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Abstract

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

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Objectives: To identify and prioritise key areas of clinical uncertainty regarding the medical management of non-ST elevation acute coronary syndrome (ACS) in current UK practice.

Data sources: Electronic databases. Consultations with clinical advisors. Postal survey of cardiologists.

Review methods: Potential areas of important uncertainty were identified and 'decision problems' prioritised. A systematic literature review was carried out using standard methods. The constructed decision model consisted of a short-term phase that applied the results of the systematic review and a long-term phase that included relevant information from a UK observational study to extrapolate estimated costs and effects. Sensitivity analyses were undertaken to examine the dependence of the results on baseline parameters, using alternative data sources. Expected value of information analysis was undertaken to estimate the expected value of perfect information associated with the decision problem. This provided an upper bound on the monetary value associated with additional research in the area.

Results: Seven current areas of clinical uncertainty (decision problems) in the drug treatment of unstable angina patients were identified. The agents concerned were clopidogrel, low molecular weight heparin, hirudin and intravenous glycoprotein antagonists (GPAs). Twelve published clinical guidelines for unstable angina or non-ST elevation ACS were identified, but few contained recommendations about the specified decision problems. The postal survey of clinicians showed that the greatest disagreement existed for the use of small molecule GPAs, and the greatest uncertainty existed for decisions relating to the use of abciximab (a large molecule GPA). Overall, decision problems concerning the GPA class of drugs were considered to be the highest priority for further study. Selected papers describing the clinical efficacy of treatment were divided into three groups, each representing an alternative strategy. The strategy involving the use of GPAs as part of the initial medical management of all non-ST elevation ACS was the optimal choice, with an incremental cost-effectiveness ratio (ICER) of £5738 per quality-adjusted life-year (QALY) compared with no use of GPAs. Stochastic analysis showed that if the health service is willing to pay £10,000 per additional QALY, the probability of this strategy being cost-effective was around 82%, increasing to 95% at a threshold of £50,000 per QALY. A sensitivity analysis including an additional strategy of using GPAs as part of initial medical management only in patients at particular high risk (as defined by age, ST

depression or diabetes) showed that this additional strategy was yet more cost-effective, with an ICER of £3996 per QALY compared with no treatment with GPA. Value of information analysis suggested that there was considerable merit in additional research to reduce the level of uncertainty in the optimal decision. At a threshold of £10,000 per QALY, the maximum potential value of such research in the base case was calculated as £12.7 million per annum for the UK as a whole. Taking account of the greater uncertainty in the sensitivity analyses including clopidogrel, this figure was increased to approximately £50 million.

Conclusions: This study suggests the use of GPAs in all non-ST elevation ACS patients as part of their initial medical management. Sensitivity analysis showed that virtually all of the benefit could be realised by treating only high-risk patients. Further clarification of the optimum role of GPAs in the UK NHS depends on the availability of further high-quality observational and trial data. Value of information analysis derived from the model suggests that a relatively large investment in such research may be worthwhile. Further research should focus on the identification of the characteristics of patients who benefit most from GPAs as part of medical management, the comparison of GPAs with clopidogrel as an adjunct to standard care, follow-up cohort studies of the costs and outcomes of high-risk non-ST elevation ACS over several years, and exploring how clinicians' decisions combine a normative evidence-based decision model with their own personal behavioural perspective.

Contents

List of abbreviations

ACC	American College of Cardiology
ACS	acute coronary syndrome
ADP	adenosine diphosphate
AHA	American Heart Association
AMI	acute myocardial infarction
BCS	British Cardiac Society
BMA	British Medical Association
BNF	British National Formulary
CABG	coronary artery bypass graft
CAD	coronary artery disease
CAPTURE	c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina
CCTR	Cochrane Controlled Trials Register
CCU	coronary care unit
CDSR	Cochrane Database of Systematic Reviews
CEAC	cost-effectiveness acceptability curve
CEC	clinical events committee
CHD	coronary heart disease
CI	confidence interval
CK-MB	creatine kinase MB fraction
CPI	Conference Papers Index
CRD	Centre for Reviews and Dissemination
CSANZ	Cardiac Society of Australia and New Zealand
CURE	Clopidegral in Unstable Angina to Prevent Recurrent Ischemic Events
D	dominance
DARE	Database of Abstracts of Reviews of Effectiveness
DEC	Development and Evaluation Committee
DGH	district general hospital
DM	diabetes mellitus
E	equivocal
ED	extended dominance
EPIC	Evaluation of 7E3 for the Prevention of Ischemic Complications
EPILOG	Evaluation in Percutaneous Transluminal Coronary Angioplasty to Improve Long-Term Outcome with abciximab GP IIb/IIIa blockade
EPISTENT	Evaluation of Platelet IIb/IIIa Inhibitor for Stent
EQ-5D	EuroQol 5 Dimensions
ERASER	Evaluation of Reopro And Stenting to Eliminate Restenosis
ESPRIT	Enhanced Suppression of Platelet Receptor GP IIb-IIIa using Integrelin Trial
EVPI	expected value of perfect information
GI	gastrointestinal
GPA	glycoprotein IIb/IIIa antagonist
GUSTO	Global Use of Strategies To open Occluded coronary arteries in acute coronary syndromes
HES	Hospital Episode Statistics
HR	hazard ratio
ICD	International Classification of Diseases
ICER	incremental cost-effectiveness ratio
IHD	ischaemic heart disease

continued

List of abbreviations *continued*

IMPACT	Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis
LMWH	low molecular weight heparin
LOS	length of stay
LYG	life-year gained
MI	myocardial infarction
NA	not applicable
NC	not covered
NHAR	Nottingham Heart Attack Register
NHF	National Heart Foundation
NICE	National Institute for Health and Clinical Excellence
NR	not reported
NRR	National Research Register
NS	not significant
NSF	National Service Framework
OR	odds ratio
PARAGON	Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network
PCI	percutaneous coronary intervention
PRAIS-UK	Prospective Registry of Acute Ischaemic Syndromes in the UK
PRISM	Platelet Receptor Inhibition in Ischemic Syndrome Management
PRISM-PLUS	Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms
PTCA	percutaneous transluminal coronary angioplasty
PURSUIT	Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RESTORE	Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis
revasc.	revascularisation
RR	relative risk
RRR	relative risk reduction
SD	standard deviation
SE	standard error
TIMI	Thrombolysis in Myocardial Infarction
TVR	target vessel revascularisation
UA	unstable angina
UFH	unfractionated heparin
VOI	value of information
WTP	willingness to pay

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

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

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

Objectives

The objectives of this study were:

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

Methods

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

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

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

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

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

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

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

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

Results

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

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

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

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

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

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

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

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

Conclusions

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

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

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

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

Chapter 1
Introduction

Background

The purpose of this section is to set the context for the work described in subsequent chapters. First, the clinical definition and current understanding of the pathology of unstable angina (UA) will be described briefly. Next, the limited information available about the incidence of the condition in the UK and its costs to the NHS will be reviewed. Finally, the prognosis and pattern of current management in the UK will be described.

What is UA?

Unstable angina is a clinical syndrome rather than a specific pathological diagnosis. It has been defined as "ischaemic type chest pain that is more frequent, severe, or prolonged than the patient's usual angina symptoms, occurs at rest or minimal exertion, or is difficult to control with drugs".[1]

This is not a precise definition. Pain is a subjective experience, and syndromes whose definitions depend on the recognition of changes in the intensity or frequency of pain are likely to be subject to considerable observer variation. UA represents a spectrum, each extreme of which is more easily defined than UA itself (*Figure 1*).

At the less severe end of the spectrum, UA merges with stable angina. Stable angina is pain that occurs in response to factors such as exercise, emotional excitement or cold in a predictable and repeated manner. At the other end of the spectrum, when severe, UA cannot usually be distinguished on history and examination alone from acute myocardial infarction (AMI). Severe UA and AMI therefore represent a single clinical entity for which the term acute coronary syndrome (ACS) is now commonly used.

On the basis of the initial resting ECG, ACS patients can be divided into two groups for which distinct management strategies have emerged. The first of these are patients whose ECG shows ST segment elevation; the second are those whose ST segments are normal, depressed or uninterpretable owing to a conduction disorder such as bundle branch block. The first group of patients, almost all of whom will be found later to have had a full-thickness AMI, will benefit from thrombolytic drugs administered as quickly as possible; the second group does not appear to benefit from such treatment. It is the second group with which this report is concerned.

Some of the second group will later be shown to have suffered an AMI, usually a partial thickness or subendocardial AMI. In others the initial ischaemia causing the pain will subside without having caused any irreversible damage to the myocardium. These may be regarded as 'true' UA cases. Recent publications refer to the group as a whole as 'unstable angina/non-ST elevation acute myocardial infarction'; in this report 'unstable angina' will be used as shorthand. *Figure 2* summarises the current generally accepted terminology for different types of ACS.

The prognosis of UA in a case series is highly dependent on the case definition. If this is loose, such that all grades of UA are included, prognosis will be much better than if the definition is restricted only to those more severe cases, which are initially indistinguishable from AMI.

Pathological basis of UA

The key pathological event in UA is usually the rupture of a pre-existing atheromatous plaque in the wall of a major coronary artery. Atheromatous plaques are slowly growing collections of cholesterol and fibrous tissue in the wall of an artery. Before a plaque ruptures, it may have caused substantial narrowing of the lumen of the artery, such that blood flow is insufficient

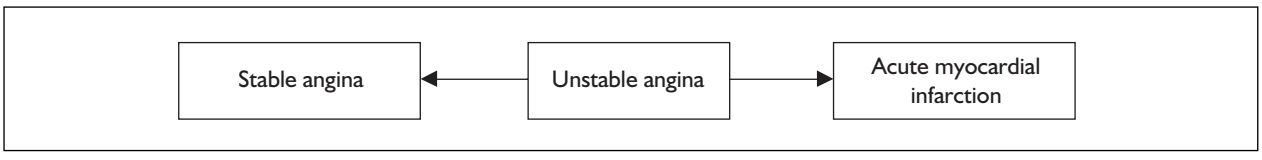

FIGURE 1 *Spectrum of unstable angina*

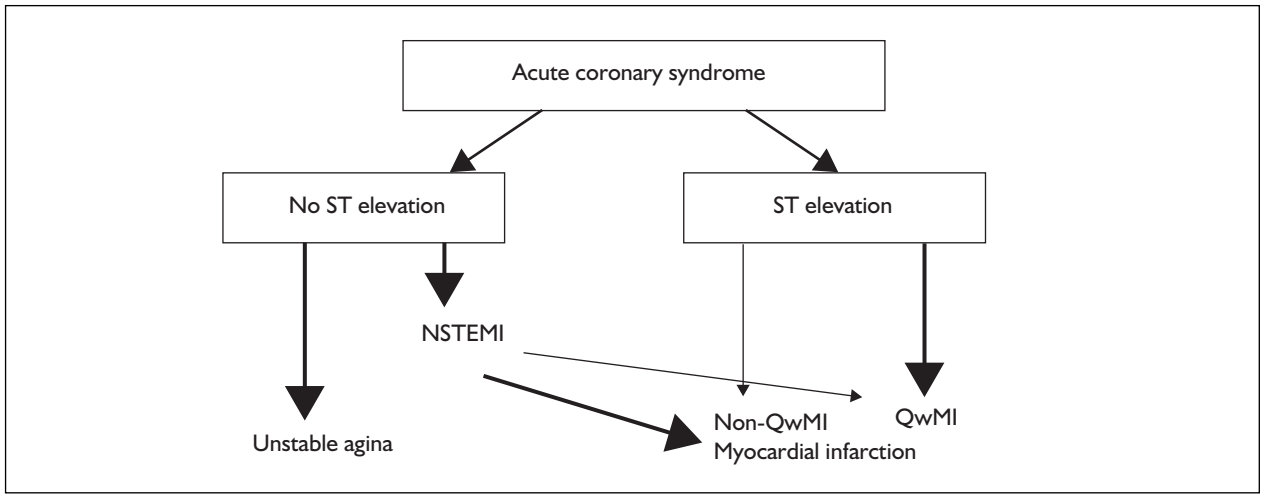

FIGURE 2 *Classification of ACS. NSTEMI, non-ST elevation myocardial infarction; QwMI, Q-wave myocardial infarction. Adapted from Braunwald* et al. *(2000).*[2]

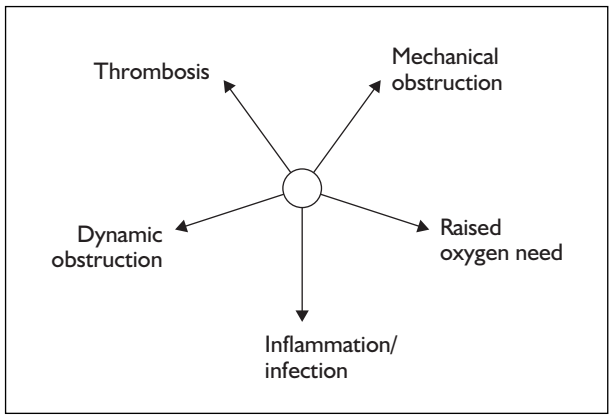

FIGURE 3 *Five factors causing UA. Adapted from Braunwald (1998).*[4]

when cardiac output is raised. This may have resulted in stable angina, or may have been asymptomatic.

The stimuli that precipitate the rupture of a plaque are not well understood, but the events that may follow this are. Platelet adherence to the exposed intima, platelet aggregation and blood coagulation all combine to form thrombus which narrows the lumen of the artery and limits blood supply to distal myocardium. If the thrombus is sufficient to obliterate or almost obliterate all blood flow through the affected artery, a volume of myocardium is likely to be irreversibly damaged, resulting in an AMI. If some blood flow continues, the amount of myocardium irreversibly damaged may be smaller, resulting in a less than full-thickness infarction, or no irreversible damage at all. Angioscopic studies suggest that plaques may remain unstable for up to 1 month following an AMI.[3]

The degree of ischaemia and amount of irreversible damage, if any, that may occur following the disruption of a plaque depend on the balance between oxygen supply and demand in the affected myocardium. In all, five factors are recognised that may affect this (*Figure 3*). Although all five factors may contribute to some extent, the formation of thrombus is the most common cause[4] and the target of most recent innovations in medical treatment.

The balance between oxygen supply and demand is a dynamic one, and one that may change over time. Hence the pain of UA may be controlled by initial medical management, only to recur several hours later when oxygen demands rise or thrombus is re-created at the site of the disrupted plaque. Recurrent ischaemia is associated with ECG abnormalities, and the number and duration of such episodes can be detected by continuous ST-segment monitoring. Not all ischaemic episodes so detected are symptomatic: in the placebo arm of one recent trial, 37 out of 163 (23%) UA patients had one or more episodes lasting for at least 1 minute during the 24–36-hour observation period, but in 24 (15%) patients these were all asymptomatic.[5]

Besides AMI, there are two other important acute complications of UA. First, small parts of thrombus may become detached, forming emboli that travel down the artery and block smaller branches distally; this may result in multiple small areas of microinfarction. This process may explain the release into the bloodstream of markers of myocardial damage such as troponins which, as described below, indicate a poor prognosis.

The second important complication besides AMI is left ventricular failure and circulatory shock, when blood pressure is reduced and cardiac output is insufficient to meet essential metabolic needs. In the one large recent trial that has reported in detail on this complication, 2.5% of UA patients were affected, of whom 65.8% died within 30 days. The death rate in patients without shock was 2.0%.[6]

Incidence of UA

The subjective nature of UA and the difficulty of distinction from other conditions at both ends of its spectrum of severity mean that only rough estimates of incidence are possible.

NHS Hospital Episode Statistics (HES)[7] have included a specific category for UA since the adoption of the International Classification of Diseases, 10th revision (ICD-10) in 1995. On this basis, the incidence is about 1000 cases per million total population per year or about 10 per acute hospital per week. The extent to which this is an underestimate because UA is coded as AMI or non-specific chest pain is unknown. However, estimates suggest that about one-third of AMI admissions are due to non-Q-wave infarctions,[3] so contributing about another 600 per million total population per year to the hospital workload.

Hospital admission for all cases of UA is recommended,[8] but may not always occur. This is a further cause of underestimation that is of unknown size.

Alternative estimates of incidence are two to three times higher than that derived from HES, similar in magnitude to those reported from the USA and Canada.[3]

Trends in incidence in the UK are difficult to establish. There is a consensus among clinicians that UA is becoming more common,[3] but the annual series of HES figures is difficult to interpret because of potential confounding by changes in coding practice. In the USA, the National Hospital Discharge Survey showed an apparent four-fold rise in UA episodes between 1980 and 1989.[3] In the UK, the HES rate increased by 66% from its 1995/96 figure to 2000/01,[7] the most recent year for which figures are currently available.

Possible explanations for a rising incidence are increased awareness of the condition, due in part to recent health education encouraging patients with acute chest pain to seek prompt medical attention. Another possibility is that more effective treatment for coronary heart disease (CHD), while reducing the incidence and case-fatality of AMI, has increased the numbers at risk of UA. There is some evidence to support this from trial populations,[3] although the extent to which this can be extrapolated to the general population is uncertain.

Costs of UA

Besides the direct costs of acute care for UA that fall on the NHS, costs accrue to patients and their families, and to the economy as a whole owing to lost productivity. The costs of complications such as AMI, delayed treatments such as revascularisation and rehabilitation should also be considered.

Recent estimates of the total cost of circulatory diseases including CHD are £3800 million per year for the NHS and £3000 million to industry in terms of working days lost.[7] The proportion of this due to UA and its complications is difficult to establish.

The average cost of an inpatient episode of care for angina (stable and unstable not distinguished) in different hospitals as quoted in official statistics ranged from £156 to £1123.[9] These figures include elective readmissions for revascularisation as well as acute care, and some patients will have more than one inpatient episode per UA event, for example if they are transferred from one hospital to another for specialised care.

Prognosis of UA

As described above, the main acute complications of UA are AMI, left ventricular failure and ventricular arrythmias, any of which may be fatal. In the longer term, once the disrupted plaque has stabilised, the range of outcomes for the UA patients, but not necessarily their frequency, will be the same as for other groups of patients with established CHD, for example those with stable angina or previous myocardial infarction (MI).

Determination of the frequency of adverse events in both the short and long term in the general population of UA patients is beset by the same difficulties as the measurement of the incidence of the condition. In-hospital mortality could be derived from HES, but the usual practice of delaying coding until the end of an episode of care will produce bias, as patients who die are more likely to be coded as AMIs. Population-based cohort studies of the incidence of CHD similarly will assume that all deaths following acute chest pain are due to AMI.

Almost all information about the prognosis of UA is therefore derived from case series constructed by secondary care clinicians or randomised controlled trials (RCTs). While case series may be representative of all UA patients, RCTs are less so, as they tend to exclude older patients and those with significant co-morbidities. However, RCTs tend to have an explicit case definition and smaller losses to follow-up.

Adverse event rates in trials depend not only on case definition (restriction to severe UA meaning higher rates), but also on how soon after the onset of symptoms patients are diagnosed as UA and recruited (delay meaning lower rates, as adverse events are common soon after the onset of symptoms that may precede recruitment).

Overall mortality rates in the placebo arms of recent RCTs vary from 3.0% to 4.5%[10,11] at 30 days, and average 7.0% at 6 months. Rates for MI over the same periods range from 4.3 to 13.5%, and 10.5%[12] to 14%[11] at 30 days and 6 months, respectively. Equivalent 6-month rates in the most recent UK case series were 7.4% for mortality and 7.3% for incident AMI.[13]

Another adverse outcome frequently reported in RCTs is severe recurrent angina or refractory ischaemia. The exact definition varies between trials, but cardiac pain lasting for at least 10 minutes associated with ST-segment changes is usually a required part of it. Reported 30-day rates for this outcome vary from 10.8%[10] to 15%.[14] Equivalent rates in the recent UK case series were 3.3% at discharge and 17.0% at 6 months.

Although case series and trials provide information of limited generalisability concerning overall adverse event rates, they do provide accurate data about relative risks in different patient subgroups. Identification of which UA patients are at highest risk has been important to clinicians, so that where resources for costly treatments are limited they can be most efficiently deployed, and where costs are not an issue, the benefits of treatment over the possible harms of treatment can confidently be predicted. A considerable body of literature on this topic is available.[15] For example, analysis of survival in two large RCTs, PURSUIT (platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) and ESSENCE, showed that the critical features associated with an increased risk of death were older age, positive serum markers such as troponins, more severe chronic angina before admission, chest crackles and ST-segment depression on the admission ECG.[2] A risk score that can be calculated at presentation and does not require a computer has now been developed.[16]

Recent clinical guidelines produced by specialist societies in the USA[2] and the UK[8] have combined this body of evidence with expert opinion to produce an operational classification of UA patients into three risk groups, recommending for each a different management plan. This evidence and related recommendations are summarised later in this background section. These classifications are not entirely evidence based; indeed the US guideline acknowledges that "estimation of the short-term risks … is a complex multivariable problem that cannot be fully specified in a … rigid algorithm".[2]

Multivariate analysis of a recent UK case series of 1046 unselected UA patients confirmed the main findings of previous analyses.[13] In particular, the adjusted 6-month rate for death or non-fatal MI was 2.2 times higher in those aged 60–70 years than those younger than 60, and 3.5 times greater in those aged over 70 than in those younger than 60 years. Other significant predictors on adverse 6-month outcome were ST depression or bundle branch block on the admission ECG [odds ratio (OR) = 5.0], male gender (OR = 1.6), low systolic blood pressure on admission and history of heart failure, diabetes or prior percutaneous coronary intervention (PCI). Troponin levels, which form an important part of risk stratification in all recently published guidelines, were only measured in 4.6%, and so could not be assessed.

Current management of UA

The aims of the management of UA have recently been described as:[17]

- to relieve pain and ischaemia
- to prevent death and MI
- to identify people at high risk requiring revascularisation
- to facilitate early hospital discharge in people at low and medium risk
- to modify risk factors; to prevent death, MI and recurrent ischaemia after discharge from hospital, with minimum adverse effects.

Three related perspectives on the care of UA patients can be distinguished. These are:

- management as derived from published evidence (RCTs and systematic reviews)[17]

TABLE 1 *Recommended management of UA in the NSF for CHD[19]*

The interventions that patients with **unstable angina** should usually receive, unless contraindicated, are

General measures
- bed rest, oxygen, pain relief, ECG and haemodynamic monitoring

Anti-thrombotics
- aspirin (300 mg, if not already given, then 150 mg daily)
- heparin (i.v. heparin for 2–5 days or subcutaneous low molecular weight heparin)

Anti-ischaemics
- β-blocker
- nitrates
- calcium antagonists (usually reserved for second or third line therapy after β-blockers and nitrates, or when β-blockers are contraindicated)

Reassess risk
- reassess 12–24 hours after admission to hospital to determine further management

Continuing care
- as for AMI

- management as recommended in the guidelines of specialist societies[18]
- management as currently observed in a recent UK case series.[13]

For some interventions these three perspectives coincide; for others there are important differences. This section describes the extent of concordance for each of the main interventions normally used in the acute phase of management. The CHD National Service Framework (NSF) describes a range of interventions that UA patients "should usually receive unless contraindicated". These are shown in *Table 1*.

Antiplatelet agents

There is strong evidence that aspirin reduces the combined end-point of vascular death, AMI or stroke in UA,[20] and both US and UK guidelines contain a class 1 recommendation to this effect. However, in a recent UK case series, aspirin was not used in 13% of patients in-hospital and in 22% at 6 months. Some of these patients, but probably not all, will have been allergic to the drug or unable to tolerate it because of gastrointestinal effects.

Clopidogrel and ticlodipine are alternative antiplatelet agents, with a different mechanism of action. Use of the latter agent has declined since reports of occasional severe and irreversible neutropenia.[21] The US guidelines recommend that one or other drug is used when aspirin is contraindicated; the UK guidelines do not mention this, and the extent of use in the UK was not reported in the recent case series. The CURE trial,[22] published after the present work was started, shows that clopidogrel is effective in combination with aspirin, and guidelines are being modified accordingly.[2]

Antithrombotic agents

Unfractionated heparin (UFH) is a recognised standard treatment for UA, although the evidence from RCTs that it has any additional effect to that of aspirin is marginal.[17] Low molecular weight heparin (LMWH) (which is simpler to administer) has been shown to add benefit to aspirin, but head-to-head comparisons with UFH have shown no significant differences.

The US guideline recommends either UFH or LMWH; the UK guideline LMWH alone. The recent UK case series showed that UFH was used in 28% of patients, LMWH in 38% and both in 6%. However, 28% of patients did not receive any type of heparin.

Nitrates, β-blockers and calcium antagonists

The evidence base about use of these agents is at present inadequate, making it difficult to reach definite conclusions on their value.[17] However, specialist consensus is that intravenous nitrates and oral β-blockers should be used as part of initial management of UA patients unless contraindicated. This is recommended in both US and UK specialist guidelines and in the NSF. In the recent UK case series, intravenous nitrates were used in 31% and other forms (oral or buccal) in 79%; for β-blockers and calcium antagonists the rates in-hospital were 50% and 54%, respectively.

Glycoprotein antagonists

The evidence base for the use of glycoprotein antagonists in UA is reviewed systematically in Chapter 2 of this report. In essence, RCTs have shown small decreases in the composite rates of death, AMI or refractory ischaemia, but subgroup analyses of one of these trials suggest that the effect may be reduced when revascularisation rates are relatively low, as in the UK. Subgroup analysis has also demonstrated an enhanced effect in UA patients with raised troponin levels, and little or no effect in those with normal troponins.

US and UK specialist guidelines both recommend the use of these agents in high-risk patients. They

TABLE 2 *NICE guidance on glycoprotein inhibitors (November 2000)*[23]

This guidance applies to patients with unstable angina or non-Q-wave myocardial infarction and those patients undergoing acute or elective percutaneous coronary intervention.

- For high-risk patients with unstable angina or non-Q-wave myocardial infarction the intravenous use of the glycoprotein IIb/IIIa inhibitors (consistent with current UK licensing), in addition to aspirin and low (adjusted) dose unfractionated heparin, is recommended.
- In unstable angina, raised blood levels of troponin should be used to identify those at high risk.
- For patients undergoing acute or elective percutaneous coronary intervention, the intravenous use of GP IIb/IIIa inhibitors (consistent with current UK licensing) is recommended.

are not mentioned in the NSF but were the subject of a National Institute for Health and Clinical Excellence (NICE) appraisal process; this was planned when the NSF was being drafted. The results of this appraisal were published in November 2000 (*Table 2*). The PRAIS-UK case series reported on the care of patients between May 1998 and February 1999 and use of these agents was restricted to adjunct use to PCI in 1.8% of patients.

Coronary angiography with a view to PCI or coronary artery bypass surgery

Unlike the other interventions described above, coronary angiography followed by revascularisation requires special equipment and training, which is not available in all hospitals. When first introduced, both PCI and coronary artery bypass grafts (CABGs) were used only when medical treatment had failed to control ischaemia; however, routine angiography followed by revascularisation in suitable cases is now proposed as a rational strategy for all patients without contraindications, given the pathological basis of UA.

The evidence base for an early invasive approach as opposed to a conservative one is conflicting; angina and readmission rates were reduced in two RCTs, but combined mortality and AMI rates were not significantly reduced.[17] A more recent trial including the use of glycoprotein antagonists in conjunction with the early invasive approach has produced more encouraging results.[24]

UK guidelines and the NSF suggest early coronary angiography only in cases where UA is recurrent or refractory to medical treatment, whereas US guidelines suggest that an early invasive approach may be applied to all hospitalised patients. In the recent UK case series, only 10% of patients underwent angiography during their index admission.

Aims and objectives of study

The overall aims of the research were:

- to identify and prioritise key decision problems about the medical management of non-ST elevation ACS in current UK practice
- to undertake a systematic review of relevant RCTs and previous economic evaluations
- to construct a decision-analytical model for the most important problem, and populate this using the results of the systematic review and observational UK data
- to identify priorities for, and the value of, specific future research, using value of information techniques.

The objectives were:

- to construct a list of decision problems concerning the management of UA for possible study (shown below)
- to examine published clinical practice guidelines concerning these decision problems
- to assess the degree of uncertainty currently perceived by clinicians in the NHS concerning these decision problems
- on the basis of the above, to select the most relevant decision problem
- to identify management options in the current NHS relevant to the chosen decision problem, and construct a decision-analytical model
- to undertake a systematic review of trials to estimate selected model parameters
- to identify the most appropriate unpublished data, to estimate model parameters not available from the systematic review
- to examine the robustness of the model's conclusions using sensitivity analysis
- to use the expected value of perfect information (EVPI) technique to recommend further research help to inform priority-setting regarding further research.

The initial literature review and consultation with clinicians identified the following key decision problems, at the time when the research was considered for funding:

1a. Should a platelet adenosine diphosphate (ADP) receptor inhibitor (e.g. clopidogrel) be routinely used instead of aspirin for acute and long-term treatment?

1b. Should a platelet ADP receptor inhibitor be routinely used in aspirin-intolerant patients?
2a. Should subcutaneous LMWH replace intravenous heparin in all UA patients?
2b. Should routine use of intravenous hirudin replace intravenous heparin?
3a. Should intravenous IIb/IIIa inhibitor therapy be used routinely in particular high-risk patients as part of initial management?
3b. Should intravenous IIb/IIIa inhibitor therapy be used in high-risk patients only when not eligible for early revascularisation?
3c. Should intravenous IIb/IIIa inhibitor therapy be used routinely for all patients in whom revascularisation by PCI is planned?

This list of decision problems was used as the starting point for the prioritisation process, which is described in the following section.

Methods used to prioritise decision problems

Three sources of information were used together to prioritise the decision problems:

- consultations with clinical advisors (see Appendix 1 for names and specialities)
- review of clinical guidelines and policy documents
- postal survey of cardiologists.

The first of these was an informal process, which is not described further. The latter two involved more systematic data collection and are described below.

Review of clinical guidelines and policy documents

Objectives

The objective of this section of the review was to identify UK and international clinical guidelines and policy documents on the treatment of UA. The review included completed and ongoing systematic reviews commissioned to inform policy and carried out by organisations such as the NHS Centre for Reviews and Dissemination (CRD) and international equivalents.

Methods

Searches were carried out in January 2001. British Library staff searched the SIGLE database; all other literature searches were carried out by staff of the Nuffield Institute for Health with guidance from the CRD. Sources were searched back to 1994, the year in which the original Agency for Health Care Policy and Research guideline was published.[25] Most of the sources are websites with very basic interfaces. Simple subject terms (e.g. 'unstable angina', 'acute coronary syndromes') were therefore more appropriate than complex search strategies. The databases and search strategies used were as follows:

- UK databases and websites; search terms and strategies
  - NICE; simple subject terms
  - NHS HTA Programme; simple subject terms
  - DEC (Development and Evaluation Committee); simple subject terms
  - SIGN (Scotland) (Scottish Intercollegiate Guidelines Network); simple subject terms
  - Eguidelines; simple subject terms
  - HMIC (Health Management Information Consortium); angina* AND (guid* or policy or health-policy)
- International databases and websites; search terms and strategies
  - SIGLE (EU); simple subject terms
  - NHS CRD databases [DARE (Database of Abstracts of Reviews of Effectiveness), HTA, NHS EED (NHS Economic Evaluations Database)]; simple subject terms
  - TRIP (Turning Research Into Practice); simple subject terms
  - National Guideline Clearing House (USA); angina-unstable*:me
  - AHRQ (USA) (Agency for Healthcare Research and Quality); "angina, unstable"[mesh] AND guidelines
  - Cochrane Library; angina, unstable/AND (guidelines/OR practice guidelines/OR health policy/)
  - Pubmed (Pre-MEDLINE only); angina, unstable/AND (guidelines/OR practice guidelines/OR health policy/)
  - HealthSTAR; angina, unstable/AND (guidelines/OR practice guidelines/OR health policy/).

Search results

Twelve documents were identified. Ten of these were guidelines and two were systematic reviews carried out as part of the NICE technology appraisal.[23] Of the guidelines, six were from the UK,[9,18,26–29] two were from the USA[2,25] and two were from Australia.[30,31] One of the UK guidelines[29] was an update of another.[28]

Table 3 summarises the guidelines' answers to the seven key decision problems listed in the previous section: yes, no, equivocal or not covered. *Table 4* deals with each of the seven decision problems in

TABLE 3 *Extent to which clinical guidelines address selected decision problems*

Guideline	Commissioning details/outline of recommendations on UA/ACS	Treatment questions						
		1a	1b	2a	2b	3a	3b	3c
BCS, 2001:[18] Guideline for the management of patients with ACS without persistent ECG ST segment elevation	UA/non-Q-wave MI accounts for 120,000 UK hospital admissions every year Patients whose condition has stabilised, but who are at high risk of death or further cardiac events, should be referred for coronary angiography	No	NC	Yes (A)	NC	Yes (A)	NC	Yes (A)
Braunwald *et al*., 2000:[2] ACC/AHA guidelines for the management of patients with UA and non-ST-segment elevation MI (USA)	Summary of recommendations published in *Circulation*	No	Yes (A)	E	NC	Yes (A)	NC	Yes (A)
NHF/CSANZ, 2000:[31] Clinical practice guidelines diagnosis and management of UA (Australia)	Summary of recommendations published in the *Medical Journal of Australia*	No (A)	E	EI	No	E	NC	Yes (A)
NICE, 2000:[23] Guidance on the use of glycoprotein IIb/IIIa inhibitors in the treatment of acute coronary syndromes	For high-risk patients with UA/non-Q-wave MI, intravenous use of GPAs (in addition to aspirin and unfractionated heparin) is recommended Raised blood levels of troponin should be used to identify high-risk UA patients For patients undergoing acute/elective PCI, intravenous use of GPAs is recommended	NC	NC	NC	NC	Yes	NC	Yes
McDonagh *et al*., 2000:[9] Systematic review of clinical and cost-effectiveness of GPAs in medical management of UA*	Report produced by NHS CRD and commissioned by the NHS HTA programme on behalf of NICE This review informs the NICE guidance on GPAs (see above)	NC	NC	NC	NC	Yes/ not certain	NC	NC
Fischer *et al*., 2000:[27] Clinical and cost-effectiveness of GPAs in association with PCI*	Report produced by NHS CRD and commissioned by the NHS HTA programme on behalf of NICE This review informs the NICE guidance on GPAs (see above)	NC	NC	NC	NC	NC	NC	Yes/ not certain
DEC, 2000:[29] Dalteparin and enoxaparin for UA and non-Q-wave MI: update	LMWH offer important advantages over UEH in terms of convenience and time saved to both patients and staff Short-term treatment of unstable CAD using enoxaparin is strongly supported Short-term treatment of unstable CAD using dalteparin is not proven	NC	NC	Yes (A)	NC	NC	NC	NC
DEC, 1999:[28] LMWH (dalteparin and enoxaparin) compared with UFH for UA and non-Q-wave MI	Following discussion with the NHS Executive this report was withdrawn	–	–	–	–	–	–	–

continued

TABLE 3 *Extent to which clinical guidelines address selected decision problems (cont'd)*

Guideline	Commissioning details/outline of recommendations on UA/ACS	Treatment questions						
		1a	1b	2a	2b	3a	3b	3c
Eccles *et al*., 1998:[32] North of England evidence-based guideline development group guideline on use of aspirin as secondary prophylaxis for vascular disease in primary care	Patients with suspected UA to be treated with 75 mg aspirin daily for 18 months They should then be treated in accordance with the accompanying recommendations on stable angina	No (A)	NC	NC	NC	NC	NC	NC
NHS Executive, Northern and Yorkshire Regional Office, 1998:[26] Guidelines for the management of patients with IHD	UA in primary care: give aspirin and refer patient to hospital UA in secondary care: treat with heparin, aspirin and/or antianginal drugs High-risk patients: refer for angiography with a view to revascularisation (PCI or CABG)	NC	EI	NC	NC	NC	NC	NC
National Health and Medical Research Council, 1996:[30] Clinical practice guidelines: diagnosis and management of unstable angina (Australia)	Updated and adapted for Australian use from Braunwald's AHCPR guideline (see below)	NC	Yes (B)	EI	NC	NC	NC	Yes (A)
Braunwald *et al.,* 1994,[33] Unstable angina: diagnosis and management. Clinical practice guideline (USA)	Many suspected UA patients can be discharged home after adequate evaluation Patients with acute IHD judged to be at intermediate or high risk of complications should be hospitalised for careful monitoring of their clinical course Intravenous thrombolytic therapy should not be administered without evidence of AMI Non-invasive assessment of prognosis aids selection of appropriate therapy Coronary angiography is appropriate for patients judged to be at high risk of cardiac complications or death based on their clinical course or results of non-invasive testing	NC	Yes (B)	NC	NC	NC	NC	NC

BCS, British Cardiac Society; ACC, American College of Cardiology; AHA, American Heart Association; NHF, National Heart Foundation; CSANZ, Cardiac Society of Australia and New Zealand; NC, not covered; E, equivocal; CAD, coronary artery disease; IHD, ischaemic heart disease.

TABLE 4 *Details of guideline content for selected decision problems*

Guideline	Answers and treatment recommendations	Notes
Question 1a: Should a platelet ADP receptor inhibitor (e.g. clopidogrel) be routinely used instead of aspirin for acute and long-term treatment?		
BCS, 2001[18]	No (A): all confirmed ACS patients should be given aspirin unless contraindicated	Alternatives to aspirin not discussed
Braunwald *et al.*, 2000[2]	Acute, No (A): "antiplatelet therapy should be initiated promptly. Aspirin is the first choice and is administered a.s.a.p. after presentation and continued indefinitely" Postdischarge, No (A): "aspirin 75 to 325 mg/day in the absence of contraindications"	Contraindications to aspirin are briefly outlined
NHF/CSANZ, 2000[31]	No (A): "aspirin should be given to all patients unless there is	The cost of clopidogrel precludes its general use when aspirin has proven efficacy in cardiovascular disease
Eccles *et al.*, 1998[32]	No (A): "patients with suspected UA should be treated with 75 mg aspirin daily for 18 months", then in accordance with the accompanying recommendations on stable angina	Based on trials published before the introduction of newer antiplatelet treatments (e.g. clopidogrel)
NHMRC, 1996[30]	No (A): "all patients … should receive regular aspirin … unless a definite contraindication is present …"	Guideline pre-dates introduction of clopidogrel
Braunwald *et al.*, 1994[25]	No (A): "all patients with UA should receive aspirin unless they have documented hypersensitivity …"	Guideline pre-dates introduction of clopidogrel
Question 1b: Should a platelet ADP receptor inhibitor be routinely used in aspirin-intolerant patients?		
Braunwald *et al.*, 2000[2]	Acute, Yes (A): clopidogrel or ticlopidine "should be administered to patients unable to take aspirin …" Postdischarge, Yes (A): "clopidogrel 75 mg/day in patients with a contraindication to aspirin"	Clopidogrel is preferable to ticlopidine as it has a better safety profile
NHF/CSANZ, 2000[31]	Yes (D, but see note): "clopidogrel may be a useful alternative when there is intolerance to aspirin"	Falls short of recommending clopidogrel routinely for all aspirin-intolerant patients
Eccles *et al.*, 1998[32]	No (A): "the benefits of using aspirin in the secondary prophylaxis of vascular disease considerably outweigh the attributable risks of gastrointestinal or cerebrovascular bleeding" No (D): "use of aspirin in the secondary prophylaxis of vascular disease is cost effective"	Recommendations "apply only in the absence of recognised cautions …", etc., documented in BNF; they also pre-date newer agents, e.g. clopidogrel
NHMRC, 1996[30]	Yes (B): "patients unable to take aspirin … may be started on ticlopidine 250 mg twice per day"	"Initial treatment with heparin is especially important in these patients" due to delayed onset of antiplatelet activity; pre-dates clopidogrel
Braunwald *et al.*, 1994[33]	Yes (B): "patients unable to take aspirin … should be started on ticlopidine 250 mg twice a day …"	Guideline pre-dates introduction of clopidogrel

continued

TABLE 4 *Details of guideline content for selected decision problems (cont'd)*

Guideline	Answers and treatment recommendations	Notes
Question 2a: Should subcutaneous LMWH replace intravenous heparin in all UA patients?		
BCS, 2001[18]	Yes (A): "LMW heparin should be given for at least two days, and for up to eight days or longer in cases of recurrent ischaemia or where myocardial revascularisation is delayed or contraindicated"	Notes that subcutaneous LMWH is easier to use than intravenous UFH
Braunwald *et al.*, 2000[2]	E: "parenteral anticoagulation with intravenous UF heparin or with subcutaneous LMW heparin should be added to antiplatelet therapy with aspirin, or a thienopyridine (clopidogrel or ticlopidine)"	No general recommendations on UFH versus LMWH are given
NHF/CSANZ, 2000[31]	No: high-risk patients to be treated with aspirin plus "either LMW heparin or i.v. tirofiban with UF heparin (A)"; however, i.v. tirofiban plus UFH are preferred where LMWH fails (D) or when an invasive strategy is planned (A)	"Enoxaparin is superior to UF heparin in reducing death and MI (A), whereas dalteparin and nadroparin are not (A)"; levels of risk defined
DEC, 1999[28]	Yes (A): RCTs demonstrate that enoxaparin has clinical and cost advantages over UFH. There is not yet adequate trial evidence to compare dalteparin with UFH	"Cost implications are likely to depend on local revascularisation practice"
NHMRC, 1996[30]	No (A): i.v. heparin to be started as soon as intermediate/high-risk UA is diagnosed; however, "subcutaneous heparin might be considered as an alternative to i.v. heparin" during acute intensive management, and LMWH might be considered both during and after the acute intensive phase of management	Tables, etc., included to help define level of risk
Braunwald *et al.*, 1994[33]	No (A): "beta blockers and i.v. heparin are indicated for patients with intermediate- and high-risk UA …"	Guideline pre-dates introduction of LMWH
Question 2b: Should routine use of intravenous hirudin replace intravenous heparin?		
NHF/CSANZ, 2000[31]	No	Hirudin is "not available for clinical use in Australia"
Question 3a: Should intravenous IIb/IIIa inhibitor therapy be used routinely in particular high-risk patients as part of initial management?		
BCS, 2001[18]	Yes (A): "Treatment with an intravenous small molecule platelet glycoprotein IIb/IIIa inhibitor for up to 96 hours should be given to ACS patients at high risk of an adverse outcome"	Small molecule = tirofiban or eptifibatide
Braunwald *et al.*, 2000[2]	Yes (A): "A platelet GP IIb/IIIa receptor antagonist should be administered … to patients with continuing ischaemia or with other high-risk features"	Guideline includes tables, etc., to support risk assessment
NHF/CSANZ, 2000[31]	Equivocal: either IV tirofiban with UFH or LMWH alone recommended for high-risk patients (A)	Table for risk stratification provided, but no guidance on choosing between the two alternative strategies for high-risk patients

continued

TABLE 4 *Details of guideline content for selected decision problems (cont'd)*

Guideline	Answers and treatment recommendations	Notes
NICE, 2000[23]	Yes: "For high-risk patients with UA/non-Q-wave MI, intravenous use of GP IIb/IIIa inhibitors …, in addition to aspirin and low (adjusted) dose UF heparin, is recommended"	Ideally, "raised blood levels of troponin should be used to identify those at high risk"; alternative markers of "high risk" are also described
[**Question 3b** was omitted, as it was not addressed by any guidelines]		
Question 3c: Should intravenous IIb/IIIa inhibitor therapy be used routinely for all patients in whom revascularisation by PCI is planned?		
BCS, 2001[18]	Yes (A): "An intravenous platelet glycoprotein IIb/IIIa inhibitor should be administered to ACS patients with elevated cardiac troponin who are scheduled to undergo PCI using UF heparin"	Treatment should commence before intervention
Braunwald *et al.*, 2000[2]	Yes (A): "A platelet GP IIb/IIIa receptor antagonist should be administered … to patients in whom a PCI is planned"	Eptifibatide and tirofiban are approved for this use. Abciximab may also be used for 12–24 hours in patients scheduled to have a PCI within 24 hours
NHF/CSANZ, 2000[31]	Yes (A): "i.v. tirofiban and UF heparin are particularly recommended in high-risk patients for whom an invasive strategy is planned"	Risk stratification table and decision trees on invasive strategies are provided
NICE, 2000[23]	Yes: "For patients undergoing acute or elective PCI, the intravenous use of GP IIb/IIIa inhibitors … is recommended"	Economic evaluations suggest a cost-effectiveness range of £7000–11,500 per LYG
NHMRC, 1996[30]	Yes (A): "patients with UA undergoing PTCA should be treated with peri-procedural platelet IIb/IIIa receptor antagonists and pre-treatment heparin"	

BNF, British National Formulary; LYG, life-year gained.

turn and describes the guideline recommendations in more detail. Where possible, recommendations are categorised as A, B, C or D (see below) according to the strength of the evidence on which they are based:[32]

Categories of strength used in guideline statements

Strength of evidence:

Ia evidence from meta-analysis of RCTs
Ib evidence from at least one RCT
IIa evidence from at least one controlled study without randomisation
IIb evidence from at least one other type of quasi-experimental study
III evidence from descriptive studies, such as comparative studies, correlation studies and case–control studies
IV evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

Strength of recommendations:

A directly based on category I evidence
B directly based on category II evidence or extrapolated recommendation from category I evidence
C directly based on category III evidence or extrapolated recommendation from category I or II evidence
D directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence.

