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Rapid review

A rapid and systematic review of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists in the medical management of unstable angina

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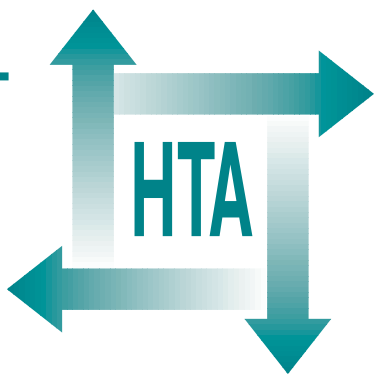
Health Technology Assessment
NHS R&D HTA Programme



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A rapid and systematic review of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists in the medical management of unstable angina

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Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases usage differs in the literature, but the term has a constant meaning throughout this review.

ACS Acute coronary syndrome

Agonist A drug that both binds to receptors and has an intrinsic effect; a drug that triggers an action from a cell or a drug

Aneurysm A localised dilatation of the lumen of a blood vessel. The most common sites of aneurysms are the aorta and the vessels of the brain

Angina pectoris A severe acute attack of cardiac pain

Angioplasty Procedure during which a balloon is passed into the artery and inflated to enlarge it and increase blood flow. Also called percutaneous transluminal angioplasty

Antagonist A drug that nullifies the effect of another drug

Anticoagulant A pharmaceutical that helps to stop the blood from clotting

aPTT Activated partial thromboplastin time. Control measure used during treatment with heparin

Arteriogram A radiographic technique involving a radiopaque contrast material that can be seen on X-ray and therefore is injected into a blood vessel for the purpose of identifying the vessel's anatomy on X-ray

Atherosclerosis A major disease of the arteries characterised by deposition of organised lipid and platelets at the intima of arteries. This deposition narrows the lumen for blood flow and also reduces the elasticity of the blood vessels. Hypertension, high levels of cholesterol in the blood and cigarette smoking are the major risk factors for atherosclerosis

Beta-adrenergic antagonist Also called beta blockers. These drugs inhibit the action of certain types of neurones that stimulate beta receptors

Bias Deviation of results or inferences from the truth, or processes leading to such deviation. Any trend in the collection, analysis, interpretation, publication or review of data that can lead to conclusions that are systematically different from the truth

Blinding A procedure used in clinical trials to avoid the possible bias that might be introduced if the patient and/or doctor knew which treatment the patient would be receiving. If neither the patient nor the doctor is aware of which treatment has been given, the trial is termed 'double-blind'. If only one of the patient or doctor is unaware, the trial is called 'single-blind'

Bypass surgery Creating an alternate route for blood to pass an obstruction (commonly used to describe heart surgery to bypass the coronary artery)

CABG Coronary artery bypass graft. A surgical procedure that involves replacing diseased (narrowed) coronary arteries with veins obtained from the patient's lower extremities (autologous graft)

CAD Coronary artery disease. Gradual blockage of the coronary arteries

CAPTURE Chimeric 7E3 Antiplatelet Therapy in Unstable Angina Refractory to Standard Treatment.* The name of a particular study

Cardiac catheterisation A procedure involving the introduction of a catheter into the right or left side of the heart to study the pressures in the central vein, across the valves of the arteries and in the chambers of the

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continued

heart. The volumes in the cardiac chamber during the cardiac cycle and the patency of the coronary artery are also measured by observing the flow pattern of radiographic dye injected through the catheter

CCTR Cochrane Controlled Trials Register*

CDSR Cochrane Database of Systematic Reviews*

Cerebrovascular disease Damage to the blood vessels in the brain, which can result in a stroke

CHD Coronary heart disease*

CHF Congestive heart failure*

CI Confidence interval. A measure of the precision of statistical estimates

CK-MB Creatine kinase, myocardial band (fraction)

Coagulation Clotting of the blood. A complex reaction that depends on a series of biochemical components and platelets in the blood

