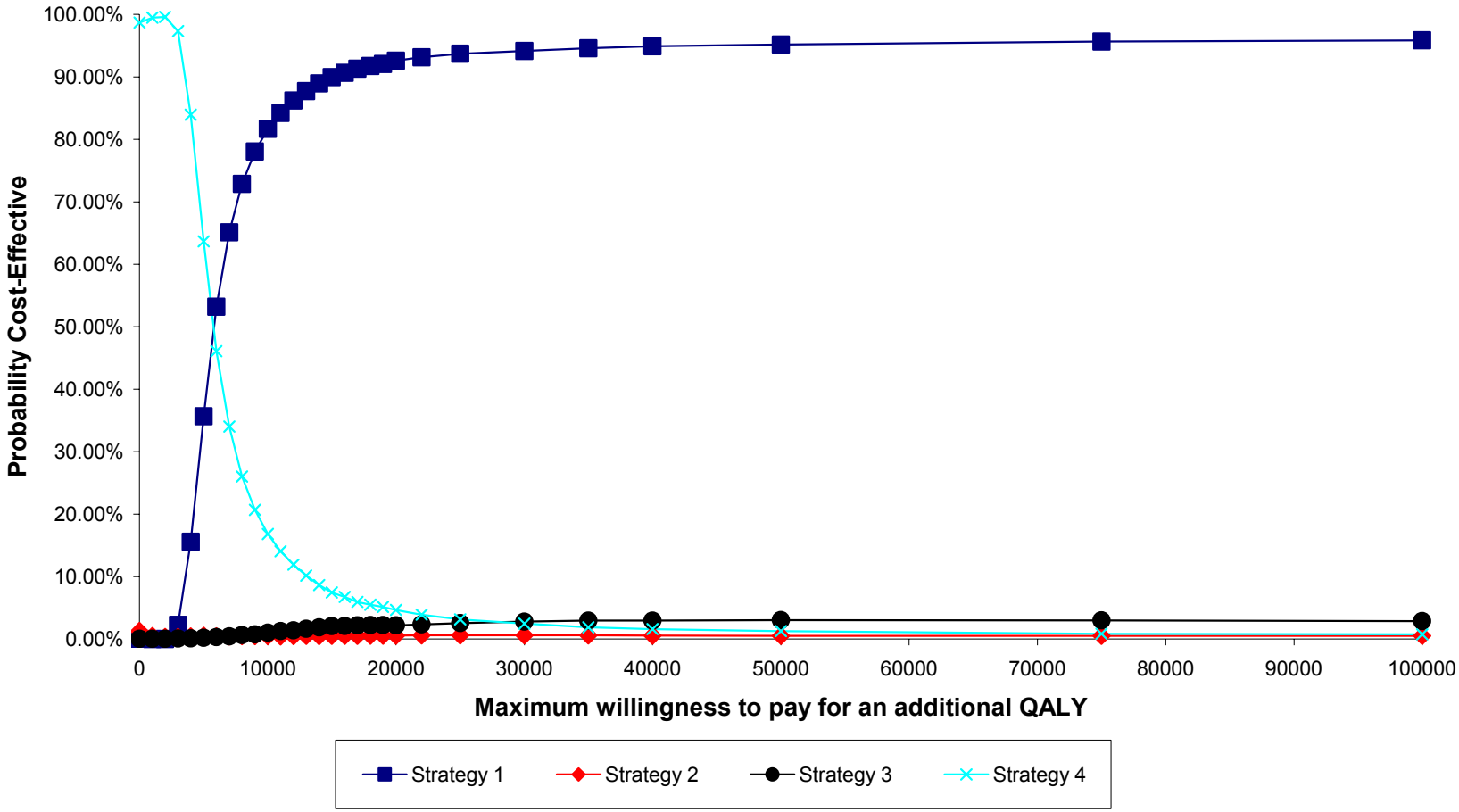


Figure 4. Base-case results in the form of a cost-effectiveness acceptability curve. This shows the probability that each strategy is more cost-effective than the others conditional on a different maximum willingness to pay for an additional QALY



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