The CRD and NICE reviews marked with an asterisk in *Table 3* are not included in *Table 4*.

These are literature reviews carried out to inform the NICE guidance,[23] and as such examine the current state of knowledge about glycoprotein IIb/IIIa antagonists (GPAs) rather than make recommendations on their use.

Conclusions from review of guidelines

Clinical guidelines were less helpful in the identification of areas of uncertainty than anticipated. There are two main reasons:

- Several guidelines were published before some of the drugs featured in the shortlist of decision problems became available for the management of non-ST elevation ACS.
- Guidelines lacked the detail necessary to address the decision problems.

There were no absolute conflicts between guidelines; that is, "yes" and "no" in response to the same decision problem.

Survey of clinicians

Background and aim

One of the overall goals of the research was to ensure that the focus of the model and systematic review was as relevant as possible to actual NHS practice. To be relevant, the focus needed to be on a decision problem around which there was genuine uncertainty.

The review of clinical guidelines did not clearly distinguish the level of uncertainty associated with each of the shortlisted problems. A survey of clinicians was therefore undertaken, with the aim of identifying:

- the extent to which cardiologists agreed on whether the relevant drugs should be used in particular cases
- their perceptions of how much uncertainty was associated with these hypothetical treatment decisions.

Method

A one-page self-completed questionnaire was mailed to 385 consultant cardiologists who were listed as such on a database for medical mail companies that was obtained from the Royal College of Physicians. The questionnaire was sent at the end of February 2001. The covering letter stated that this was a survey of consultant cardiologists' opinions on current practice in the management of UA, to assist with a health technology assessment. Only responses received before the presentation of the CURE trial in late March 2001 were analysed and no attempts were made to contact non-responders.

The first part of the questionnaire consisted of brief descriptions of four hypothetical patients with UA, and a list of possible treatments (clopidogrel in place of aspirin, unfractionated heparin, low molecular weight heparin, and glycoprotein antagonists). Respondents were asked to state in each case whether or not they would administer each treatment and the degree of certainty they held about each decision, using a Likert scale from 1, completely uncertain, to 6, completely certain This was not a previously validated instrument. The hypothetical cases are listed below:

1. A 78-year-old man with chest pain for 4 hours before admission to a district general hospital (DGH). ST-segment depression anteriorly and troponin positive. Patient declined intervention.
2. A 77-year-old woman with history of previous MI and peripheral vascular disease, admitted with several hours of chest pain to a DGH. ST depression anteriorly and troponin positive. Continues to have chest pain 48 hours after admission. Accepted for angiography; proceed within the next 24 hours.
3. A 60-year-old woman with diabetes, two previous MIs and known diffuse CAD. Not suitable for angioplasty or CABG. Admitted with unstable angina. ST depression and troponin positive and the pain is not settling.
4. A 45-year-old man, no previous history, admitted to his local DGH with chest pain at rest. ST depression in the inferolateral leads, continues to have pain and ST depression in the same territory. Accepted for angiography; proceed within the next 24 hours.

The choice of responses is shown in *Table 5*.

This statement preceded the second part of the questionnaire:

> "The National Institute of Clinical Excellence [NICE] recommended the use of intravenous glycoprotein IIb/IIIa antagonists in the following situations:
>
> 1. High-risk patients with unstable angina or non-Q-wave myocardial infarction
> 2. Patients undergoing acute or elective percutaneous coronary intervention."

In the second part of the questionnaire respondents were asked to estimate what

TABLE 5 *Choice of responses*

(All receive analgesia, aspirin, β-blockers and i.v. nitrates)	Would you administer this treatment?	Degree of certainty with which you hold your opinion
Clopidogrel (in place of aspirin)	Y/N	6 5 4 3 2 1
UFH	Y/N	6 5 4 3 2 1
LMWH	Y/N	6 5 4 3 2 1
Abciximab	Y/N	6 5 4 3 2 1
Small molecule GPA	Y/N	6 5 4 3 2 1

proportion of ACS cases in their own institution would receive GPAs (a) before any decision on angiography and proceed, and (b) after a decision on angiography and proceed. They were asked to make this estimate for (a) now and (b) in 6 months' time. A similar question was asked about use in conjunction with elective PCI as the guidance also recommended this.

Respondents were also asked about their preference between the currently licensed GPAs. To examine the characteristics of respondents, they were asked whether they practised in a DGH or a cardiac centre or teaching hospital, whether they were interventionists or non-interventionists, and their year of primary qualification.

Results

Ninety-seven questionnaires were returned, a response rate of 25%. Thirty-seven per cent of these responses were from teaching hospitals or cardiac centres, 36% described themselves as interventionists and 44% obtained their basic medical qualification in 1980 or before.

The results of the first part of the questionnaire are shown in *Table 6* with the percentage of No or Yes answers, and the certainty scores No and Yes responses, together with a mean weighted score.

There was low intended use of clopidogrel, with moderate certainty scores. Use of clopidogrel was greater in the higher risk cases 2 and 4, possibly in anticipation of stent placement during the intervention. There was also a strong preference for LMWH instead of UFH. The low use of UFH increased in the patients who were accepted for angiography and proceed.

Overall, there was high intended use of GPAs. This is despite lower certainty scores than for the other agents, as shown in *Figure 4*. There was 92% and 93% overall use of GPAs for the two patients who were accepted for angiography and proceed (cases 2 and 4), with about 50% of respondents choosing small molecule GPA and the other 50% choosing abciximab. For the two cases who were not undergoing intervention, the overall use of GPAs was 57% in case 1 and 76% in case 3, with the vast majority of respondents choosing small molecule GPA.

Figure 4 summarises the degree of certainty for Yes and No answers for the various possible treatments, and the overall score for each drug. These were: clopidogrel = 4.82, UFH = 5.21, LMWH = 5.48, abciximab = 4.78, small molecule GPA = 4.69.

The results of the second part of the questionnaire are shown in *Table 7*, as the percentage of cardiologists who expected to be using GPAs, in their own clinical settings, in less than 20%, 20–49%, 50–89% and at least 90% of the time, now and 6 months later.

Discussion

A specific focus for the review was sought, based on both clinical priority and existing uncertainties. Review of the pathophysiology of UA highlights the great importance of thrombus formation in disease causation. Consequently, treatments designed to prevent thrombus assume a clear importance. Secondarily, it is apparent that there is an absolute need for RCTs to permit evaluation of the effectiveness of any given treatment strategy. Once again, these have most frequently evaluated treatments that are able to prevent thrombus formation.

Published guidelines for the treatment of UA patients were reviewed to identify areas of consensus and also areas of uncertainty. This evaluation was influenced by the date on which the guidelines were drafted, and also the scope of treatment options selected for comment. No absolute discordance in recommendations was found, but more recent clinical evidence had not been available at the time that many of the guidelines were drafted. Consequently, the reviewers also sought to evaluate the current views of practising clinicians, regarding both priority

TABLE 6 *Responses to case vignettes*

	No (%)	Yes (%)	Certainty (out of 6) No	Certainty (out of 6) Yes	Mean certainty (out of 6)
Question 1 Clopidogrel	90	10	4.7	4.9	4.7
UFH	86	14	5.2	5.7	5.3
LMWH	8	92	4.1	5.6	5.5
Abciximab	93	7	4.6	4.5	4.6
Small molecule GPA	44	56	3.9	5	4.5
Question 2					
Clopidogrel	71	29	4.8	5.0	4.9
UFH	71	29	5.0	5.3	5.1
LMWH	22	78	4.9	5.6	5.5
Abciximab	48	52	4.5	5.0	4.8
Small molecule GPA	45	55	4.2	5.2	4.8
Question 3					
Clopidogrel	70	30	4.9	4.6	4.8
UFH	85	15	5.2	5.3	5.2
LMWH	7	93	4.3	5.6	5.5
Abciximab	94	6	4.8	4.8	4.8
Small molecule GPA	25	75	4.2	4.8	4.7
Question 4					
Clopidogrel	65	35	4.8	5.1	4.9
UFH	72	28	5.2	5.5	5.3
LMWH	23	77	5.1	5.6	5.5
Abciximab	40	60	4.6	5.2	5.0
Small molecule GPA	49	51	4.3	5.4	4.9

Certainty scale: 1 = completely uncertain; 6 = completely certain.

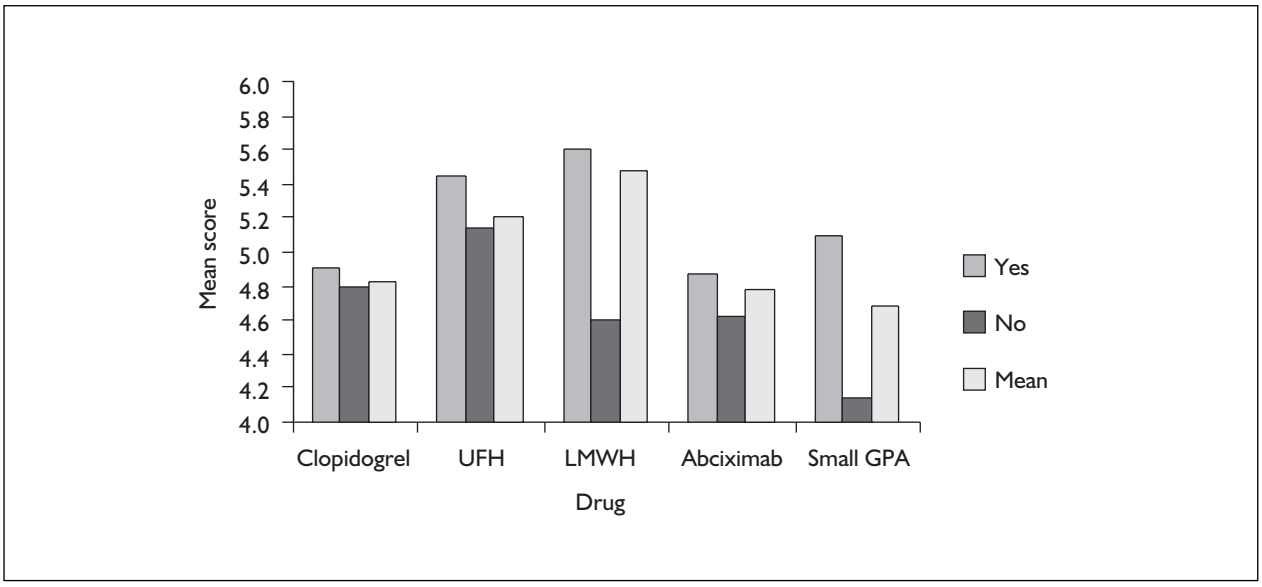

FIGURE 4 *Mean certainty by drug and intended usage*

TABLE 7 *Estimated present and future rates of use of GPAs*

	< 20%	20–49%	50–89%	⩾90%
Elective PCI now	60%	23%	11%	6%
Elective PCI in 6 months	28%	38%	26%	8%
UA before decision on angiography now	88%	6%	3%	3%
UA before decision in 6 months	35%	48%	9%	8%
UA after decision now	69%	13%	13%	5%
UA after decision in 6 months	28%	35%	25%	12%

The wording of the first question was "In your institution, for patients undergoing elective PTCA, do you administer a IIb/IIIa antagonist? (a) In < 20%, (b) In 20–50%, (c) In 50–90%, (d) In > 90%", with corresponding wording for the other questions.
PTCA, percutaneous transluminal coronary angioplasty.

areas (based on perceived benefits for patients) further selected on the basis of ongoing uncertainty.

The first part of the questionnaire showed low rates of use of clopidogrel, which was not surprising given that this pre-dated publication of the results of the CURE trial.[22] Although intended rates of use of GPAs were higher, there was greater uncertainty than for any of the other treatments.

The second part of the questionnaire showed clinicians' expectations of an increase in use of GPAs over a period of 6 months. However, this increase did not match their rate of use of these drugs in the hypothetical cases in the first part of the questionnaire or NICE's recommendations. The explanation for this is either that clinicians did not believe that their hospitals could implement the NICE guidelines or it may reflect their degree of uncertainty about appropriate use expressed in the first part of the questionnaire, or that not all patients seen in routine practice were captured by the case scenarios.

Conclusion of the decision problem prioritisation

Use of glycoprotein antagonists in patients with UA was identified as the priority area for decision modelling on the following basis:

- Review of pathophysiological and pharmacological data showed that these drugs act to prevent thrombus formation in an innovative and potent manner, that is, selective inhibition of platelet IIb/IIIa receptors.
- Review of published guidelines showed incompleteness and uncertainty with regard to the best strategy for use of GPAs in patients with UA.
- In the clinical survey the average 'certainty index' for both large and small molecule GPAs was lower than for other drugs considered. The magnitude of the differences observed was small and whether such differences in responses to a postal questionnaire can validly be extrapolated to the NHS as a whole is uncertain.
- Only a small minority of cardiologists surveyed stated that GPAs were used in accordance with the NICE guidance at present, and expectations of change over the following 6 months were for only a modest increase. Even if there had been extreme response bias such that all non-responders were highly compliant with NICE guidance, which seems unlikely, it would still suggest that about one-third of hospitals were non-compliant. This discordance between NICE guidance and intended practice suggested that the decision was a problematic one and that a model might be useful in helping to refine future policy.
- Reports in the medical and popular media stated that some cardiologists had expressed the opinion that NICE guidance on GPAs was incorrect. The main debate at the BCS Conference in Manchester 2000 was a motion supporting the NICE guidance and this was rejected on a show of hands by over 95% of those present.

The decision model

Background

The aim of developing a decision-analytical model was to inform the development of practice in the current NHS. The initial[9,27] and updated[33] rapid reviews of GPAs for this indication for the NICE had identified serious limitations in published cost-effectiveness analyses.

Their 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 the UK. This is particularly important with GPAs, because of the possibility that much of their effectiveness arises in conjunction with PCIs, the use of which is traditionally lower in the UK than in many developed countries.[8] Hence, baseline clinical event rates, relative risk reductions (RRRs), resource utilisation, costs and, therefore, cost-effectiveness may differ in the UK from those estimated in published studies.

A second problem is the short follow-up of the trials, typically no more than 6 months and often as little as 30 days. However, the use of GPAs to reduce the risk of mortality and non-fatal AMI 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 none of the early GPA trials included a prospective economic evaluation as part of their design. Existing cost-effectiveness studies usually relate changes in costs, conditional on the use of GPAs, to differential outcomes that 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 (QALYs) 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, and a new model was required.

Relationship between the model and updated systematic review

The decision-analytical model builds on the trial-based evidence summarised in the updated systematic review.[34] 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 is systematically to identify, summarise and critically appraise the results of all relevant studies. The model has been designed to address specific issues faced by a decision-maker in assessing the potential cost-effectiveness of GPAs in ACS. It assesses the relevance of all 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.

Treatment strategies under comparison

Four treatment strategies have been identified as being relevant options for the use of GPAs in ACS, the first three of which are the same as those used to classify the trials found in the systematic review:

- 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 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. UFH or LMWH, aspirin, nitrates and analgesia), without the use of GPA.

Full details of the model are provided in Chapter 3. The next chapter describes the results of the systematic review undertaken to inform the parameters of the model relating to the effectiveness of GPAs in each of the alternative treatment strategies.

Clinical involvement

Clinicians were involved at all stages of the model development and generation of results and conclusions. There were three main levels of clinician involvement.

First, one of the applicants (AH) was a practising cardiologist. He was involved at all stages from inception through to final publication of the

results. He supervised an audit of PTCA in Leeds which was used in the model.

Second, clinicians from two other cardiology centres (Nottingham and the Royal Brompton) supplied data that were used in the model, contributed to the analysis and interpretation, and are joint authors of this report.

Finally, there was a wider group of clinical advisors, who participated in two half-day meetings to consider preliminary results and advise on the range of sensitivity analyses undertaken. The membership of this group is listed in Appendix 1.

Chapter 2

Systematic review

This chapter describes the systematic literature review that was undertaken in preparation for the decision model.

The rationale, aims and methods of the review are described here in full, but only part of the results are presented in detail, as most of these have already been published in a separate HTA monograph as an updated Technology Assessment Review for NICE.[34] The review of economic literature relating to the use of glycoproteins in ACS patients is also contained in that monograph.[34]

Aims

The aims of the systematic review were:

- to identify and update if necessary previous systematic reviews of effectiveness, and economic evaluations of cost-effectiveness, that appeared relevant to the decision problem selected for modelling
- to identify and appraise relevant studies of clinical effectiveness, that is, RCTs of the use of GPAs in high-risk non-ST elevation ACS
- to extract and pool data for use in the decision model.

Rationale: requirements of the decision model

As described in Chapter 1, the decision problems chosen for modelling were as follows:

- Should GPAs be used routinely in particular high-risk patients as part of initial management?
- Should GPAs be used in high-risk patients only when early revascularisation is not considered suitable?
- Should GPAs be used routinely for all patients in whom early PCI is planned?

It was concluded that the systematic review should ideally include the following:

- RCTs of GPAs as part of initial medical management in specified high-risk groups, with and without consideration for early PCI
- RCTs of GPAs for all patients scheduled for early PCI.

The main difficulty anticipated in the conduct of the review was the definition of high-risk patients. "Estimation of the level of risk [in UA] is a multivariable problem that cannot be accurately quantified" (Braunwald and colleagues, 2000,[2] p. 979), so the definition of high risk was not expected to be consistent between trials. Moreover, trials may not report separate results for high-risk groups or may not include details of how such patients were defined.

Any definition of high-risk groups chosen for use here therefore needed to take account of these uncertainties. A highly specific definition, for example based on raised troponin measurements, would offer the advantage of corresponding closely to the actual decision problem chosen, but would limit the amount of evidence available to be considered.

The review of clinical guidelines and other background (see Chapter 1) suggested that such a definition would result in very few trials being eligible for inclusion, so a much more inclusive definition was adopted: "those patients with non-ST elevation ACS either implicitly or explicitly identified as being at greater risk of adverse outcomes (death or non-fatal MI) than the overall population of ACS patients from which the study patients are drawn". Using this approach, acute hospital admission in itself could be taken to imply high risk because low-risk patients might be discharged from the accident and emergency department or managed as outpatients.

It was recognised that this might produce a very heterogeneous set of results, some trials including only patients definitely at high risk and others with a much more varied risk profile. It was therefore decided that a key requirement for the systematic review would be to record whether a high-risk group or groups had been defined, and if so how this had been done. It was anticipated that a sensitivity analysis of the results could then be undertaken, according to whether high risk had

been defined, and if so how precisely. In practice, this was possible only to a limited extent (see section 'Use of GPAs as part of initial medical management in high-risk ACS patients only', p. 57).

It was decided that the results of previous systematic reviews (if applicable) and the present searches should be able to identify subgroup analyses of high-risk groups as well as main reports. This did not affect the construction of search strategies (shown in Appendix 2), but extended the criteria normally used to choose papers from search results for further consideration.

The decision model required separate effectiveness results for each major clinical outcome rather than a composite measure. Nevertheless, such measures are favoured in trial reports because of the increased statistical power that they provide. Rates for adverse events such as bleeding were also required. Ideally, the model would also incorporate costs and quality of life measurements from the trials. The abstraction pro forma (see Appendix 3) was designed to include such details if available.

To maximise the number of patients included, trials of all intravenous glycoprotein agents were included, whether or not the agent concerned was currently licensed in the UK. The preliminary work to identify the key decision problem (see Chapter 1) had assumed a common class effect for intravenous GPAs and this was not challenged by the clinical advisors, although the biology of small molecule agents shows some important differences compared with abciximab.

Oral agents were excluded as they constitute a different subclass; early results had shown high rates of bleeding and a lack of effectiveness and none of the clinicians consulted considered that their use in the UK NHS was likely.

Previous systematic reviews

The Cochrane Database of Systematic Reviews (CDSR) and DARE were used to identify previous systematic reviews: details of the search strategies are shown in Appendix 4. The authors were also aware of two systematic reviews commissioned by NICE as part of its appraisal of GPAs undertaken in 2000,[9,27] which were too recent to be included on these databases. During the project, other papers were also discovered, which reviewed two or more GPA trials or combined their results. Where relevant, these are included below. Some of these papers may have been overlooked, as no systematic review for material of this type was conducted.

Towards the end of the project, an individual patient meta-analysis was published of one particular type of trial, concerning GPAs as part of initial medical management.[35] This is not described here, but was used in sensitivity analysis of the results of the decision model (see section 'Sensitivity analyses using alternative sources of baseline data', p. 53).

Two completed reviews and three protocols were found on CDSR. Neither of the completed reviews was appropriate for this study. One of the three protocols was relevant;[36] a copy of the completed review (which has since been published[9]) was obtained from the authors. The search on DARE identified one further relevant review.[37]

Both reviews are summarised in *Table 8*, together with the NICE reviews and three others, which were discovered non-systematically. The extent to which each review appeared to meet the requirements of the present study is shown in the final column.

Conclusions regarding previous systematic reviews and approach to the present review

The following conclusion was drawn.

- McDonagh[9] and Fischer[27] (the previous NICE reviews) between them provided a comprehensive search strategy, which would have identified all relevant RCTs and published subgroup analyses up to their respective cut-off dates. None of the previous reviews provided sufficient detail about the definition of high risk and how this affected results

The authors therefore decided on the following approach to the present systematic review.

- Update searches were performed using a combination of the search strategies of the NICE reviews to identify main reports and subgroup reports published more recently.
- The search output of the NICE reviews was re-examined to identify any subgroup reports that had been excluded by these reviews. (Some subgroup reports were included by McDonagh, but it was unclear whether all such reports had been.)
- In light of the results from main reports and initial findings of the decision model, this re-examination was limited to four main high-

TABLE 8 *Previous systematic reviews*

Details of review	Trials and data included	Relevance to chosen decision problem
Bhatt and Topol, 2000[37] Review to determine optimal role of GPAs in the treatment of ACS	Ten double-blind RCTs of GPAs vs placebo	Search strategy comprehensive; very little detail on subgroups (only UA and troponins); search for subgroup analysis not systematic; lamifiban trials not included
Bosch and Marrugat, 2001[36] Protocol for a Cochrane review on GPAs for ACS and PCI	RCTs, with/without blinding, of GPAs in patients with UA or AMI or undergoing PCI	Included use of GPAs as adjunct to stenting for all CHD, not just non-ST elevation ACS; no details on high-risk subgroups
McDonagh *et al.*, 2000[9]		Search strategy comprehensive; high-risk subgroup results limited to troponins
Fischer *et al.*, 2000[27]		Search strategy comprehensive; no subgroup results
Brown *et al*., 2000[38] Effect of GPAs on individual end-points (death, MI, refractory ischaemia and major bleeding) at 30 days in the management of UA or non-Q-wave MI	Meta-analysis of five RCTs of GPAs vs placebo	Search strategy not comprehensive; no subgroup results; did not look at use of GPAs as an adjunct to PCI
Cho *et al.*, 2000[39] Pooled analysis of RCT data on safety/efficacy of abciximab in women undergoing PCI	Data from EPIC, EPILOG and EPISTENT RCTs	Restricted to women; no systematic searching undertaken; use of GPAs in the medical management of ACS not considered
Dasgupta *et al*., 2000[40] Pooled analysis investigating occurrence of thrombocytopenia when GPAs are used in the management of ACS or PCI	Eight large RCTs of GPAs vs placebo; also case reports (total of 42 patients with thrombocytopenia)	Search strategy comprehensive; only included trials that reported on thrombocytopenia; excluded lamifiban trials

EPIC, Evaluation of 7E3 for the Prevention of Ischemic Complications; EPILOG, Evaluation in PCTA to Improve Long-term Outcome with abciximab GP IIb/IIIa blockade; EPISTENT, Evaluation of Platelet IIb/IIIa Inhibitor for Stent.

risk features: older age (70 years or older), troponin positivity, diabetes and ST depression on the admission ECG. These features were chosen in conjunction with the clinical advisory group, as representing the most important indicators of high risk about which data could be reasonably expected to have been published. The age cut-off of 70 years was derived from analysis of UK observational data [Prospective Registry of Acute Ischaemic Syndromes in the UK (PRAIS-UK)], which showed a discontinuity at that age in the relationship between age and outcome.[13] The re-examination was further limited to trials using GPAs as part of initial medical management, because these were the group of trials with relatively small effect sizes in whom it was anticipated that separate results from high risk subgroups may have an appreciable effect on the decision model.

- Lead authors of reports without subgroup results, or with inadequate detail for use in the decision model, were contacted once by letter and once by e-mail to request additional information. This produced only limited results (see below).
- Trials were classified into three groups, depending on the timing of use of GPA: (1) as part of initial medical management (strategy 1); (2) once scheduled for early invasive management (strategy 2); and (3) as an adjunct to PCI at the time of the procedure or up to 1 hour beforehand (strategy 3). These strategies formed the structure of the decision model described in Chapter 3.
- Outcomes that were needed for the decision model were abstracted.

Search strategy, quality assessment and data pooling

The following databases were searched for studies of effectiveness:

- MEDLINE
- EMBASE
- National Research Register (NRR)
- Conference Papers Index (CPI)
- Cochrane Controlled Trials Register (CCTR)
- Controlled-trials.com

The main database searches were carried out between 31 January and 2 February 2001, using strategies equivalent to a combination of the previous NICE searches but excluding oral agents. See Appendix 2 for details of databases, strategies and dates covered.

Two reviewers independently assessed titles and abstracts obtained from the update searches for inclusion, and re-examined output from the original NICE searches as described above. Any discrepancies were resolved by discussion. The criteria used to identify papers for further consideration were the same as those used for the NICE reviews, except that reports of subgroups were also included. Trials of the use of GPAs in conjunction with PCI were eligible if they included patients with UA. Economic evaluations met relevance criteria if they were cost-effectiveness analysis (including cost minimisation), cost–utility analysis or cost–benefit analysis of an intravenous GPA in UA or ACS, using any definition. Economic analyses of a GPA in conjunction with coronary angioplasty were included as long as UA or ACS patients were included in the trial population.

Data was abstracted by one reviewer and checked by another (see the template for effectiveness studies in Appendix 3: changes from the NICE template are shown in italics); data originally extracted for the NICE reviews were re-extracted to ensure that all information relevant for the modelling exercise was available. A third reviewer checked all data re-extraction and resolved any discrepancies in new data extraction.

Study quality assessment

All trials included in the review were assessed using a list of items indicating components of internal validity in a standardised fashion (Appendix 5). This is identical to that used in the CRD review for NICE;[9] hence, quality assessment of studies previously included in that review was not repeated.

Details on treatment, patients included and outcome phenomena were included in the main data extraction template (see Appendix 3). Two reviewers independently scored the internal and external validity. The reviewers were not blinded for names of authors, institutions, journals or the outcomes of the trials.

Pooling of data

Although the designs of the trials (see previous HTA monograph[9] and below) showed considerable heterogeneity suggesting that pooling of results was not advisable using the normal criteria for meta-analysis, the decision model required the best available overall estimates of the RRRs associated with each of the three groups of trials.

Results from each trial were therefore pooled across groups using a random effects analysis. This meant that both the uncertainty in the estimates of relative risk from each trial and the between-trial heterogeneity would be accounted for. Where a trial had more than one treatment arm, the arm that appeared most likely to be relevant to current NHS practice was selected; details are given in the results section below.

Not all trials published results at the time-point required for model input, namely 6 months. Where this was the case, RRRs at 30 days were used instead (four out of seven strategy 1 trials;[10,11,14,40] no strategy 2 trials; four out of 10 strategy 3 trials[42–45]). If neither 30-day nor 6-month data were available the trial was excluded; this applied to one small trial only.[46]

The effect of pooling data from two separate time-points was assessed by extrapolating the RRR for trials only reporting this at 30 days to 6 months using an exponential model. This made little difference.

Pooling of smaller groups of trials using similar methods was undertaken as required for particular sensitivity analyses as detailed in Chapter 3.

Search results

The previous reviews for NICE had identified a total of 17 relevant trials, published in 25 separate papers, three of which were subgroup analyses. One of these trials (Schulman and colleagues 1996[46]) only reported outcomes at 24 hours and so was unsuitable for use in the model. Another (PARAGON B[43]) has only been published as an abstract, but the full manuscript was supplied by the lead investigator for this review. Re-examination of the original search output for the previous reviews (1815 items) using the methods

TABLE 9 *Numbers of included papers (trials) by type and source*

Source	Update searches including websites	Miscellaneous[a]	McDonagh et *al.*[9]	Fischer et *al.*[27]
RCTs main reports	2 (2)	1 (1)[b]	5 (5)	15 (10)
RCTs subgroup reports	15 (6)[c]	1 (1)[d]	3 (2)[e]	–
Economics (excluding industry submissions)	6	3[f]	5	17

[a] Papers identified through means other than formal database searches.
[b] Unpublished PARAGON B manuscript supplied by lead investigator.
[c] PURSUIT: Hasdai (2000),[6,48] Akkerhuis (2000),[50] Dyke (2000),[51] Lincoff (2000),[52] Roe (2000),[53] Boersma (2000);[54] PRISM-PLUS: Theroux (2000);[55] PARAGON B: Newby (2001);[49] CAPTURE. Hamm (1999);[47] EPILOG: Cura (1999);[56] Keriakes (1998);[57] Kleiman (1998).[58] EPISTENT: Cho (2000);[59] Lincoff (2000).[60]
[d] Unpublished data (Topol EJ) concerning unstable angina patients in EPIC.
[e] PURSUIT: Mahaffey (1999);[61] McClure (1999).[62] PRISM: Heechen (1999).[63]

described above revealed four further subgroup reports that had not been included in the original reviews.[35,47–49] The update searches generated a total of 353 hits, of which 291 remained after duplicates were removed. Of these, 235 were suitable for transfer to a Reference Manager database. A total of 40 full papers was then obtained for closer examination. Of these, six economic studies and 12 subgroup reports of RCTs were selected.

Fifty-six hits (those from the CPI, Controlled-trials.com and the NRR) were unsuitable for transfer to Reference Manager. They were therefore printed out and examined by two reviewers in collaboration. Most of these referred to work in progress. Two appeared potentially relevant but on further investigation one was ineligible (CACHET) and the other had already been identified (GUSTO IV).

To ensure that no important late-breaking or ongoing clinical trials had been missed, additional searches of the following web-based registries were carried out on 15 May 2001:

- ACC, annual conference 2001, late-breaking clinical trials
- AHA, late-breaking clinical trials 2001
- BCS, annual conference 2001
- Cardiosource, ongoing and unpublished trials.

For URLs and search strategies, see Appendix 6. The following relevant completed trials were identified: GUSTO IV, ESPRIT, TARGET and TACTICS-TIMI18. No relevant ongoing trials were identified. Data from the above trials were subsequently obtained from published reports. GUSTO IV was a strategy 1 trial. ESPRIT and TARGET were strategy 3 trials. TARGET was not suitable for use in the decision model, as it was a head-to-head comparison of two GPAs. TACTICS was also unsuitable as GPAs were used in both arms.

In summary, *Table 9* shows the number of completed studies (including separately published subgroup analyses) featured in the present review.

Results: individual trials and subgroup reports

As described above, trials were classified according to which of the three strategies they most closely represented. *Table 10* shows the main and subgroup reports by strategy, and the subject of each subgroup report included.

Apart from the lamifiban trials (the first three trials listed under strategy 1), results from all the main reports are presented in the HTA monograph detailing the updated Technology Assessment Review for NICE[34] and so are not reproduced here.

Detailed abstraction of the lamifiban trials is shown in Appendix 7, the nine subgroup reports from PURSUIT in Appendix 8 and the subgroup reports from other trials in Appendix 9.

Lamifiban

Lamifiban is a small molecule GPA similar in pharmacokinetics to tirofiban and eptifibatide. Unlike the latter two agents, lamifiban is not licensed for use in the UK and so was not included in the recent NICE update review.[34] However, for the purpose of the decision model it was decided

TABLE 10 *Trials and subgroup reports by strategy*

Strategy and name	Main report(s)	Subgroup report(s); subject
Strategy 1: initial medical management		
Canadian Lamifiban Study	Theroux, *Circulation* – 1996[14]	–
PARAGON A	*Circulation* 1998[11]	–
PARAGON B	Conference proceedings[44]	Newby, 2001,[49] troponin status
PURSUIT	*N Engl J Med* 1998[65]	Boersma, 2000;[54] relation between baseline characteristics and outcome Hasdai, 2000;[48] outcomes by age group Hasdai, 2000;[6] cardiogenic shock Akkerhuis, 2000;[50] geographical variations Dyke, 2000;[51] early CABG Roe, 2000;[53] insignificant CAD Lincoff, 2000;[52] regional analysis of US patients Mahaffey, 1999;[61] analysis of stroke McClure, 1999;[62] analysis of thrombocytopenia
PRISM	*N Engl J Med* 1998[10]	Heeschen, 1999;[63] troponin status
PRISM-PLUS	*N Engl J Med* 1998[12]	Theroux, 2000;[55] diabetic patients
GUSTO IV	*Lancet* 2001[41]	–
Strategy 2: once scheduled for acute PCI		
CAPTURE	*Lancet* 1997[66]	Hamm, 1999;[47] troponin status
Strategy 3: adjunct to PCI		
EPIC	*N Engl J Med* 1994[67] *Lancet* 1994[68] *JAMA* 1997[69]	–
IMPACT II	*Lancet* 1997[45]	–
ESPRIT	*JAMA* 2001[70]	–
Harrington	*Am J Cardiol* 1995[71]	–
RESTORE	*Circulation* 1997[72]	–
EPILOG	*N Eng J Med* 1997[73] *Circulation* 1999[74]	Cura, 2000;[56] patients with complex lesions Kereiakes, 1998;[57] use of unplanned stents Kleiman, 1998;[58] diabetic patients
EPISTENT	*Lancet* 1998[75]	Cho, 2000;[59] diabetic women Lincoff, 2000;[60] diabetic patients Cura, 2000;[56] patients with complex lesions
ERASER	*Circulation* 1999[76]	–
Galassi	*Cardiologia* 1999[43]	–
Chen	*Chin Med J* 2000[42]	–

PARAGON, Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network; PRISM, Platelet Receptor Inhibition in Ischemic Syndrome Management; PRISM-PLUS, Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms; GUSTO, Global Use of Strategies To open Occluded coronary arteries in acute coronary syndromes; CAPTURE c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina; IMPACT, Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis; ESPRIT, Enhanced Suppression of Platelet Receptor GP IIb-IIIa using Integrelin Trial; RESTORE, Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis; ERASER, Evaluation of Reopro And Stenting to Eliminate Restenosis.

to include all intravenous agents within the class regardless of their licence status, so a brief description of the lamifiban trials and their results is included here, comparing these to the other agents. This is based on findings on lamifiban published by McDonagh and colleagues in the original NICE review.[9]

Three trials have been published:

- Phase II dose-finding study of approximately 200 patients, published in 1996
- Phase II/III study of approximately 2000 patients in 1998 comparing high- and low-dose lamifiban
- Phase III study using an intermediate dosage, completed in 1999 but not yet published in full.

The Phase II study[14] had a slightly lower validity assessment than the Phase II/III studies (PARAGON A[11] and PARAGON B[44]). There was imbalance among the groups with regard to baseline characteristics and prognostically significant variables, which were not adjusted for in the analysis of end-points. Other items not fully addressed were blinding (patients and persons implementing interventions) and registration of cointerventions, such as antianginal medications.

Four dose levels were tested against placebo. The results are presented separately, but were analysed based on low-dose (1 and 2 μg per minute combined) and high-dose (4 and 5 μg per minute combined) groups. A primary end-point was not stated. There were very few deaths or MIs during study drug infusion.

PARAGON A compared heparin alone with two doses of lamifiban (high and low) with or without heparin. This was a dose-finding Phase II/III study that was meant to identify the dose of lamifiban to be studied in a Phase III study (PARAGON B). The primary end-point was a composite end-point of death from any cause and non-fatal MI in the first 30 days. Secondary end-points were death and MI at 30 days, death and MI at 6 months, and death at 1 year. The validity assessment of this Phase II/III trial was lower than the Phase III study. Procedures of randomisation were not described, and blinding of patients and persons implementing interventions was not clear. Two per cent of patients assigned to lamifiban and 0.9% of patients assigned to placebo did not receive study drug.

Overall, 3% and 6.7% were lost to follow-up at 6 months and 1 year, respectively. The numbers lost in each treatment group were not stated. In addition, 73 participants were excluded from further analysis because of no events at 6 months and shorter than expected follow-up (<120 days). These patients were counted as lost to follow-up. Correspondence with a study investigator did not result in further clarification.

PARAGON B compared lamifiban with placebo. Outcomes were defined at 30 days postrandomisation. Based on the PARAGON A trial, PARAGON B used a 500-μg bolus of lamifiban followed by a 72-hour infusion that was dose-adjusted to renal function. Doses of 1 or 2 μg per minute were given depending on the calculated creatinine clearance rate.

The effect of lamifiban on death at 30 days and 6 months can be seen in *Figures 5* and *6*, respectively. Six-month results are only published for PARAGON B. Effect sizes are similar to other small molecule GPAs; none shows a statistically significant difference from placebo.

Effects on non-fatal MI at 30 days and 6 months can be seen in *Figures 7* and *8*, respectively. Results are similar to other small molecule GPAs.

Effects on the rates of revascularisation (PCI and CABG) during the first 30 days after admission can be seen in *Figures 9* and *10*. Theroux and colleagues[14] did not report this outcome. As with other GPAs used for strategy 1, there is a suggestion of lower rates associated with treatment, but this is not statistically significant.

As with other GPAs, the main concerns for adverse effects of lamifiban were related to an extension of its pharmacological effect: major and minor bleeding, and thrombocytopenia. The effect of lamifiban on the rates of major bleeds can be seen in *Figure 11* (PARAGON B did not report on this). As with other GPAs, there is evidence of an increased rate of major bleeds, but the number needed to harm is large, approximately 250. Other details are shown in Appendix 7.

In conclusion, lamifiban exhibits similar results to the other small molecule GPAs reviewed in the other HTA monograph.[34]

Pooled estimates (strategy 1)

To apply results of the review in the decision model, pooled estimates of the effect of GPAs for each strategy were required.