Coagulopathy A defect in the blood clotting mechanism

Co-intervention In a randomised controlled trial, the application of additional diagnostic or therapeutic procedures to members of either the experimental or reference group, or to both groups

Composite end-point Several different possible outcomes or events associated with individuals in a medical investigation

Confounding (1) The masking of an actual association or (2) false demonstration of an apparent association between the study variables when no real association between them exists

Cost–benefit analysis An attempt to give the consequences of the alternative interventions a monetary value. In this way, the consequences can be more easily compared with the costs of the intervention. This type of analysis involves measuring individuals' 'willingness to pay' for given outcomes and can be quite difficult

Cost-effectiveness analysis An assessment in which consequences of the alternative interventions are measured in natural units, such as years of life gained. The consequences are not given a monetary value

Cost-minimisation When two alternative interventions are found to have equal clinical efficacy or outcomes (consequences), therefore the only difference between the two is cost. This analysis is sometimes considered a subtype of cost-effectiveness analysis

Cost-offset analysis A special type of cost–benefit analysis

Cost–utility analysis An assessment in which the consequences of alternatives are measured in 'health state preferences', which are given a weighting score. In this type of analysis, different consequences are valued in comparison with each other, and the outcomes (e.g. life-years gained) are adjusted by the weighting assigned. In this way, an attempt is made to value the quality of life associated with the outcome so that life-years gained become quality-adjusted life-years gained

Counterpulsation A technique for assisting the circulation by decreasing the afterload of the left ventricle and augmenting the diastolic pressure. It may be achieved by intra-aortic balloon or by implanting a special pumping device in the chest, or externally by applying a negative pressure to the lower extremities during cardiac systole

CPI Conference Papers Index

Creatinine An end-product of protein metabolism found in the blood and urine, which can be used to help assess if the kidneys are working adequately

DARE Database of Abstracts of Reviews of Effectiveness

DEC Development and Evaluation Committee

Diastolic Relating to the phase during which the heart relaxes (e.g. diastolic pressure)

Diathesis A constitution or condition of the body that makes the tissues react in special ways to certain extrinsic stimuli and thus tends to make the person unusually susceptible to certain diseases

Dipyridamole nuclear stress test Myocardial perfusion imaging for patients who cannot exercise

Ecchymosis A livid or black-and-blue spot, produced by the extravasation or effusion of blood into the areolar tissue from a contusion

ECG Electrocardiogram. A recording of the electrical signals from the heart

ECU European currency unit*

End-point A clearly defined outcome or event associated with an individual in a medical investigation. A simple example is the death of a patient

EPIC Evaluation of 7E3 for the Prevention of Ischemic Complications.* The name of a particular study

Exercise stress test A treadmill or cycle-ergometer test that records heart rate, ECG and other data. Workload is gradually increased until an increase in workload is no longer followed by an increase in oxygen consumption, thus identifying the individual's maximal oxygen uptake. The test allows the prescription of exercise based on the individual's actual, rather than estimated, heart rate or aerobic capacity

Exertional angina The sensation of chest pain, brought on by physically or emotionally stressful situations

External validity The ability to generalise the results from an experiment to a larger population

GI bleeding Any bleeding that may occur along the course of the gastrointestinal tract

GU bleeding Genitourinary bleeding

GUSTO Global Use of Strategies to Open Occluded Arteries. The name of a particular series of studies

Haematemesis The vomiting of blood

Haematochezia The passage of bright red blood via the rectum

Haematoma A localised collection of blood, usually clotted, in an organ, space or tissue, due to a break in the wall of a blood vessel

Haematuria The finding of blood in the urine

Haemoptysis The expectoration of blood or of blood-stained sputum

Haemorrhage The escape of blood from the vessels; bleeding. Small haemorrhages are classified according to size as petechiae (very small), purpura (up to 1 cm) and ecchymoses (larger). The massive accumulation of blood within a tissue is called a haematoma

Haemorrhagic stroke Stroke due to excessive blood loss

Haemostasis The arrest of bleeding, either by the physiological properties of vasoconstriction and coagulation, or by surgical means

Hazard ratio Measure of relative risk used in survival studies

Heparin Sulphated mucopolysaccharide that inhibits the action of thrombin on fibrinogen by potentiating antithrombins, thereby interfering with the blood clotting cascade

Heterogeneity A term used to mean that the variation of a measurement within a group is different from the variation of that same measurement within other groups

Holter monitoring A test that measures the heart rhythm (ECG) over a 24-hour period while the patient records their symptoms and activities in a diary. A small portable ECG device is contained in a pouch worn around the neck or waist. After the test is complete, a correlation is made between the symptoms (or activities) recorded and the ECG pattern that was obtained simultaneously

Homeostasis The maintenance of equilibrium of the internal body functions in response to external changes

Hypotension The condition of an individual's blood pressure being lower than normal

ICU Intensive care unit*

IDEA Internet Database of Evidence-Based Abstracts and Articles

continued

continued

IMPACT Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis.* The name of a particular study

INAHTA International Network of Agencies for Health Technology Assessment

Intention-to-treat analysis A method of data analysis in which the primary tabulations and companion summaries of outcome data are by assigned treatment, regardless of treatment adherence

Interim analysis A formal statistical term indicating an analysis of data performed part-way through a study

Internal validity The degree to which a study is logically sound and free of confounding variables

Intravenous Administered into a vein

Ischaemia Deficiency of blood in an organ or body part, usually due to obstruction of the arterial blood supply or inadequate blood flow, leading to hypoxia (oxygen deficiency) in the tissue

Kaplan–Meier curves Product limit method. A non-parametric method of compiling life or survival tables, developed by Kaplan and Meier in 1958. This method combines calculated probabilities of survival and estimates to allow for censored observations, which are assumed to occur randomly. The intervals are defined as ending each time an event (e.g. death or withdrawal) occurs and are therefore unequal

Killip class Classification of the severity of chronic heart failure

LBBB Left bundle branch block.* A term used in ECG monitoring

Log-rank test Significance test for comparing the survival experience of two or more distinct groups, as expressed by their survival curves

Melaena The passage of dark stools containing blood, which can indicate bleeding from the lower intestine

Meta-analysis A quantitative method for combining the results of many studies into one set of conclusions

MI Myocardial infarction. An infarction caused by obstruction of blood circulation to a region of the heart; results from permanent damage to an area of the heart muscle. Also called a heart attack

MIMS *Monthly Index of Medical Specialties*

Mitral regurgitation The back flow of blood from the left ventricle into the left atrium through a defective mitral bicuspid valve

Monoclonal antibody A biological response modifier with unique 'homing device' properties. Identical monoclonal antibody molecules are produced by a single clone of cells or cell line

Mortality rate The proportion of deaths in a population or in a specific number of the population

NHSEED NHS Economic Evaluations Database

NICE National Institute for Clinical Excellence

Nitrates A group of medications that relax smooth muscle, dilate veins, lower blood pressure and improve blood flow through the coronary arteries

NNH Number need to harm

NNT Number needed to treat. In clinical treatment regimens, the number of patients with a specified condition who must follow the specified regimen for a prescribed period in order to prevent occurrence of specified complications or adverse outcomes of the condition. Mathematically equal to 1 divided by the risk difference

NSAID Non-steroidal anti-inflammatory drug*

OPUS-TIMI Orbofiban in Patients with Unstable Coronary Syndromes, Thrombolysis in Myocardial Infarction. The name of a particular study

OR Odds ratio

PARAGON Platelet IIb/IIIa Antagonist for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network. The name of a particular study

PCI Percutaneous coronary intervention

Percutaneous revascularisation The surgical restoration of blood supply (e.g. by means of a vascular graft or prosthesis)

Petechiae Small red spots on the skin that usually indicate a low platelet count

Phase II trial A study with a small number of patients diagnosed with the disease for which the drug is being studied. In this study phase, the safety of the new drug is tested. Early effectiveness data are also collected for various doses of the drug