Some trials contained more than one intervention arm, so a decision about which arm to use in the

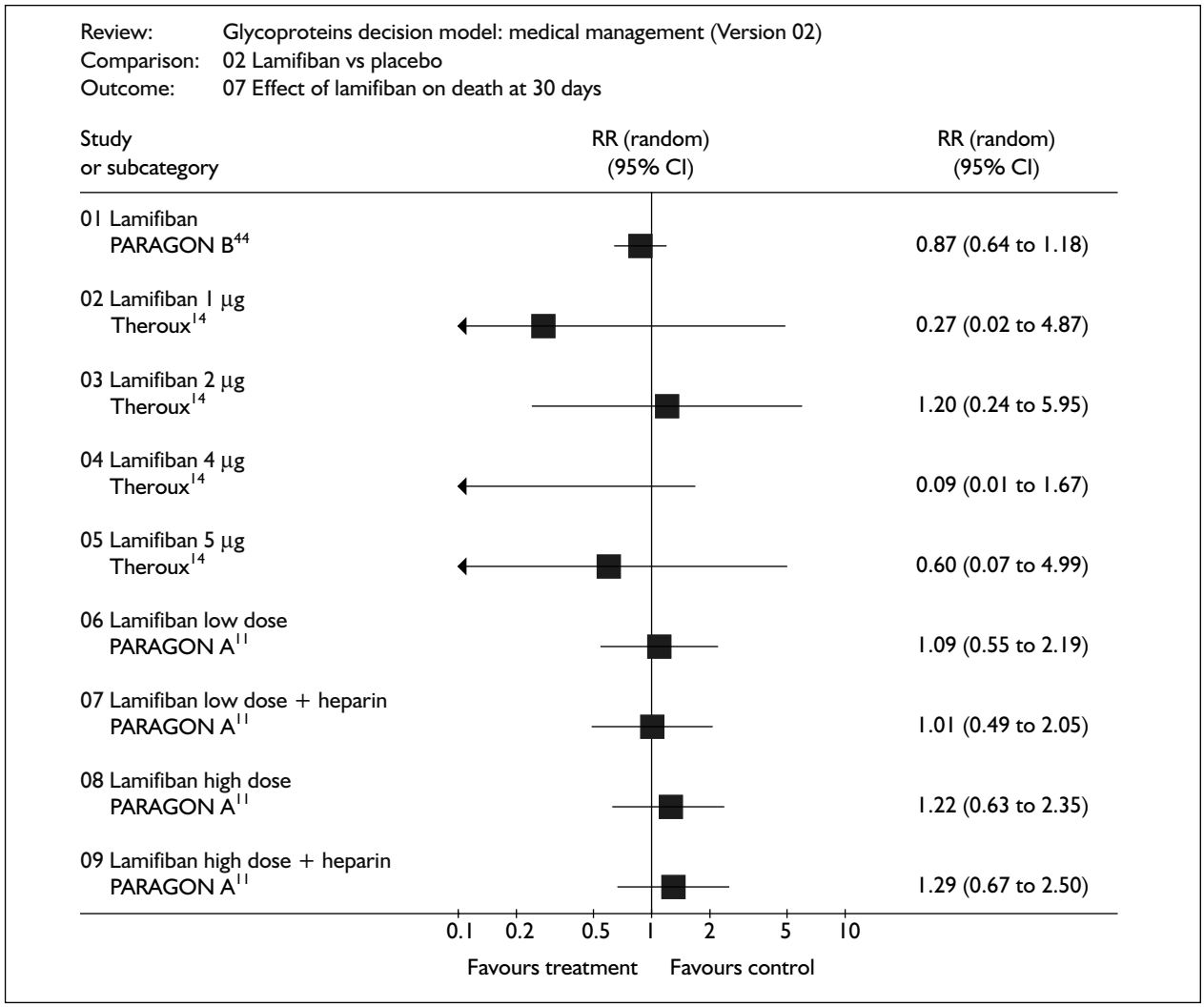

FIGURE 5 *Effect of lamifiban on 30-day death rates for patients receiving glycoproteins as part of medical management (strategy 1)*

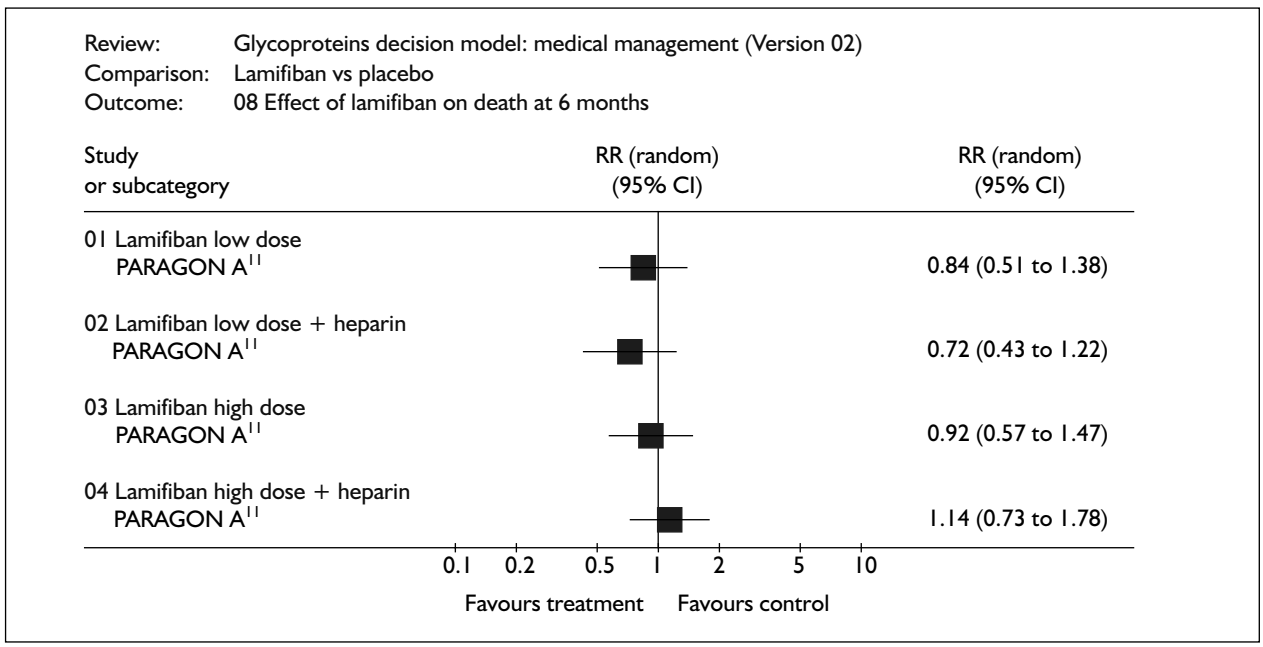

FIGURE 6 *Effect of lamifiban on 6-month death rates for patients receiving glycoproteins as part of medical management (strategy 1)*

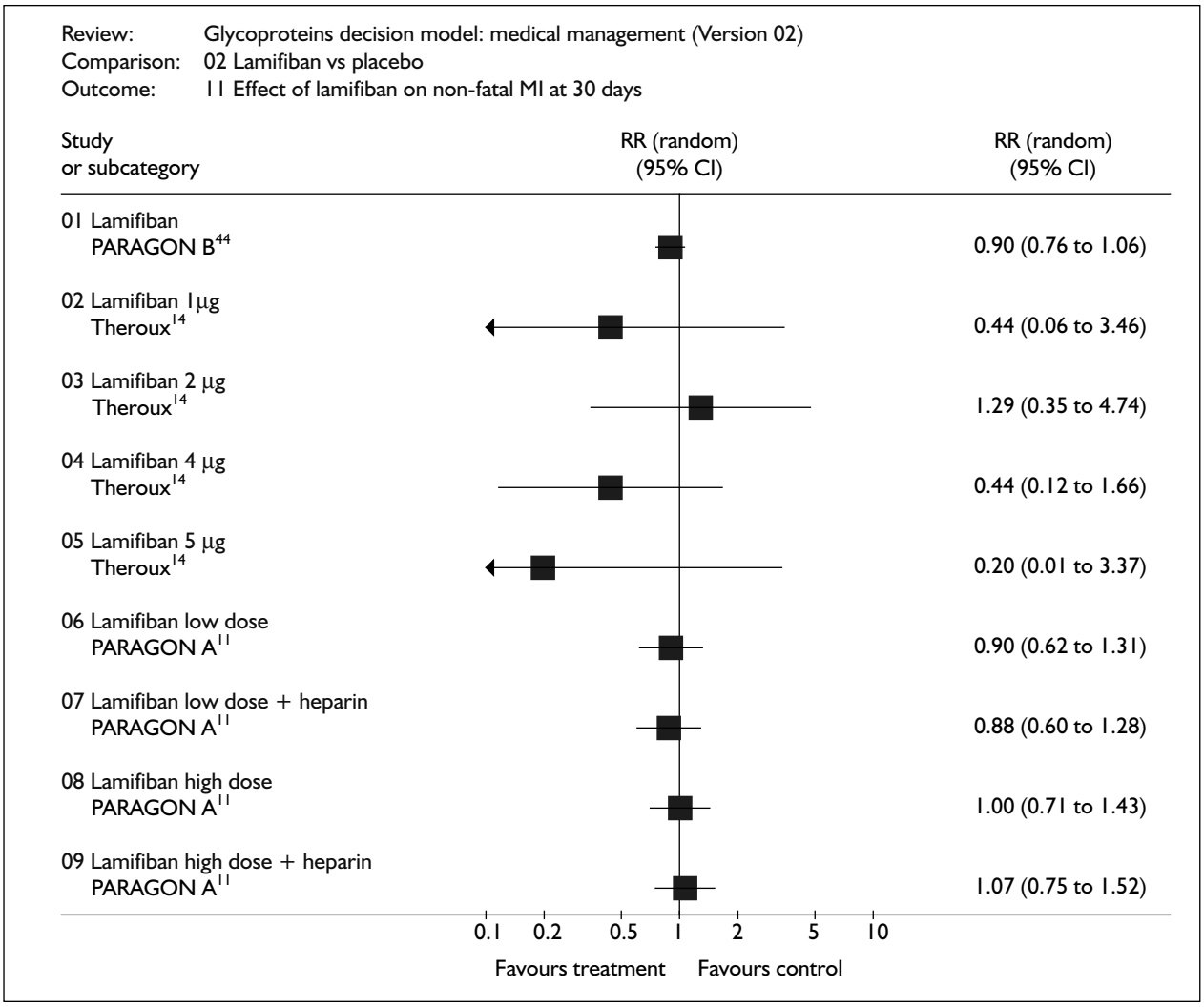

FIGURE 7 *Effect of lamifiban on 30-day non-fatal MI for patients receiving glycoproteins as part of medical management (strategy 1)*

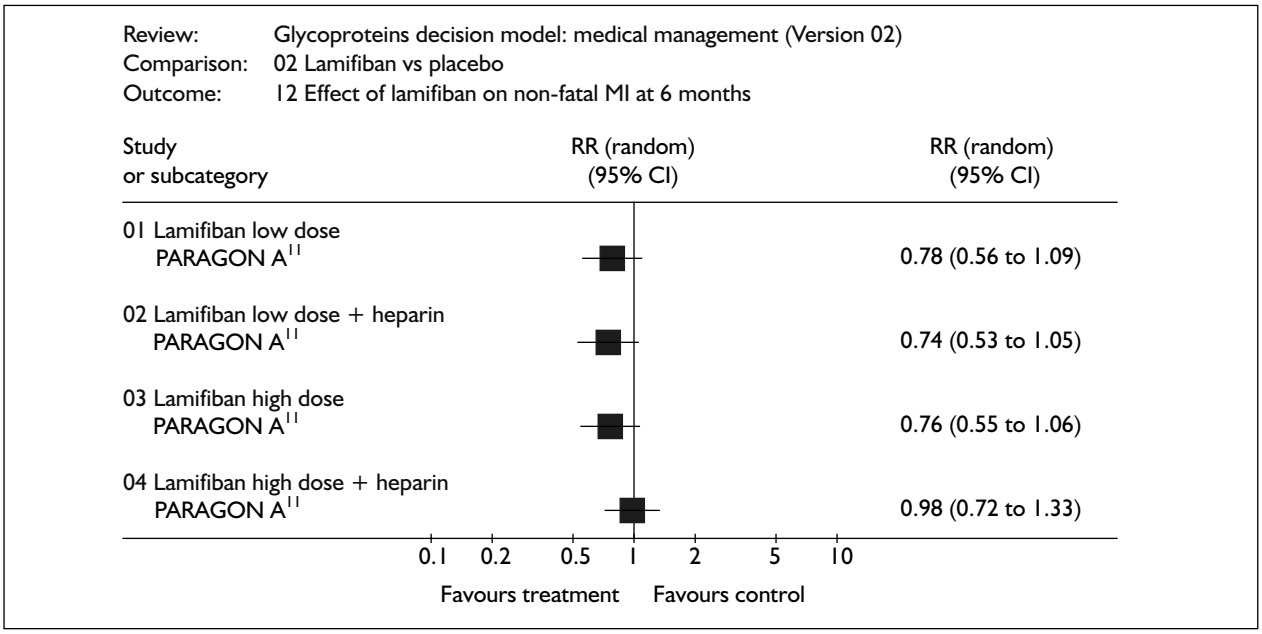

FIGURE 8 *Effect of lamifiban on 6-month non-fatal MI for patients receiving glycoproteins as part of medical management (strategy 1)*

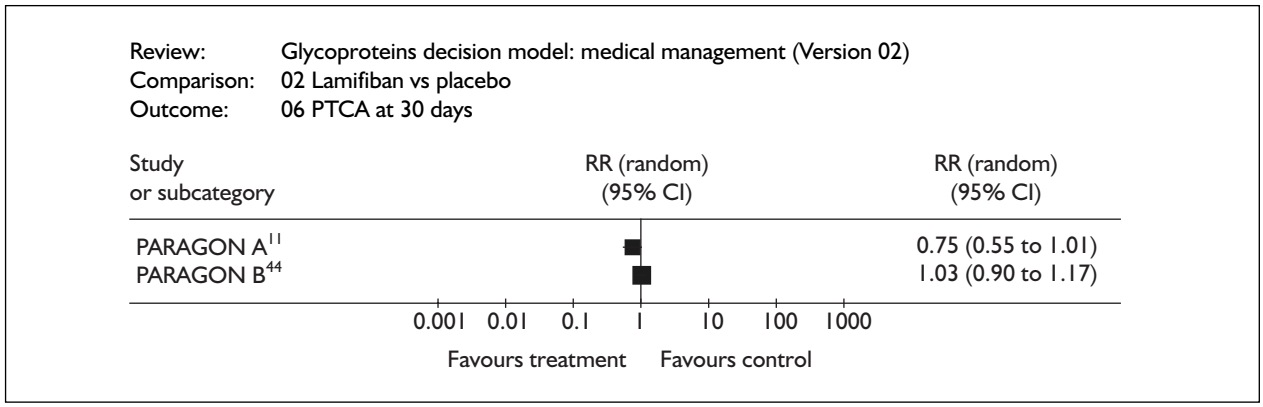

FIGURE 9 *Effect of lamifiban on PCI for patients receiving glycoproteins as part of medical management (strategy 1)*

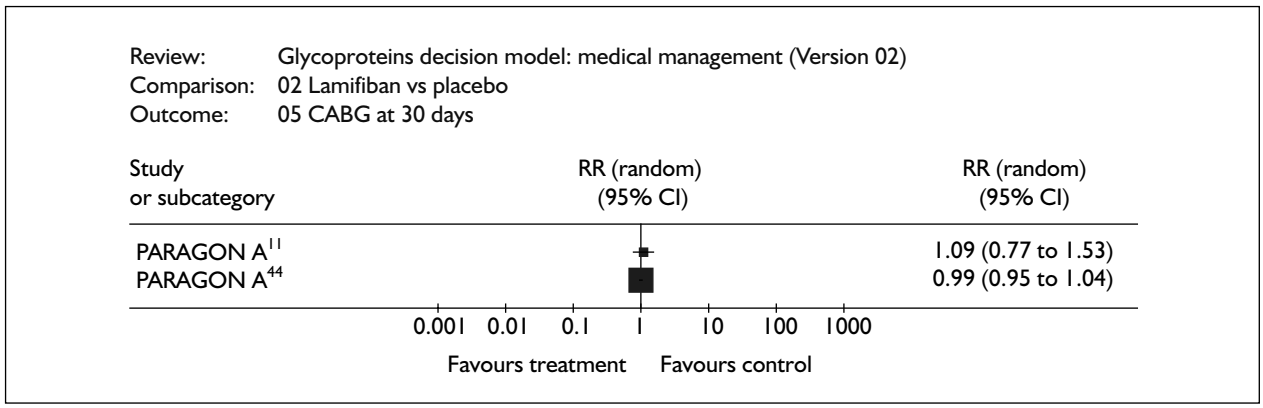

FIGURE 10 *Effect of lamifiban on CABG for patients receiving glycoproteins as part of medical management (strategy 1)*

pooled estimates of effect had to be made. For strategy 1, this applied to Theroux and colleagues,[14] PARAGON A,[11] and GUSTO IV.[41] In each case, clinical advisors were consulted to determine which arm best represented how the drug would most likely be used in the NHS.

The resultant plots of pooled relative risk are presented in *Figures 12–15*. The pooled estimate of the relative risk of major bleed, also needed for the decision model, is shown in *Figure 16*.

Pooled estimates (strategy 2)

No pooling of results for strategy 2 was needed, as CAPTURE[66] was the only relevant trial. RRRs for the decision model were taken directly from the results for CAPTURE, as shown in the previous HTA monograph.[34]

The CAPTURE trial selected a particularly high-risk group of patients. All had refractory UA, that is, recurrent ischaemia during treatment with intravenous heparin and nitrates, and had undergone angiography which showed significant CAD including a culprit lesion suitable for angioplasty. The study infusion (abciximab or placebo) was started 18–24 hours before PCI was scheduled and continued until 1 hour afterwards. The primary end-point of death, MI or urgent reintervention for ischaemia, was reduced at 30 days (11.3% in abciximab group, 15.9% in placebo group, $p = 0.012$), but the decision model specified the use of results after 6 months' follow-up if available. These results were less positive: although the rate of MI was less in the treatment arm than in the control arm (6.6% versus 9.3%, respectively), the death rate at 6 months was higher in the treatment arm (2.8% versus 2.2% in the control arm). As a result, strategy 2 was not favoured in the decision model.

Pooled estimates (strategy 3)

As for strategy 1, pooled estimates were required for the model of the RRRs for death, non-fatal MI and repeat revascularisation during the first 6 months after the index presentation. As before, several trials had more than one treatment arm and a decision had to made which one should be included in the pooled analysis. In general, the chosen arm was that which administered the GPA (usually Reopro) in the manner in which it has

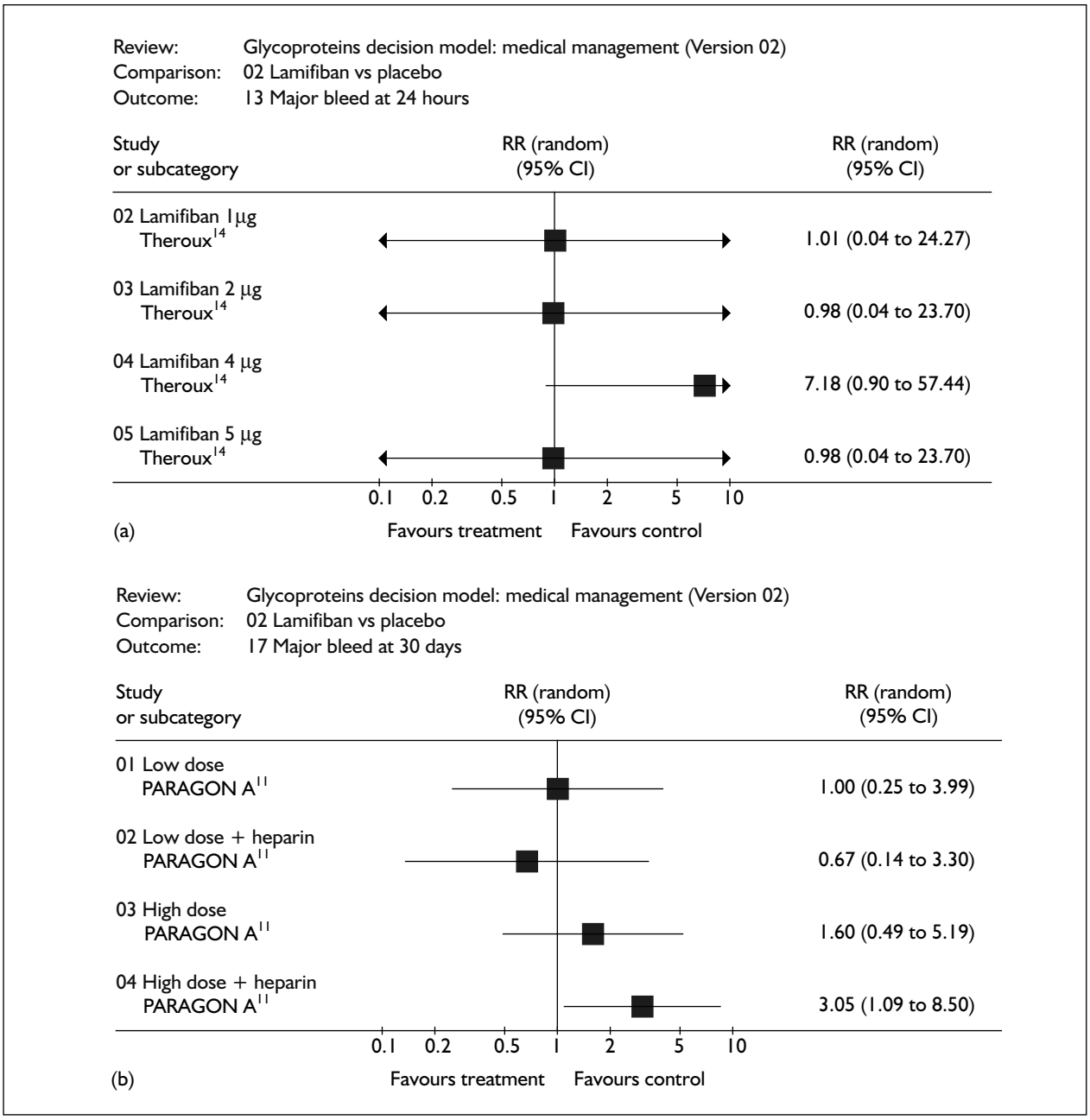

FIGURE 11 *Effect of lamifiban on major bleeding for patients receiving glycoproteins as part of medical management (strategy 1)*

been licensed in the UK, that is, a bolus at the time of PCI followed by a 12-hour infusion. For EPISTENT,[75] the treatment arm with the better outcome (abciximab plus stent) was selected. For EPILOG,[73,74] the treatment arm with the low dose of heparin was selected.

The results of the pooling for strategy 3 trials are shown in *Figures 17–21*.

Subgroup analyses

Doctors are faced with individual patients, about whom they have to make a treatment decision. Consequently, mean data, derived from heterogeneous populations of patients with UA, do not necessarily reflect the risks and benefits within subsets of patients. Mechanistically, GPAs act by blocking platelet aggregation. Consequently, they are likely to be most effective when there is a the potential for a large amount of thrombus formation. Based on Virchow's triad of factors influencing thrombus formation (abnormalities in blood clotting, blood flow, the vessel wall),[77] it may be possible clinically to identify subsets of patients at increased risk of thrombus who in turn derive a greater net benefit from treatment.

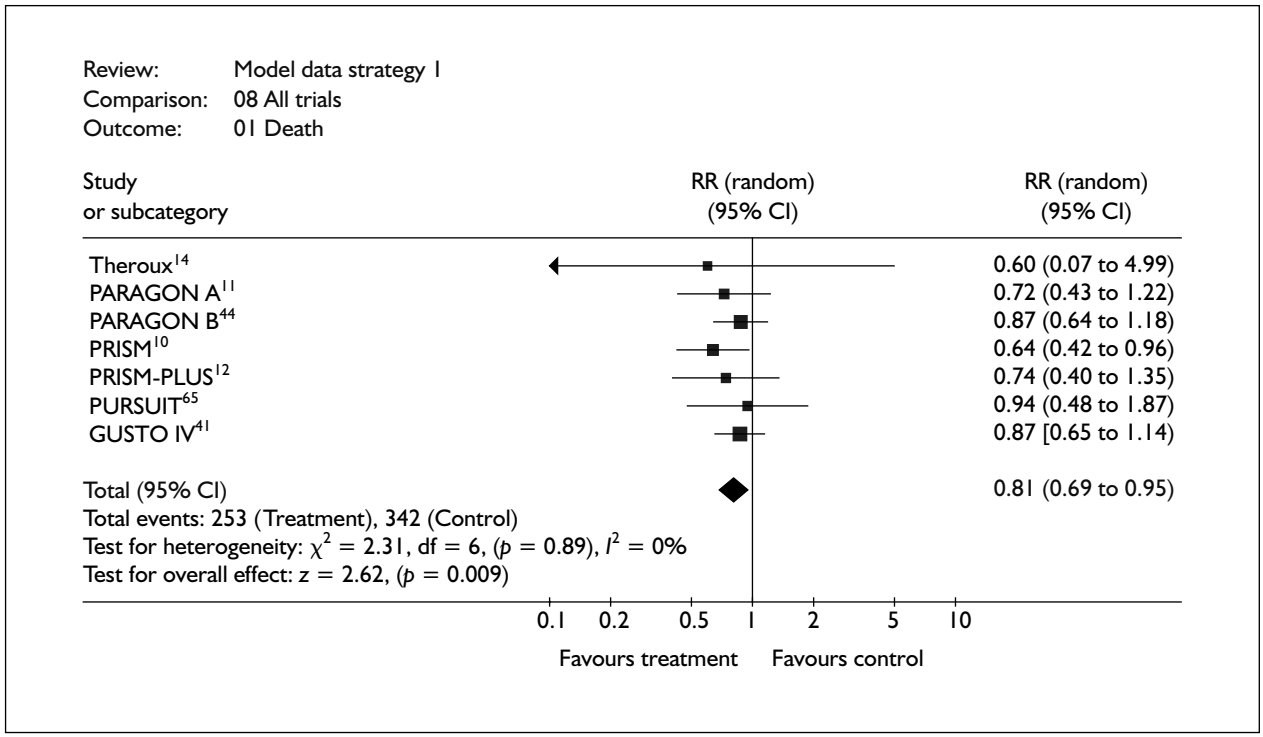

FIGURE 12 *Pooled effect of glycoproteins on death in strategy 1 trials*

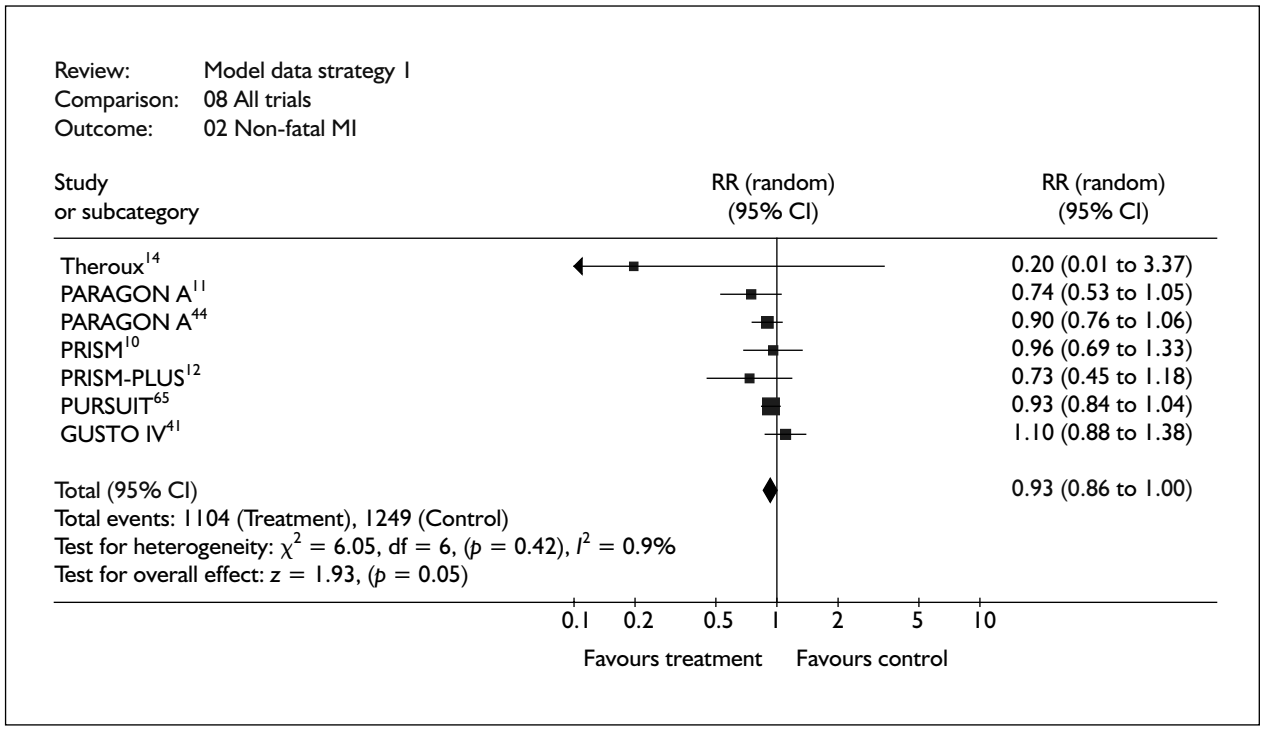

FIGURE 13 *Pooled effect of glycoproteins on non-fatal MI in strategy 1 trials*

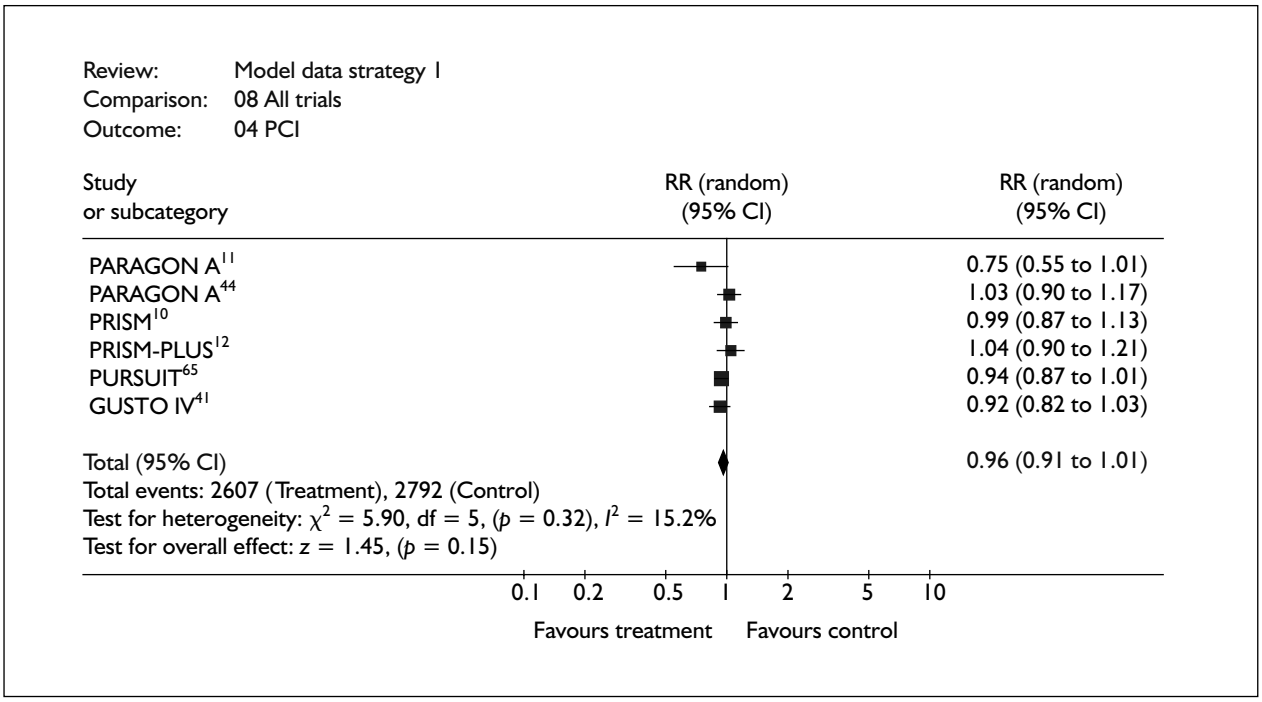

FIGURE 14 *Pooled effect of glycoproteins on rate of PCI in strategy 1 trials*

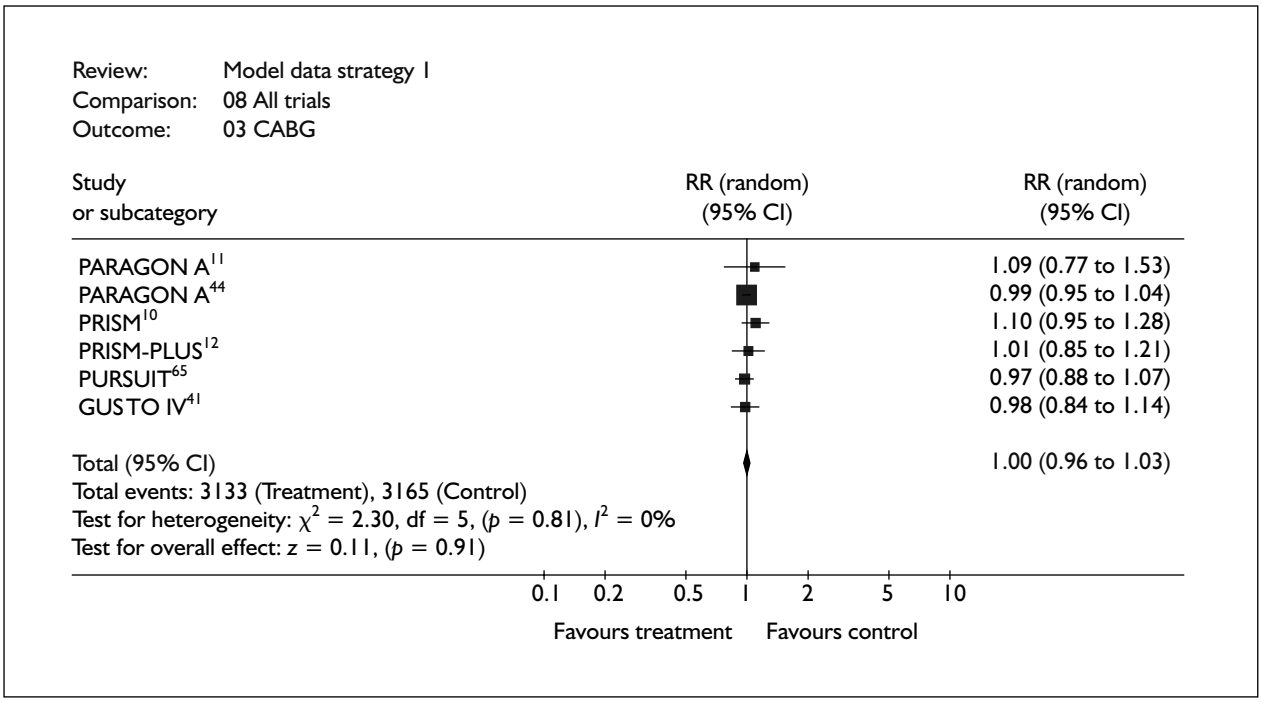

FIGURE 15 *Pooled effect of glycoproteins on rate of CABG in strategy 1 trials*

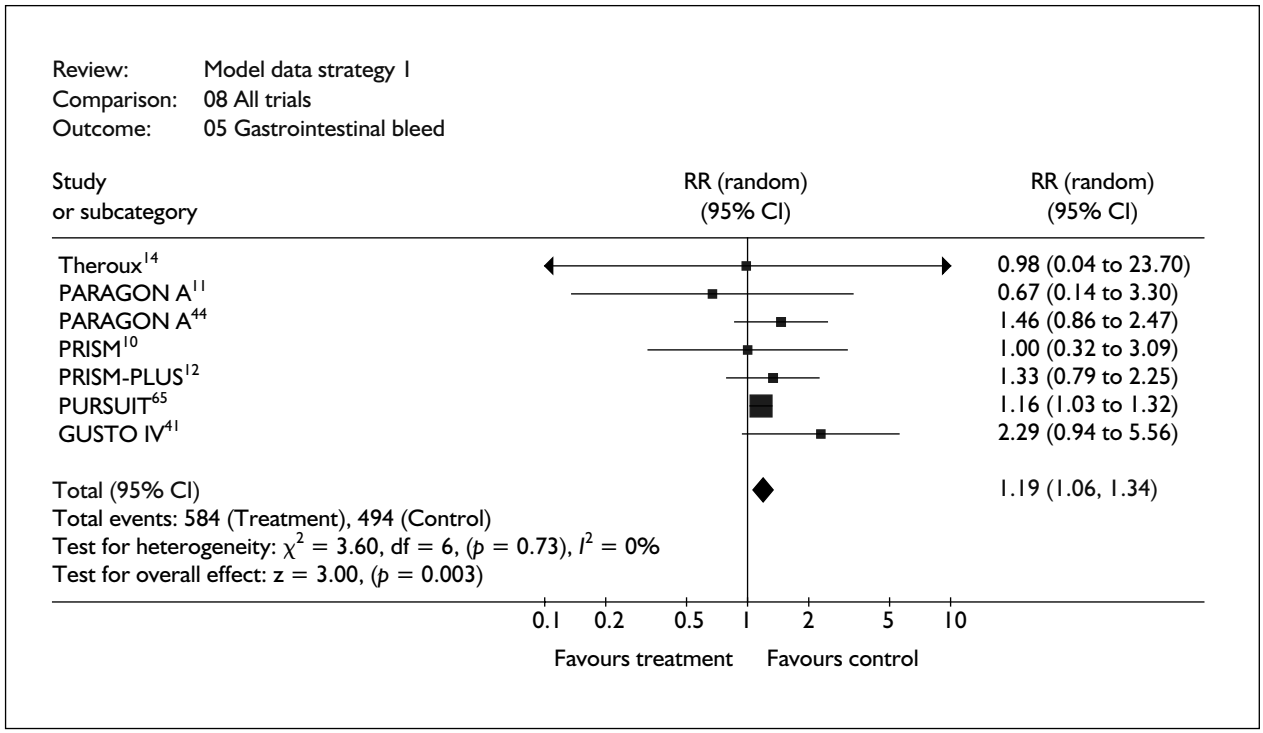

FIGURE 16 *Pooled effect of glycoproteins on rates of major bleeding in strategy 1 trials*

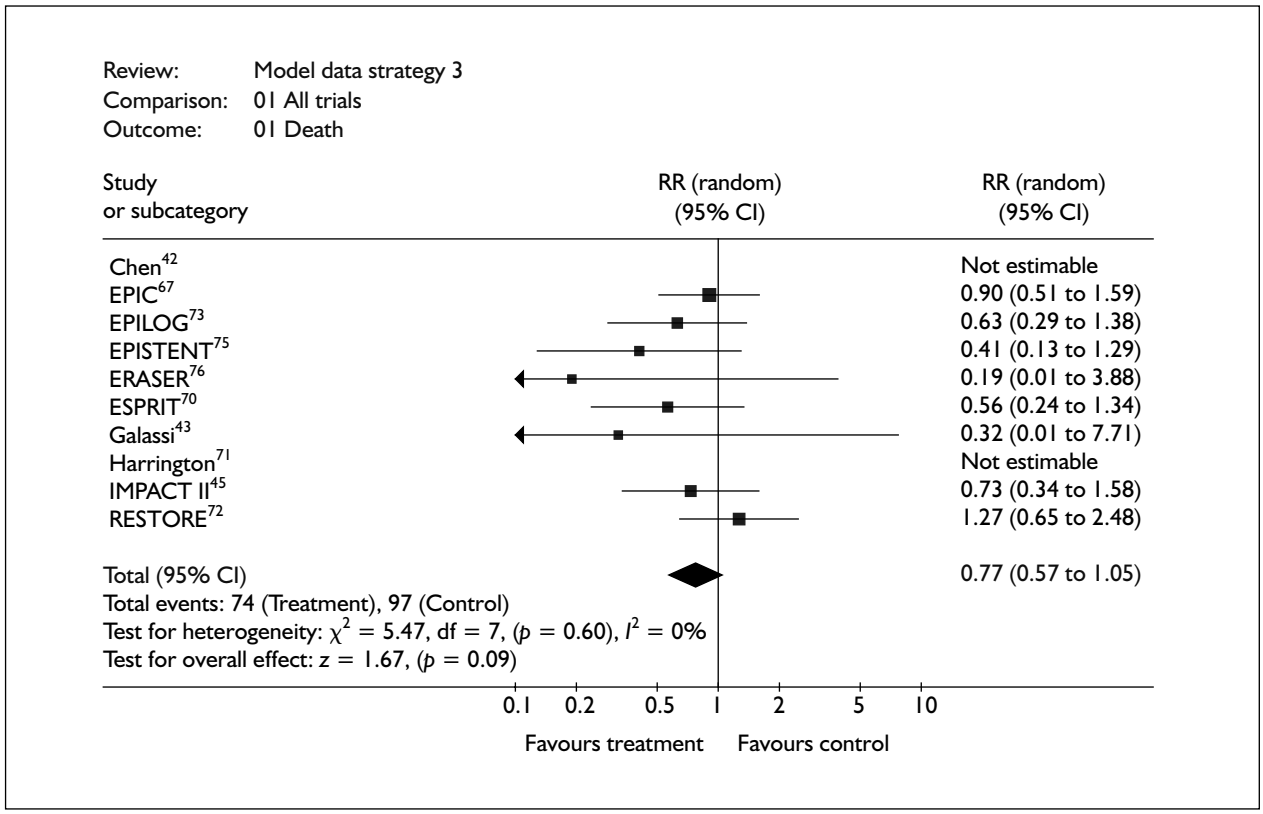

FIGURE 17 *Pooled effect of glycoproteins on death in strategy 3 trials*

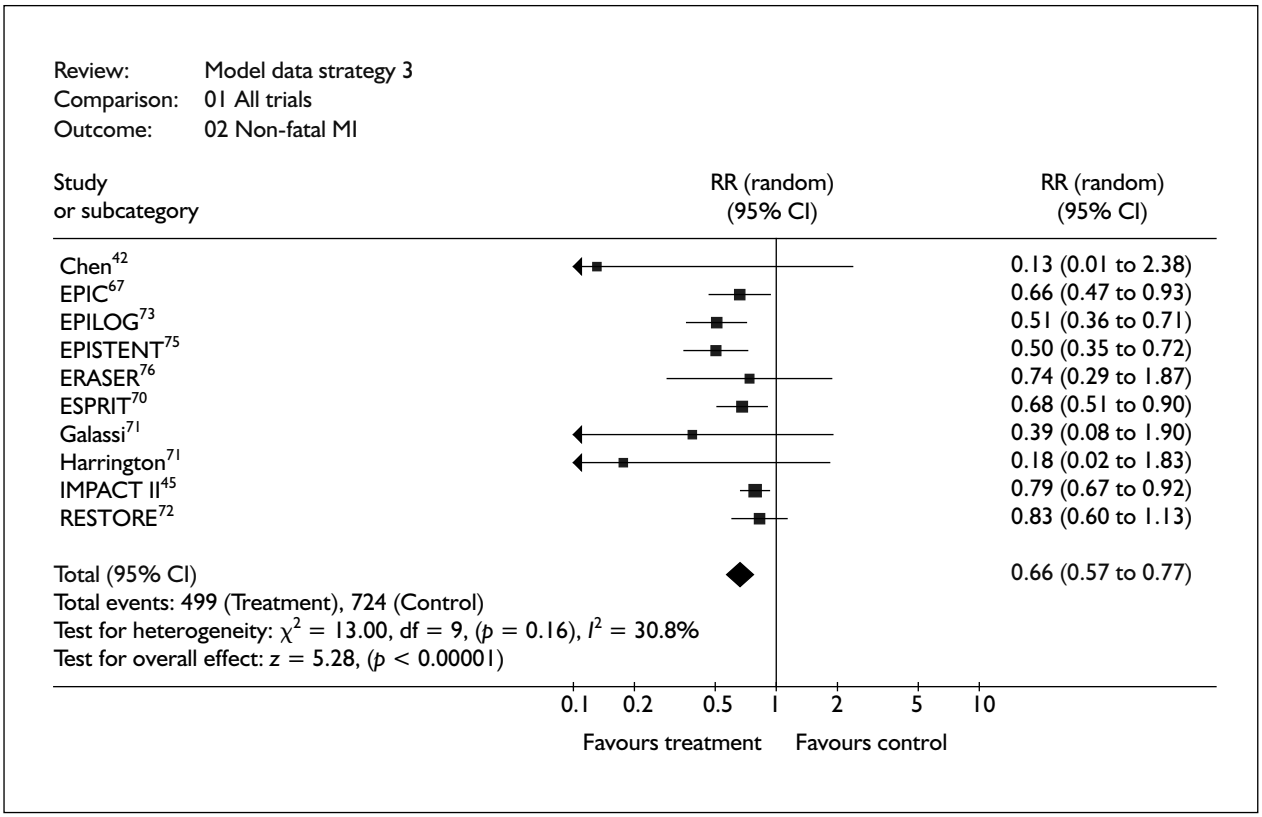

FIGURE 18 *Pooled effect of glycoproteins on MI in strategy 3 trials*

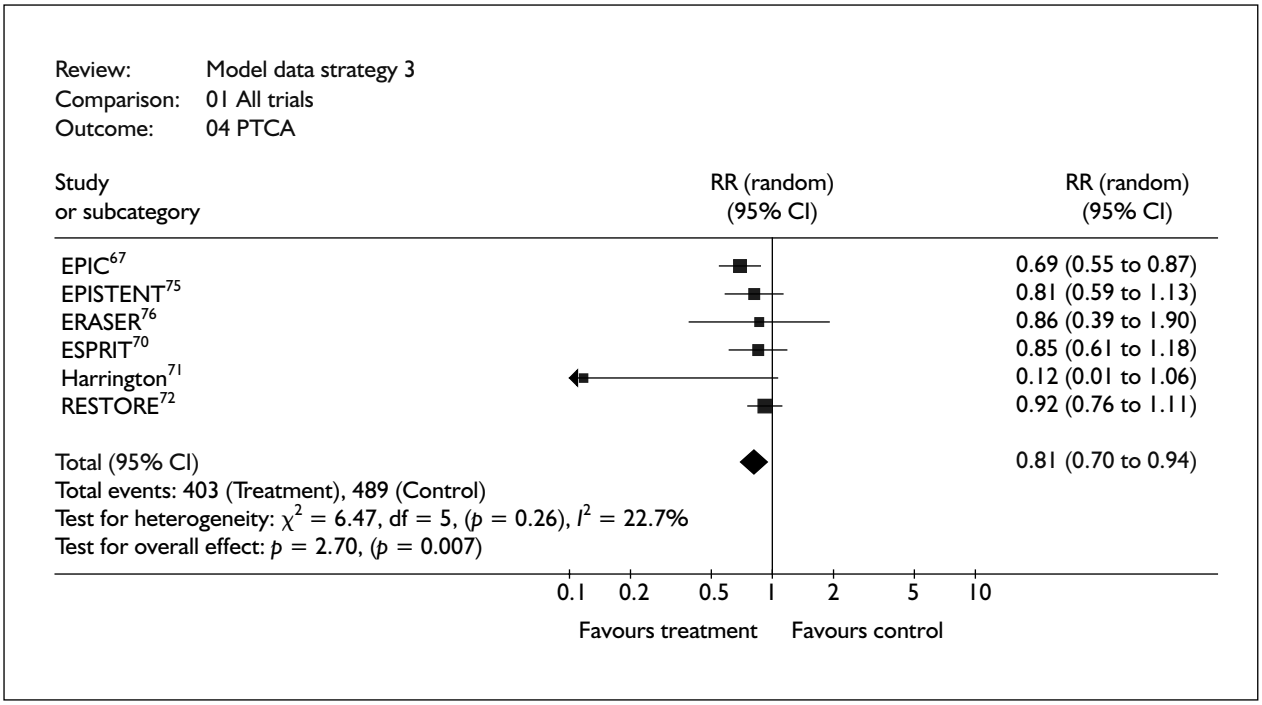

FIGURE 19 *Pooled effect of glycoproteins on PCI in strategy 3 trials*

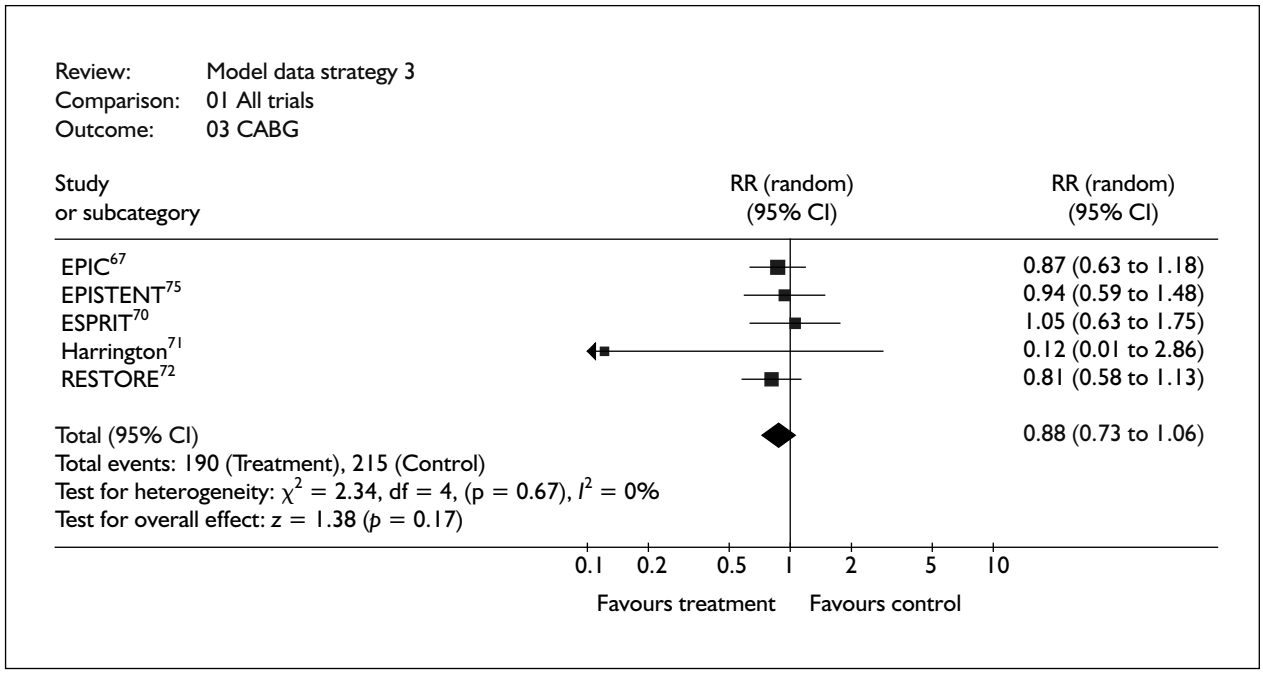

FIGURE 20 *Pooled effect of glycoproteins on CABG in strategy 3 trials*

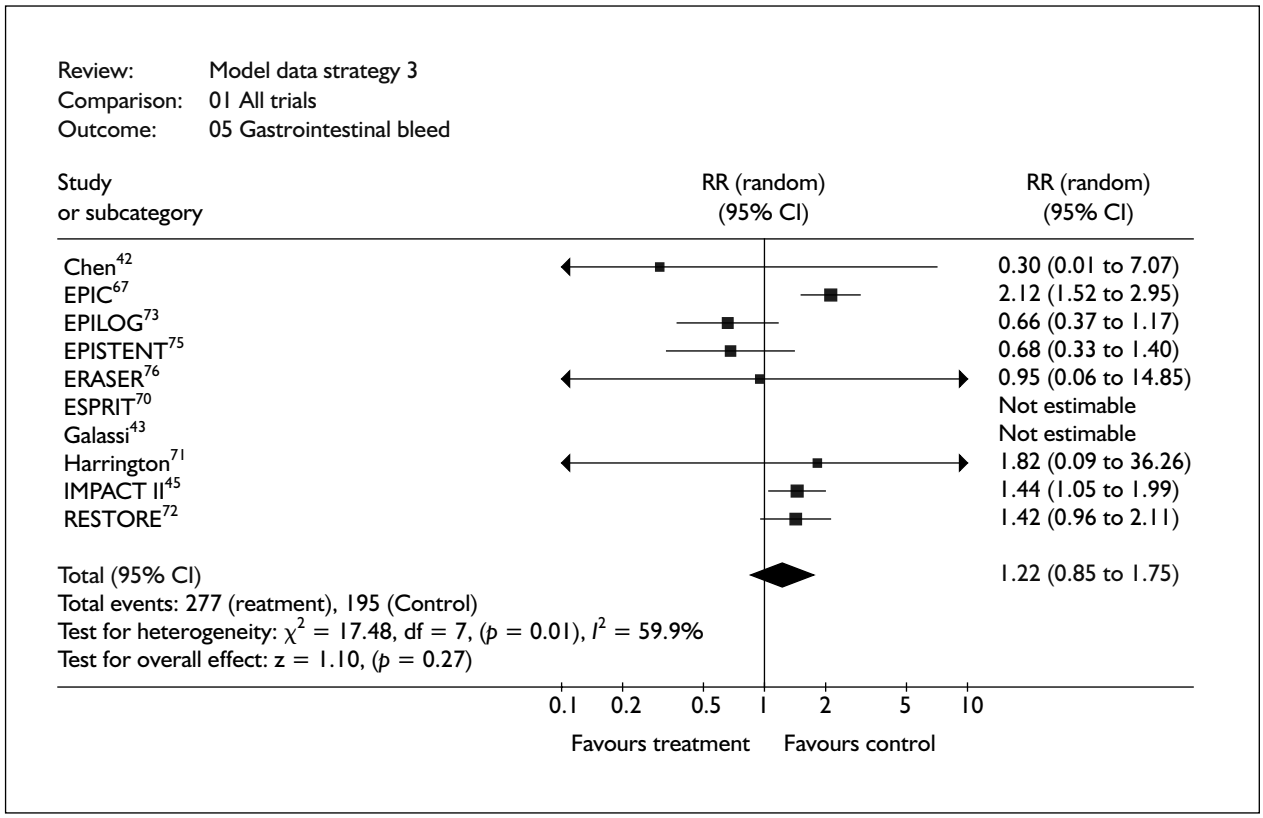

FIGURE 21 *Pooled effect of glycoproteins on major bleeding in strategy 3 trials*