Phase III trial A study with a large number of patients diagnosed with the disease for which the drug is being studied. In this study phase, the drug is tested against a placebo or alternative treatment

Placebo A 'dummy' treatment administered to the control group in a controlled clinical trial, in order to distinguish the specific and non-specific effects of the experimental treatment (i.e. the experimental treatment must produce better results than the placebo in order to be considered effective)

Plaque Any patch or flat area. Atheromatous plaque is a swelling on the inner surface of an artery produced by lipid deposit

Platelet A blood cell that helps to control bleeding by inducing clotting

PRISM Platelet Receptor Inhibition in Ischemic Syndrome Management. The name of a particular study

PRISM-PLUS PRISM in Patients Limited to Very Unstable Signs and Symptoms. The name of a particular study

PTCA Percutaneous transluminal coronary angioplasty. Dilatation of a coronary vessel by means of a balloon catheter inserted through the skin and into the lumen of the vessel to the site of the narrowing, where the balloon is inflated to flatten plaque against the arterial wall

PURSUIT Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy. The name of a particular study

***p*-value** In the context of significance tests, the *p*-value represents the probability that a given difference will be observed in a study sample when, in reality, such a difference does not exist in the relevant population. Small *p*-values indicate stronger evidence to reject the null hypothesis of no difference

QALY Quality-adjusted life-year. A term originally developed in cancer studies to balance poor quality of life (possibly with long life expectancy) with good quality of life (possibly with short life expectancy)

Q wave A negative deflection at the onset of a QRS complex in an ECG. An abnormal Q wave spans 0.04 seconds or more in duration and reaches more than 25% of the amplitude of the adjacent R wave

Random allocation A method for forming treatment and control groups, particularly in the context of a clinical trial. Patients receive the active treatment or placebo on the basis of the outcome of a chance event, for example, tossing a coin

RCT Randomised controlled trial.* This type of study is designed to measure the efficacy and safety of particular types of healthcare interventions, by randomly assigning people to one of two or more treatment groups and, when possible, blinding them and the investigators to the treatment that they are receiving. The outcome of interest is then compared between the treatment groups. Such studies are designed to minimise the possibility of an association due to confounding and to remove many sources of bias present in other study designs. However, such studies are not infallible, and there are areas of methodological concern: selection bias (bias in the way patients are assigned to experimental groups), issues relating to reproducibility of results, bias introduced by co-interventions and bias in assessing the outcomes

RD Risk difference*

Regression Regression method for modelling survival times. The outcome variables are whether or not the event of interest has occurred, and if so, after what period of time, or if not, the duration of follow-up. The

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model predicts the hazard or risk of the event in question at any given time. Also called proportional hazard model

Relative risk The proportion of diseased people among those exposed to the relevant risk factor, divided by the proportion of diseased people among those not exposed to the risk factor

Revascularisation The restoration of blood supply, either naturally (e.g. by wound healing) or surgically (e.g. by means of a vascular graft or prosthesis)

RRR Relative risk reduction.* An alternative way of expressing relative risk (RR). It is calculated as follows:

$$RRR = (1 - RR) \times 100\%$$

The RRR can be interpreted as the proportion of the initial or baseline 'risk' that was eliminated by a given treatment or intervention, or by avoidance of exposure to a risk factor

ScHARR School of Health and Related Research

SHPIC Scottish Health Purchasing Information Centre

SIGN Scottish Intercollegiate Guidelines Network

ST elevation Elevation of the ST segment of an ECG

Stent A tube used by a surgeon to drain fluids or relieve an obstruction

Stratification The division of a population into parts known as strata, particularly for the purpose of enhancing comparability

SYMPHONY Sibrafiban versus Aspirin to Yield Maximum Protection from Ischemic Heart Events Post-acute Coronary Syndromes. The name of a particular study

TACTICS Treat Angina with Aggrastat (tirofiban) and Determine Cost of Therapy with Invasive or Conservative Strategy. The name of a particular study

Thrombocytopenia A decrease in the number of platelets in the blood, resulting in the potential for increased bleeding and decreased clotting ability

Thrombolysis The mechanism by which thrombi are dissolved by a series of events, the most important of which involves the local action of plasmin within the substance of the thrombus. Intracoronary thrombolysis refers to the lysis of clots by thrombolytic agents introduced into the coronary arteries for the treatment of myocardial infarction

Thrombus An aggregation of blood factors, primarily platelets and fibrin, with the entrapment of cellular elements, which frequently causes vascular obstruction at the point of its formation. Some authorities thus differentiate thrombus formation from simple coagulation or clot formation

Ticlopidine An inhibitor of platelet aggregation

TIMI Thrombolysis (and Thrombin Inhibition) in Myocardial Infarction. The name of a particular series of studies

TRIP Turning Research Into Practice

Unstable angina Angina pectoris in which the cardiac pain has changed in pattern

Vasoconstrictor A chemical that causes the narrowing of blood vessels so that less blood is able to flow through at a time

Vasospasm A sudden decrease in the internal diameter of a blood vessel that results from contraction of smooth muscle within the wall of the vessel

Warfarin Synthetic inhibitor of prothrombin activation and therefore an inhibitor of blood clotting. It is also used as a rat poison

* Used only in tables, figures or appendices

Executive summary

Background

Unstable angina represents a spectrum of clinical states that fall between stable angina and acute myocardial infarction (MI). It includes angina at rest (typically lasting more than 20 minutes), new-onset angina (within 2 months of onset), increasing angina (increased frequency, longer duration and at lower thresholds), variant angina (ST-segment elevation) and angina occurring more than 24 hours post-MI.

Glycoprotein IIb/IIIa is a receptor on the platelet membrane. This receptor is the final common pathway of platelet aggregation, which is considered to be a major factor in thrombus formation and MI. Therefore, in theory, antagonists of glycoprotein IIb/IIIa could play a very important role in the treatment of unstable angina. Glycoprotein IIb/IIIa antagonists can be used in conjunction with percutaneous coronary intervention (PCI), but this review is limited to their use in patients for whom PCI is not planned. These drugs can be administered intravenously over a few days during the acute episode and orally over several weeks. This review considers both routes of administration.

Epidemiology

Although classification problems complicate reliable estimation, it is likely that between 60,000 and 180,000 new cases of unstable angina occur in the UK each year. Patients with unstable angina have a high risk of MI and death.

Methods

A systematic review of the literature, involving a range of databases, was conducted. Full details are described in the main report.

Results

Number and quality of studies

Evidence from randomised trials was found for six glycoprotein IIb/IIIa antagonists: tirofiban, eptifibatide, lamifiban, sibrafiban, orbofiban and lefradafiban. Focussing on Phase III trials, the literature search found five trials dealing with the intravenous use of tirofiban, eptifibatide or lamifiban, and four trials dealing with the oral use of sibrafiban, orbofiban or lefradafiban. The assessment of the quality of the studies was hindered by a lack of detailed reporting on study methods, most notably on the methods of treatment allocation and the handling of missing values in the data analysis. If inadequate reporting does not reflect inadequate study conduct, the trials generally seem to be of good quality.

Benefits and adverse effects

The results for the three main outcomes at 30 days (MI, death and the composite end-points) from the Phase III trials of the intravenous glycoprotein IIb/IIIa antagonists are summarised in *Table A*.

For the composite end-points measured at 30 days, the trials investigating the intravenous use of the drugs tended to show small to very small benefits and slightly higher rates of side-effects associated with the glycoprotein IIb/IIIa antagonists. For tirofiban alone, the risk was actually slightly increased in one trial (PRISM-PLUS). Because many of the results were not statistically significant, the 95% CIs for many of the NNT values include infinity. Therefore, the NNT data quoted here should be interpreted with **caution**.