Clinical trials are designed to be optimal with regard to a primary end-point such as death or death plus MI. The numbers required in the study relate directly to the net change in the frequency of this primary end-point at a certain time. Conventional trial methodology requires this primary hypothesis to be fully defined before the start of the trial, and not redefined and tested after the trial is finished. Subgroup analysis can be predefined and indeed accommodated in the design by prerandomisation stratification. Only two trials performed this. These were PURSUIT[61,65,78,79] and GUSTO IV-ACS.[42] No trial stratified according to clinical indicators, such as raised versus normal plasma troponin, male versus female, young versus old patients, prior diabetes versus no prior diabetes, or ST depression versus no ST depression on ECG. Nevertheless, most trials have reported their data for subgroups. On an individual trial basis these may be viewed as being unreliable owing to the post hoc nature of the hypothesis being tested and the reduced statistical power (increased uncertainty) of most subgroups. Consequently, the decision model detailed in Chapter 3 used the Boersma meta-analysis based on patient-level data[35] as a primary source of subgroup data.

The Boersma paper indicates the following differential effects of GPAs: (1a) trend towards reduced benefit with increasing age [$p = 0.1$, not significant (NS)]; (2) net benefit in males but net harm in females [hazard ratio (HR) for males 0.81 but for females 1.15, $p < 0.0001$]; (3) no differential effect according to region of world where patient was recruited; (4) slightly greater effect in diabetics versus non-diabetics (HR 0.88 versus 0.93, $p = 0.48$, NS); (5) no clear trend regarding smoking status; (6) no clear difference based on prior MI; (7) possible greater benefit if prior heart failure versus no prior heart failure (HR 0.86 versus 0.90, $p = 0.69$, NS); (8) slight net harm if prior CABG versus no CABG (HR 1.03 versus 0.90, $p = 0.20$, NS); (9) slight increased benefit if prior PTCA versus no prior PTCA (HR 0.85 versus 0.92, $p = 0.48$, NS); (10) greater benefit if ST depression on ECG versus no ST depression (HR 0.83 versus 0.98, $p = 0.06$, NS); (11) no trend with incrementing systolic blood pressure; (12) slightly greater benefit in patients with low versus high heart rate (HR 0.86 versus 0.92, $p = 0.5$, NS); and (13) slightly greater effect if normal creative kinase MB fraction (CK-MB) versus raised CK-MB (HR 0.94 versus 0.98, $p = 0.55$, NS). Of these data, only the differential effect in males versus females and patients with ST depression versus no ST depression are worthy of further consideration.

Plasma troponin measurements were not available in 11,540 patients treated with GPAs and 8802 controls patients from the same trials. Troponin measurements were available for 6756 patients treated with GPA and 4303 matching controls. Of these, a positive value was present in 3113 patients randomised to GPA treatment and 1851 patients randomised to the control arms. There was a differential effect of GPA treatment in patients with positive versus negative baseline troponin (HR 0.85 versus 1.17, $p = 0.045$). The trend towards harm in troponin-negative patients was of the same order as that seen for females (HR 1.15; see above). However, while the effect in females had 95% confidence intervals (CIs) that do not overlap 1.0 (i.e. statistically significant harm), the 95% CIs for troponin-negative patients do overlap 1.0 (0.94 to 1.44).

The authors of the meta-analysis address the issue of apparent significant harm to females by pointing out that this is a subgroup analysis and hence may mislead as a result of chance (even despite statistical significance at $p < 0.05$). They also report data based on troponin positivity (prerandomisation) and the subsequent recourse to revascularisation (postrandomisation). While troponin-negative males and females have a hazard ratio of greater than 1.0 (indicating control better than GPA), this is more marked in females. Furthermore, it is suggested that this may relate to the fact that females and troponin-negative patients are less likely to undergo revascularisation. If this were indeed the explanation, then it would offer support to strategies 2 and 3. Furthermore, taking the data on females as a whole would argue against strategy 1 (routine treatment for all). However, troponin-positive females may derive a very slight benefit from GPA (HR 0.93, 95% CI 0.68 to 1.28), although there is clear failure to achieve statistical significance.

In conclusion, the differential effect of GPAs based on plasma troponin levels is credible based on pathophysiological considerations (more thrombus, so troponin positive, so more scope for thrombus inhibition). The more marked differential effect in men than in women is much harder to understand. In discussion, Boersma and colleagues imply a very novel view that the pathological basis of UA in men and women may be fundamentally different. Namely, if GPA medication works by inhibiting thrombus and women have reduced net benefit, this implies that they may have less thrombus. This implies that other mechanisms, such as coronary arterial

spasm, may be important in such cases, and unresponsive to platelet inhibition. It is certainly reasonable to suggest that based on current data, troponin-positive men and women should not be treated differently. However, it is much harder to justify routine treatment of troponin-negative patients in general, and women in particular.

Overall, there is probably insufficient information for a reliable estimate of effectiveness to be constructed for subgroups that could be used in the decision model. This is true even in the case of gender and also the prespecified indicators of high risk (old age, diabetes, ST depression and troponin positivity) for which the original NICE search output was re-examined. For example, only two of the nine trials of strategy 1 have published adequate information about effectiveness in troponin-positive patients. Several other trials publish data on their composite outcome for particular high-risk groups, but these are not sufficient to be useful for modelling. Principal investigators were contacted in such cases to try to obtain a breakdown of the composite into its component parts, but without success. *Table 10* shows that the information available from subgroups varies greatly from trial to trial. Details of the results that could be abstracted from each report are shown in Appendices 8 and 9.

Discussion

The purpose of this systematic review was to obtain the best possible estimates of the effectiveness of GPAs for use in the decision-analytical model. As a result, there were some distinctive features of the methods, which are discussed below.

The first feature is the selection of trials to be included. Previous systematic reviews conducted for NICE[23,27,34] only considered drugs that were licensed for use in the UK, but the present review included all agents that were judged to have a common class effect, namely intravenous GPAs, to maximise the numbers of patients on which the modelling would be based. Small molecule GPAs (lamifiban, tirofiban and eptifibatide) could arguably be considered a separate subclass from abciximab; this was taken into account in the decision model by undertaking sensitivity analyses in which the effectiveness parameter was restricted to specific trials. In the case of strategy 3, previous reviews[27,36] have included trials of GPA as an adjunct to PCI for all indications; in this case the review was restricted to trials that include at least some, if not all, UA patients.

The second feature is the selection of certain outcome measures for pooling. The reviewers chose to produce pooled estimates for each strategy only for those outcomes that could be directly used in the decision model, namely death, non-fatal MI, major bleeding and separate estimates for revascularisation by CABG or PCI. This meant that not all results discovered in the review were included. For example, many trials included data on recurrent ischaemia during the follow-up period; this was not included as an outcome in the decision model and so was not included in the pooling. Another reason why trials could not be fully exploited for the model, in particular for subgroups, was that only composite outcomes were reported. An assumption could have been made that effect sizes observed for composite outcomes applied equally to each constituent part (usually death and non-fatal MI), but the data for trials for which both sorts of data are available show that this would be unsafe. Another problem with such a disaggregation would be the derivation of confidence limits or other uncertainty estimates that are necessary for a stochastic determination of cost-effectiveness. This was a key feature of the present approach. Towards the end of this work an individual patient-level meta-analysis of strategy 1 trials was published,[35] which enabled analysis of a particularly high-risk subgroup (see p. 57).

The third feature is the approach used to pool data. No formal tests of heterogeneity were undertaken before proceeding to a meta-analysis, but a random effects analysis was undertaken regardless of the extent of variation in results of individual trials. This produced an estimate of the effectiveness and its uncertainty that could be used in the decision model, which took account of all available data. Any alternative approach would have involved making a judgement about which particular trials should be included and excluded, and there seemed no straightforward basis on which to make such judgements. In pooling data from trials with more than one treatment arm, the arm was selected that advice suggested represented how the drugs were most likely to be used in the NHS. In the case of strategy 1, this produced less conservative estimates than the individual patient meta-analysis that subsequently became available.[35] The effect of this was examined in a sensitivity analysis (see Chapter 3, p. 49).

Chapter 3
Decision model

Model overview

The model was developed to estimate costs from the perspective of the UK NHS, and health outcomes in terms of life-years and QALYs. For the main analysis, a lifetime time horizon is 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 6 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 their surviving the first 6 months after the acute episode.

The model is probabilistic in that input parameters are entered into the model as probability distributions to reflect second order uncertainty; that is, uncertainty in mean costs and outcomes, and in probabilities.[80] 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 2000/01 price base is used, and annual discount rates of 6% for costs and 2% for benefits are adopted based on UK guidance.[81]

Probabilistic analysis requires distributions for the input parameters in the model to be specified. The distribution represents the uncertainty in the estimation of each parameter (e.g. a more diffuse distribution reflects a higher level of uncertainty). Consequently, the quality and quantity of information available can be reflected in the probability distributions assigned to each input parameter in the model. The objective of probabilistic analysis is to calculate the combined impact of the model's various uncertainties to determine a probability distribution for the possible model outcomes.

Short-term model

Model structure

The short-term model is structured as a decision tree as shown in *Figure 22*. 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 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 may 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–G, H–I and O–T). Three mutually exclusive outcomes are modelled: non-fatal MI, death, and all other survivors with no definite evidence of AMI during the 6-month period.

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.[34] 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.[8] 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 baseline event rates, specific for UK practice, were constructed from an alternative data source, PRAIS-UK.[13] 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

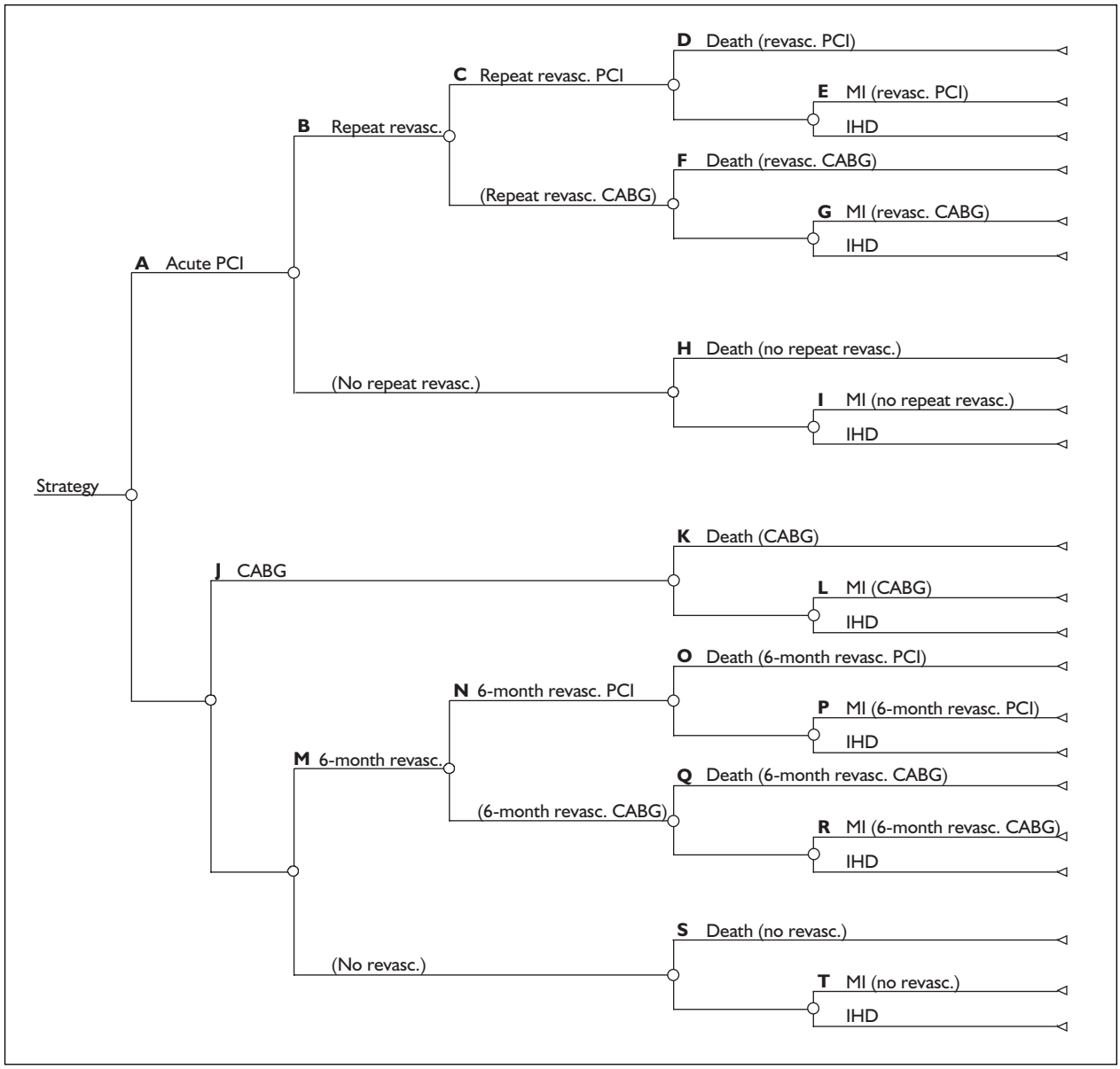

FIGURE 22 *Structure of the short-term model. revasc., revascularisation.*

phase of their ACS were based on a relatively small number of patients (n = 53). For this reason, an audit of UA patients undergoing acute PCI at a large UK cardiac centre (Leeds) was undertaken. All acute PCIs (n = 213) performed in the calendar year 2000 were identified from the angiography suite database. Case notes were obtained from medical records for 211 (99%) patients (two patients were excluded owing to a lack of case-note data). Data were abstracted using a standard pro forma by a specialist registrar in cardiology, including diagnosis (ST elevation MI or non-ST elevation ACS), 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 (n = 99). When 6-month follow-up data were not available from the case notes, patients or their relatives were contacted by telephone to ascertain this. In total, 112 patients from the Leeds audit met the inclusion criteria and were included in the analysis. 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 11 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

TABLE 11 *Baseline probabilities used in the short-term model taken from PRAIS-UK and the Leeds audit (node labels relate to the decision tree in* Figure 22*)*

Node	Description	Probability	Parameters of 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			
	Undergoing PCI in acute period	0.00	0.01	52.99
	Undergoing CABG in acute period	0.02	1	46
	No initial revasc.	0.01	12	921

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 data sets 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 subsample, and β the number of patients who did not experience the event.

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 12*. In part, resource use relates directly to the clinical events shown in *Figure 22*, specifically to revascularisation using PCI or CABG. In addition, mean length of inpatient 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 6 months but outside the acute period, length of stay data were not collected in PRAIS-UK. For PCI undertaken outside the acute period, a fully allocated cost for the procedure was applied from published estimates,[82] while for CABG it was 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 is 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 log-normal 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 are incorporated into the model based on costs estimated in NHS hospitals in England.[83] 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 11*. Although some trials suggest

TABLE 12 *Resource use associated with the short-term model taken from PRAIS-UK*

Item of resource use	Probability	Parameters of beta distribution	
		α	β
Angiography when:			
Undergoing PCI in acute period	0.96	51	2
Undergoing CABG in acute period	0.81	38	9
No initial revasc.	0.21	193	740
CCU stay when:			
Undergoing PCI in acute period	0.38	20	33
Undergoing CABG in acute period	0.61	28	18
No initial revasc.	0.41	375	543
	Mean	**SD**	
Length of inpatient stay			
Undergoing PCI in acute period	10.30	8.04	
Undergoing CABG in acute period	15.28	12.32	
No initial revasc.	5.45	4.78	
Length of CCU stay component			
Undergoing PCI in acute period	3.70	4.12	
Undergoing CABG in acute period	4.71	6.61	
No initial revasc.	2.11	1.95	

CCU, coronary care unit; SD, standard deviation.

an excess risk of stroke in patients treated with GPAs,[34] 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 (NHAR; see Transition probabilities, below). 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 13*, together with the sources of those data. These unit costs are used, together with the resource use in *Figure 22* and *Table 12*, to generate an overall mean cost (and standard deviation) of each of the pathways in *Figure 22*.

Effectiveness and costs of GPAs

The relative risks (RRs) associated with GPAs are based on the trials identified as part of the update systematic review.[34] 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 that included at least some patients with ACS or UA are included in the model. *Table 14* summarises the trials included for each strategy, to estimate the relative risks of GPAs.

In the systematic review undertaken for NICE,[34] it was argued that heterogeneity between trials, with regard to drugs studied, types of patient 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 the discussion at the end of this chapter 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

TABLE 13 *Unit costs used in the analysis*

Unit cost	Unit	Base-case value	Source
PCI	Procedure	£1,410.04	Schulpher *et al.*, 2002[82]
CABG	Procedure	£4,902.22	Schulpher *et al.*, 2002[82]
Repeat PCI	Per diem	£2,976	Schulpher *et al.*, 2002[82]
Angiogram	Procedure	£748.25	Schulpher *et al.*, 2002[82]
Cardiac ward	Day	£157.47	Schulpher *et al.*, 2002[82]
Non-cardiac ward	Day	£244.00	Schulpher *et al.*, 2002[82]
CCU	Day	£459.04	Schulpher *et al.*, 2002[82]
Outpatient	Visit	£59.70	Schulpher *et al.*, 2002[82]
Cardiac day case	Visit	£108.58	Schulpher *et al.*, 2002[82]
Non-cardiac day case	Visit	£182.00	Schulpher *et al.*, 2002[82]
Guidewire	Item	£61.75	Schulpher *et al.*, 2002[82]
Stent	Item	£599.01	Schulpher *et al.*, 2002[82]
Guiding catheter	Item	£37.05	Schulpher *et al.*, 2002[82]
Blood	Unit	£85.00	Specific NHS trust
Full blood count	Item	£4.00	Specific NHS trust
Endoscopy	Item	£246.00	Delaney *et al.*, 2000[84]
Tirofiban	12.5-mg vial	£146.11 (+ VAT)	BMA, 2001[85]
Eptifibatide	20-mg vial	£15.54 (+ VAT)	BMA, 2001[85]
Eptifibatide	75-mg vial	£48.84 (+ VAT)	BMA, 2001[85]
Abciximab	10-mg vial	£280.00 (+ VAT)	BMA, 2001[85]
Omeprazole	28-tab pack, 10 mg	£18.91	BMA, 2001[85]
Clopidogrel	28-tab pack, 75 mg	£35.31	BMA, 2001[85]

BMA, British Medical Association.

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 were incorporated into the model without adjustment, which is equivalent to assuming that relative risks are transportable across healthcare systems while the baseline risks in those studies are not. Given the small number of trials for each strategy, it is possible that a type 2 error may have occurred. This was indirectly examined by a sensitivity analysis using relative risks from a patient-level meta-analysis of strategy 1 trials[86] as discussed in Chapter 2 (p. 36). Further details are shown in Appendix 10.

The relative risks taken from the trials are shown in *Table 14* 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 log-normal distributions to allow for uncertainty in the parameters. Three important assumptions were necessary in developing these estimates of treatment effect, as detailed below.

- Trials relating to the three strategies used particular GPAs, which may not be used in routine practice in the UK.[34] 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 were 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. A sensitivity analysis was performed using just the small molecule GPAs for strategy 1.
- 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

TABLE 14 *Relative risks from the trials used in the model*

Trial	Options (*n*)	RR (95% CI)					
		Non-fatal MI	Death	Revasc.[a]	PCI[a]	CABG[a]	GI bleed
Strategy 1	GUSTO IV abciximab[b] (7800)[41]	1.10 (0.88 to 1.38)	0.87 (0.65 to 1.14)	0.94 (0.87 to 1.02)	0.92 (0.82 to 1.03)	0.98 (0.84 to 1.14)	2.29 (0.94 to 5.56)
	PARAGON A lamifiban (2282)[11]	0.73 (0.53 to 1.05)	0.72 (0.43 to 1.22)	NR	0.75 (0.55 to 1.01)	1.09 (0.77 to 1.53)	0.67 (0.14 to 3.30)
	PARAGON B lamifiban[b] (5225)[44]	0.90 (0.76 to 1.06)	0.87 (0.64 to 1.18)	NR	1.03 (0.90 to 1.17)	1.00 (0.88 to 1.14)	1.46 (0.86 to 2.47)
	PRISM tirofiban[b] (3232)[10]	0.96 (0.66 to 1.40)	0.64 (0.42 to 0.96)	NR	0.99 (0.87 to 1.13)	1.10 (0.95 to 1.28)	1.00 (0.32 to 3.09)
	PRISM-PLUS tirofiban (1915)[12]	0.73 (0.45 to 1.18)	0.74 (0.40 to 1.35)	NR	1.04 (0.90 to 1.21)	1.01 (0.85 to 1.21)	1.33 (0.79 to 2.25)
	PURSUIT eptifibatide[b] (9461)[65]	0.93 (0.84 to 1.04)	0.94 (0.48 to 1.87)	NR	0.94 (0.87 to 1.01)	0.97 (0.88 to 1.07)	1.16 (1.03 to 1.32)
	Theroux lamifiban[b] (365)[14]	0.20 (0.01 to 3.37)	0.60 (0.07 to 4.99)	NR	NR	NR	0.98 (0.04 to 23.70)
Pooled[c]		0.93 (0.86 to 1.00)	0.81 (0.69 to 0.95)	0.94 (0.87 to 1.02)	0.96 (0.91 to 1.01)	1.00 (0.94 to 1.03)	1.19 (1.06 to 1.34)
Strategy 2	CAPTURE abciximab (1265)[66]	0.70 (0.48 to 1.03)	1.22 (0.61 to 2.46)	1.02 (0.84 to 1.24)	1.04 (0.84 to 1.29)	0.76 (0.49 to 1.17)	2.02 (1.02 to 4.00)
Pooled[c]		0.70 (0.48 to 1.03)	1.22 (0.61 to 2.46)	1.02 (0.84 to 1.24)	1.04 (0.84 to 1.29)	0.76 (0.49 to 1.17)	2.02 (1.02 to 4.00)
Strategy 3	Chen abciximab[b] (42)[42]	0.13 (0.01 to 2.38)	NR	NR	NR	NR	0.3 (0.01 to 7.07)
	EPIC abciximab (2099)[67]	0.66 (0.47 to 0.93)	0.90 (0.51 to 1.59)	0.77 (0.65 to 0.92)	0.69 (0.55 to 0.87)	0.87 (0.63 to 1.18)	2.12 (1.52 to 2.95)
	EPILOG abciximab (2792)[73]	0.51 (0.36 to 0.71)	0.63 (0.29 to 1.38)	0.98 (0.81 to 1.18)	NR	NR	0.66 (0.37 to 1.17)
	EPISTENT abciximab (2399)[75]	0.50 (0.35 to 0.72)	0.41 (0.13 to 1.29)	0.86 (0.66 to 1.33)	0.81 (0.59 to 1.13)	0.94 (0.59 to 1.48)	0.68 (0.33 to 1.40)
	ERASER abciximab (225)[76]	0.74 (0.29 to 1.87)	0.19 (0.01 to 3.88)	0.86 (0.39 to 1.90)	0.86 (0.39 to 1.90)	NR	0.95 (0.06 to 14.85)
	ESPRIT eptifibatide (2064)[70]	0.68 (0.51 to 0.90)	0.56 (0.24 to 1.34)	NR	0.85 (0.61 to 1.18)	1.05 (0.63 to 1.75)	NR
	Galassi abciximab[b] (106)[43]	0.39 (0.08 to 1.90)	0.32 (0.01 to 7.71)	NR	NR	NR	NR
	Harrington eptifibatide[b](73)[71]	0.18 (0.02 to 1.83)	NR	NR	0.12 (0.01 to 1.06)	0.12 (0.01 to 2.86)	1.82 (0.09 to 36.26)
	IMPACT II eptifibatide[b] (4010)[45]	0.79 (0.67 to 0.92)	0.73 (0.34 to 1.58)	NR	NR	NR	1.44 (1.05 to 1.99)
	RESTORE Tirofiban (2141)[72]	0.83 (0.60 to 1.13)	1.27 (0.65 to 2.48)	NR	0.92 (0.76 to 1.11)	0.81 (0.58 to 1.13)	1.42 (0.96 to 2.11)
Pooled[c]		0.66 (0.57 to 0.77)	0.77 (0.57 to 1.05)	0.87 (0.76 to 0.98)	0.81 (0.70 to 0.94)	0.88 (0.73 to 1.06)	1.22 (0.85 to 1.75)

[a] Repeat revascularisation rate for strategies 2 and 3.
[b] Trials that only report at 30 days follow-up. For the base-case analysis, it was assumed that the 30-day relative risks remain the same at 6 months.
[c] Based on random effects meta-analysis.
GI, gastrointestinal; NR, not reported.

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 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 end-points including death). This may have overestimated the benefits; a sensitivity analysis using the more conservative results from the Boersma meta-analysis[86] was therefore performed.

- 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, it was assumed that the RRRs 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 6 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 owing to its relative simplicity.

The acquisition costs of the three licensed GPAs are shown in *Table 13*. The costs of lamifiban are not included as it is not licensed for use in the UK. These are based on undiscounted prices from the BNF.[85] 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 70-kg person. It was assumed that part-vials cannot be used. The overall costs [including value added tax (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 72 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 £534.74 for eptifibatide and £515.04 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.

Long-term model

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. First, 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. Second, 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 that can be compared across treatment areas. The most frequently used generic measure for this purpose is the QALY. 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 (6-month) model in one of two disease states: those who have 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.

Structure

The long-term model takes the form of a four-state Markov process, as illustrated in *Figure 23*. 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 1 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.

Transition probabilities

The transition probabilities used in the long-term model are shown in *Table 15* and are based on a cycle length of 1 year. The annual probability of non-fatal MI and death is 1.8% and 7.5%, respectively, for IHD patients. The probability of

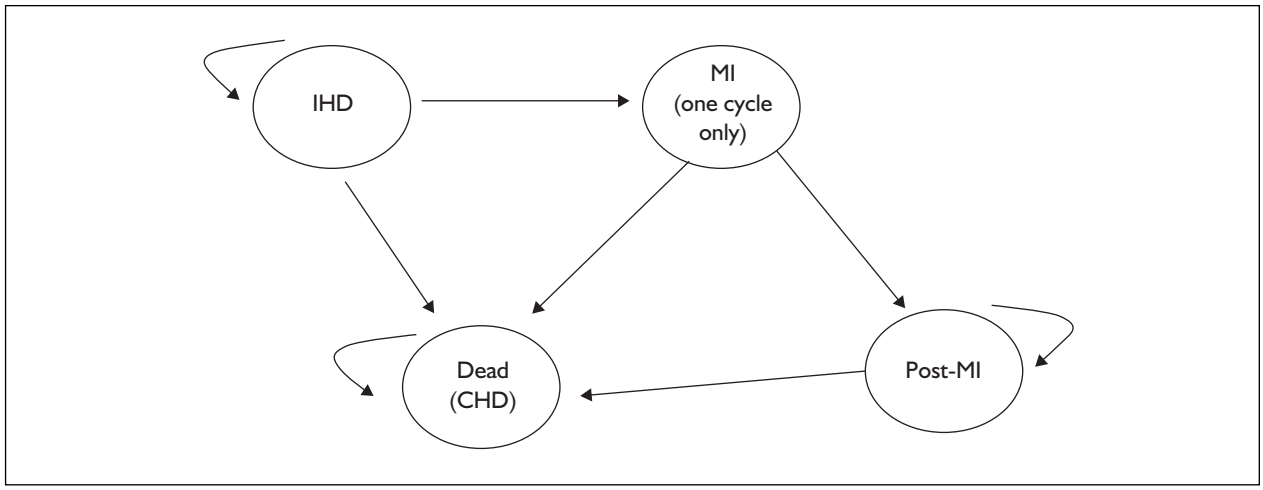

FIGURE 23 *Structure of the long-term model*

TABLE 15 *Annual transition probabilities used in the long-term model (95% CI)*

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

death in the first year following non-fatal MI is 21%, and for subsequent years is 7.2%. These probabilities are assumed to be 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 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 prehospital and inhospital events, admission and discharge data, risk-factor profiles and follow-up plans.[38,87] 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. These were chosen because they were years in which extensive additional follow-up had already been conducted. The subgroup of patients used comprised those classified on the NHAR as having an initial working diagnosis, made by the admitting clinician, of typical ischaemic pain or angina on cardiac presentation (rule out MI), or patients who were suspected of having had an MI, but had not. Diagnostic coding was based on enzyme and ECG findings during the index admission. The 1992 cohort included 979 patients and had 5 years' follow-up data for survival. Subsequent MIs between 1992 and 1997 in these patients were identified through the hospitals' patient administration systems, by searching for discharge codes of MI (ICD-9 = 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 were 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 were calculated by assuming an exponential survival distribution (i.e. fixed hazard). The hazard rates were converted into annual transition probabilities (plus variance) using standard techniques.[88] The uncertainty associated with each transition probability was characterised by a log-normal distribution.[89] Owing 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 known. 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 transitions.

Costs in the long-term model

Costs were 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 was 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 inpatient stays (cardiac and non-cardiac) and associated length of stay, day-case and outpatient visits. Hospital inpatient stays, which included time on CCU, were recorded, although the amount of time spent in CCU was not. For the purpose of this analysis, it was 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 16*. As for the short-term model, the uncertainty in resource use in the long-term model is characterised by beta distributions (to reflect the proportion of patients using a particular resource item) and log-normal distributions (to reflect the intensity of use). The beta distribution is a continuous distribution bounded by the limits of the interval 0–1. Uncertainty in the beta distribution is characterised by two parameters: beta (α, β), where α represents the number of patients experiencing an event and β is the total number of patients in whom a particular event does not occur. The log-normal distribution is a continuous distribution bounded at the lower end by zero and with no positive upper bound. The properties of the log-normal distribution are particularly appropriate to modelling resource-use data such that the resulting estimates are positive and reflect the positive skew typically seen in the sample data.

Quality adjustment

To estimate QALYs, it is necessary to quality-adjust the period for which the average patient is alive within the model using an appropriate utility or preference score. Ideally, utility data are required that 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 exists providing estimates of utilities associated with IHD and MI. These include baseline utilities [based on responses to the EuroQol 5 Dimensions (EQ-5D)] from patients randomised into trials evaluating alternative forms of management for stable angina[90] and direct utility assessments as part of trials looking at thrombolytic therapies.[91] However, none of these sources provides separate estimates of the three relevant states in the long-term model based on consistent valuation methods. In the base-case analysis, it is assumed that the health states of all patients who are alive are valued, on average, at the same utility regardless of which 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 based on a previously reported estimate from a reanalysis of the cost-effectiveness of alternative thrombolytic therapies using data from the GUSTO trial.[92] Uncertainty in the utility estimate is characterised using a beta distribution.

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

TABLE 16 *Resource use and costs for the long-term model based on data from the NHAR*

	IHD[a]			MI[b]			Post-MI[c]		
	No. of patients	Average total LOS/no. of visits	SD	No. of patients	Average total LOS/no. of visits	SD	No. of patients	Average total LOS/no. 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					
PCI	2			3					
CABG	7			1					
Average health state cost (SD)[d]	£1421 (£944)			£3966 (£1722)			£1587 (1091)		

[a] 252 patients, 113,222 patient-days follow-up.
[b] 27 patients, 7248 patient-days follow-up.
[c] 15 patients, 2993 patient-days follow-up.
[d] Based on the Monte Carlo simulation.
LOS, length of stay.

patient can be calculated for each strategy, as well as the mean lifetime costs. The age of the patients in the model is not incorporated 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.[34]

Similarly, the model does not formally include the results of any particular subgroups 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 subgroups. A sensitivity analysis was carried out to examine strategy 1 just for high-risk patients.

The results of the model are presented in two ways. First, mean lifetime costs and QALYs of the four strategies are presented and their cost-effectiveness is compared, estimating incremental cost-effectiveness ratios as appropriate, using standard decision rules.[93] The advantage of entering input parameters as uncertain variables is that this uncertainty can be propagated 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.[94,95] These show the probability that each strategy is more cost-effective than the other three using alternative values for the maximum value that the health service is willing to pay for an additional QALY in these patients.

The model was developed in Excel with the Crystal Ball 'add-on'. The Monte Carlo simulation was run for 10,000 iterations. The model was 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 were 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:

- variation in the sources of data used to populate the base-case model
- variation in the baseline event rates using non-UK-specific sources of data
- the inclusion of additional strategies to those considered in the base-case model.

Table 17 summarises the key assumptions used in the base-case analysis and how these were varied in the sensitivity analyses.

Results

Results of the short-term model

Table 18 details the results of the short-term model. Despite the relative risks of death and non-fatal MI being most favourable for strategy 3, strategy 1 yields the lowest probability of leaving the short-term model in either with non-fatal MI or dead. 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 £2526 per patient, as opposed to strategies 2 and 3, which cost around £2130. 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, £525 and £989, respectively.

Base-case results of the long-term model

Table 19 presents the analysis of the incremental cost-effectiveness ratio (ICER) for the base-case analysis. The ICER examines the additional costs that one strategy incurs 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.[93]

- The strategies are ranked in terms of cost (from the least expensive to the most costly).
- If a strategy is more expensive and less effective than the previous strategy, then this strategy is said to be dominated and is excluded from the calculation of the ICERs.
- 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.
- 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 24* 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 £5738 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.

Although 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 25* presents the base-case results in the form of 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 19*). The results of the CEACs incorporate the uncertainty within the model in relation to both the estimates of mean costs and QALYs, and the maximum WTP for an additional QALY. The CEACs demonstrate that the probability that strategy 1 is cost-effective increases as the maximum WTP 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 WTP is £50,000. Consequently, the results from the base-case analysis demonstrate that if the health service

TABLE 17 *Details of key elements of the base-case analysis and how these are varied in the sensitivity analysis*

Elements	Position in base-case analysis	Variation in sensitivity analysis
Variation in the sources of data used to populate the base-case model		
Time horizon of model	50 cycles (50 years)	Five 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 RRs (which are assumed also to apply at 6 months)	Only those trials that report outcomes at 6 months Focus on those trials evaluating drugs most likely to be used for given strategy: strategy 1 risk reductions based on pooled results of eptifibatide and tirofiban trials (excluding lamifiban and abciximab trials); strategy 2 same as base case; strategy 3 based on abciximab trials only (excluding tirofiban and eptifibatide trials) Base case but cost strategy 3 as mean of tirofiban and eptifibatide for 12-hour infusion Base case except: strategy 1 RRs based on pooled results of eptifibatide and tirofiban trials (excluding lamifiban and abciximab trials); strategy 3 based on pooled results of eptifibatide and tirofiban (excluding abciximab trials), cost as mean of tirofiban and eptifibatide for 12-hour infusion Base case but relative risk data for strategy 3 based on EPIC subgroup analysis of UA patients
Utilities used to calculate QALYs	Assumption of mean utility of 0.8 (95% CI 0.6 to 0.94) for all non-death states in the long-term model based on data from GUSTO[41]	Assumption of fixed utility of 1.0 for all non-death states (i.e. life-years analysis) 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[90] 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	PRAIS data only Leeds audit data on parameters collected during the audit, otherwise use PRAIS Baseline data derived from patient-level meta-analysis
RR data used in strategy 1	Pooled RRs reported in trials	RRs taken from patient-level meta-analysis[35] for strategy 1; base case for strategies 2–4
Variation in the sources of baseline event data		
Baseline event data	UK-specific data derived from PRAIS-UK and Leeds cohort	New baseline event data derived from control group data reported in Boersma.[35] Same RRs applied as in base-case model Baseline event data derived as above. Separate RRs applied to strategy 1 to patient undergoing/not undergoing acute-PCI from patient-level meta-analysis
Variation in the choice of comparators		
Medical management of high-risk patients only	Not considered	Add medical management of high-risk patients only as a fifth strategy in the model
Clopidogrel	Not considered	Add clopidogrel as a fifth strategy in the model using published RR estimates[22] Add clopidogrel as a fifth option and use RR data from patient-level meta-analysis[35] in strategy 1

TABLE 18 *Results of the short-term model: probabilities (95% CI)[a] of leaving the 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	0.8906 (0.8681 to 0.9104)	0.8764 (0.8558 to 0.8958)	0.8774 (0.8572 to 0.8963)	0.8764 (0.8562 to 0.8955)
Dead	0.0623 (0.0465 to 0.0817)	0.0758 (0.0593 to 0.0915)	0.0739 (0.0591 to 0.0907)	0.0742 (0.0594 to 0.0911)
Non-fatal MI	0.0471 (0.0349 to 0.0612)	0.0488 (0.0366 to 0.0628)	0.0487 (0.0366 to 0.0625)	0.0493 (0.0372 to 0.0631)
Expected cost per patient	£2528 (£1724 to £4344)	£2139 (£1331 to £3952)	£2156 (£1349 to 3969)	£2106 (£1301 to £3916)

[a] Based on mean and 2.5 and 97.5 percentiles from the Monte Carlo simulation.

TABLE 19 *Base-case estimates of mean lifetime costs and QALYs for the four strategies, together with incremental analysis*

				Probability cost-effective for maximum WTP[a]		
Strategy	Cost	QALY	ICER	£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] Probability that each strategy is more cost-effective than the others conditional on different maximum willingness to pay (WTP) for an additional QALY.
[b] ICER strategy 3 versus strategy 4.
D, dominated; ED, option ruled out by extended dominance.

is prepared to pay over £5738 per QALY then strategy 1 is always the optimal decision.

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 20 details the results of each individual sensitivity analysis undertaken to assess the robustness or 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 in 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 20* 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 that 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 £8915 per QALY. This increase is primarily driven by the less favourable risk reduction associated with death (0.89, 95% CI 0.63 to 1.25) in comparison to the base-case analysis (0.84, 95% CI 0.71 to 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 offered in the

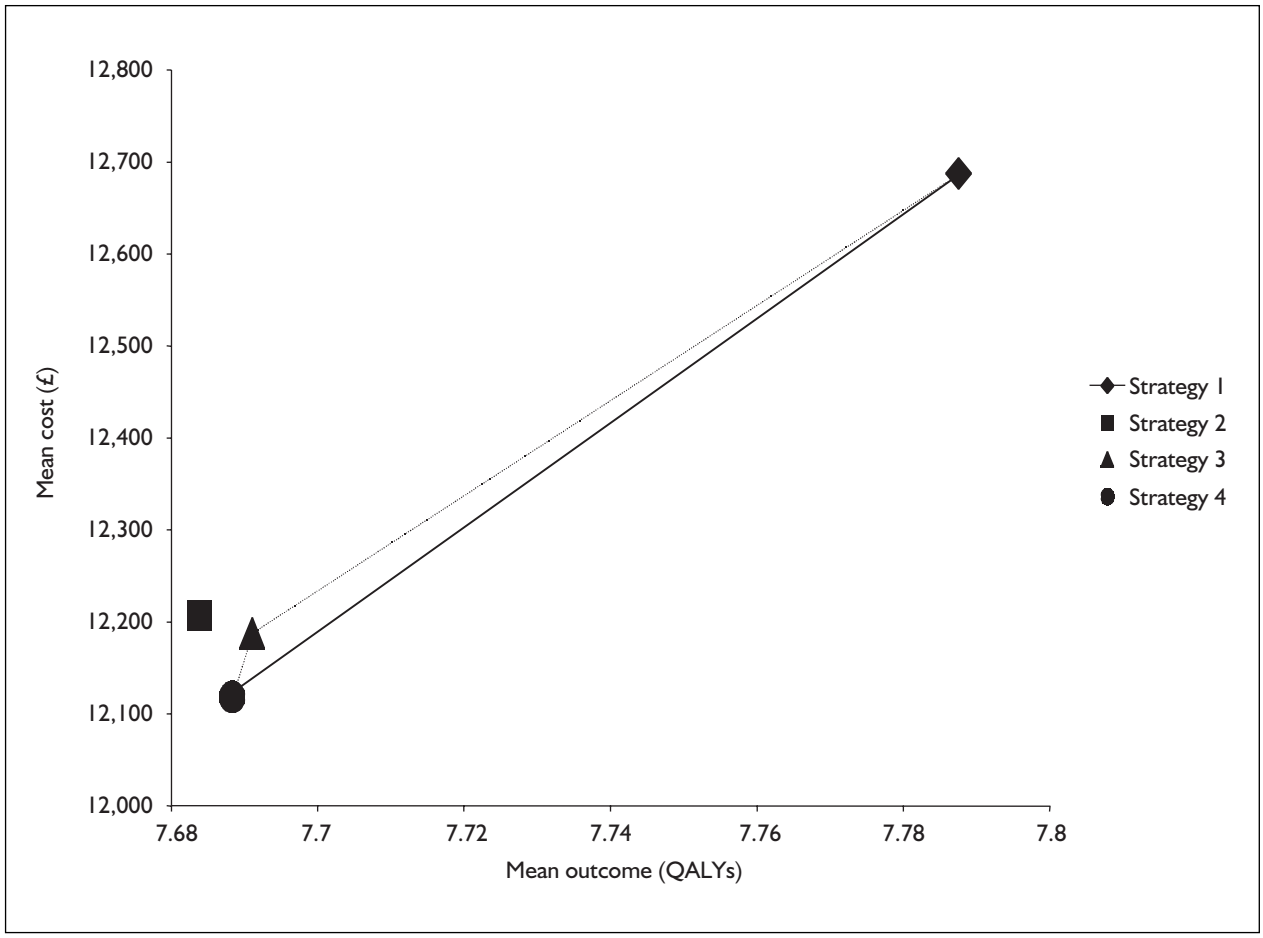

FIGURE 24 *Graphical representation of the mean costs and outcomes of the four strategies*

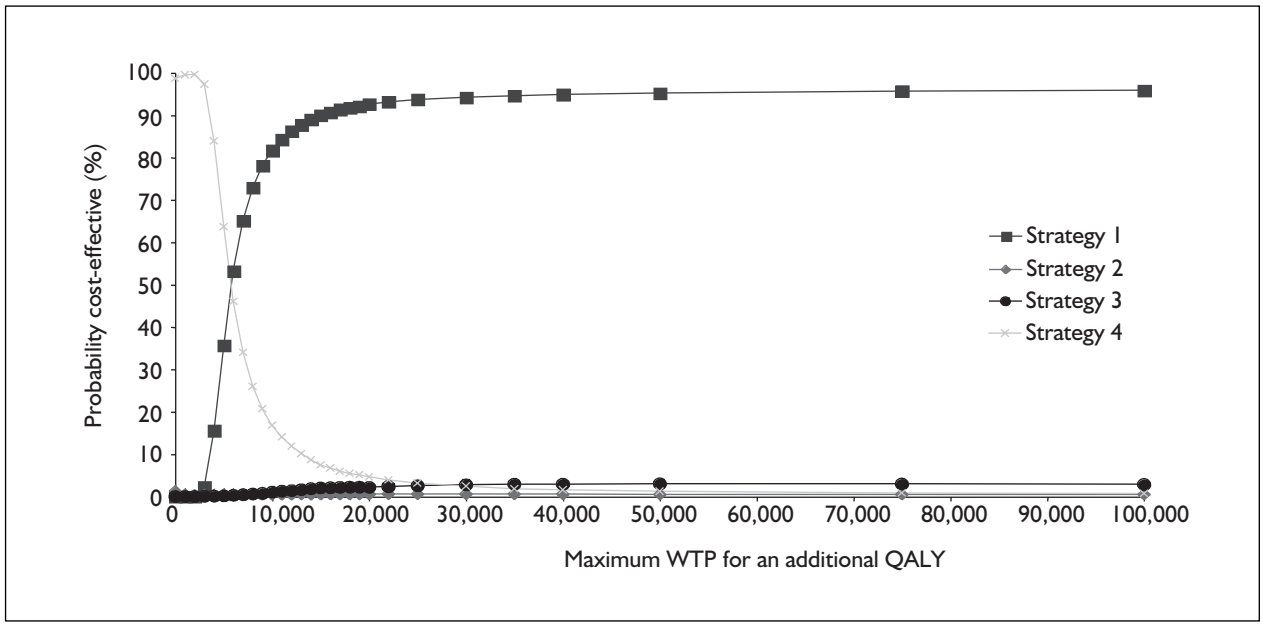

FIGURE 25 *Base-case CEAC*

TABLE 20 *Results of the sensitivity analyses using data summarised in* Table 17

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	Five 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 RRs of GPAs	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
	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
	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 RRs of GPAs	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
	Strategy 3: EPIC subgroup analysis of UA 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	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
	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

continued

TABLE 20 *Results of the sensitivity analyses using data summarised in* Table 17 *(cont'd)*

Element	Sensitivity analysis	Strategy	Cost	QALY	ICER	Probability cost-effective for maximum WTP[a] £10,000	£30,000	£50,000
	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	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
	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
RR 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] Probability that each strategy is more cost-effective than the others conditional on different maximum WTP for an additional QALY.
[b] ICER strategy 3 versus strategy 4.

context of strategy 1 in the NHS) increased the ICER marginally to £5824 per QALY.

The effect of using LYG 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 £4605, while reducing the utility weight for these states from 0.8 in the base case to 0.65 increased the ratio to £7005 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 ICER by only £8 to £5730 per QALY.

The results of the base-case model were based on the baseline risks derived by combining two separate 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 explore the impact of the assumptions used to derive the pooled estimates of relative risk for strategy 1, a separate sensitivity analysis was undertaken 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).[35] 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 that 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 ratios for death and non-fatal MI were 0.91, 95% CI 0.81 to 1.03, and 0.92, 95% CI 0.85 to 1, respectively, as opposed to the base-case estimates of relative risks of 0.84, 95% CI 0.71 to 0.98, and 0.94, 95% CI 0.87 to 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 RRRs for these two small-molecule GPAs are equivalent to the pooled RRRs 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. A head-to-head comparison of abciximab and tirofiban has been carried out, and showed that abciximab was more effective. This has not been used here. The purpose of the results presented here is to illustrate the sensitivity of the results of strategy 3 to the assumptions made in the base-case analysis, not to compare directly 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 UA. Owing 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 UA patients within EPIC,[96] 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 owing 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 20* indicate that 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.

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 and non-fatal MI). To address these limitations, the model was rerun using baseline event data from the recently published patient-level meta-analysis undertaken by Boersma and colleagues.[35]

In addition to the potential uncertainty in relation to the baseline data, two further sensitivity analyses were 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 prespecified indicators of high risk (e.g. age, diabetes, ST depression or positive baseline troponin levels). However, the recent meta-analysis undertaken by Boersma and colleagues[35] 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.

Methods used to derive new baseline event rates

New baseline event probabilities were derived from the control group data of the Boersma patient-level meta-analysis. Since the meta-analysis only reported event rates at 30 days, an extrapolation was required to apply these data to the 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 they had undergone an intervention within 5 days of randomisation. Using these 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 21 summarises the baseline event rates for death and non-fatal MI using the alternative data sources for the three patient groups considered in the short-term model. Both the 30-day event data reported in the Boersma paper and the

TABLE 21 *Comparison of baseline event rates between UK-specific sources used in the base-case model and non-UK-specific sources derived from Boersma[35]*

Revasc. group	Event	Base-case model: 6-month event rates (from PRAIS and Leeds)	Boersma: 30-day event rates	Boersma: 6-month event rates (extrapolated from 30-day rates)
Acute PCI	Death	3.3%	1.99%	5.62%
	Non-fatal MI	3.6%	12.77%	19.27%
Acute CABG	Death	10.6%	4.54%	8.14%
	Non-fatal MI	6.4%	22.46%	28.79%
No acute revasc.	Death	7.1%	3.97%	7.53%
	Non-fatal MI	4.7%	6.77%	13.43%

TABLE 22 *Relative risk reductions (95% CI) used in sensitivity analysis for strategy 1*

Revasc. group	Event	Baseline RRs	Separate RR for acute PCI/no acute PCI
Acute PCI	Death	0.84 (0.71 to 0.98)	0.83 (0.53 to 1.29)
	Non-fatal MI	0.94 (0.87 to 1.02)	0.80 (0.65 to 0.95)
Acute CABG	Death	0.84 (0.71 to 0.98)	0.91 (0.81 to 1.04)
	Non-fatal MI	0.94 (0.87 to 1.02)	0.95 (0.86 to 1.03)
No acute revasc.	Death	0.84 (0.71 to 0.98)	0.91 (0.81 to 1.04)
	Non-fatal MI	0.94 (0.87 to 1.02)	0.95 (0.86 to 1.03)

extrapolated event data at 6 months are 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 non-fatal MI 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 non-fatal MI is now higher in the acute PCI group using the new baseline data (19.27% versus 13.43% compared with 3.6% versus 4.7%).

Results of sensitivity analyses using alternative sources of baseline data

Two separate sensitivity analyses were undertaken using the new baseline event data. The first analysis applied the same relative risks as in the base case from the main report. The second analysis applied the relative risks reported in the Boersma paper to strategy 1 and used separate relative risks for those patients undergoing/not undergoing acute PCI (i.e. PCI within 5 days). *Table 22* provides details of the relative risks used in the two separate analyses for strategy 1.

Neither of the additional sensitivity analyses using the revised baseline event data results in a change in 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 23* 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, increases the ICER of strategy 1 from £5738 to £5753. The slight increase in uncertainty surrounding this decision is reflected in the lower probability that 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 both changing 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 £5667 to £9609. 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.

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

Two sensitivity analyses were undertaken to examine the impact of including a fifth strategy besides the four in the base case. These were: use as part of initial medical management only in a high-risk subgroup; and use of clopidogrel in all patients instead of GPA. Each is now presented in turn.

TABLE 23 *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	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
	Strategy 1 RR based on patient-level meta-analysis: differential RR applied to acute PCI/no acute PCI	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 24 *Sensitivity analysis including an alternative medical management strategy based on the use of GPAs in high-risk patients only*

				Probability cost-effective for maximum WTP		
Strategy	**Cost**	**QALY**	**ICER**	**£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	£3,996	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

Use of GPAs as part of initial medical management in high-risk ACS patients only

An additional subgroup analysis in Boersma[35] reported on the rate of death and non-fatal MI 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 MI 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 greater than or equal to 0.1 $\mu g\ l^{-1}$ (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. Owing 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, owing 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 RRRs are applied to low-risk strategy 1 patients, including those undergoing PCI. This is a limitation; in current practice, all patients without contraindications undergoing acute PCI for ACS will receive abciximab.

Using data from PRAIS-UK, high-risk status was determined by the presence of at least one of the following characteristics: age at least 70 years, 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 24* 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 £3996. 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 appears to be a small additional QALY benefit for use in all patients compared with 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. Owing 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 RRRs

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.

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 (300 mg 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.

The relative risks applied in the model based on the CURE trial were as follows: all-cause death 0.92 (95% CI 0.79 to 1.05), non-fatal MI 0.77 (95% CI 0.67 to 0.89), all revascularisation 0.92 (95% CI 0.85 to 0.98) and major bleeding 1.38 (95% CI 1.13 to 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[35] 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 £6978.

The results of the base-case model appear highly sensitive to the inclusion of clopidogrel as a fifth alternative strategy (*Table 25*). 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.

Discussion

Here, the focus is on the discussion of the decision model. For discussion of how its results fit with current practice in the NHS, and the implications for further research, see Chapter 5.

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/LYG 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 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 one. 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, and may be an artefact because the extra strategy of giving GPAs just to high-risk patients assumed that low-risk patients would never receive GPA, even if they underwent PCI. 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 either to 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 practice, clopidogrel and GPAs may be used in combination in high-risk cases. This represents yet another strategy that at present cannot be modelled because there are no trial data with which to estimate RRRs.

The results of the decision model should not be seen as contradictory to the findings of the systematic review. Although the systematic review highlighted the uncertainty in the effectiveness of GPAs in the medical management of ACS (caused in part by the conflicting results of some of the trials, in particular GUSTO IV), no attempt was

TABLE 25 *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	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
	Add clopidogrel as a fifth option and 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] Probability that each strategy is more cost-effective than the others conditional on different maximum WTP for an additional QALY.
[b] ICER clopidogrel versus strategy 4.
[c] ICER strategy 3 versus strategy 4.
clop., clopidogrel.

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.[35] The results of this analysis support the conclusion that GPAs reduce the incidence of death and MI 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.

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. A detailed examination of these studies can be found in the previous HTA monograph.[34] A summary is presented here.

Part of the reason why there have been few previous UK cost-effectiveness analyses is 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[34] of economic studies of GPAs in the medical management of ACS, which estimated cost per LYG in UK patients, was contained in the Schering-Plough submission to the earlier rapid review in 2000.[97] The 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 multinational 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 using similar methods,[98] LYG 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 £8179 to £11,079 per LYG, 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 ICERs for strategy 1 here are similar to those in the Schering Plough submission: £4605–10,343 based on a lifetime analysis here, compared with £8179–11,079 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.[27,34] These studies included data from several trials that 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 that 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.[64] 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 LYG for abciximab of £3554 for EPISTENT, £6247 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 was £13,191 for EPILOG and £11,196 for EPISTENT (assuming a lower reduction in mortality for both trials). Cost per QALY estimates ranged between £6941 and £9053 for EPILOG and £3949 and £5151 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 subgroup analysis of UA 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.

Technical limitations of the model

This section discusses specific limitations from the technical perspective of what an ideal model should contain. The clinical relevance of these limitations is discussed further in Chapter 5 (section 'Summary of key results', p. 74).

The first limitation to note 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 AMI. The relative risks used here to model strategy 3 were taken from trials that included any patients with UA, but it is recognised that the resulting pooled estimates of relative risk will reflect considerable heterogeneity. The only trial giving results in a subgroup of UA 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 for 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. In addition, there were not enough data to make it sensible to consider recurrent MI as a separate state; instead, this was included in the post-MI state (see *Figure 23*). Despite these assumptions, the average life expectancy of 9.59 years predicted by the extrapolation model does not appear unreasonable compared with 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. No other source of data on long-term UK survival following an episode of unstable angina, with and without MI at 6 months, was available to undertake further validation.

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 the UK). However, the different selection processes used in both the trials and observational cohorts inevitably mean 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 and non-fatal MI. 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 was not possible formally to incorporate this additional benefit for the following reasons: (1) both the definition and the actual reporting of recurrent ischaemia are inconsistent in strategy 1 trials; (2) there is no information on recurrent ischaemia in relation to strategy 3 trials owing to the inclusion of non-ACS patients; and (3) 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.[22] The current baseline used in the model for strategy 4 assumes 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 with standard therapy alone is shown to be cost-effective, then the current baseline comparator used in the model may be inappropriate. Although the potential 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. A further limitation regarding clopidogrel is that in practice it may be used in combinations with GPAs. This is discussed further in Chapter 5 (section 'Interpreting the results of the analysis', p. 76).

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 £4605 and £11,671 (the range for the analyses using a lifetime extrapolation is £4605–10,343). 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), the ICER ranges between £11,160 and £45,308 per QALY gained (the range for the analyses using a lifetime extrapolation is £11,160–38,350).

Chapter 4

Value of information analysis

Background

Healthcare decision-making is inevitably undertaken under conditions of uncertainty. There is uncertainty in terms of both the resource implications (and hence costs) of alternative healthcare technologies and their associated outcomes. This chapter explores the implications of the uncertainty associated with the cost-effectiveness of the use of GPAs in ACS patients by undertaking value of information (VOI) analysis. This analysis produces an upper limit to the value of future research that could be undertaken to reduce the uncertainty associated with a decision regarding the adoption of GPAs.

Using a Bayesian decision-theoretical approach, the decision to adopt any healthcare technology or management strategy is separated from the decision regarding the funding of future research to obtain further information to inform that adoption decision. Adoption decisions are based on expected costs and benefits (i.e. the ICER relative to some maximum WTP for a unit of health gain on the part of the health service), irrespective of the uncertainty surrounding that decision. In other words, the optimal strategy given current information (the a priori decision) is the one with the maximum expected payoff.[99] This rule is consistent with the objective of maximising health benefit from a given budget, assuming that the health technologies under investigation (here strategies 1–4 in the decision model) are mutually exclusive and that one of the technologies must be chosen.[100] Basing adoption decisions on alternative rules, such as those of classical inference, imposes costs to society in terms of benefits forgone by continuing with an inferior technology (in terms of expected costs and benefits) when a superior technology is available. However, this maximisation rule implicitly assumes no sunk costs and complete reversibility in decision-making, although these elements can be incorporated into the formulation of the payoff statistic.[101]

In decision theory, payoffs are expressed in terms of net benefits. These can be expressed in monetary (μ) or outcome (η) terms, by simply incorporating a threshold monetary value of outcome (λ) explicitly:

$$\mu = (\lambda * \text{QALY}) - \text{Cost}$$
$$\eta = \text{QALY} - (\text{Cost} * \lambda^{-1})$$

where λ represents the amount that society (or, more narrowly, the health service) is prepared to pay for an additional unit of outcome and is considered unknown. For this reason, it is considered as exogenous and analyses are presented for a range of λ.

A cost-effectiveness acceptability frontier provides a useful graphical representation of the uncertainty associated with the adoption decision. It depicts the uncertainty associated with the optimal decision over a range of λ values.[94] Although CEACs detail the probability of cost effectiveness for a particular strategy, the outer set of the acceptability curves cannot be used to identify the optimal decision at each value of λ. This is because the strategy with the highest probability of being optimal does not necessarily have the highest expected net benefit, and will only do so when the distribution of net benefits is symmetrical.[94,102]

Information from further research is considered valuable to a decision-maker, as it will reduce the uncertainty associated with the decision regarding healthcare service provision.[102] However, the decision to obtain further information should be based on criteria such that the costs of obtaining further information should not outweigh the benefits.[103]

The benefits of obtaining further information by funding future research can be expressed, at the limit, as the expected costs of uncertainty associated with the adoption decision (the optimal strategy under current conditions of uncertainty). This is based on two elements: the level of uncertainty associated with the adoption decision and the costs associated with making an incorrect decision. The first of these can be calculated as the probability that the adoption decision is wrong (the error probability). The second is measured by net benefits forgone as a result of making an incorrect decision (opportunity losses). If net benefits are expressed in monetary terms, the resultant value represents the maximum monetary amount that

society should be willing to pay to reduce the uncertainty surrounding the adoption decision. This value can be compared directly with the costs associated with gathering further information to determine whether further research in the area is potentially worthwhile.[102] It is important to note that the resultant value represents an upper bound on the expected benefits of obtaining further information, and observing a value greater than the costs of additional research is only a necessary, but not sufficient, condition for conducting further research. It is when the expected benefits of sampling exceed the costs, and the societal net benefits of sampling are positive, that further research will be efficient. This information can be obtained from the expected value of sample information (see Claxton and Thompson[104] for details).

Methods

The expected cost of uncertainty associated with the a priori decision is equivalent to the EVPI because perfect information eliminates the possibility of making an incorrect decision. Following the methods described by Fenwick and colleagues,[102] a non-parametric approach to determining the costs of uncertainty associated with the adoption decision is used:

$$\text{Cost of uncertainty of adoption decision} = \text{EVPI} = E(NB_{s**}) - E(NB_{s*})$$

where NB_s is the net benefit associated with strategy S, expressed in monetary units, S^* is the strategy chosen with existing information (adoption decision), and S^{**} is the strategy chosen with perfect information.

The use of Monte Carlo simulation allows the expected costs of uncertainty associated with the initial adoption decision to be expressed as the proportion of iterations in which the uncertainty within the model results in an adoption decision other than that resulting from maximising expected net benefits (the adoption decision). The benefits forgone are simply the difference in net benefits between the optimal strategy for a given iteration and the net benefit of the strategy identified as optimal in the adoption decision. The expectation of benefits forgone over all iterations represents the EVPI for a patient with ACS.

The overall value of information for a population of ACS patients is determined by applying the patient-level EVPI to the number of patients who would be affected by the information (i.e. incidence of ACS) over the anticipated lifetime of the technology:

$$EVPI^* \sum_{t=1}^{T} \frac{I_t}{(1+r)^t}$$

where I is the incidence in the period, t is the period, T is the total number of periods for which information from research would be useful, and r is the discount rate.

NHS HESs suggest that the incidence of UA is around 1000 cases per million total population per year, or about 10 per acute hospital per week.[105] Based on current estimates of the UK population, this implies an annual incidence of around 59,756.[106] The population-level EVPI is estimated using this value and assumes that the information would be valuable for 5 years. A 6% annual rate of discount is applied.

Patient and population EVPI are calculated for the base-case model and for the sensitivity analyses detailed in *Tables 11–25*. Results are reported separately for the three types of variation described in Chapter 3.

Results

Base-case model

Figure 26 details the cost-effectiveness acceptability frontier for the base-case model. The minimum point represents a switch point in the optimal decision. This is where the level of uncertainty in the optimal decision is greatest owing to the error probability that the optimal decision is cost-effective reaching a maximum. Up to this point, strategy 4 is optimal. Beyond this point, strategy 1 is optimal.

The results of the VOI analysis of the base-case model suggest that there is considerable value in obtaining further information on the input parameters to the model (*Figure 27*). At a λ value of £10,000, the EVPI is close to £48 per patient. This rises to £58 per patient when λ is £50,000. At a population level, the total EVPI is between £12,730,720 and £15,423,628 for these values of λ (*Table 26*).

As shown in *Figure 27*, the EVPI reaches a local maximum at the point where the λ value is equal to the ICER for the adoption decision of strategy 1 relative to strategy 4 (£5738 per additional

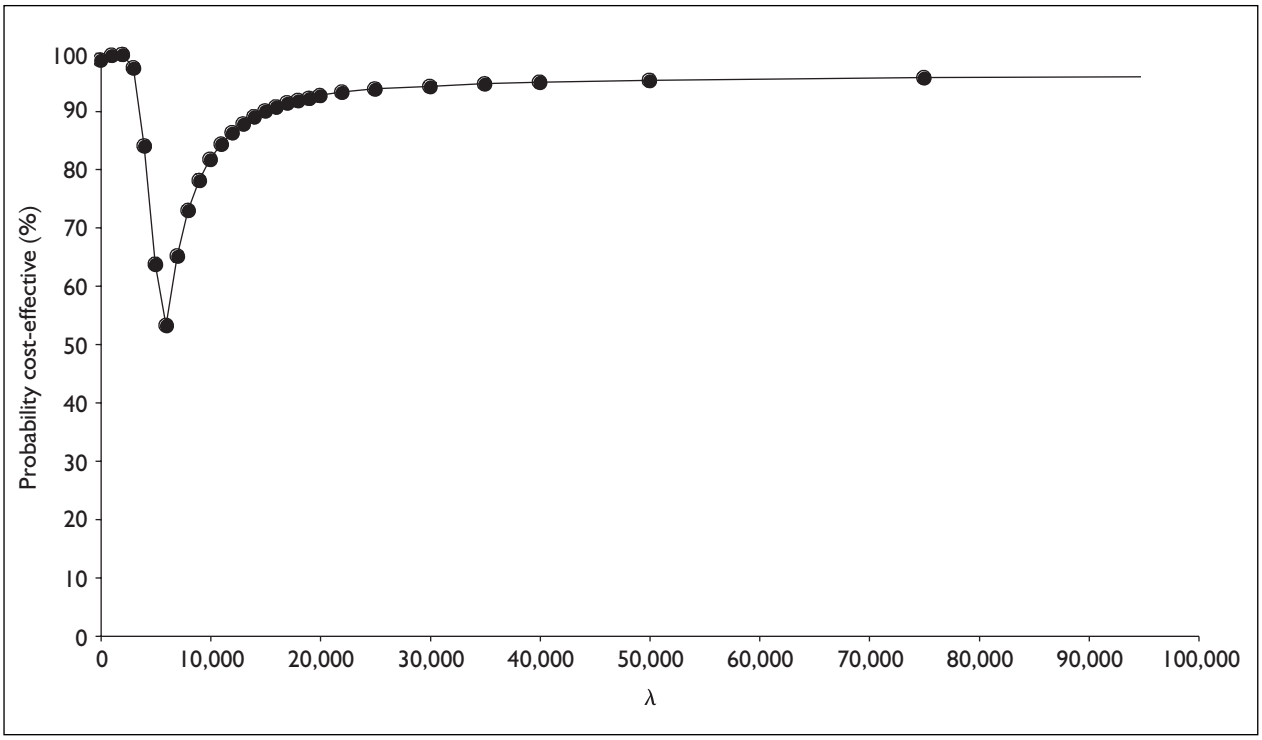

FIGURE 26 *Cost-effectiveness acceptability frontier for base-case model*

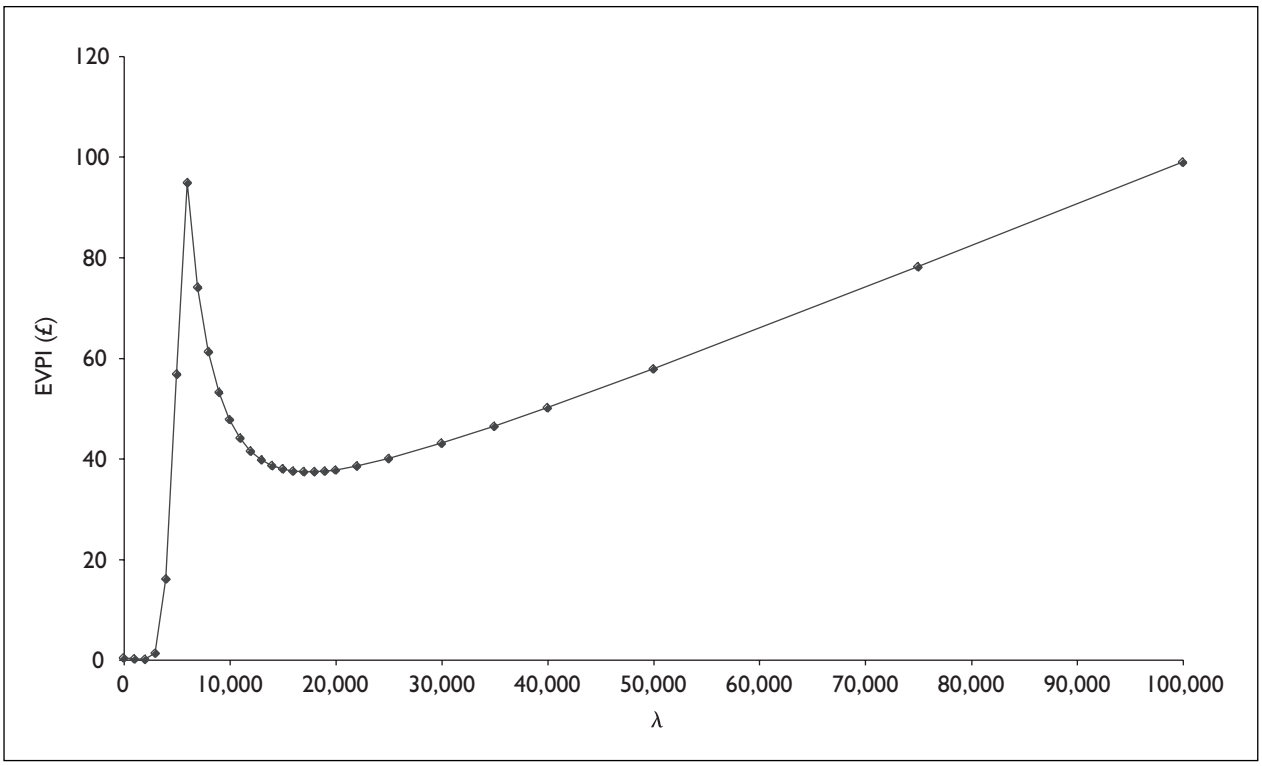

FIGURE 27 *Patient EVPI for base-case model*

TABLE 26 *Patient and population EVPI for selected values of lambda: base-case model and sensitivity analyses summarised in* Table 20

		Patient-level EVPI			Population EVPI[a]		
Element	**Sensitivity analysis**	**£10,000**	**£30,000**	**£50,000**	**£10,000**	**£30,000**	**£50,000**
Base-case model		£47.71	£42.97	£57.81	£12,730,702	£11,464,710	£15,423,628
Time horizon of model	Five cycles	£48.04	£35.73	£35.89	£12,819,196	£9,534,363	£9,577,106
Trials included in pooled estimates of RRs of GPAs	Only trials reporting outcomes at 6 months	£382.15	£859.47	£1364.23	£101,903,751	£229,319,839	£363,999,256
	Focus on drugs most likely to be used	£199.79	£408.63	£638.92	£53,307,320	£109,029,382	£170,473,615
	Cost of strategy 3 changed to average of eptifibatide/tirofiban	£48.23	£43.73	£58.57	£12,869,531	£11,667,626	£15,626,100
	Pooled results of eptifibatide and tirofiban for strategies 1 and 3	£200.69	£411.98	£644.44	£53,547,403	£109,923,272	£171,947,018
	Strategy 3 = EPIC subgroup analysis of UA patients	£50.26	£50.41	£70.03	£13,410,986	£13,449,923	£18,684,185
Utilities used to calculate QALYs	Life-year analysis	£39.36	£47.23	£66.46	£10,501,479	£12,601,646	£17,732,957
	Utilities reduced to 0.649 for all non-dead states	£95.09	£48.32	£57.11	£25,370,967	£12,893,758	£15,239,260
	Utility decrement of 5% on MI/post-MI states	£46.01	£40.77	£54.71	£12,276,808	£10,878,327	£14,597,915
Rate of PCI during ACS phase	Increase to 10%	£47.69	£41.90	£56.62	£12,725,109	£11,180,813	£15,107,640
Source of baseline data	PRAIS only	£50.09	£44.45	£58.85	£13,366,034	£11,860,342	£15,700,869
	Leeds PCI audit	£46.97	£39.70	£52.71	£12,532,799	£10,593,238	£14,064,322
RR data for strategy 1	Patient-level meta-analysis for strategy 1	£142.13	£146.01	£191.35	£37,923,638	£38,959,063	£51,055,913

[a] Assuming incidence = 59,756, discount rate = 6% and information useful for 5 years.

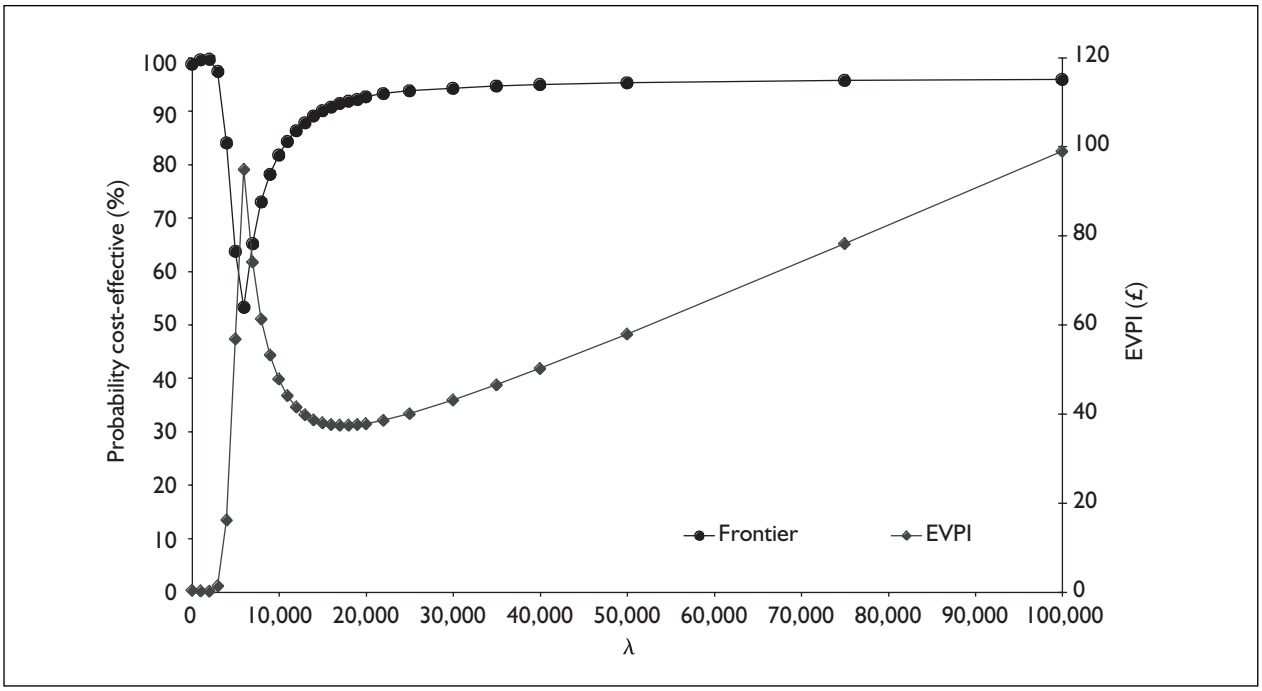

FIGURE 28 *EVPI versus acceptability frontier for base-case model*

QALY). Up to this value, EVPI is increasing. This is because the uncertainty surrounding the a priori adoption decision is increasing (error probability increasing), as is the value applied to the consequences of the uncertainty (λ). After this point, the uncertainty in the adoption decision decreases, but the costs associated with making an incorrect decision are increasing. The overall effect on the EVPI depends on the interaction between these terms. In this case, as λ approaches £18,000 the EVPI falls, implying that the probability of an incorrect decision is reducing at a rate that is sufficient to outweigh the increasing costs of making an incorrect decision. After this point, the EVPI increases as λ increases, demonstrating that while the error probability is still falling, this is now being outweighed by the costs of making an incorrect decision. The relationship between the cost-effectiveness acceptability frontier and the EVPI is demonstrated clearly in *Figure 28*. When uncertainty in the decision to adopt strategy 1 is the greatest (i.e. the probability of strategy 1 being cost-effective, given that it is optimal, is at a minimum), the EVPI reaches a local maximum.

Sensitivity analyses

Sensitivity analyses on alternative assumptions relating to the sources of data used in the base-case model

Table 26 details the results of the sensitivity analyses. Under alternative assumptions regarding the sources of data used in the base-case model, changes in the source of relative risk estimates have most impact on EVPI. The biggest effect is to increase EVPI to between £382.15 and £1364.23 per patient when trials reporting at 6 months only are used for the relative risk estimates. The EVPI is reduced in just one scenario: at low values of λ, the EVPI falls when outcomes are measured in life-years (to between £39.36 and £66.46 per patient).

Altering the assumptions regarding the utility values used to calculate QALYs results in marginal changes to the EVPI. When outcomes are valued using life-years gained (i.e. no quality adjustment), the mean difference in outcome between strategies 1 and 4 magnifies. This results in less uncertainty surrounding the a priori decision and a lower EVPI when λ is valued at £10,000 compared with the base-case model. Equally, when a lower utility estimate is used to estimate QALYs (i.e. 0.649 as opposed to 0.80 used in the base-case model), the benefit of strategy 1 over strategy 4 is reduced and the optimal strategy becomes more uncertain. Under this scenario the EVPI is £95 per patient, almost double that of the base-case model.

Changes in the relative risks associated with the use of GPAs have the most marked effect on EVPI. This is most noticeable when only trials reporting at 6 months are used to derive the relative risk estimates. If society is prepared to pay £10,000

per additional QALY gained, the EVPI under this scenario is £382 per patient (approximately £101,963,751 for a population). This increase over the base-case model is likely to be due to the wider confidence intervals on the relative risk estimates, driven primarily by a lower number of trials used to calculate the pooled estimates.

Applying relative risks from the patient-level meta-analysis[35] to strategy 1 increases the level of uncertainty within the model, especially at low values of λ. This is because the estimates of relative risk derived from the meta-analysis are more conservative for strategy 1 than those used in the base-case model. Consequently, the probability of strategy 1 being optimal is lower (higher error probability) than in the base-case model. The impact of this is to increase the EVPI across the entire range of values of λ. Using these alternative relative risk reductions for strategy 1 increases the EVPI per patient from £48–58 (£12.7–15.4 million for the population) in the base-case model to £142–191 per patient (£37.9–51 million for the population) using the revised relative risks, for values of λ between £10,000 and £50,000.

Sensitivity analyses relating to changes in the source of baseline data

Changing the source of the baseline event data to that reported by Boersma and colleagues[35] has a small effect on the EVPI (*Table 27*). Although a change in baseline event rates is reflected in each of the strategies, the event rates are considerably higher than in the baseline model, and the overall effect is a marginal increase in the uncertainty regarding the optimal strategy. [As baseline data are applied to each strategy simultaneously (alone on strategy 4, in combination with relative risk data from strategies 1–3), changes to the source of baseline data do not lead to any marked changes in the relative differences in cost and outcomes between the strategies.] When the relative risks applied to strategy 1 are altered to reflect the differential risks according to whether or not a PCI has been undertaken, the EVPI rises to between £190 and £364 per patient (approximately £51–97 million for the ACS population). This can be explained by the increase in the probability that strategy 4 is cost-effective when λ is £10,000, and similarly for strategy 3 when λ is at least £30,000.

Sensitivity analyses relating to additional management strategies

Changing the structure of the model to incorporate additional management strategies results in dramatic increases in EVPI. *Table 28* details the VOI analysis for these sensitivity models.

Considerable uncertainty is introduced into the model when the option of medical management for high-risk patients only is assessed alongside the previous four strategies. In this sensitivity analysis, the optimal decision depends on the value placed on outcomes. *Figure 29* details the EVPI and acceptability frontier for this sensitivity analysis. The switch-points between optimum strategies occur at the ICER values (approximately £4000 and £91,000), and are reflected by a change in the gradient of the slope of the EVPI, and local minima on the frontier. The frontier shows that beyond the initial switch-point, where the optimal strategy changes from strategy 4 to managing high-risk patients only, the uncertainty associated with the optimal strategy centres around 50%. This explains why the EVPI is high: the probability of an incorrect decision is in the order of 50% and the costs associated with an incorrect decision (i.e. λ) are increasing. At a population level, the EVPI exceeds £571 million (λ = £50,000), suggesting considerable value in further information to inform a decision in this instance.

When clopidogrel is added to the model, the range of EVPIs increases compared with the base case to between £157 and £587 per patient. This is because there are only small differences in cost and outcome between the clopidogrel option and strategy 1. Although strategy 1 remains the optimal decision, there is around a one-third probability that clopidogrel is cost-effective. This uncertainty explains the high EVPI. When the relative risks for strategy 1 are altered to reflect the more conservative estimates reported by Boersma, the EVPI values increase further (£192–1153 per patient). On average, clopidogrel dominates strategy 1, but the differences are so modest that there are several iterations of the model where strategy 1 yields the highest net benefit and the a priori decision leads to opportunity losses.

Discussion

Discussion of results

The decision regarding the most efficient use of GPAs in non-ST elevation ACS patients is based on a rule of maximisation. The strategy with highest net benefit, expressed in monetary terms, represents the most efficient use of resources under current conditions of uncertainty (the a

TABLE 27 *Patient and population EVPI for selected values of lambda: alternative source of baseline data*

Element	Sensitivity analysis	Patient-level EVPI			Population EVPI[a]		
		£10,000	£30,000	£50,000	£10,000	£30,000	£50,000
Patient-level meta-analysis as the source of baseline data	Same RR as applied in base-case model	£56.62	£59.00	£82.04	£15,106,269	£15,742,419	£21,889,828
	Strategy 1 RR based on patient-level meta-analysis: differential RR applied to acute PCI/no acute PCI	£190.66	£254.59	£364.67	£50,871,782	£67,928,156	£97,300,188

[a] Assuming incidence = 59,756, discount rate = 6% and information useful for 5 years.

TABLE 28 *Patient and population EVPI for selected values of lambda: alternative management strategies*

Element	Sensitivity analysis	Patient-level EVPI			Population EVPI[a]		
		£10,000	£30,000	£50,000	£10,000	£30,000	£50,000
Strategies under investigation	Add GPAs in medical management for high-risk patients only as a fifth option	£333.21	£1230.74	£2142.26	£88,905,247	£328,381,713	£571,591,764
	Add clopidogrel as a fifth option	£157.01	£365.24	£587.25	£41,892,997	£97,452,124	£156,690,736
	Add clopidogrel as a fifth option and use patient-level meta-analysis for RR for strategy 1	£192.34	£657.60	£1153.08	£51,318,833	£175,458,417	£307,661,841

[a] Assuming incidence = 59,756, discount rate = 6% and information useful for 5 years.

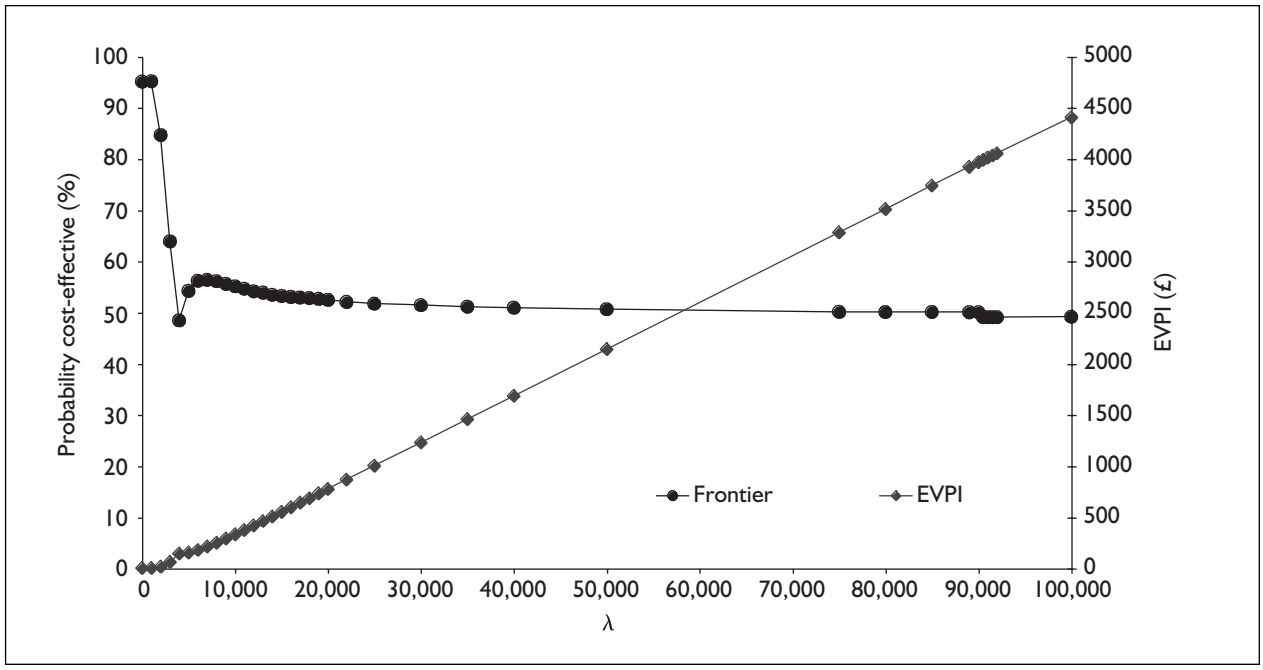

FIGURE 29 *EVPI and cost-effectiveness acceptability frontier for sensitivity analysis applying a fifth option of medical management for high-risk patients only*

priori decision). The uncertainty within the model is used to quantify the potential value of future research to reduce the uncertainty associated with the a priori decision. Financial losses associated with making the adoption decision are expressed as the difference between the maximum payoff and the payoff associated with the a priori decision over each iteration of the model. The expectation of opportunity losses represents the limit of the potential value of future research to reduce that uncertainty as opportunity losses are equivalent to the EVPI and perfect information eliminates the possibility of making an incorrect decision.

The EVPI for the base-case model indicates that there is potentially considerable value in further research to reduce the uncertainty associated with the a priori decision. Using base-case assumptions, EVPI is between £47.71 and £57.81 per patient for λ values between £10,000 and £50,000. At a population level, the EVPI necessarily depends on assumed estimates of annual incidence. HES suggest that the incidence of UA is around 1000 per million of the UK population. Applying these estimates indicates that the potential maximum value of future research is in the region £12.7–15.4 million. Moreover, it is reported that as many as one-third of AMI admissions relate to non-Q-wave infarctions. Therefore, it may be appropriate for an additional 600 per million to be included on these incidence estimates.[3] This would increase the population EVPI to between £20.4 and £24.7 million.

Calculation of EVPI for the sensitivity analyses offers a guide to which input parameters of the model may affect the uncertainty associated with the a priori decision. EVPI is relatively insensitive to changes in outcome valuation, baseline risk, the time horizon of the model and PCI rate, but fluctuates greatly under alternative assumptions regarding the pooled estimates of relative risk and when additional management strategies are included in the model.

Application of the relative risks derived in the patient-level meta-analysis[35] increased EVPI by approximately 300%. This increase is primarily driven by the more conservative estimates of relative risk and the consequent reduction in the additional benefit of strategy 1 over strategy 4. When the information base regarding relative risk estimates is reduced, and trials only reporting at 6 months are included in the pooled estimates, the EVPI increases dramatically to between £382 and £1364 per patient (£102–364 million for the population). However, these results must be interpreted with caution, as deliberately omitting already available data will artificially inflate the potential value of future research, as some of the information that would be derived from the 'future research' is already available, and simply not being used. In this instance, the inflated EVPI is due to the more conservative estimates of the relative

risks associated with death and MI and the wider confidence intervals on these relative risk estimates due to the smaller number of trials included in the pooled estimates. This indicates the importance of making decisions on the basis of all available data.

Modelling an additional strategy where high-risk patients only are treated with GPAs as part of medical management gives rise to considerable uncertainty. The optimal decision depends on the value placed on outcome; as λ increases, the model suggests that a wider population should be treated with GPAs as part of medical management. At low values of λ, the uncertainty lies in the decision between not using GPAs and treating high-risk patients only. As λ increases beyond £3993 (ICER of optimal decision) the probability that the optimum strategy is cost-effective never exceeds 60%, leading to opportunity losses in the order of £333–2142 per patient. The results suggest that there is potential value in further research to identify the subgroups of patients who benefit most from the use of GPAs alongside medical management. However, it is important that these results are interpreted with caution and viewed as indicative, as the definition of high risk was not consistent across baseline and relative risk estimates in the model. The definition of high risk used for the systematic review is highlighted in Chapter 2 (section 'Rationale: requirements of the decision model', p. 19).

When clopidogrel is added as a fifth strategy, there is considerable uncertainty in the model because of the small relative differences in cost and outcome between clopidogrel and GPAs as part of medical management. Currently, there are no trials under way that make a head-to-head comparison of clopidogrel and GPAs. The EVPI of the model ranged between £157 and £587 per patient when clopidogrel was added to the base-case model and between £192 and £1153 per patient when the relative risks for strategy 1 were taken from Boersma.[35] These results are indicative of the need for research comparing GPAs with other relevant adjunct medications, but again should be interpreted with caution as the relative risk estimates for clopidogrel were not identified as part of the systematic review.

The decision-theoretical work presented in this chapter can be extended in two important ways to help to identify the appropriate designs for additional research. First, the EVPI for individual parameters in the model can be estimated.[100,107] Second, the expected net benefits of sampling information can be estimated to assess the optimum sample size in future studies.[104]

Conclusion

The population EVPI for the base-case model was £12.7–15.4 million for the UK as a whole, suggesting that further research in this area is likely to be of significant value. Sensitivity analyses indicate that EVPI is most sensitive to the addition of further management strategies. Potential future research in this area should be directed towards the identification of the characteristics of patients who benefit most from GPAs and the comparison of GPAs with clopidogrel as an adjunct to standard care.

Chapter 5

Discussion and conclusions

The discussion is structured in the following manner. The first section highlights aspects of the methodology which, to the authors' knowledge, have not been applied before in the UK HTA programme. The next section presents a summary of the key results. The final section discusses how and why these findings diverge from recommended and current practice within the NHS at present, and what future research is indicated as a result.

Methodological developments

This study consciously adopted an explicit set of methods that differ from those typically used in many health technology assessments based on secondary analysis of existing data. The key methods used are described below.

Explicit methods to identify the most important decision problem before conducting a systematic review

To provide a useful basis for decision-making regarding the use of healthcare technologies, it is important that there is an explicit statement of the decision problem. Specifically, clarity is required about the relevant patient population and the full range of competing interventions that require comparison. This study was presented with a general research question: 'What is the cost-effectiveness of different management strategies for patients with UA?'

To identify a focused decision question which, when answered, would provide the most valuable information to UK decision-makers, two pieces of preliminary work were undertaken: first, a review of international clinical guidelines in UA to identify the areas of uncertainty regarding the most appropriate form of management; and second, a survey of clinical opinion with a similar objective, but enabling more detailed responses, in particular, regarding the alternative management strategies with which GPAs could be used. Given more time and research resources, this preliminary work could have included more detailed surveys and interviews with other types of decision-makers (e.g. primary care trusts). The process used to identify 'the right question' suggests that this is an important area of methodological research.

The use of a decision model to structure the decision problem and data acquisition

On the basis of the preliminary work, an explicit decision problem was identified: to identify whether alternative management strategies involving GPAs were cost-effective in the management of non-ST elevation ACS. To address this question a decision-analytical model was developed as a framework for synthesising existing information.[106] Although the use of decision models is now more common in secondary research, the model that was developed for this study had some important features that have not been widely adopted. First, the model was probabilistic; that is, the uncertainty in all input parameters was explicitly quantified and incorporated into the model, and the joint uncertainty in these parameters was propagated through the model using Monte Carlo simulation. This allowed the uncertainty in the cost-effectiveness results (and hence in the decision about appropriate management) to be made explicit using CEACs. Furthermore, uncertainty was characterised without reliance on standard rules of inference, which rely on ultimately arbitrary *p*-value thresholds that are inconsistent with the objective of maximising health gain from limited resources.[100]

Second, although a considerable amount of trial data was identified in the systematic review, these data exhibited important limitations for UK decision-making. In particular, there were no head-to-head comparisons of the competing GPA strategies, and the control groups in these predominantly non-UK trials were unlikely to reflect standard management of patients in the UK. To address these limitations, baseline risks were taken from UK sources and pooled relative treatment effects were taken from the trials. Furthermore, meta-regression was undertaken to explore whether the assumption of a constant relative treatment effect was reasonable.

Third, to overcome the relatively short time horizons in the study (typically no more than 6 months) and the use of intermediate clinical outcomes (deaths, MIs, etc.) rather than ultimate measures of health gain (quality-adjusted survival

duration), an extrapolation model was also developed. This was based on a Markov model and populated using clinical and resource-use data from a UK longitudinal cohort study.

An explicit framework to provide information on future research priorities

The use of probabilistic modelling provides a formal way of estimating the cost of the uncertainty in existing information in terms of (1) the probability of making a wrong decision about the most appropriate form of management for these patients, and (2) the 'cost' of that wrong decision in terms of resources and forgone health gain. This cost of uncertainty can be seen as the maximum value of further research: the EVPI. This can be seen as a reference point for judging the value of further research such as clinical trials: a necessary condition for specific further research studies to be cost-effective is that their fixed costs are lower than the EVPI. The probabilistic modelling also provides insight into the parameters to which the decision about 'best management' is particularly sensitive. This also provides important information for future research prioritisation and design.

Summary of key results

The aims of the study were:

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

The key results will be now be presented under each of these aims.

Prioritisation of decision problems

The shortlist identified at the proposal stage identified decision problems concerning the use of clopidogrel (as an alternative to aspirin), LMWH, direct thrombin inhibitors and GPAs. Clopidogrel as an addition to aspirin was not considered as no results from the CURE study were available at the time (December 2000).

Although the mean certainty expressed by clinicians in how these drugs should be used in case vignettes was high (between 4 and 5 on a scale from 1 to 6), the type of drugs for which there was least certainty was GPAs. The criticism that was expressed about the NICE guidance on GPAs published in September 2000, and the suggestion from the present survey that it was not expected to be widely adopted, were additional reasons why GPAs were considered to be the highest priority decision problem.

This judgement was made in March 2001; if the prioritisation exercise were conducted at a different point in time its results might well differ, given the frequency with which relevant RCTs and other types of study are published.

Systematic review of randomised controlled trials and previous economic evaluations

The systematic review was designed to focus on 'high-risk' patients, in whatever way that was defined by the authors of the studies, as is explained more fully in Chapter 2 (section 'Rationale: requirements of the decision model', p. 19). In addition to the papers discovered for the systematic reviews undertaken in 2000 for the technology assessment review for NICE,[9] two RCTs and six economic studies were identified; 12 subgroup trial reports were also found. The new publications did not substantially alter the findings of the previous reviews. There was insufficient detail and consistency in the reporting of high-risk subgroups to provide reliable estimates of effect size for use in the model.

An individual patient-level meta-analysis of the strategy 1 trials was published after this systematic review had been completed[35] and this provided information that could be used to reflect event risks in high-risk patients (see below).

Decision model

Four treatment strategies were evaluated: GPAs as part of initial medical management (strategy 1); GPAs in patients with planned PCIs, where GPAs are started when a decision to undertake PCI has been made (strategy 2); GPAs as an adjunct to PCI at the time of PCI or up to 1 hour before the procedure (strategy 3); and no use of GPAs (strategy 4).

Strategy 1 generated an extra 0.1 QALYs per patient for an extra cost of £560 per patient compared with no use of GPAs, giving an ICER of £5667. Strategy 2 was more expensive and less

effective than strategy 3; it was, therefore, dominated and unequivocally less cost-effective than one or more alternative strategies. Strategy 3 showed a benefit over no use of GPAs but was less cost-effective than strategy 1, generating, on average per patient, only 0.002 extra QALYS for an extra £77 compared with strategy 1 (ICER £33,478), which means that it is subject to extended dominance with respect to strategy 1. Hence, as long as the health service is willing to pay at least £5667 per additional QALY, strategy 1 is the most cost-effective strategy. When reflecting uncertainty in mean costs and QALYs, if the health service is prepared to pay £10,000 per additional QALY, the probability that strategy 1 is the most cost-effective choice is around 82%, increasing to 95% if the maximum WTP is £50,000.

A range of sensitivity analyses was undertaken, few of which resulted in substantive changes to the base-case conclusions described above. The following sensitivity analyses showed the most important changes.

- Use of RRRs for strategy 1 from the recent patient-level meta-analysis[35] rather than the present systematic review roughly doubled the ICER of strategy 1 and reduced the probability that it was cost-effective at the same £10,000 threshold from 82% to 48%.
- Initial medical management with GPAs only to high-risk patients (defined as those who were diabetics, were aged over 70 years or who had ST depression on their admission ECG) reduced the ICER of strategy 1 by about 40% and increased the probability that initial medical management was the most cost-effective choice to 94% at the £10,000 threshold. However, only the RRR for strategy 1 could be adjusted to high-risk patients alone, owing to the lack of suitable data for strategies 2 and 3.
- Use of clopidogrel, in the dosage and with the effects on outcome suggested in the CURE trial, is cost-effective compared with no use of GPAs, but not to the same extent as strategy 1.
- The only sensitivity analysis in which strategy 1 was not the most cost-effective option was a two-way analysis including clopidogrel as a fifth strategy and using the more conservative RRRs for strategy 1 from the Boersma meta-analysis[35] rather than the present review. In this analysis, strategy 1 was dominated by the clopidogrel strategy in that it cost an extra £160 per patient but produced 0.002 fewer QALYs.

VOI analysis

The uncertainty within the decision model is used to quantify the potential value of future research to reduce the uncertainty associated with the decision regarding which strategy to adopt based on current information. The EVPI for the base-case model indicates that there is potentially considerable value in further research to reduce the uncertainty associated with the a-priori decision: EVPI ranged between £47.71 and £57.81 per patient for λ values between £10,000 and £50,000, respectively, under base-case assumptions. At a UK population level, this translates into potential maximum value of future research in the region of £12.7–15.4 million.

The EVPI analysis can indicate which input parameters have a particularly large impact on the uncertainty associated with the adoption decision. EVPI fluctuates most significantly under alternative assumptions regarding the pooled estimates of relative risk and when additional management strategies are included in the model. Application of the relative risks derived in the patient-level meta-analysis[35] increased EVPI by approximately 300%. This increase was primarily driven by the more conservative estimates of relative risk and the consequent reduction in the additional benefit of strategy 1 over strategy 4.

Modelling an additional strategy where high-risk patients only are treated with GPAs as part of medical management gives rise to considerable uncertainty. The optimal decision depends on the value placed on outcome; as λ increases, the model suggests that a wider population should be treated with GPAs as part of medical management. The results suggest that there is potential value in further research to identify the subgroups of patients who benefit most from the use of GPAs as part of medical management. However, it is important that these results are interpreted with caution and viewed as indicative, as the definition of high risk was not consistent across baseline and relative risk estimates in the model.

When clopidogrel is added as a fifth strategy, there is considerable uncertainty in the model because of the small relative differences in cost and outcome between clopidogrel and GPAs as part of medical management. The EVPI of the model ranged between £157 and £587 per patient when clopidogrel was added to the base-case model, and between £192 and £1153 per patient when the relative risks for strategy 1 were taken from Boersma.[35] These results are indicative of the

need for research comparing GPAs with other relevant adjunct medications.

Interpreting the results of the analysis

As with any primary or secondary analysis it is important to consider issues that influence the interpretation of the study's results.

How the results compare with current NHS policy and practice

The first issue to consider is how the results of the analysis compare with existing clinical policy and practice in the UK. Current, NHS policy for the management of non-ST elevation ACS, as described in the NSF for CHD, published in March 2000, is shown in *Table 1* (Chapter 1). No reference is made to GPAs. Guidance to the NHS from NICE on the use of GPAs in ACS was published in September 2000.[23] At the time of writing (May 2002) a review of this guidance was in progress, in part based on analysis described here and elsewhere[34] (this has now been published[108]). The 2000 guidance recommends the use of GPAs in high-risk patients and also in conjunction with PCI. High risk is to be determined by raised serum troponin measurement.

The survey of UK cardiologists detailed in this report and consultations with clinical advisors suggest that current practice differs from that recommended in the following ways.

- In a few DGHs, GPAs may not be used at all. Only those patients considered to be sufficiently high risk that they require urgent transfer to a tertiary centre may be judged to be at sufficient risk to merit the use of GPAs, and the actual prescription decision may be left to the receiving hospital. At the tertiary centre a small molecule GPA may not be prescribed if the investigation is imminent, because the use of abciximab (the large molecule GPA) is anticipated at the time of PCI. This approach is equivalent to strategy 3 in the decision model. If the patient is found on angiography not to be suitable for PCI, no GPA may be given.
- In some DGHs, GPAs may be administered only to those patients in whom a decision has been made to perform urgent angiography, either locally or after transfer. This policy is consistent with current guidelines issued by the BCS,[18] which recommend that patients at sufficient risk should receive both GPAs and urgent intervention. The definition of what risk is sufficient is, however, more demanding than simply a raised troponin level, as suggested by the NICE guidelines: "recurrent symptoms or ECG changes or other indication of high risk" are also required. This approximates to strategy 2 of the decision model with the use of a small molecule GPA.
- In other DGHs, small molecule GPAs will be used in all patients considered to be sufficiently high risk, whether or not PCI is to be performed. However, much depends on the threshold used to define high risk. The threshold will differ from the base-case version of strategy 1 of the decision model in that, unlike that base-case scenario, not all patients with non-ST elevation ACS will be treated. Indeed, the threshold may be set higher than the high-risk version of strategy 1 undertaken in the sensitivity analysis (baseline risk from patients with diabetes or aged over 70 years or ST depression on ECG; treatment effect from patients with raised troponin).
- Some high-risk patients may receive both a small molecule GPA as part of their initial medical management and abciximab (large molecule GPA) at the time of PCI. None of the strategies in the decision model follow this policy owing to the complete absence of treatment effect data from trials.

Although this may be a reasonable summary of existing clinical practice in the NHS with respect to GPAs in non-ST elevation ACS, the pattern of practice is likely to change month by month as the clinical significance of newly published findings is considered. For example, the apparently large gender difference in the effectiveness of GPAs demonstrated by the recent meta-analysis,[35] which appeared to show that, on average, men have a higher risk of events following GPAs, may mean that the drugs are rarely prescribed to women with non-ST elevation ACS, although a differential policy is not advocated by the authors of the meta-analysis. However, the fact that, in high-risk patients with raised troponin, women are expected to benefit complicates that interpretation of the data. It may be predicted that fewer patients will receive GPA as part of initial medical management as more of them receive clopidogrel. However, limited cost-effectiveness evidence exists on that drug, and the model presented here suggests that the cost-effectiveness of GPAs and clopidogrel is finely balanced.

If this summary of current practice is accurate, the analysis presented here suggests that there should be an expansion in the use of GPAs in non-ST

elevation ACS as defined in the model as strategy 1. There is clearly room for discussion (and further research) about the threshold used to define high risk, but the definition used in the model (baseline risk from patients with diabetes or aged over 70 years or ST depression on ECG; treatment effect from patients with raised troponin) may embrace a higher proportion of patients than covered by existing practice. The analysis suggests that any widespread use of GPAs only once a decision has been made to undertake urgent PCI, or only at the time of PCI, is not cost-effective and should be curtailed in preference to earlier use as medical management.

Limitations of the analysis

As with any analysis, there are limitations of the model presented here and these should be considered as part of the process of interpreting the results.

Limitations in the available data

The data used were the best available in the UK. The principal source of the baseline probabilities of the short-term model was PRAIS-UK.[13] This study was designed to be representative of all UA patients admitted to 56 DGHs. Each hospital was instructed to recruit 20 consecutive patients who met the inclusion criteria.

Selection bias may have occurred in this study for two reasons. First, although the initial sample of hospitals was randomly selected, if a chosen hospital refused to participate, the identification of a substitute was not random. Second, there was no validation that the 20 cases chosen by each hospital were consecutive as intended.

The most probable direction of such bias would arguably be to exclude cases who were particularly unwell, so that the risks of death or subsequent MI may have been underestimated. In turn, this implies a possible underestimation of the absolute benefit of strategy 1 (i.e. the treatment of all patients). Hence, the cost-effectiveness of strategy 1 might be greater than that reported here, and the optimal decision to use strategy 1 may be even more probable than the results suggest.

Definition of high-risk patients

The initial review of clinical guidelines showed a consensus that if GPAs were to be used as part of initial medical management this should be in high-risk cases only (see section 'Rationale: requirements of the decision model', p. 19). The survey of clinicians to assess which particular types of medication for non-ST elevation ACS should be studied concerned high-risk patients only. There was no suggestion that the management of 'low-risk' patients was an area of uncertainty that was worth modelling. However, as described in the last section, the threshold used to define high risk is crucial to the cost-effectiveness of GPAs, and this is also highly uncertain.

Statements in clinical guidelines that high-risk patients should receive a particular treatment imply that a clear distinction can be drawn between high-risk patients and others. Yet, as described in Chapter 1 (section 'What is UA?', p. 1), non-ST elevation ACS represents a spectrum from 'pure' UA to AMI and any dichotomy between 'high risk' and 'low risk' is artificial. US guidelines[109] state that risk stratification is a "complex multivariable problem" and provide a list of factors to be taken into account. UK guidelines[18] are similar. A raised serum troponin level has been suggested as a simple marker of high risk,[110] but even with this single factor there is evidence of a gradient rather than a clear dichotomy into 'positive' and 'negative'. Furthermore, anecdotal evidence suggests that there are patients whose chest pain resolves rapidly after admission and appear in all respects to be low risk apart from a positive troponin level. The original NICE guidance on GPAs[23] appeared to suggest that such patients should receive GPAs, which was partly responsible for subsequent criticisms.

The confusion over what constitutes high risk reflects that in the clinical literature. Previous reviews had noted that most GPA trials recruited a heterogeneous group of patients. The present systematic review aimed to identify high-risk patients within each trial and the results for such patients. Only one trial, GUSTO IV,[41] specifically recruited high-risk patients. None of the trials explicitly identified a high-risk group, but to varying extents did report results in subgroups that were at higher risk than average.[34] These results were not considered usable for the model. This was because, first, there was a lack of consistency in the definition of subgroups, for example by age, and, second, not all trials have published results for the relevant subgroups. Approaches made to primary investigators to supply unpublished information were unsuccessful. Some key indicators of high risk, for example troponin levels, were not reported at all in some trials or reported only in selected participants.

The modelling reported here was, therefore, as limited as the clinical evidence in offering a clear

threshold for high risk that could, with certainty, guide clinical practice. However, the model showed that, on average, the use of GPAs in non-ST elevation ACS, as in strategy, 1 is cost-effective and use of the drug in this group appears justified. It further showed that focusing the drug on patients at higher risk was even more cost-effective, but further research is necessary to provide a clearer indication of the optimal threshold to define high risk.

Gender effect of GPAs

As reported in Chapter 2, Boersma and colleagues' patient-level meta-analysis[35] reported a subgroup analysis that revealed apparent harm to women from GPAs. The authors of the meta-analysis addressed this issue by pointing out that this is a subgroup analysis and hence may mislead as a result of chance (even despite statistical significance at $p < 0.05$). In addition, they report data based on troponin positivity (prerandomisation) and the subsequent recourse to revascularisation (postrandomisation). While troponin-negative men and women have a hazard ratio of greater than 1.0 (indicating control better than GPA), this is more marked in women. Furthermore it is suggested that this may relate to the fact that women, and troponin-negative patients, are less likely to undergo revascularisation. Boersma and co-workers imply a very novel view that the pathological basis of UA in men and women may be fundamentally different. Namely, if GPA medication works by inhibiting thrombus and women have reduced net benefit, this implies that they may have less thrombus. This implies that other mechanisms, such as coronary arterial spasm, may be important in such cases, and are unresponsive to platelet inhibition.

As described above, it has not been possible to reflect the full complexity of information about subgroups in the model and further research is required in this regard.

The role of clopidogrel

With regard to clopidogrel, sensitivity analyses suggest that if a choice had to be made between either GPA for all patients (high and low risk) or clopidogrel for all such patients, the clopidogrel option may or may not be more cost-effective, depending on which set of RRRs for strategy 1 trials is applied. However, the decision problem is more complex than this. This is because, first, GPAs will be used in high-risk patients only. Second, in practice, it is not 'either/or' between GPAs and clopidogrel, as these drugs may be used together. Ideally, the decision model would have examined different options for use of GPAs against a background of other medical treatment that included clopidogrel, assuming that its use in this way will become routine. In practice, this is not possible without additional data. Further research would be needed to reveal the most appropriate combination of these drugs.

A behavioural perspective

The analysis reported here is essentially, and properly, a normative one. It explores what rationally should be done for a patient presenting with certain symptoms, in the light of all relevant available data and values. However, it is not directly the facts of a situation that drive an individual professional's response to it, but rather his or her perceptions. These need not be precisely aligned with the facts. Indeed, there is a good deal of evidence from medical and other studies to show that the 'mental model' of a situation that drives an individual's response to it is very likely to be distorted from the reality, often in quite significant and predictable ways.

Thus, in seeking models to support good decision-making in relation to the initial medical management of non-ST elevation ACS, a further dimension to address is the functioning of normative decision support models within a working context that will almost inevitably reflect biased perceptions as well as realities. Assessing, in a specific context such as the current one, the extent of biases at different stages in the overall set of decisions that determine a patient's treatment regimen, and how to take account of them in framing guidelines and decision support, represents an interesting and potentially important extension of the current work.

Recommendations for future research

The VOI analysis reported in Chapter 4 suggests that the EVPI associated with the use of GPAs in non-ST elevation ACS is high: under base-case assumptions, EVPI ranged between £47.71 and £57.81 per patient for λ values between £10,000 and £50,000, respectively (£12.7–15.4 million per year for the total ACS population in the UK). This suggests that further research is likely to represent significant value to the health service, although further analysis is needed to establish the optimal design of that research.

The VOI analysis presented here, together with the more descriptive discussion of the results of this study presented in this chapter, suggest that potential future research should be directed towards:

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

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Contribution of authors

Mike Robinson (Senior Lecturer in Public Health) was responsible for the overall coordination. Stephen Palmer (Senior Research Fellow) carried out modelling. Mark Sculpher (Professor Health Economics) was responsible for the modelling and the coordination of the Centre for Health Economics input. Zoe Philips (Lecturer in Economics) carried out modelling. Laura Ginnelly (Research Fellow) carried out the literature review and modelling. Amanda Bowens (Evidence-based Healthcare Researcher) carried out the literature review. Su Golder (Information Officer) carried out literature searches. Khaled Alfakih (Specialist Registrar in Cardiology) was responsible for the survey of clinicians and Leeds audit. Ameet Bakhai (Consultant Cardiologist) carried out analysis of PRAIS-UK. Chris Packham (Senior Clinical Lecturer) carried out analysis of NHAR. Nicola Cooper (MRC Research Fellow) carried out modelling. Keith Abrams (Professor of Medical Statistics) was responsible for evidence synthesis and modelling. Alison Eastwood (Senior Research Fellow) was responsible for the design of the literature reviews. Alan Pearman (Professor of Management Decision Analysis) was responsible for the original application for research. Marcus Flather (Director, Clinical Trials and Evaluation Unit) and David Gray (Reader in Medicine and Honorary Consultant Physician Epidemiology and Health Services Research Unit) provided general clinical advice. Alistair Hall (Professor of Clinical Cardiology) carried out clinical input.

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Appendix 1

Membership of the clinical advisory group

Name	Affiliation	Discipline
Professor Stephen Ball	University of Leeds	Academic Cardiology
Dr Philip Batin	Pinderfields Hospital, Wakefield	DGH Cardiology
Professor Andrew Davies	University of Leeds	General Medicine/Cardiology
Professor Simon Capewell	University of Liverpool	Epidemiology/Public Health
Dr Allan Harris	Haxby Group Practice	General Practice
Dr Jim McLenachan	Leeds Teaching Hospitals NHS Trust	Interventional Cardiology

Appendix 2

Search strategies

MEDLINE on SilverPlatter

(January 2000 to December 2000)

Cost-effectiveness strategy (searched on 31 January 2001)

1. "Platelet-Glycoprotein-GPIIb-IIIa-Complex"/ all subheadings
2. abciximab*
3. reopro*
4. aggrastat*
5. eptifibatide*
6. intrifiban*
7. integrelin*
8. tirofiban*
9. (gp* or glycoprotein*) near (iib* near iiia*)
10. integrin* near (iib* near iiia*)
11. lamifiban or ro 44-9883
12. sibrafiban or ro 44-3888 or ro 48-3657 or xubix
13. fradafiban or bibu
14. lefradafiban
15. xemilofiban or sc-54701A or sc-54684A
16. orbofiban or sc-57099B
17. explode "Angina-Pectoris"/ all subheadings
18. angina
19. explode "Myocardial-Infarction"/ all subheadings
20. myocard*
21. infarct*
22. myocard* infarct*
23. heart attack*
24. coronary syndrome*
25. crescendo
26. cost effect*
27. cost benefit*
28. economic evaluation*
29. technology assessment*
30. pharmacoeconomic*
31. cost util*
32. explode "Economics"/ all subheadings
33. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
34. #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25
35. #26 or #27 or #28 or #29 or #30 or #31 or #32
36. #33 and #34 and #35

Clinical effectiveness strategy (searched on 31 January 2001)

1. "Platelet-Glycoprotein-GPIIb-IIIa-Complex"/ all subheadings
2. abciximab*
3. reopro*
4. aggrastat*
5. eptifibatide*
6. intrifiban*
7. integrelin*
8. tirofiban*
9. (gp* or glycoprotein*) near (iib* near iiia*)
10. integrin* near (iib* near iiia*)
11. lamifiban or ro 44-9883
12. sibrafiban or ro 44-3888 or ro 48-3657 or xubix
13. fradafiban or bibu
14. lefradafiban
15. xemilofiban or sc-54701A or sc-54684A
16. orbofiban or sc-57099B
17. explode "Angina-Pectoris"/ all subheadings
18. angina
19. explode "Myocardial-Infarction"/ all subheadings
20. myocard*
21. infarct*
22. myocard* infarct*
23. heart attack*
24. coronary syndrome*
25. crescendo
26. explode "Clinical-Trials"/ all subheadings
27. (clin* near trial*) in ti ab
28. ((singl* or doubl* or treble* or tripl*) near (blind* or mask*)) in ti ab
29. "Placebos"/ all subheadings
30. random* in ti ab
31. placebo* in ti ab
32. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
33. #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25
34. #26 or #27 or #28 or #29 or #30 or #31
35. #32 and #33 and #34
36. UD >= "200006"
37. #35 and (UD >= "200006")

EMBASE on SilverPlatter

(January 2000 to December 2000)

Cost-effectiveness strategy (searched on 31 January 2001)

1. "fibrinogen-receptor"/ all subheadings
2. "fibrinogen-receptor-antagonist"/ all subheadings
3. "abciximab"/ all subheadings
4. "eptifibatide"/ all subheadings
5. "tirofiban"/ all subheadings
6. fibrinogen-receptor* in ti ab
7. abciximab* in ti ab
8. eptifibatide* in ti ab
9. tirofiban* in ti ab
10. reopro* in ti ab
11. intrifiban* in ti ab
12. integrelin* in ti ab
13. aggrastat* in ti ab
14. integrin* near (IIb* near iiia*)
15. (glycoprotein* or gp*) near (iib* near iiia*)
16. lamifiban or ro 44-9883
17. sibrafiban or xubix or ro 44-3888 or ro 48-3657
18. fradafiban or bibu
19. lefradafiban
20. xemilofiban or sc-54701a or sc-54684a
21. orbofiban or sc-57099b
22. explode "angina-pectoris"/ all subheadings
23. angina in ti ab
24. explode "heart-infarction"/ all subheadings
25. myocard* infarct*
26. coronary syndrome*
27. crescendo
28. explode "economic-evaluation"/ all subheadings
29. cost effect*
30. cost benefit*
31. economic evaluation*
32. technology assessment*
33. pharmacoeconomic*
34. cost util*
35. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21
36. #22 or #23 or #24 or #25 or #26 or #27
37. #28 or #29 or #30 or #31 or #32 or #33 or #34
38. #35 and #36 and #37
39. #38 and (UD > "20000427")

Clinical effectiveness strategy (searched on 31 January 2001)

1. "fibrinogen-receptor"/ all subheadings
2. "fibrinogen-receptor-antagonist"/ all subheadings
3. "abciximab"/ all subheadings
4. "eptifibatide"/ all subheadings
5. "tirofiban"/ all subheadings
6. fibrinogen-receptor* in ti ab
7. abciximab* in ti ab
8. eptifibatide* in ti ab
9. tirofiban* in ti ab
10. reopro* in ti ab
11. intrifiban* in ti ab
12. integrelin* in ti ab
13. aggrastat* in ti ab
14. integrin* near (IIb* near iiia*)
15. (glycoprotein* or gp*) near (iib* near iiia*)
16. lamifiban or ro 44-9883
17. sibrafiban or xubix or ro 44-3888 or ro 48-3657
18. fradafiban or bibu
19. lefradafiban
20. xemilofiban or sc-54701a or sc-54684a
21. orbofiban or sc-57099b
22. explode "angina-pectoris"/ all subheadings
23. angina in ti ab
24. explode "heart-infarction"/ all subheadings
25. myocard* infarct*
26. coronary syndrome*
27. crescendo
28. explode "Clinical-Trials"/ all subheadings
29. (clin* near trial*) in ti ab
30. ((singl* or doubl* or trebl* or tripl*) near (blind* or mask*)) in ti ab
31. Placebos
32. placebo* in ti ab
33. random in ti ab
34. "randomized-controlled-trial"/ all subheadings
35. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21
36. #22 or #23 or #24 or #25 or #26 or #27
37. #28 or #29 or #30 or #31 or #32 or #33 or #34
38. #35 and #36 and #37
39. #38 and (UD > "20000427")

Cochrane Library on CD-ROM (searched on 31 January 2001)

(2000, Issue 3 to 2001, Issue 1)

The Cochrane Database of Systematic Reviews (CDSR) and the Cochrane Controlled Trials Register (CCTR) were searched via the Cochrane Library CD-ROM using the following search strategy. The results were then limited for each issue to 'new this issue' in order not to duplicate results from the previous searches:

1. (GLYCOPROTEIN* or GP*) near IIB*
2. GPIIB*
3. ABCIXIMAB or REOPRO
4. EPTIFIBATIDE or INTRIFIBAN
5. INTEGRELIN or INTEGRILIN
6. TIROFIBAN or AGGRASTAT
7. LAMIFIBAN or SIBRAFIBAN
8. XUBIX or FRADAFIBAN
9. LEFRADAFIBAN or BIBU
10. XEMILOFIBAN or ORBOFIBAN
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

NRR on CD-ROM (searched on 31 January 2001)

(2000, Issue 3 to 2000 Issue 4)

The following search was conducted and the search limited to 'new this issue':

1. (GLYCOPROTEIN* or GP*) near IIB*
2. GPIIB*
3. ABCIXIMAB or REOPRO
4. EPTIFIBATIDE or INTRIFIBAN
5. INTEGRELIN or INTEGRILIN
6. TIROFIBAN or AGGRASTAT
7. LAMIFIBAN or SIBRAFIBAN
8. XUBIX or FRADAFIBAN
9. LEFRADAFIBAN or BIBU
10. XEMILOFIBAN or ORBOFIBAN
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

Current Controlled Trials on the Internet (searched on 31 January 2001)

http://www.controlled-trials.com/

'glycoprotein* or abciximab or reopro or eptifibatide or intrifiban or integrelin or integrilin or tirofiban or aggrastat or lamifiban or sibrafiban or xubix or fradafiban or lefradafiban or bibu* or xemilofiban or orbofiban'

CPI on DIALOG (searched on 02 February 2001)

(1973 to November 2000)

S abciximab?
S reopro?
S aggrastat?
S eptifibatide?
S intrifiban?
S integrelin? or integrilin?
S tirofiban? or aggrastat?
S (gp? or glycoprotein?) (2w) (iib?(w)iiia?)
S integrin? (w) (iib? (w) iiia?)
S lamifiban? or ro(w)44(w)9883 or ro(w)44(w)9883 or ro449883
S sibrafiban? or xubix or ro(w)44-3888 or ro(w)44(w)3888 or ro44388 or ro(w)48-3657 or ro(w)48(w)3657 or ro483657
S fradafiban? or BIBU(w)52
S lefradafiban? or BIBU(w)104
S xemilofiban? or SC-54701A or SC-54684A or SC(w)54701A or SC54701A or SC(w)54684A or SC54684A
S orbofiban? or SC-57099B or SC(w)57099B or SC57099B
s s1:s15
s s16 and ud>20001805

Appendix 3

Abstraction pro forma for RCTs

This pro forma is based on the NICE review protocol. Modifications of NICE headings are shown in italics.

Study details

Study (Author, year)	Study design; *any subgroup analyses?*	Definition of high-risk group (if any)	Inclusion criteria	Interventions (specified by protocol)	*Length of observation period before PCI*	*Timing of drug administration before PCI*	Follow-up duration

Characteristics of participants (*specify separately for high-risk patients*)

Study (Author, year)		No. of subjects enrolled (total and high risk)	*No. of subjects lost to follow-up*	Median age *range, and standard deviation*	Prognosis indicators *n* (%) and standard deviation for continuous variables, e.g. blood pressure, heart rate
	Arm 1 Arm 2				

Other medication (*specify separately for high-risk patients*)

Study (Author, year)		Selected antianginal medication[a] before enrolment, *n* (%)	Selected antianginal medication[a] after enrolment, *n* (%)
	Arm 1		

[a] Selected antianginal drugs to be considered: antiplatelet agents (aspirin, ticlodipine, clopidogrel); anticoagulants (UFH, LMWH, enoxaprin, daltrepin).

Outcomes: definitions and measures

Study (Author, year)	Acute myocardial infarction	Severe recurrent angina/refractory ischaemia	Death	Measurement of quality of life	Composite outcome	Major/minor bleeding	Other, e.g. stroke

Outcomes (*specify separately for high-risk patients*)

Study (Author, year)	*High risk or all?*	Acute myocardial infarction	Severe recurrent angina/refractory Ischaemia	Death	Measurement of quality of life	Composite outcome	Other
	Arm 1 Arm 2						

Adverse effects (*specify separately for high-risk patients*)

Study (Author, year)	Fatal bleeding episodes	Haemorrhagic strokes	Major bleeding episodes	Minor bleeding episodes	Any bleeding	Other adverse effects requiring treatment

Appendix 4

Search for previous systematic reviews

The following databases were searched on 22 January 2001 to identify any systematic reviews on GPAs published after the CRD's HTA report.[9]

CDSR (via Cochrane Library 2000, Issue 4)
DARE (via the CRD website at http://www.york.ac.uk/inst/crd/)

The search strategies used were the same as those used by CRD and included all GP agents, whether licensed or unlicensed, oral or intravenous. The strategy for the Cochrane database was as follows:

#1 ABCIXIMAB or REOPRO or EPTIFIBATIDE or INTRIFIBAN or INTEGRELIN or INTEGRILIN
#2 TIROFIBAN or AGGRASTAT or LAMIFIBAN or SIBRAFIBAN or XUBIX or FRADAFIBAN
#3 LEFRADAFIBAN or BIBU* or XEMILOFIBAN or ORBOFIBAN
#4 ((GLYCOPROTEIN* or GP*) near IIB*) or GPIIB*
#5 #1 or #2 or #3 or #4

DARE was searched via the CRD website as this version is more up to date than that available via the Cochrane Library software. The search strategy used for DARE was as follows (the results of each search line were examined separately owing to a software problem which prevented search combining):

ABCIXIMAB or REOPRO or EPTIFIBATIDE or INTRIFIBAN or INTEGRELIN or INTEGRILIN or TIROFIBAN or AGGRASTAT or LAMIFIBAN SIBRAFIBAN or XUBIX or FRADAFIBAN or LEFRADAFIBAN or BIBU or XEMILOFIBAN or ORBOFIBAN

GLYCOPROTEIN or GP(w)IIB

Appendix 5

Quality checklist for RCTs

	Studies
A Internal validity	
1 Selection of prognostically homogeneous study population	
2 Blinding of persons to assess inclusion criteria	
3 Prestratification on prognostically relevant variables	
4 Random allocation (description of procedure)	
5 Registration of loss to follow-up	
6 Blinding of patients	
7 Blinding of persons who implement interventions	
8 Registration of cointerventions that bear on outcome for each group	
9 Blinding of persons who assess treatment effects	
10 Check to what extent blinding was successful	
B Data description and analysis	
11 Measures of central tendency and their confidence intervals (e.g. SE or SD)	
12 Statistical measures	
13 Way in which missing values were dealt with	
14 Intention-to-treat analysis	
15 Distributions of baseline characteristics	
16 Way in which any imbalance in prognostic variables was accounted for	

+, Item properly addressed; -, item not properly addressed or not stated; +/-, item partially addressed; ?, unknown.

Appendix 6

Searches for late-breaking trials

Websites and search strategies for ongoing trials (searched on 15 May 2001)

American College of Cardiology, annual conference 2001, late-breaking clinical trials, available at: http://www.acc.org/2001ann_meeting/home.htm

American Heart Association, late-breaking clinical trials 2001, available at: http://www.scientificsessions.org/abstracts/lateBreakingClinicalTrials.oft

British Cardiac Society, annual conference 2001, available at: http://www.bcs.com/conference/conference.html

Cardiosource, database of ongoing and unpublished trials, available at: http://www.cardiosource.com/site.mash?left=&m1=3&m2=4&right=/trials/trialsearch.asp

The Cardiosource database was searched using the terms ANGINA and ACUTE in the 'Disease' field; the remaining websites were simply title-scanned for relevant trials.

Appendix 7

Detailed abstraction from main reports of lamifiban studies

PARAGON A investigators (1998)[11]

Study details

Study (Author, year)	Study design; any subgroup analyses?	Definition of high-risk group (if any)	Inclusion criteria	Interventions (specified by protocol)	Length of observation period before PCI	Timing of drug administration before PCI	Follow-up duration
PARAGON A, 1998[11]	Multicentre (international), double-blind, placebo-controlled RCT (Phase II/III)	NA	Chest discomfort (within previous 12 hours) associated with transient or persistent ST-segment depression (≥ 0.5 mm), T-wave inversion or transient (30 minutes) ST-segment elevation (≥ 0.5 mm)	1. Low-dose lamifiban, 300-mg bolus followed by 1 μg per minute 2. Low-dose lamifiban plus heparin 3. High-dose lamifiban, 750-mg bolus followed by 5 μg per minute 4. High-dose lamifiban plus heparin Control: adjusted-dose heparin plus placebo lamifiban Study drugs infused for a minimum of 3 and a maximum of 5 days. If PCI was performed on day 5, an additional 12–24 hours was allowed. Heparin dosing: if >80 kg, 5000-unit bolus, followed by 1000 unit per hour infusion; if <80 kg, 60 units kg^{-1} bolus followed by 12 units kg^{-1} infusion. All patients received aspirin (80–325 mg) at enrolment and daily thereafter. Median drug administration: 72 hours	NA	NA	30 days, 6 months

NA, not applicable.

Characteristics of participants (specified separately for high-risk patients)

Study (Author, year)		No. of subjects enrolled (total and high risk)	No. of subjects lost to follow-up[a]	Median age (25th, and 75th percentiles) (years)	Prognosis indicators (%) and SD for continuous variables, e.g. blood pressure, heart rate						
					Previous MI	Previous PCI	Previous CABG	Hyper-tension	Diabetes	Blood pressure (mmHg)	Heart rate (bpm)
PARAGON A, 1998[11]	1: Low-dose lamifiban	378	Not stated	65 (55, 72)	37	11	10	20	52	135 (120–150) systolic, 80 (70–90) diastolic	74 (63–82)
	2: Low-dose lamifiban plus heparin	377	Not stated	66 (57, 74)	31	7	11	20	49	40 (120–150) systolic, 80 (70–90) diastolic	73 (64–84)
	3: High-dose lamifiban	396	Not stated	66 (57, 73)	36	8	11	18	45	137 (120–150) systolic, 80 (70–87) diastolic	72 (62–82)
	4: High-dose lamifiban plus heparin	373	Not stated	67 (57, 74)	35	9	10	16	48	140 (124–150) systolic, 80 (70–90) diastolic	72 (62–83)
	Control: Placebo plus heparin	758	Not stated	66 (58, 73)	35	9	11	17	49	135 (120–150) systolic, 80 (70–88) diastolic	72 (62–82)

[a] 3.0% and 6.7% of patients were lost to follow-up at 6 months and 1 year, respectively; the numbers lost to follow-up were not stated.
bpm, beats per minute.

Other medication (specified separately for high-risk patients)

Study (author, year)		Selected antianginal medication before randomisation (%)	Selected antianginal medication after randomisation (%)
PARAGON A, 1998[11]	1: Low-dose lamifiban	Not stated	Aspirin: 99–100% in all groups. Heparin: according to protocol
	2: Low-dose lamifiban plus heparin	Not stated	Aspirin: 99–100% in all groups. Heparin: according to protocol
	3: High-dose lamifiban	Not stated	Aspirin: 99–100% in all groups. Heparin: according to protocol
	4: High-dose lamifiban plus heparin	Not stated	Aspirin: 99–100% in all groups. Heparin: according to protocol
	Control: Placebo plus heparin	Not stated	Aspirin: 99–100% in all groups. Heparin: according to protocol

Outcomes: definitions and measures

Study (Author, year)	AMI	Severe recurrent angina/ refractory ischaemia	Death	Measurement of quality of life	Composite outcome	Major/minor bleeding	Other, e.g. stroke
PARAGON A, 1998[11]	Not defined	Not a reported end-point in this trial			All-cause mortality and non-fatal MI (or reinfarction)	Major not defined, intermediate = red blood cell transfusion or >5 g haemoglobin drop without haemodynamic compromise	

Outcomes (specified separately for high-risk patients and subgroup analysis)

Study (Author, year)		Time-point	AMI, *n* (%)	Death, *n* (%)	Composite outcome, *n* (%)	Other: revascularisation rate during hospitalisation		
						Coronary angiography (%)	Emergency PCI, *n* (%)	CABG (%)
PARAGON A, 1998[11]	1: Low-dose lamifiban	30 days 6 months	36 (9.5) ? (11.1)	12 (3.2) ? (5.6)	41 (10.8) ? (14.7)	50	15 (1.6)	10
	2: Low-dose lamifiban plus heparin	30 days 6 months	35 (9.3) ? (10.5)	11 (2.9) ? (4.8)	39 (10.3) ? (12.6)	50	13 (2.1)	12
	3: High-dose lamifiban	30 days 6 months	42 (10.6) ? (12)	14 (3.5) ? (6.1)	46 (11.6) ? (14.8)	47	13 (1.5)	10
	4: High-dose lamifiban plus heparin	30 days 6 months	43 (11.3) ? (13.9)	14 (3.8) ? (7.6)	46 (12.3) ? (18)	51	12 (1.6)	12
	Control: Placebo plus heparin	30 days 6 months	80 (10.6) 102 (14.3)	22 (2.9) 51 (6.6)	89 (11.7) 131 (17.9)	53	17 (2.4)	11

Adverse effects (specified separately for high-risk patients and subgroup analysis)

Study (Author, year)		Time-point	Fatal bleeding episodes	Stroke (%)	Major bleeding episodes (%)	Minor bleeding episodes (%)	Any bleeding (%)	Other adverse effects: thrombocytopenia (%)
PARAGON A, 1998[11]	1: Low-dose lamifiban	30 days		1.1	0.8	2.9		2.1
	2: Low-dose lamifiban plus heparin	30 days		1.1	0.5	5.8		0.8
	3: High-dose lamifiban	30 days		0.8	1.3	8.4		1.8
	4: High-dose lamifiban plus heparin	30 days		0.5	2.4	9.2		0.8
	Control: Placebo plus heparin	30 days		0.4	0.8	4.4		1.1

PARAGON B: Harrington and colleagues (2000)[71]

Study details

Study (Author, year)	Study design; any subgroup analyses?	Definition of high-risk group (if any)	Inclusion criteria	Interventions (specified by protocol)	Length of observation period before PCI	Timing of drug administration before PCI	Follow-up duration
Harrington *et al.*, 2000[44]	Multicentre (international), double-blind, placebo-controlled RCT (Phase III)	NA	Patients presenting with an ACS without ST-segment elevation, onset of chest pain within 12 hours and either ECG evidence of ischaemia or a positive cardiac marker	1: Lamifiban 500-μg bolus, followed by infusion with dose adjustment based on renal function (range 1.0–2.0 μg per minute, depending on creatinine clearance). Control: placebo Study drug infused for 72 hours. All patients received aspirin (or other antiplatelet agent) and heparin (either UFH or LMWH) at physician's discretion. LMWH was used in over one-third of the total cohort. Heparin dose was adjusted according to patients' weight	NA	NA	30 days, 6 months

Characteristics of participants (specified separately for high-risk patients)

Study (Author, year)		No. of subjects enrolled (total and high risk)	No. of subjects lost to follow-up	Median age (range) (years)	Prognosis indicators (%) for continuous variables, e.g. blood pressure, heart rate			
					Previous MI	Previous PCI	Previous CABG	CHF
Harrington *et al.*, 2000[44]	1: Lamifiban	2628	0.3% at 30 days	63 (54–72)	29	15	13	11
	Control: Placebo	2597	0.1% at 30 days	64 (55–72)	31	14	13	11

Other medication (specified separately for high-risk patients)

Study (author, year)		Selected antianginal medication before randomisation, *n* (%)		Selected antianginal medication after randomisation, *n* (%)	
		Antiplatelet agents	**Heparin**	**Antiplatelet agents**	**Heparin**[a]
Harrington *et al.*, 2000[44]	1: Lamifiban	Not stated	Not stated	Aspirin 2548 (92) Clopidogrel/ticlopidine 658 (25)	UFH 2297 (88) LMWH 931 (36)
	Control: Placebo	Not stated	Not stated	Aspirin 2525 (92) Clopidogrel/ticlopidine 666 (26)	UFH 2270 (88) LMWH 904 (35)

[a] UFH and LMWH were not mutually exclusive.

Outcomes: definitions and measures

Study (Author, year)	AMI	Severe recurrent angina/ refractory ischaemia	Death	Measurement of quality of life	Composite outcome	Major/minor bleeding	Other, e.g. stroke
Harrington *et al.*, 2000[44]	No revasc.: CK-MB (or total CK) ≥ 2 times upper normal limit, or new significant Q waves in two contiguous leads Post-PCI/bypass: CK-MB (or total CK) ≥ 3 or ≥ 5 times upper normal limit, respectively, or new significant Q waves in two contiguous leads	1. Recurrent chest pain at rest occurring >2 hours after start of drug and lasting for ≥ 20 minutes 2. New/increased ischaemic changes on the ECG 3. Unplanned/urgent revasc. within 24 hours of episode of ischaemic pain			Primary: death, MI or severe recurrent ischaemia Secondary: death or MI	Major: intracranial haemorrhage, or any that leads to haemodynamic compromise requiring intervention Intermediate: any that leads to transfusion or ≥ 5 g dl^{-1} decrease in haemoglobin	

Outcomes (specified separately for high-risk patients and subgroup analysis)

Study (Author, year)			AMI (%)	Severe recurrent angina/ refractory ischaemia (%)	Death (%)	Measurement of quality of life	Composite outcome, *n* (%)		Other: revascularisation, *n* (%)		
							Primary	Secondary	Angiography	Any PCI	Bypass surgery
Harrington *et al.*, 2000[44]	1: Lamifiban	30 days	8.8	1.5	2.9		310 (11.8)	279 (10.6)	1670 (64)	726 (28)	400 (15)
	Control: Placebo	30 days	9.8	1.5	3.3		332 (12.8)	299 (11.5)	1659 (65)	701 (27)	385 (15)

Adverse effects (specified separately for high-risk patients and subgroup analysis)

Study (Author, year)			Fatal bleeding episodes	Haemorrhagic stroke (%)	Major bleeding episodes (%)	Minor ('intermediate') bleeding episodes (%)	Any bleeding	Other adverse effects[a]
Harrington *et al.*, 2000[44]	1: Lamifiban	30 days		1.1	1.3	14		
	Control: Placebo	30 days		0.6	0.9	11.5		

[a] Incidence of 'severe' thrombocytopenia was low, but slightly higher in the lamifiban group; however, the difference was not statistically significant.

Theroux and colleagues (1996)[14]

Study details

Study (Author, year)	Study design; any subgroup analyses?	Definition of high-risk group (if any)	Inclusion criteria	Interventions (specified by protocol)	Length of observation period before PCI	Timing of drug administration before PCI	Follow-up duration
Theroux *et al.*, 1996[14]	Multicentre (Canada), double-blind, placebo-controlled RCT (Phase II)	NA	Chest pain at rest or at minimal exercise of ≥ 5 minutes in duration in the 24 hours preceding randomisation, as well as evidence of CAD by ECG ST-T changes, documentation of a previous MI, a thallium-201 exercise test or coronary angiography Only patients aged <75 years	1: Lamifiban 150-μg bolus followed by 1 μg per minute 2: Lamifiban 300-μg bolus followed by 2 μg per minute 3: Lamifiban 600-μg bolus followed by 4 μg per minute 4: Lamifiban 750-μg bolus followed by 5 μg per minute Control: placebo Study drug infused for 72–120 hours (mean 84 hours). Dose reduction of 10% for patients <70 kg, 20% if <60 kg, 30% if <50 kg. Aspirin 325 mg given to all patients at randomisation and daily thereafter. Intravenous heparin left to the discretion of treating physician, but the decision was made before randomisation. Heparin was adjusted to twice the control activated partial thromboplastin time value. Antianginal drugs were recommended, but not required	NA	NA	During infusion (72–120 hours) and at 1 month

Other medication (specified separately for high-risk patients)

Study (Author, year)		No. of subjects enrolled (total and high risk)	No. of subjects lost to follow-up	Median age ± SD (years)	Prognosis indicators (%) for continuous variables, e.g. blood pressure, heart rate				
					Previous MI	Hypertension	Diabetes	CHF	Ischaemic ECG
Theroux *et al.*, 1996[14]	1: Lamifiban 1 μg per minute	40	Not stated	59 ± 9	58	23	23		60
	2: Lamifiban 2 μg per minute	41	Not stated	63 ± 9	41	24	20		68
	3: Lamifiban 4 μg per minute	120	Not stated	61 ± 10	50	33	23		67
	4: Lamifiban 5 μg per minute	41	Not stated	61 ± 9	54	34	27		59
	Control: Placebo	123	Not stated	59 ± 11	63	33	20		67

Other medication (specified separately for high-risk patients)

Study (author, year)		Selected antianginal medication before randomisation, (%)		Selected antianginal medication after randomisation, (%)	
		Heparin	Aspirin	Heparin	Aspirin
Theroux *et al*, 1996[14]	1: Lamifiban 1 μg per minute	20	All	"An additional 6% evenly distributed among the groups"	All
	2: Lamifiban 2 μg per minute	22	All	"An additional 6% evenly distributed among the groups"	All
	3: Lamifiban 4 μg per minute	18	All	"An additional 6% evenly distributed among the groups"	All
	4: Lamifiban 5 μg per minute	22	All	"An additional 6% evenly distributed among the groups"	All
	Control: Placebo	20	All	"An additional 6% evenly distributed among the groups"	All

Outcomes: definitions and measures

Study (Author, year)	AMI	Severe recurrent angina/ refractory ischaemia	Death	Measurement of quality of life	Composite outcome	Major/minor bleeding	Other, e.g. stroke
Theroux *et al*, 1996[14]	Recurrent chest pain ≥ 30 minutes in duration after randomisation, ECG changes, a new elevation or re-elevation of CK-MB fraction values to ≥ 1.5 times the previous values	Recurrent ischaemia at rest or minimal exercise, with objective documentation of ischaemic ST changes Refractory ischaemia despite maximal medication treatment requiring urgent angioplasty or bypass			Death, MI, or ischaemia requiring intervention (PCI or CABG)	Major bleeding: intracranial haemorrhage, cardiac tamponade, a decrease in blood haemoglobin of ≥ 5 g dl^{-1} or the need for blood transfusion Minor bleeding: all bleeding affecting the patients' daily activities Other bleeding (e.g. minor bruises, self-limiting mucosal bleeding) were classified as insignificant	

Outcomes (specified separately for high-risk patients and subgroup analysis)

Study (Author, year)		Time-point	AMI, *n* (%)	Severe recurrent angina/refractory ischaemia, *n* (%)	Death, *n* (%)	Measurement of quality of life, *n* (%)	Composite outcome, *n* (%)	Other
Theroux *et al*., 1996[14]	1: Lamifiban 1 μg per minute (*n* = 40)	Infusion	0	3 (7.3)	0		1 (2.5)	
		30 days	1 (2.4)	6 (14.6)	0		3 (7.3)	
	2: Lamifiban 2 μg per minute (*n* = 41)	Infusion	1 (2.5)	5 (12.5)	0		2 (4.9)	
		30 days	3 (7.5)	9 (22.5)	2 (5)		7 (17.5)	
	3: Lamifiban 4 μg per minute (*n* = 120)	Infusion	0	18 (15)	0		4 (3.3)	
		30 days	3 (2.5)	22 (18.3)	0		12 (10)	
	4: Lamifiban 5 μg per minute (*n* = 40)	Infusion	0	2 (4.9)	0		1 (2.4)	
		30 days	0	3 (7.3)	1 (2.4)		3 (7.3)	
	Control: Placebo (*n* = 128)	Infusion	2 (1.6)	15 (12.2)	1 (0.8)		10 (8.1)	
		30 days	7 (4.9)	19 (14.6)	5 (4.1)		19 (14.6)	

Adverse effects (specified separately for high-risk patients and subgroup analysis)

Study (Author, year)		Time-point	Fatal bleeding episodes, *n* (%)	Haemorrhagic strokes, *n* (%)	Major bleeding episodes, *n* (%)	Minor bleeding episodes, *n* (%)	Any bleeding, *n* (%)	Other adverse effects requiring treatment
Theroux *et al.*, 1996[14]	1: Lamifiban 1 μg per minute (*n* = 40)	Drug infusion + 24 hours			0	0		
	2: Lamifiban 2 μg per minute (*n* = 41)	Drug infusion + 24 hours			0	6 (14.6)		
	3: Lamifiban 4 μg per minute (*n* = 120)	Drug infusion + 24 hours			7 (5.8)	14 (11.7)		
	4: Lamifiban 5 μg per minute (*n* = 40)	Drug infusion + 24 hours			0	7 (17.1)		
	Control: Placebo (*n* = 128)	Drug infusion + 24 hours			1 (0.8)	2 (1.6)		

Appendix 8

Detailed abstraction from PURSUIT subgroup reports

PURSUIT substudy of geographical variations in outcomes: Akkerhuis and colleagues (2000)[50]

Study details

Study (Author, year)	Definition of high-risk group (if any)	Inclusion criteria	Interventions (specified by protocol)	Length of observation period before any PCI	Timing of administration of drug before PCI	Follow-up duration
Akkerhuis *et al.*, 2000[50]		Ischaemic chest pain within previous 24 hours, and either ECG changes suggestive of ischaemia or CK-MB fraction above upper limit of normal for that hospital	1. 180 μg kg^{-1} bolus plus infusion of 2.0 μg kg^{-1} per minute eptifibatide 2. i.v. bolus plus infusion of placebo Study drug infused over 72 hours, continued up to 96 hours if PCI performed at end of 72-hour treatment period	72 hours		30 days

Characteristics of participants (specified separately for high-risk patients)

Study (Author, year)		No. of subjects enrolled (total)	No. of subjects lost to follow-up	Median age (25th and 75th percentiles)	Prognosis indicators (%) for continuous variables, e.g. blood pressure, heart rate					
					Hypertension	Diabetes	Prior MI	Prior CHF	Prior PCI	Prior CABG
Akkerhuis *et al.*, 2000[50]	Western Europe	3697	Not stated	65 (56, 71)	46	18	28	8	10	9
	Eastern Europe	1541	Not stated	65 (56, 71)	62	26	37	20	3	2
	North America	3827	Not stated	63 (54, 71)	61	27	34	10	21	20
	Latin America	396	Not stated	60 (51, 67)	63	23	37	8	5	6

Other medication (specified separately for high-risk patients)

Study (Author, year)		Selected antianginal medication before enrolment (%)				Selected antianginal medication after enrolment *n* (%)
		Aspirin	β-Blockers	ACE inhibitors	Heparin infusion	
Akkerhuis *et al.*, 2000[50]	Western Europe	94	68	23	88	Discretion of treating physician
	Eastern Europe	95	65	41	80	Discretion of treating physician
	North America	91	66	27	97	Discretion of treating physician
	Latin America	95	55	33	77	Discretion of treating physician

ACE, angiotensin converting enzyme.

Outcomes: definitions and measures

Study (Author, year)	AMI	Death	Composite outcome
Akkerhuis *et al.*, 2000[50]	ECG abnormalities or CK-MB elevation. Single CK-MB value elevated above the upper limit of normal Following PCI or surgical intervention enzyme levels required to be 3 or 5 times upper limit of normal Investigators' definition of MI also used	As noted	Death or MI according to clinical events committee

Outcomes (specified separately for high-risk patients and subgroup analysis)

Study (Author, year)		Time-point	Death (%)		Composite (%)		CEC >2 (%)		CEC >3 (%)		CEC >5 (%)		Investigator (%)	
			Eptifi-batide	Placebo	Eptifi-batide	Placebo	Eptifi-batide	Placebo	Eptifi-batide	Placebo	Eptifi-batide	Placebo	Eptifi-batide	Placebo
Akkerhuis *et al.*, 2000[50]	Western Europe	72 hours	0.4	0.9	4.6	5.8	3.7	4.7	3.3	4.0	2.2	3.1	2.1	3.6
	Eastern Europe	72 hours	0.7	1.2	10.3	10.2	6.2	6.5	5.0	5.6	3.2	3.8	3.0	4.5
	North America	72 hours	0.4	0.6	2.9	4.1	2.6	3.5	2.4	3.1	1.9	2.5	2.0	3.1
	Latin America	72 hours	1.0	1.5	3.7	8.2	2.6	8.2	1.6	6.7	1.6	5.1	1.0	5.6

CEC, clinical events committee.

Outcomes (specified separately for high-risk patients and subgroup analysis)

Study (Author, year)		Time-point	Death (%)		Composite (%)		CEC >2 (%)		CEC >3 (%)		CEC >5 (%)		Investigator (%)	
			Eptifi-batide	Placebo	Eptifi-batide	Placebo	Eptifi-batide	Placebo	Eptifi-batide	Placebo	Eptifi-batide	Placebo	Eptifi-batide	Placebo
Akkerhuis *et al.*, 2000[50]	Western Europe	Events reported between 3 and 30 days	4.1	4.4	11.7	11.5	9.9	9.7	9.1	9.5	8.1	8.4	8.2	8.5
	Eastern Europe	Events reported between 3 and 30 days	6.7	4.8	14.3	12.7	14.3	12.7	10.4	8.5	9.4	7.4	10.0	9.5
	North America	Events reported between 3 and 30 days	3.9	4.9	9.7	11.4	9.7	11.4	8.0	10.3	8.0	9.6	6.8	7.9
	Latin America	Events reported between 3 and 30 days	13.5	5.2	18.4	10.3	18.4	10.3	17.5	7.9	16.4	7.2	14.7	7.3

PURSUIT subgroup analysis of age of patients: Hasdai and colleagues (2000)[48]

Study details

Study (Author, year)	Study design; any subgroup analyses?	Definition of high-risk group (if any)	Inclusion criteria/ exclusion criteria	Interventions (specified by protocol)	Follow-up duration
Hasdai *et al.*, 2000[48]	Study looking at impact of age on clinical outcomes of patients in PURSUIT trial	–	See PURSUIT	Eptifibitide vs placebo	30 days

Characteristics of participants

Study (Author, year)	Age (years)	No. of subjects enrolled (total and high risk)	No. of subjects lost to follow-up	Prognosis indicators, *n* (%)						
				Current smoker	Previous MI	History of CAD	History of CHF	History of hypertension	History of diabetes	Prior CABG
Hasdai *et al.*, 2000[48]	<50	1324	Not stated	769 (58%)	324 (25%)	661 (50%)	52 (4%)	553 (42%)	172 (13%)	87 (7%)
	50–59	2184	Not stated	893 (41%)	620 (28%)	876 (40%)	152 (7%)	1115 (51%)	409 (19%)	236 (11%)
	60–69	3049	Not stated	717 (24%)	1065 (35%)	1022 (34%)	342 (11%)	1790 (59%)	767 (25%)	411 (13%)
	70–79	2398	Not stated	266 (11%)	857 (36%)	676 (29%)	395 (16%)	1466 (61%)	692 (29%)	347 (14%)
	≥80	506	Not stated	32 (6%)	198 (40%)	88 (18%)	106 (21%)	314 (62%)	123 (24%)	53 (10%)

Other medication

Study (Author, year)	Selected antianginal medication[a] before enrolment	Selected antianginal medication[a] after enrolment
Hasdai *et al.*, 2000[48]	See PURSUIT	See PURSUIT

[a] Selected antianginal drugs to be considered: antiplatelet agents (aspirin, ticlodipine, clopidogrel); anticoagulants (UFH, LMWH, enoxaprin, daltrepin).

Outcomes: definitions and measures

Study (Author, year)	Age (years)	Time-point	Death, *n* (%)		MI, *n* (%)		Death or MI, *n* (%)		Bleeding, *n* (%)	
			Eptifibitide	Placebo	Eptifibitide	Placebo	Eptifibitide	Placebo	Eptifibitide	Placebo
Hasdai *et al.*, 2000[48]	<50	30 days	5 (0.8)	6 (0.9)	54 (8.2)	63 (9.5)	57 (8.7)	64 (9.6)	30 (4.6)	26 (3.9)
	50–59	30 days	15 (1.4)	16 (1.5)	100 (9.0)	138 (12.8)	107 (9.7)	148 (13.8)	102 (9.2)	73 (6.8)
	60–69	30 days	45 (3.0)	54 (3.5)	188 (12.6)	203 (13.0)	212 (14.3)	235 (15.0)	207 (13.9)	182 (11.7)
	70–79	30 days	71 (5.8)	78 (6.6)	194 (15.9)	194 (16.5)	223 (18.3)	237 (20.1)	227 (18.6)	163 (13.8)
	≥80	30 days	29 (11.7)	23 (9.0)	57 (22.9)	46 (17.9)	73 (29.3)	61 (23.7)	43 (17.3)	26 (10.1)

PURSUIT subgroup analysis of stroke: Mahaffey and colleagues (1999)[61]

Outcomes (incidence of stroke by 30-day follow-up)

Study (Author, year)		Type of stroke, *n* (%)				
		Primary haemorrhagic	Non-haemorrhagic	Cerebral infarction plus haemorrhagic conversion	Uncertain	Total
Mahaffey *et al.*, 1999[61]	1: Eptifibatide (*n* = 6209)	4 (< 0.1)	33 (0.5)	2 (< 0.1)	1 (< 0.1)	40 (0.6)
	Control: Placebo (*n* = 4739)	2 (< 0.1)	33 (0.7)	1 (< 0.1)	3 (< 0.1)	39 (0.8)
	Total (*n* = 10,948)	6 (< 0.1)	66 (0.6)	3 (< 0.1)	4 (< 0.1)	79 (0.7)

PURSUIT regional analysis of US-enrolled patients: Lincoff and colleagues (2000)[52]

Characteristics of participants (specified separately for high-risk patients)

Study (Author, year)		No. of subjects enrolled in USA	No. of subjects lost to follow-up	Median age (range) (years)	Prognosis indicators (%) for continuous variables, e.g. blood pressure, heart rate						
					Previous MI	Previous PCI	Previous CABG	Previous CHF	Diabetes	Systolic blood pressure	Diastolic blood pressure
Lincoff *et al.*, 2000[52]	1: Eptifibatide	1756	0.7% at 6 months for total US subgroup	63 (53–71)	33.4	21.1	19.9	10.3	25.3	127 (113–142) mmHg	70 (61–80) mmHg
	Control: Placebo	1766		63 (53–71)	34.6	21.3	20.7	10.8	28.2	128 (113–143) mmHg	70 (61–80) mmHg

Other medication (specified separately for high-risk patients)

Study (Author, year)		Selected antianginal medication before enrolment (%)		Selected antianginal medication after enrolment (%)		
		Aspirin	Heparin	Aspirin	Heparin	Ticlopidine
Lincoff *et al.*, 2000[52]	1: Eptifibatide	Not stated	Not stated	94.2	97.2	26.5
	Control: Placebo	Not stated	Not stated	94.0	96.9	26.1

Outcomes (specified separately for high-risk patients and subgroup analysis

Study (Author, year)		Time-point	AMI (%)	Severe recurrent angina/refractory ischaemia (%)	Death (%)	Measurement of quality of life (%)	Composite outcome (%)	Other (%)
Lincoff *et al.*, 2000[52]	1: Eptifibatide (n = 1756)	96 hours	6.0		0.6		6.4	
		7 days	8.2		1.4		9.1	
		30 days	10.2		3.0		11.9	
		6 months	12.6		5.0		15.2	
	Control: Placebo (n = 1766)	96 hours	8.9		1.1		9.6	
		7 days	10.8		2.0		12.1	
		30 days	13.3		3.5		15.4	
		6 months	15.5		5.5		18.9	

Outcomes, continued (procedures during initial hospitalisation)

Study (Author, year)		Time-point	Procedures (%)				
			Cardiac catheterisation	PCI			Cardiac bypass
				Any	Within first 72 hours	Stent	
Lincoff *et al.*, 2000[52]	1: Eptifibatide	During initial hospitalisation	81.8	34.4	26.6	18.3	19.6
	Control: Placebo	During initial hospitalisation	81.8	35.4	26.0	18.0	20.1

Adverse effects (specified separately for high-risk patients and subgroup analysis)

Study (Author, year)		Time-point	Fatal bleeding episodes (%)	Haemorrhagic strokes (%)	Major bleeding episodes, TIMI (%)	Minor bleeding episodes, TIMI (%)	Any bleeding, TIMI (%)	Other adverse effects requiring treatment (%)
Lincoff *et al.*, 2000[52]	1: Eptifibatide	During initial hospitalisation			16.4	17.8		
	Control: Placebo	During initial hospitalisation			14.3	9.7		

TIMI, thrombolysis in myocardial Infarction.

PURSUIT subgroup analysis of patients stratified according to severity of CAD: Roe and colleagues (2000)[53]

Characteristics of participants (specified separately for high-risk patients)

Study (Author, year)		No. of subjects enrolled	No. of subjects lost to follow-up	Median age (range) (years)	Prognosis indicators (%) for continuous variables, e.g. blood pressure, heart rate							
					Previous MI	Previous PCI	Previous CABG	Previous CHF	Previous angina	Diabetes	Hypertension	Smoker
Roe *et al.*, 2000[53]	1: Significant CAD	5071	–	63 (55–70)	33.8	18.2	15.9	8.2	83.3	23.9	55.6	30.1
	2: Mild CAD	366	–	58 (50–67)	20.5	15.6	0.3	7.4	72.7	13.1	55.2	31.1
	3: No CAD	330	–	54 (47–63)	5.5	1.2	0.3	5.5	69.5	10.3	50.3	30.3

Outcomes (specified separately for high-risk patients and subgroup analysis)

Study (Author, year)		Time-point	Severity of CAD	AMI (%)	Severe recurrent angina/refractory ischaemia (%)	Death (%)	Measurement of quality of life (%)	Composite outcome (%)	Other (%)
Roe *et al.*, 2000[53]	1: Eptifibatide (n = 2869)	30 days	Significant CAD	14.1		2.9		15.6	
			Mild CAD	5.4		0.5		5.4	
			No CAD	1.2		0.0		1.2	
	Control: Placebo (n = 2898)	30 days	Significant CAD	16.6		3.7		18.3	
			Mild CAD	6.1		0.6		6.6	
			No CAD	1.8		1.2		3.0	

PURSUIT subgroup analysis of patients who underwent immediate CABG (i.e. within 2 hours of cessation of study drug): Dyke and colleagues (2000)[51]

Characteristics of participants (specified separately for high-risk patients)

					Prognosis indicators (%) for continuous variables, e.g. blood pressure, heart rate						
Study (Author, year)		No. of subjects enrolled (total and high risk)	No. of subjects lost to follow-up	Median age ± SD (years)	Previous MI	Previous PCTA	Previous CABG	Smoking	Diabetes	Hypertension	Non-Q-wave MI at presentation
Dyke *et al.*, 2000[51]	1: Eptifibatide	32	Not stated	61.5 ± 1.92	41	1	6	28	16	66	44
	Control: Placebo	46	Not stated	61.1 ± 1.45	31	18	13	33	22	67	43

Outcomes (specified separately for high-risk patients and subgroup analysis)

Study (Author, year)		Time-point	AMI, *n* (%)	Severe recurrent angina/refractory ischaemia, *n* (%)	Death, *n* (%)	Measurement of quality of life, *n* (%)	Composite outcome, *n* (%)	Other, *n* (%)
Dyke *et al.*, 2000[51]	1: Eptifibatide (*n* = 32)	96 hours	7 (21.9)		0		7 (21.9)	
		7 days	7 (21.9)		0		7 (21.9)	
		30 days	7 (21.9)		2 (6.3)		9 (28.1)	
	Control: Placebo (*n* = 46)	96 hours	18 (39.1)		1 (2.2)		19 (41.3)	
		7 days	19 (41.3)		1 (2.2)		20 (43.5)	
		30 days	21 (45.7)		3 (6.5)		22 (47.8)	

Adverse effects (specified separately for high-risk patients and subgroup analysis)

Study (Author, year)		Time-point	Fatal bleeding episodes, *n* (%)	Haemorrhagic strokes, *n* (%)	Major bleeding episodes, TIMI, *n* (%)	Minor bleeding episodes, TIMI, *n* (%)	Any bleeding, TIMI, *n* (%)	Other: transfusions, *n* (%)
Dyke *et al.*, 2000[51]	Eptifibatide	Not stated			20 (63)			Packed red blood cells: 19 (59.4) Platelets: 10 (31.3)
	Control: Placebo	Not stated			29 (64)			Packed red blood cells: 25 (56.5) Platelets: 17 (37)

PURSUIT subgroup analysis of outcomes among patients (n = 237, 2.5% of total) who developed cardiogenic shock after enrolment: Hasdai and colleagues (2000)[6]

Cardiogenic shock defined as systolic blood pressure <90 mmHg for ≥1 hour not responsive to fluid resuscitation alone, felt to be secondary to cardiac dysfunction and associated with signs of hypoperfusion or a cardiac index of ≤2.2 l min^{-1} m^{-2}. If systolic blood pressure increased to >90 mmHg as a result of positive inotropic agents alone in <1 hour, the event was still classified as shock.

Characteristics of participants (specified separately for high-risk patients)

Study (Author, year)		No. of subjects enrolled (total and high risk)	No. of subjects lost to follow-up	Median age (range) (years)	Prognosis indicators, n (%) for continuous variables, e.g. blood pressure, heart rate						
					Previous MI	CHF	Previous CABG	Current smoker	Diabetes	Hypertension	Angina
Hasdai *et al.*, 2000[6]	1: No shock, no MI	5027	–	63 (54–71)	1661 (33)	525 (10)	661 (13)	1319 (26)	1131 (23)	2835 (56)	4308 (86)
	2: No shock, MI	4185	–	64 (55–71)	1307 (31)	471 (11)	433 (10)	1319 (32)	957 (23)	2240 (54)	3132 (75)
	3: Shock, no MI	110	–	70 (63–74)	39 (36)	16 (15)	18 (16)	19 (17)	20 (18)	68 (62)	100 (92)
	4: Shock, MI	127	–	72 (65–76)	51 (40)	31 (24)	20 (16)	19 (15)	46 (36)	81 (64)	110 (87)

Outcomes for shock patients

Study (Author, year)		Time-point	Death (%)	
			Shock but no MI at enrolment	Shock plus MI at enrolment
Hasdai *et al.*, 2000[6]	1: Eptifibatide (n = 120)	30 days	48	69
	Control: Placebo (n = 117)	30 days	58	85

Outcomes for shock versus non-shock patients

Study (Author, year)		Time-point	Death (%)	
			Non-shock patients	Shock patients
Hasdai *et al.*, 2000[6]	1: Eptifibatide	30 days	2.0	58.5
	Control: Placebo	30 days	2.0	73.5

PURSUIT subgroup analysis of thrombocytopenia: McClure and colleagues (1999)[62]

Outcomes and adverse effects[a] (specified separately for high-risk patients and subgroup analysis)

Study (Author, year)		Mortality (%)	MI (%)	Recurrent ischaemia (%)	Stroke (%)	Any bleeding (%)	Severe bleeding (%)	Any red blood cell transfusion (%)
McClure *et al.*, 1999[62]	1: Eptifibatide, thrombocytopenia ($n = 314$)	6.7	23.9	21.0	2.9	80.0	9.9	58.3
	Control: Placebo, thrombocytopenia ($n = 319$)	8.2	30.4	23.8	3.1	71.8	5.6	53.0

[a] Events both before and after onset of thrombocytopenia; all events occurred within 30 days of randomisation, except for bleeding, which occurred only during baseline hospitalisation. Thrombocytopenia defined as platelet nadir $< 100 \times 10^9\ l^{-1}$, or a relative reduction of the nadir platelet count to <50% of baseline.

Outcomes, continued (procedures, hospitalisation, etc.)

Study (Author, year)		Percutaneous procedure (%)	CABG (%)	Incidence of rehospitalisation (%)	Median ICU stay (range) (days)	Median baseline hospital stay (range) (days)
McClure *et al.*, 1999[62]	1: Eptifibatide, thrombocytopenia ($n = 314$)	11.1	66.2	9.0	5 (3–8)	12 (8–20)
	Control: Placebo, thrombocytopenia ($n = 319$)	11.3	74.3	10.1	5 (3–8)	12 (8–20)

ICU, intensive care unit.

PURSUIT analysis of relation between baseline characteristics and the 30-day incidence of death or MI: Boersma and colleagues (2000)[54]

Study details

Study (Author, year)	Study design; any subgroup analyses?	Definition of high-risk group (if any)	Inclusion criteria	Interventions (specified by protocol)	Follow-up duration
Boersma *et al.*, 2000[54]	Analysed the relation between baseline characteristics and the 30-day incidence of death or MI in 9461 patients with ACS enrolled in the PURSUIT trial, using univariable and multivariable logistic regression	4308 patients with elevated CK-MB (classified as having MI) and remaining 5129 patients were classified as having UA	Patients were eligible if they presented within 24 hours of an episode of ischaemic chest pain (>10 minutes) and had transient ST-segment elevation (>0.5 mm), transient or persistent ST-segment depression (>0.5 mm), T-wave inversion (>1.0 mm) or elevation of CK-MB fraction above the upper limit of normal Exclusion: persistent (>30 minutes) ST-segment elevation For full inclusion criteria see PURSUIT	See PURSUIT	30 days

Characteristics of participants (specified separately for high-risk patients)

Study (Author, year)		No. of subjects enrolled (total and high risk)	No. of subjects lost to follow-up	Median age (years)	Prognosis indicators
Boersma *et al.*, 2000[54]	1: Eptifibatide Control: Placebo	See PURSUIT for full demographic data			

Other medication (specified separately for high-risk patients)

Study (Author, year)		Selected antianginal medication[a] before enrolment	Selected antianginal medication[a] after enrolment
Boersma *et al.*, 2000[54]	1: Eptifibatide Control: Placebo	See PURSUIT for data	

[a] Selected antianginal drugs to be considered: antiplatelet agents (aspirin, iclodipine, clopidogrel); anticoagulants (UFH, LMWH, enoxaprin, daltrepin).

Outcomes: definitions and measures

Study (Author, year)	AMI	Death	Composite outcome
Boersma *et al.*, 2000[54]	Within 18 hours of enrolment: ischaemic chest pain and new ST-segment elevation After 18 hours: new Q waves or new or repeated CK-MB elevations above the upper limit of normal. For patients undergoing PCI or CABG; CK-MB elevation >3 or 5 times the upper limit of normal	See PURSUIT for definition	Death and MI at 30 days

Outcomes: univariable relation between baseline characteristics and 30-day outcome

		Death		Composite outcome	
Study (Author, year)	High risk or all?	Rate (%)	OR (95% CI)	Rate (%)	OR (95% CI)
Boersma *et al.*, 2000[54]	1: Eptifibatide	3.5	UA: 1.25 (0.89 to 1.76) MI: 0.74 (0.56 to 0.99)	14.2	0.89 (0.79 to 0.99)
	Control: Placebo	3.7	1	15.7	1

Outcomes: multivariably adjusted effects of baseline characteristics and 30-day outcome

Study (Author, year)	High risk or all?	Death OR (95% CI)	Composite outcome, OR (95% CI)
Boersma *et al.*, 2001[54]	1: Eptifibatide	UA: 1.28 (0.91 to 1.81) MI: 0.79 (0.58 to 1.07)	0.90 (0.80 to 1.01)
	Control: Placebo	1	1

Appendix 9

Detailed abstraction from other subgroup reports

EPISTENT subgroup analysis of diabetic women: Cho and colleagues (2000)[59]

Study details

Study (Author, year)	Study design; any subgroup analyses?	Definition of high-risk group (if any)	Inclusion criteria	Interventions (specified by protocol)	Follow-up duration
Cho *et al.*, 2000[59]	Subgroup of 143 diabetic women from a large multicentre trial that included 2399 patients	Not reported	See EPISTENT trial	1. Stenting plus placebo 2. Stenting plus abciximab 0.25 mg kg^{-1}, followed by an infusion of 0.125 μg kg^{-1} per minute (max. dose 10 μg per minute) for 12 hours 3. Balloon plus abciximab 0.25 mg kg^{-1}, followed by an infusion of 0.125 μg kg^{-1} per minute (max. dose 10 μg per minute) for 12 hours	30 days, 6 months, 1 year

Results: participants (specified separately for high-risk patients)

Study (Author, year)		No. of subjects enrolled	No. of subjects lost to follow-up	Mean age ± SD (years)	Prognosis indicators, *n* (%)					
					Hypertension	PCI	CABG	CHF	Smoker	MI
Cho *et al.*, 2000[59]	1: Stent plus placebo	53	NR	62.4 ± 10.6	43 (81.1)	6 (11.3)	11 (20.8)	6 (11.5)	18 (34.0)	26 (49.1)
	2: Stent plus abciximab	45	NR	61.9 ± 10.6	34 (75.0)	5 (11.1)	20 (4.4)	9 (20.0)	12 (27.3)	13 (28.9)
	3: Balloon plus abciximab	45	NR	58.5 ± 10.2	35 (77.8)	7 (15.6)	20 (4.4)	6 (13.3)	17 (36.6)	11 (24.4)

Other medication (specified separately for high-risk patients)

Study (Author, year)		Antianginal medication[a] before enrolment, *n* (%)					Antianginal medication[a] after enrolment, *n* (%)
		Aspirin	β-Blockers	Ticlopidine	Nitroglycerine	Ca^{2+} channel blockers	
Cho *et al.*, 2000[59]	1: Stent plus placebo	51 (96.2)	30 (56.6)	28 (52.8)	34 (64.2)	27 (50.9)	All patients: 325 mg aspirin and weight-adjusted heparin
	2: Stent plus abciximab	41 (91.1)	31 (68.9)	26 (57.8)	27 (60.0)	21 (46.7)	
	3: Balloon plus abciximab	43 (95.6)	29 (64.4)	20 (44.4)	30 (66.7)	18 (40.0)	

[a] Antianginal drugs considered were any in the following classes: nitrates, calcium channel antagonists or β-adrenergic antagonists.

Outcomes: definitions and measures (specified separately for high-risk patients)

Study (Author, year)	AMI	Severe recurrent angina/refractory ischaemia	Death	Composite outcome	Major/minor bleeding	Other
Cho *et al.*, 2000[59]	In-hospital: new, clinically significant Q waves in two or more contiguous ECG leads or elevation in CK or CK-MB to ≥ 5 times the upper limit of normal Outpatient: occurrence of Q waves or an elevation of CK or CK-MB to >2 times the upper limit of normal			Death from any cause, MI or reinfarction, or TVR	Classified as major or minor according to the criteria used by the TIMI Study Group	

TVR, target vessel revascularisation.

Outcomes (specified separately for high-risk patients)

Study (Author, year)	All patients	Time-point	Death (%)	Composite outcome (%)	TVR (%)
Cho *et al.*, 2000[59]	1: Stent plus placebo	30 days	3.8	15.1	3.8
		6 months	3.8	24.9	15.7
		1 year	7.7	34.5	21.1
	2: Stent plus abciximab	30 days	0.0	6.7	0.0
		6 months	0.0	11.2	2.3
		1 year	0.0	13.3	4.5
	3: Balloon plus abciximab	30 days	0.0	6.7	4.4
		6 months	0.0	23.1	23.1
		1 year	4.4	28.9	26.7

Adverse effects (specified separately for high-risk patients)

Study (Author, year)		Fatal bleeding episodes (%)	Haemorrhagic strokes (%)	Major bleeding episodes (%)	Minor bleeding episodes (%)	Any bleeding (%)	Other adverse effects requiring treatment (%)
Cho *et al.*, 2000[59]	Placebo (n = 53)			6.0	2.0		
	Abciximab (n = 90)			4.5	9.1		

CAPTURE subgroup analysis of troponin status: Hamm and colleagues (1999)[47]

Study details

Study (Author, year)	Study design; any subgroup analyses?	Definition of high-risk group (if any)	Inclusion criteria	Interventions (specified by protocol)	Follow-up duration
Hamm *et al.*, 1999[47]	Subgroup of 809 patients from the CAPTURE trial, for whom serum samples taken before randomisation were available	Not stated	See CAPTURE trial Patients were excluded from this analysis if they had MI within 14 days before enrolment Patients with troponin levels >0.1 ng ml^{-1} were considered troponin T positive; those with levels ≤0.1 ng ml^{-1} were considered troponin T negative	See CAPTURE trial	72 hours, 30 days, 6 months

Results: participants (specified separately for high-risk patients)

Study (Author, year)			No. of subjects enrolled	No. of subjects lost to follow-up	Mean age ± SD (years)	Prognosis indicators, *n* (%)						
						Angina >4 weeks previously	MI 14–30 days previously	PCI	CABG	Diabetes	Hypertension	Current smoking
Hamm *et al.*, 1999[47]	1: Abciximab	Troponin T positive	136	NR	62.4 ± 10.6	57 (41.9)	4 (2.9)	16 (11.8)	2 (1.5)	18 (13.2)	48 (35.3)	56 (41.2)
		Troponin T negative	308		60.1 ± 9.3	166 (53.9)	13 (4.2)	49 (15.9)	4 (1.3)	41 (13.3)	115 (37.3)	122 (39.6)
	Control: Placebo	Troponin T positive	139	NR	62.7 ± 10.5	55 (39.6)	3 (2.2)	12 (8.6)	5 (3.6)	16 (11.5)	50 (36.0)	57 (41.0)
		Troponin T negative	307		60.9 ± 10.2	198 (64.5)	10 (3.3)	57 (18.6)	13 (4.2)	29 (9.4)	114 (37.1)	128 (41.7)

Other medication (specified separately for high-risk patients)

Study (Author, year)			Antianginal medication[a] before enrolment, *n* (%)					Antianginal medication[a] after enrolment, *n* (%)					
			Aspirin	Heparin (i.v.)	Nitrates (i.v.)	β-Blockers	Ca^{2+} channel blockers	Aspirin	Ticlopidine	Heparin (i.v.)	Nitrates (i.v.)	β-Blockers	Ca^{2+} channel blockers
Hamm *et al.*, 1999[47]	1: Abciximab	Troponin T positive	125 (91.9)	134 (98.5)	136 (100.0)	90 (66.2)	55 (40.4)	132 (97.1)	7 (5.1)	131 (96.3)	131 (96.3)	91 (66.9)	54 (39.7)
		Troponin T negative	266 (86.4)	304 (98.7)	308 (100.0)	187 (60.7)	149 (48.4)	290 (94.2)	13 (4.2)	295 (95.8)	291 (94.5)	194 (63.0)	156 (50.6)
	Control: Placebo	Troponin T positive	131 (94.2)	135 (97.1)	137 (98.6)	87 (62.6)	60 (43.2)	135 (97.1)	5 (3.6)	139 (100.0)	135 (97.1)	89 (64.0)	60 (43.2)
		Troponin T negative	286 (93.2)	306 (99.7)	307 (100.0)	194 (63.2)	184 (59.9)	299 (97.4)	15 (4.9)	300 (97.7)	302 (98.4)	186 (60.6)	180 (58.6)

[a] Antianginal drugs considered were any in the following classes: nitrates, calcium channel antagonists or β-adrenergic antagonists.

Outcomes: definitions and measures (specified separately for high-risk patients)

Study (Author, year)	AMI	Severe recurrent angina/refractory ischaemia	Death	Measurement of quality of life	Composite outcome	Major/minor bleeding	Other
Hamm *et al.*, 1999[47]	See CAPTURE trial		See CAPTURE trial		Non-fatal MI and death		

Outcomes (specified separately for high-risk patients)

Study (Author, year)	High risk or all?	Time-point	Death (%)		Composite outcome (%)		Other
			Troponin T positive	Troponin T negative	Troponin T positive	Troponin T negative	
Hamm *et al.*, 1999[47]	1: Abciximab	72 hours	–	–	3.6	4.5	
		30 days	–	–	5.8	5.2	
		6 months	2.9	1.9	9.5	9.4	
	Control: Placebo	72 hours	–	–	17.4	4.2	
		30 days	–	–	19.6	4.9	
		6 months	3.6	1.3	23.9	7.5	

PRISM-PLUS subgroup analysis of diabetic patients: Theroux and colleagues (2000)[55]

Study details

Study (Author, year)	Study design; any subgroup analyses?	Definition of high-risk group (if any)	Inclusion criteria/exclusion criteria	Interventions (specified by protocol)	Follow-up duration
Theroux *et al.*, 2000[55]	Subgroup analysis on diabetic patients from PRISM-PLUS	–	See PRISM-PLUS Patients assigned to diabetic or non-diabetic subgroup on the basis of the presence or absence of a history of diabetes mellitus at enrolment	1. Tirofiban bolus plus Infusion (0.10 μg) plus heparin 2. Tirofiban placebo + Heparin (three arms of therapy considered in main trial)	48 hours, 7 days, 30 days, 180 days

Characteristics of participants

Study (Author, year)		No. of subjects enrolled (total and high risk)		No. of subjects lost to follow-up		Mean age ± SD (years)		Prognosis indicators (%) for continuous variables, e.g. blood pressure, heart rate									
								Previous MI		Previous PCI		Previous CABG		Smoking		UA		Non-ST elevation MI	
		DM	No DM	DM	No DM	DM	No DM	DM	No DM	DM	No DM	DM	No DM	DM	No DM	DM	No DM	DM	No DM
Theroux *et al.*, 2000[55]	1: Tirofiban plus heparin	169	604	Not stated. Only patients from two of the treatment arms included in substudy		65 ± 10.2	63 ± 12.1	50	43	10	8.8	20	14	29	34	54	56	42	44
	2: Heparin	193	604			66 ± 9.8	62 ± 11.9	44	37	12	8.4	15	13	21	34	59	52	41	48

DM, diabetes mellitus.

Other medication

Study (Author, year)		Selected antianginal medication[a] before enrolment (%)				Selected antianginal medication[a] after enrolment (%)
		Nitrates	β-Blockers	Ca^{2+} calcium blockers	Insulin	
Theroux *et al.*, 2000[55]	1: Tirofiban plus heparin	DM: 88 No DM: 88	DM: 61 No DM: 53	DM: 53 No DM: 40	DM: 27 No DM: 0.5	See PRISM-PLUS; not stated for subgroup
	2: Heparin	DM: 89 No DM: 87	DM: 57 No DM: 52	DM: 50 No DM: 35	DM: 27 No DM: 0	

[a] Selected antianginal drugs to be considered: antiplatelet agents (aspirin, ticlodipine, clopidogrel); anticoagulants (UFH, LMWH, enoxaprin, daltrepin).

Outcomes: results (for diabetic patients only)

Study (Author, year)	Time-point	MI/death (%)	Severe recurrent angina/refractory ischaemia (%)	Death (%)	Measurement of quality of life (%)	Composite outcome (%)
Theroux *et al.*, 2000[55]	48 hours	0	–	–	–	7.7
	7 days	1.2	–	–	–	14.8
	30 days	4.7	–	–	–	20.1
	6 months	11.2	–	–	–	32.0
	48 hours	3.1	–	–	–	8.3
	7 days	9.3	–	–	–	21.8
	30 days	15.5	–	–	–	29.0
	6 months	19.2	–	–	–	39.9

Adverse effects (specified separately for high-risk patients)

Study (Author, year)		TIMI major bleeding (%)		TIMI minor bleeding (%)		All TIMI bleeding (%)		Other adverse effects requiring treatment
				DM	No DM	DM	No DM	
Theroux *et al.*, 2000[55]	1: Tirofiban plus heparin	0.6	1.7	7.1	11.4	9.5	13.4	NR
	2: Heparin	0.5	0.8	6.7	8.4	8.3	10.1	

EPISTENT subgroup analysis of diabetic patients: Lincoff (2000)[60]

Study details

Study (Author, year)	Study design; any subgroup analyses?	Definition of high-risk group (if any)	Inclusion criteria/exclusion criteria	Interventions (specified by protocol)	Follow-up duration
Lincoff, 2000[60]	Subgroup analysis of diabetic patients in EPISTENT trial	–	Patients undergoing urgent percutaneous coronary revascularisation, outside the setting of AMI See EPISTENT for full inclusion criteria	1. Abciximab plus Stent 2. Abciximab plus balloon 3. Placebo plus stent	30 days, 6 months

Characteristics of participants

Study (Author, year)		No. of subjects enrolled (total and high risk)	No. of subjects lost to follow-up	Mean age ± SD (years)	Prognosis indicators (%) for continuous variables, e.g. blood pressure, heart rate				
					Hypertension	CHF	Previous coronary intervention	Previous CABG	Previous MI
Lincoff, 2000[60]	Diabetic patients	491	Not stated	60.4 ± 10	68.8	9.8	14.0	10.0	47.5
	Non-diabetic patients	1908	Not stated	59.2 ± 11	48.5	3.4	15.0	8.9	49.3

Other medication

Study (Author, year)		Selected antianginal medication[a] before enrolment (%)	Selected antianginal medication[a] after enrolment
Lincoff, 2000[60]	Diabetic patients	379 (77%) patients receiving hypoglycaemic agents, insulin or both. Of the remainder, 21 patients had previously been treated with oral hypoglycaemic agents	See EPISTENT

[a] Selected antianginal drugs to be considered: antiplatelet agents (aspirin, ticlodipine, clopidogrel); anticoagulants (UFH, LMWH, enoxaprin, daltrepin).

Outcomes: definitions and measures

Study (Author, year)		Time-point	Composite outcome (%)	
			DM	Non-DM
Lincoff *et al.*, 2000[60]	1: Abciximab plus stent	30 days	5.6	5.2
		6 months	6.2	5.4
	2: Abciximab plus balloon	30 days	5.1	7.4
		6 months	7.8	7.8
	3: Placebo plus stent	30 days	12.1	10.5
		6 months	12.7	11.0

Other outcomes

Study (Author, year)			Repeat TVR (%)	
			DM	Non-DM
Lincoff, 2000[60]	1: Abciximab plus stent	180 days	8.1	8.8
	2: Abciximab plus balloon	180 days	18.4	14.6
	3: Placebo plus stent	180 days	16.6	9.0

EPILOG and EPISTENT subgroup analysis of patients with complex lesions: Cura and colleagues (1999)[56]

Study details

Study (Author, year)	Definition of high-risk group (if any)	Inclusion criteria	Interventions (specified by protocol)	Length of observation period before PCI	Timing of administration of drug before PCI	Follow-up duration
Cura *et al.*, 1999[56]	As in trials	Patients with complex coronary lesions. Patients had to fit entry criteria of the STRESS/BENESTENT trials	EPILOG: 1. Abciximab infusion for 12 hours plus heparin (ACT ≥ 300 seconds) 2. Abciximab 12 hours plus heparin (ACT ≥ 200 seconds) 3. Heparin alone EPISTENT: 1. Stent plus placebo 2. Stent plus abciximab 3. Balloon angioplasty plus abciximab four strategies analysed by substudy: 1, balloon plus placebo; 2, stent plus placebo; 3, balloon plus abciximab; 4, stent plus abciximab	–	–	30 days, 1 year

ACT, activated coagulation time.

Characteristics of participants (specified separately for high-risk patients)

Study (Author, year)		No. of subjects enrolled (total)	No. of subjects lost to follow-up	Median age ± SD (years)	Prognosis indicators (%) for continuous variables, e.g. blood pressure, heart rate				
					Diabetes	Hypertension	Current smoker	Prior MI	Prior CABG
Cura *et al.*, 1999[56]	1: Balloon plus placebo	402 UA = 70%	–	60.2 ± 11	26	59	30	48	15
	2: Stent plus placebo	424 UA = 64%	–	59.6 ± 11	22	55	39	57	15
	3: Balloon plus abciximab	1184 UA = 65%	–	60.7 ± 11	23	60	31	51	14
	4: Stent plus abciximab	399 UA = 57%	–	59.9 ± 10	23	49	37	50	11

Other medication (specified separately for high-risk patients)

Study (Author, year)		Selected antianginal medication[a] before enrolment	Selected antianginal medication[a] after enrolment
Cura *et al.*, 1999[56]	1: Balloon plus placebo	NR	NR
	2: Stent plus placebo	NR	NR

[a] Selected antianginal drugs to be considered: antiplatelet agents (aspirin, ticlopidine, clopidogrel); anticoagulants (UFH, LMWH, enoxaparin, dalteparin).

Outcomes: definitions and measures

Study (Author, year)	AMI	Severe recurrent angina/refractory ischaemia	Death	TVR	Composite outcome	Major/minor bleeding
Cura *et al.*, 1999[56]	New pathological Q waves or a value of CK or CK-MB ≥ 3 times the upper limit in the participating hospital. After discharge MI defined as occurrence of Q waves or elevation of CK or CK-MB to ≥ 2 times the upper limit of normal	–	As noted	Need to repeat revascularisation of any segment in the previously intervened vessel	Death, MI	Defined by the TIMI criteria

Outcomes (specified separately for high-risk patients and subgroup analysis)

Study (Author, year)	High risk or all?	Time-point	AMI (%)	Severe recurrent angina/refractory ischaemia (%)	Death (%)	Composite outcome (%)	Any TVR (%)
Cura *et al.*, 1999[56]	1: Total	30 days	10.3	NA	1.0	10.6	9.5
		1 year	12.0		3.2	14.2	30.5
	2: Total	30 days	11.1	NA	0.9	12.1	3.1
		1 year	13.5		3.1	15.8	18.0
	3: Total	30 days	4.9	NA	0.6	5.1	5.7
		1 year	6.4		2.1	7.6	24.4
	4: Total	30 days	6.0	NA	0.0	6.0	2.3
		1 year	7.5		0.5	8.0	19.7

Outcomes by lesion type

Study (Author, year)	High risk or all?	Time-point	TVR rate (%)	Event-free survival (%)	Composite outcome (%)
Cura *et al.*, 1999[56]	Simple lesions	1 year	15.5	79.7	7.3
	Complex lesions	1 year	23.1	70.6	10.1

Outcomes, continued

Study (Author, year)		Time-point	Any revasc. (%)	PTCA plus stent (%)	Repeat revasc. (any) at 1 year for patients treated with stents vs balloon angioplasty (%)
Cura *et al.*, 1999[56]	1: Balloon plus placebo	30 days	9.5	18.4	25.9 (arms 1 and 3)
		1 year	30.5		
	2: Stent plus placebo	30 days	3.1	98.1	18.8 (arms 2 and 4)
		1 year	18		
	3: Balloon plus abciximab	30 days	5.7	16.6	
		1 year	24.4		
	4: Stent plus abciximab	30 days	2.3	98	
		1 year	19.7		

Adverse effects (specified separately for high-risk patients and subgroup analysis)

Study (Author, year)		Time-point	Haemorrhagic strokes	Major bleeding episodes (%)	Minor bleeding episodes (%)	Any bleeding (%)	Other adverse effects requiring treatment (%)
Cura *et al.*, 1999[56]	1: Balloon plus placebo	30 days	–	4.2	–	–	–
	2: Stent plus placebo	30 days	–	1.7	–	–	–
	3: Balloon plus abciximab	30 days	–	2.0	–	–	–
	4: Stent plus abciximab	30 days	–	1.5	–	–	–

EPILOG subgroup analysis of stent use: Kereiakes and colleagues (1998)[57]

Characteristics of participants (specified separately for high-risk patients)

Study (Author, year)		No. of subjects enrolled (total)	No. of subjects lost to follow-up	Median age ± SD (years)	Prognosis indicators, *n* (%) for continuous variables, e.g. blood pressure, heart rate									
					Stable ischaemia	UA	Recent MI	History of PCI	History of CABG	Current smoker	History of high cholesterol	Diabetic hyper-tension	History of	History of CHF
Kereiakes *et al.*, 1998[57]	1: Unplanned stent	326	Not stated	60 ± 11	98 (30)	159 (49)	69 (21)	83 (26)	36 (11)	107 (33)	184 (60)	65 (20)	183 (56)	25 (8)
	2: No stent	2369	Not stated	60 ± 11	754 (32)	1130 (48)	485 (20)	592 (25)	299 (13)	768 (33)	1364 (61)	552 (23)	1406 (60)	170 (7)

Outcomes at 30 days

Study (Author, year)		Time-point	Death, MI, urgent revasc. (%) ± 95% CI		Death/MI (%) ± 95% CI		MI (%) ± 95% CI		Urgent intervention (%) ± 95% CI		Death, *n*	
			Unplanned stent	No stent	Unplanned stent	No stent	Unplanned stent	No stent	Unplanned stent	No stent	Unplanned stent	No stent
Kereiakes *et al.*, 1998[57]	1: Placebo plus standard heparin	30 days	22.6 ± 3.8	10.0 ± 1.1	20.2 ± 3.6	7.3 ± 0.9	18.6 ± 3.5	7.2 ± 0.9	9.7 ± 2.7	4.6 ± 0.8	2	4
	2: Abciximab plus low-dose heparin	30 days	8.6 ± 3.1	4.4 ± 0.7	6.2 ± 2.7	3.2 ± 0.6	6.2 ± 2.7	3.1 ± 0.6	2.5 ± 1.7	1.5 ± 0.4	0	3
	3: Abciximab plus standard heparin	30 days	9.9 ± 2.7	4.7 ± 0.8	7.4 ± 2.4	3.7 ± 0.7	7.4 ± 2.4	3.3 ± 0.6	3.3 ± 1.6	2.2 ± 0.5	0	4

Outcomes at 30 days by unplanned stent use

Study (Author, year)		Time-point	Death, MI, urgent intervention, *n* (%)	Death/MI, *n* (%)	Death, *n* (%)	MI, *n* (%)	Q-wave MI, *n* (%)	Non-Q-wave MI, *n* (%)
Kereiakes *et al.*, 1998[57]	1: Unplanned stent	30 days	47 (14.4)	39 (12.0)	2 (0.6)	37 (11.4)	3 (0.9)	34 (10.4)
	2: No stent	30 days	149 (6.3)	110 (4.6)	11 (0.5)	105 (4.4)	12 (0.5)	93 (3.9)

Outcomes at 30 days by unplanned stent use, continued

Study (Author, year)		Time-point	Urgent intervention, *n* (%)	Urgent PCI, *n* (%)	Urgent CABG, *n* (%)	Any revasc., *n* (%)	Repeat PCI, *n* (%)	Repeat CABG, *n* (%)
Kereiakes *et al.*, 1998[57]	1: Unplanned stent	30 days	18 (5.5)	11 (3.4)	8 (2.5)	27 (8.3)	18 (4.9)	13 (4.0)
	2: No stent	30 days	64 (2.7)	49 (2.1)	18 (0.8)	125 (5.3)	80 (3.4)	48 (2.0)

Outcomes at 6 months

Study (Author, year)		Time-point	Death, MI, urgent revasc. (%) ± 95% CI		Death, MI, any revasc.		Death/MI (%) ± 95% CI		TVR (%) ± 95% CI		Death, *n*	
			Unplanned stent	No stent	Unplanned stent	No stent	Unplanned stent	No stent	Unplanned stent	No stent	Unplanned stent	No stent
Kereiakes *et al.*, 1998[57]	1: Placebo plus standard heparin	6 months	24.2 ± 3.8	13.4 ± 1.2	33.1 ± 4.2	24.6 ± 1.6	21.6 ± 3.7	9.4 ± 1.0	22.2 ± 3.8	17.7 ± 1.4	4	11
	2: Abciximab plus low-dose heparin	6 months	11.1 ± 3.5	7.8 ± 0.9	23.5 ± 4.7	22.2 ± 1.5	8.6 ± 3.1	5.3 ± 0.8	14.8 ± 3.9	17.1 ± 1.3	1	9
	3: Abciximab plus standard heparin	6 months	12.5 ± 3.0	7.9 ± 1.0	25.2 ± 4.0	21.7 ± 1.5	10.0 ± 2.7	5.9 ± 0.9	13.6 ± 3.2	16.9 ± 1.4	2	11

Adverse effects (specified separately for high-risk patients and subgroup analysis)

Study (Author, year)		Time-point	Minor bleeding, *n* (%)	Major bleeding, *n* (%)	Non CABG major bleeding, *n* (%)	Non CABG minor bleeding, *n* (%)	CABG-related minor bleeding, *n* (%)	CABG-related major bleeding, *n* (%)	Any stroke, *n* (%)	Haemorrhagic stroke, *n* (%)
Kereiakes *et al.*, 1998[57]	1: Unplanned stent	30 days	36 (11)	20 (6.4)	12 (3.7)	36 (11)	1 (0.3)	9 (2.6)	0 (0.0)	0 (0.0)
	2: No stent	30 days	99 (4.2)	53 (2.2)	22 (0.9)	101 (4.3)	1 (0.0)	32 (1.4)	3 (0.1)	2 (0.1)

EPILOG subgroup analysis of diabetic patients: Kleiman and colleagues (1998)[58]

Characteristics of participants (specified separately for high-risk patients)

					Prognosis indicators, *n* (%), for continuous variables, e.g. blood pressure, heart rate								
Study (Author, year)		No. of subjects enrolled (total)	No. of subjects lost to follow-up	Median age ± SD (years)	Stable ischaemia	UA	Recent MI	History of PCI	History of CABG	Current smoker	History of high cholesterol	History of hypertension	History of CHF
Kleiman *et al.*, 1998[58]	1: Diabetic patients	638	Not stated	61 ± 10	210 (33)	326 (51)	102 (16)	168 (27)	111 (17)	156 (25)	371 (61)	470 (74)	86 (14)
	2: Non-diabetic patients	2154	Not stated	59 ± 11	675 (31)	898 (46)	476 (22)	524 (25)	237 (11)	757 (36)	1223 (61)	1181 (55)	116 (5)

Outcomes (specified separately for high-risk patients and subgroup analysis)

Study (Author, year)		Time-point	Q-wave MI, *n* (%)	Non-Q-wave MI, *n* (%)	Death, *n* (%)	Death/MI, *n* (%)	Composite outcome, *n* (%)
Kleiman *et al.*, 1998[58]	1: Diabetic patients	In hospital	3 (0.5)	27 (4.2)	3 (0.5)	32 (5)	45 (7.1)
	2: Non-diabetic patients	In hospital	12 (0.6)	108 (5)	11 (0.5)	126 (5.9)	161 (7.5)

Outcomes at 30 days

Study (Author, year)		Time-point	Composite outcome (%) ± 95% CI		Death/MI (%) ± 95% CI		Death, *n*	
			DM	Non-DM	DM	Non-DM	DM	Non-DM
Kleiman *et al.*, 1998[58]	1: Placebo plus standard heparin	30 days	12.6 ± 2.2	11.5 ± 1.2	9.4 ± 1.9	9.1 ± 1.1	3	4
	2: Abciximab plus low-dose heparin	30 days	5.7 ± 1.6	5.0 ± 0.8	3.8 ± 1.3	3.7 ± 0.7	0	9
	3: Abciximab plus standard heparin	30 days	2.5 ± 1.1	6.2 ± 0.6	1.5 ± 0.9	4.9 ± 0.6	0	4

Outcomes at 6 months

Study (Author, year)		Time-point	Composite outcome (%) ± 95% CI		Death/MI (%) ± 95% CI		TVR (%) ± 95% CI		Death, *n*	
			DM	Non-DM	DM	Non-DM	DM	Non-DM	DM	Non-DM
Kleiman *et al.*, 1998[58]	1: Placebo plus standard heparin	6 months	27.0 ± 3.0	25.4 ± 1.6	14.8 ± 2.4	10.0 ± 1.1	15.5 ± 2.4	18.9 ± 1.5	7	9
	2: Abciximab plus low-dose heparin	6 months	31.4 ± 3.2	20.3 ± 1.5	7.1 ± 1.8	5.4 ± 0.8	23.5 ± 2.9	15.1 ± 1.3	3	7
	3: Abciximab plus standard heparin	6 months	23.1 ± 3.0	21.9 ± 1.6	4.1 ± 1.4	6.9 ± 0.9	19.1 ± 2.8	15.4 ± 1.4	3	9

Outcomes, continued

Study (Author, year)		Time-point	Urgent PCI, *n* (%)	Urgent CABG, *n* (%)	Any revasc., *n* (%)	Repeat PCI, *n* (%)	Repeat CABG, *n* (%)
Kleiman *et al.*, 1998[58]	1: Diabetic patients	In hospital	16 (2.5)	3 (0.5)	42 (6.6)	28 (4.4)	15 (2.4)
	2: Non-diabetic patients	In hospital	44 (2.1)	25 (1.2)	119 (5.6)	68 (3.2)	55 (2.6)

Adverse effects (specified separately for high-risk patients and subgroup analysis)

Study (Author, year)		Time-point	Minor bleeding, *n* (%)	Major bleeding, *n* (%)	Non-CABG major bleeding, *n* (%)	Non-CABG minor bleeding, *n* (%)	CABG-related minor bleeding, *n* (%)	CABG-related major bleeding, *n* (%)	Any stroke, *n* (%)	Haemorrhagic stroke, *n* (%)
Kleiman *et al.*, 1998[58]	1: Diabetic patients	In hospital	26 (4.1)	15 (2.4)	8 (1.3)	25 (3.9)	2 (0.3)	7 (1.1)	1 (0.2)	1 (0.2)
	2: Non-diabetic patients	In hospital	114 (5.3)	65 (3.0)	29 (1.4)	114 (5.3)	4 (0.2)	37 (1.7)	2 (0.1)	1 (0.1)

PRISM subgroup analysis of troponin status: Heeschen and colleagues (1999)[63]

Outcomes (specified separately for high-risk patients and subgroup analysis)

			AMI, *n* (%)		Severe recurrent angina/refractory ischaemia, *n* (%)		Death, *n* (%)		Composite outcome (death, MI), *n* (%)	
Study (Author, year)		Time-point	Troponin-I positive	Troponin-I negative	Troponin-I positive	Troponin-I negative	Troponin-I positive	Troponin-I negative	Troponin-I positive	Troponin-I negative
Heeschen *et al.*, 1999[63]	1: Tirofiban (n = 1097)	48 hours	1 (0.3)	4 (0.5)	10 (3.3)	17 (2.1)	0	3 (0.4)	1 (0.3)	7 (0.9)
		7 days	4 (1.3)	17 (2.1)	26 (8.5)	59 (7.4)	2 (0.7)	7 (0.9)	6 (2.0)	24 (3.0)
		30 days	8 (2.6)	27 (3.6)	31 (10.2)	72 (9.1)	5 (1.6)	18 (2.3)	13 (4.3)	45 (5.7)
	Control: Heparin (n = 1125)	48 hours	9 (2.8)	5 (0.6)	30 (9.3)	24 (3.05)	2 (0.6)	0	11 (3.4)	5 (0.6)
		7 days	18 (5.6)	14 (1.8)	47 (14.5)	53 (6.6)	12 (3.7)	3 (0.4)	30 (9.3)	18 (2.2)
		30 days	22 (6.8)	21 (2.6)	48 (14.8)	60 (7.5)	20 (6.2)	18 (2.3)	42 (13.0)	39 (4.9)

PARAGON B subgroup analysis of troponin status: Newby *et al* (2001)[49]

Outcomes (specified separately for high-risk patients and subgroup analysis

Study (Author, year)		Time-point	AMI, *n* (%)		Severe recurrent ischaemia, *n* (%)		Death, *n* (%)		Composite outcome (death, MI), *n* (%)	
			Troponin I positive	Troponin I negative	Troponin I positive	Troponin I negative	Troponin I positive	Troponin I negative	Troponin-I positive	Troponin I negative
Newby *et al*., 2001[49]	1: Lamifiban	30 days	9.3	9.3	0.4	1.5	3.1	1.2	11.0	10.8
	2: Placebo	30 days	17.3	9.7	0.4	0.9	5.1	2.0	19.4	11.2

Appendix 10

Results from meta-regression analysis

To investigate whether the log relative risk in the individual trials varied with log baseline risk (i.e. the log event rate in the control group), a random effects meta-regression model was used.[111]

Strategy 1, including lamifiban trials

Mortality at 30 days

Meta-analysis regression:
no. of studies = 7
tau^2 method: reml
tau^2 estimate = 0.000

Successive values of tau^2 differ by less than 10^{-4}: convergence achieved.

	Coefficient	SE	*Z*	*p* > |*Z*|	(95% CI)
mclr	–0.0669542	0.1506245	–0.44	0.657	(–0.3621728 to 0.2282644)
_cons	–0.4181514	0.5238171	–0.80	0.425	(–1.444814 to 0.6085113)

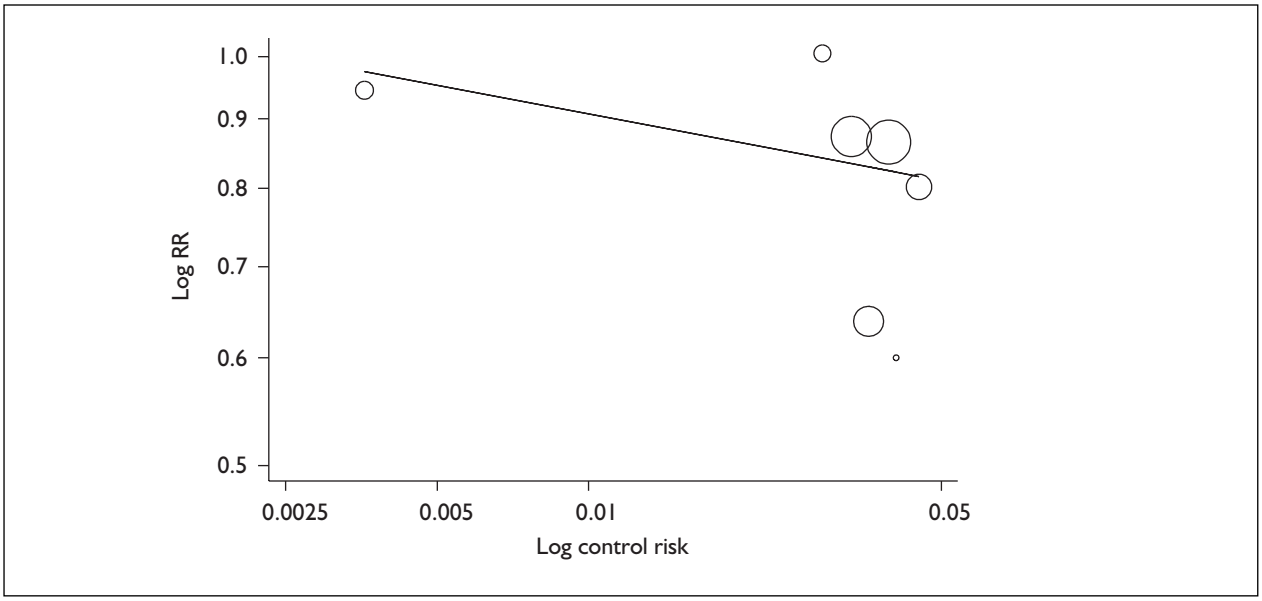

FIGURE 30 *Mortality at 30 days (strategy 1, including lamifiban trials)*

Non-fatal MI at 30 days

Meta-analysis regression:
no. of studies = 7
tau^2 method: reml
tau^2 estimate = 0.000

Successive values of tau^2 differ by less than 10^{-4}: convergence achieved.

	Coefficient	SE	Z	$p > \|Z\|$	(95% CI)
miclr	–0.0844641	0.1053033	–0.80	0.422	(–0.2908548 to 0.1219266)
_cons	–0.265705	0.2419139	–1.10	0.272	(–0.7398476 to 0.2084376)

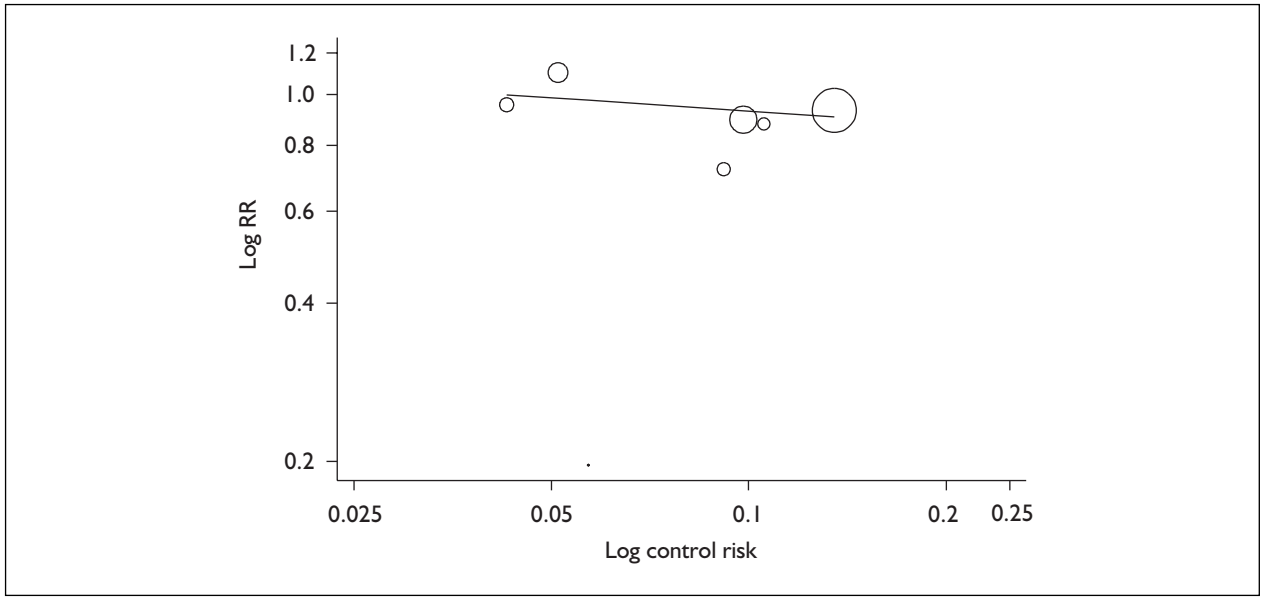

FIGURE 31 *Non-fatal MI at 30 days (strategy 1, including lamifiban trials)*

Strategy 1, excluding lamifiban trials

Mortality at 30 days

metareg mlrr mclr,wsse(mlrr_se)
Iteration 1: tau^2 = 0

Meta-analysis regression:
no. of studies = 4
tau^2 method: reml
tau^2 estimate = 0.000

Successive values of tau^2 differ by less than 10^{-4}: convergence achieved.

	Coefficient	**SE**	***Z***	***p*** **>|*Z*|**	**(95% CI)**
mclr	–0.0639614	0.1509014	–0.42	0.672	(–0.3597228 to 0.2318)
_cons	–0.4430776	0.5288631	–0.84	0.402	(–1.47963 to 0.593475)

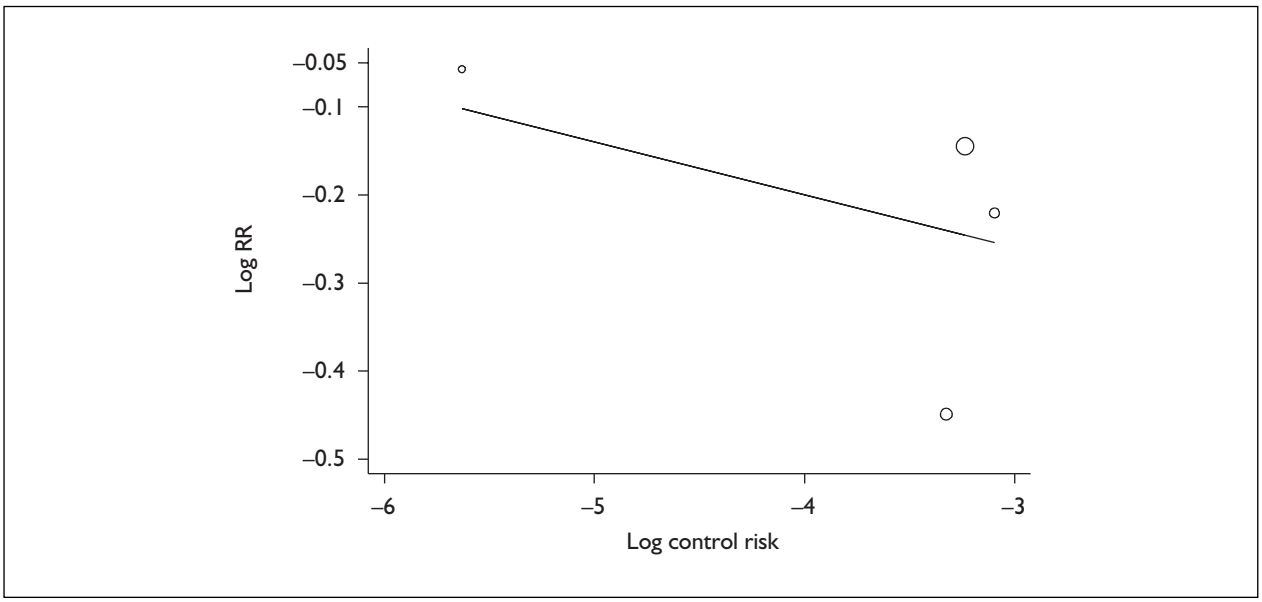

FIGURE 32 *Mortality at 30 days (strategy 1, excluding lamifiban trials)*

Non-fatal MI at 30 days

metareg milrr miclr, wsse(milrr_se)
Iteration 1: $tau^2 = 0$

Meta-analysis regression:
no. of studies = 4
tau^2 method: reml
tau^2 estimate = 0.000

Successive values of tau^2 differ by less than 10^{-4}: convergence achieved.

	Coefficient	SE	*Z*	*p* > |*Z*|	(95% CI)
miclr	–0.0937543	0.1056917	–0.89	0.375	(–0.3009063 to 0.1133977)
_cons	–0.2711912	0.2423435	–1.12	0.263	(–0.7461758 to 0.2037934)

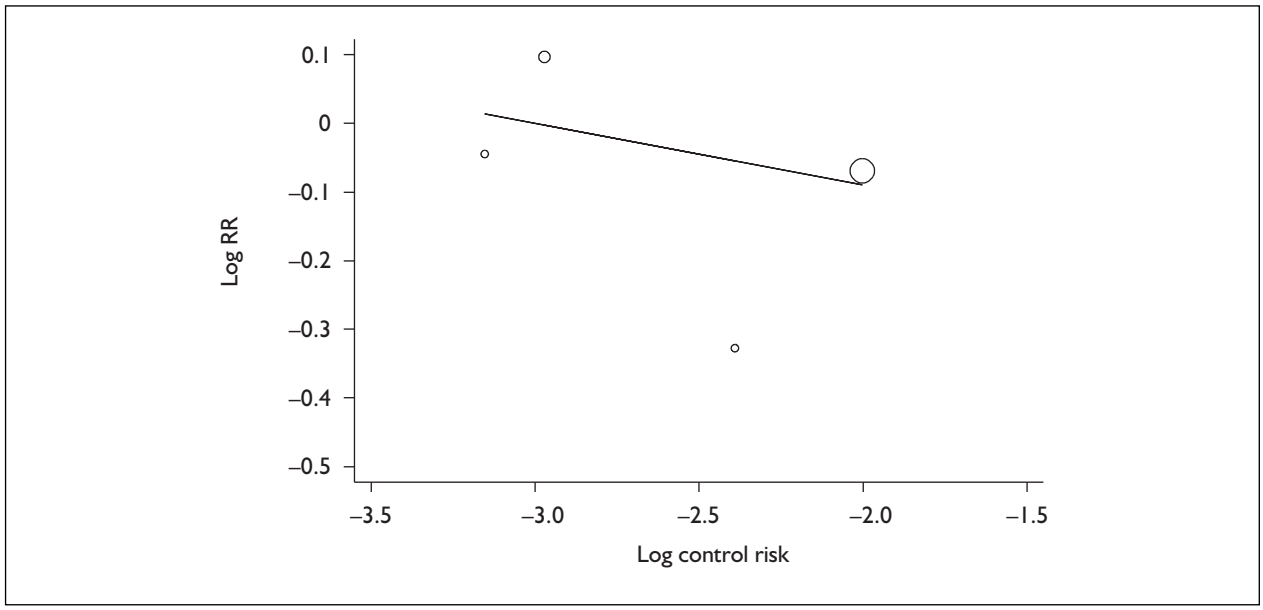

FIGURE 33 *Non-fatal MI at 30 days (strategy 1, excluding lamifiban trials)*

Strategy 3

Mortality at 30 days

Meta-analysis regression:
no. of studies = 6
tau^2 method: reml
tau^2 estimate = 0.000

Successive values of tau^2 differ by less than 10^{-4}: convergence achieved.

	Coefficient	SE	*Z*	*p* > |*Z*|	(95% CI)
mclr	0.241628	0.5764633	0.42	0.675	(–0.8882194 to 1.371475)
_cons	0.8429795	2.609682	0.32	0.747	(–4.271903 to 5.957862)

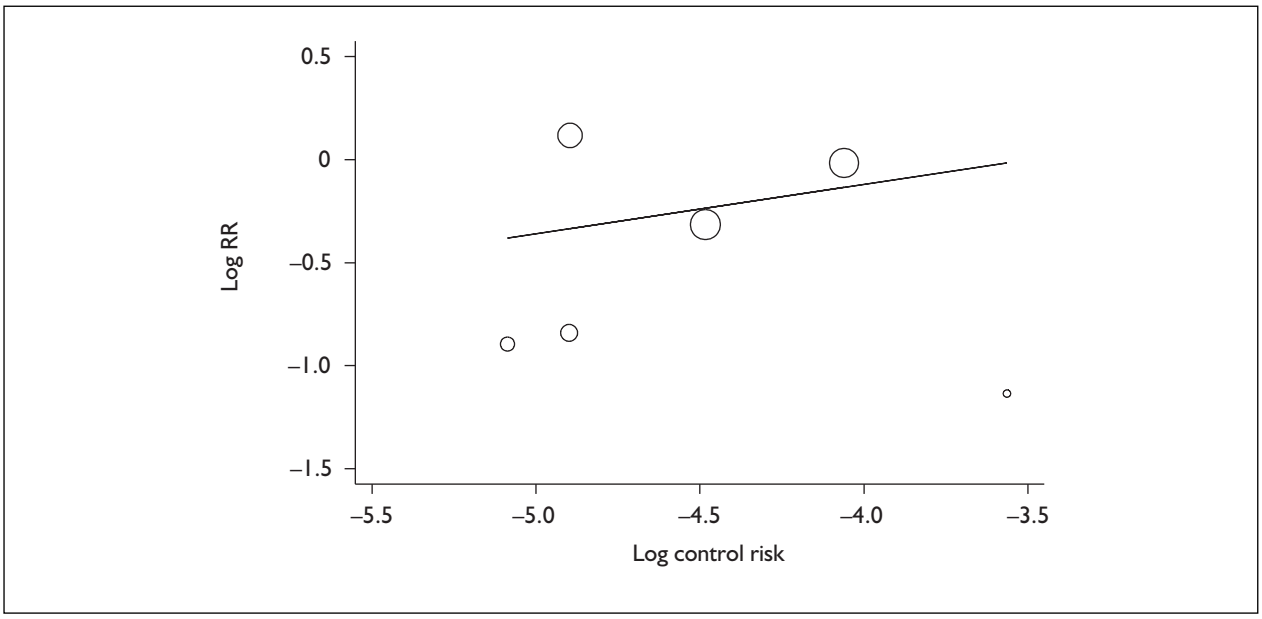

FIGURE 34 *Mortality at 30 days (strategy 3)*

Non-fatal MI at 30 days

Meta-analysis regression:
no. of studies = 8
tau^2 method: reml
tau^2 estimate = 0.0445

Successive values of tau^2 differ by less than 10^{-4}: convergence achieved.

	Coefficient	SE	*Z*	*p* > |*Z*|	(95% CI)
miclr	–1.090636	0.6593248	–1.65	0.098	(–2.382889 to 0.2016173)
_cons	–3.268273	1.662387	–1.97	0.049	(–6.526491 to –0.0100549)

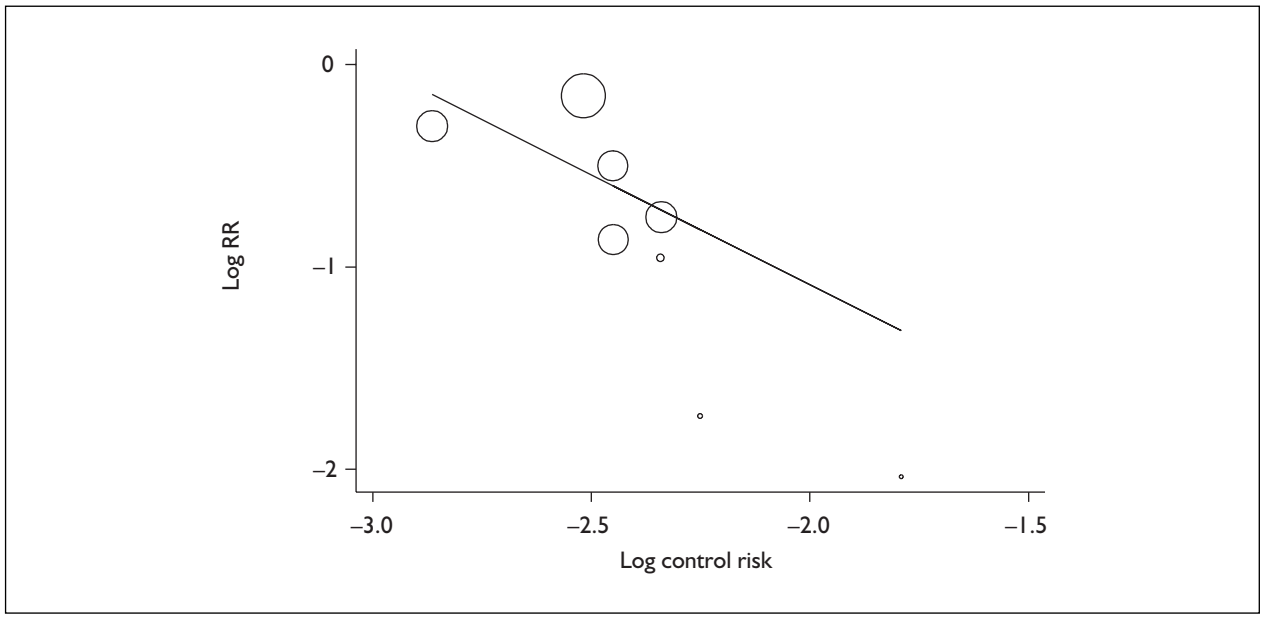

FIGURE 35 *Non-fatal MI at 30 days (strategy 3)*

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We look forward to hearing from you.

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