All the Phase III trials reported data up to 30 days. The PRISM-PLUS and PURSUIT studies also reported data at 6 months, although only the composite end-point was reported for the PURSUIT study. The risk difference in the composite end-points at 6 months remained very similar to the 30-day results; however, the eptifibatide results at 6 months no longer showed a statistically significant difference, compared with placebo. The tirofiban results for the composite end-point improved slightly, compared with heparin, although the differences remained not statistically significant. The benefits at 6 months with tirofiban were very similar for MI and slightly reduced for death, compared with the 30-day results.

The main adverse effect monitored was bleeding. The incidence of major bleeding was slightly higher in the patients treated with eptifibatide

TABLE A *Intravenous glycoprotein IIb/IIIa antagonists: results for main outcomes at 30 days*

Main outcome	Risk difference between treatment and control groups (95% CI)	NNT (95% CI)
Death		
Eptifibatide	–0.2% (–1.0% to 0.6%)	504 (105 to infinity)
Tirofiban*	–1.3% (–2.5% to –0.1%)‡	77 (40 to 729)
Tirofiban†	1.6% (–1.1% to 4.9%)	–64 (negative infinity to –91)§
Tirofiban + heparin†	–0.9% (–2.9% to 1.1%)	112 (34 to infinity)
MI		
Eptifibatide	–0.9% (–2.3% to 0.5%)	111 (44 to infinity)
Tirofiban*	–0.2% (–1.7% to 1.2%)	404 (61 to infinity)
Tirofiban†	–3.1% (–6.1% to 0.4%)	33 (16 to infinity)
Tirofiban + heparin†	–2.6% (–5.3% to 0.1%)	39 (19 to infinity)
Composite end-points		
Eptifibatide	–1.5% (–2.9% to –0.1%)‡	67 (35 to 1919)
Tirofiban*	–1.2% (–3.7% to 1.4%)	85 (27 to infinity)
Tirofiban†	1.1% (–4.0% to 6.6%)	–87 (negative infinity to –15)§
Tirofiban + heparin†	–3.8% (–7.8% to 0.2%)	27 (13 to infinity)
Lamifiban	–1.0% (–2.8% to 0.8%)	102 (37 to infinity)

CI, confidence interval; NNT, number needed to treat

* *PRISM trial*

† *PRISM-PLUS trial*

‡ *Statistically significant difference, compared with control*

§ *Number needed to harm*

compared to placebo (10.6% vs 9.1%) and in those treated with tirofiban compared to tirofiban plus heparin (4.0% vs 3.0%, in PRISM-PLUS trial). The incidence of major bleeding was equal (0.4%) in the two groups (tirofiban vs heparin) in the PRISM study. Although the data were not reported for lamifiban, the abstract of the PARAGON B trial results states that major bleeding was not higher in the lamifiban group.

The results for the trials investigating the oral administration of these drugs were consistently negative: no benefits and possibly more bleeding.

Cost-effectiveness

An unpublished economic analysis of tirofiban in the UK reported cost-effectiveness ratios of £8760 at 7 days and £9955 at 6 months per composite end-point prevented. In a further cost-offset analysis, 22% of the costs of tirofiban could be offset by the reduction of events (MI and recurrent ischaemia).

An unpublished economic analysis of eptifibatide in the UK reported that this drug was dominant to placebo in costs per life-years saved at 30 days. The cost-effectiveness analysis at 30 days resulted in an estimated saving of £213 per death or MI avoided by using eptifibatide.

It is concerning that a US-based analysis found a cost per life-year gained of over US$16,000, while the UK-based analysis found that eptifibatide is dominant (i.e. is more effective and costs less). This discrepancy is particularly a concern because the efficacy rate for the composite end-point assumed in the US-based study was 3.5% and in the UK-based study only 1%, making it even more unlikely to find eptifibatide dominant. While the PCI rate is lower in the UK than in the US, there was no difference in the rate of PCI between the treatment and placebo groups in the PURSUIT study. However, in the UK patient data, the number of percutaneous transluminal coronary angioplasty or stent procedures performed in the placebo arm was 1.8 times that of the eptifibatide group. The sample sizes for UK resource use data were small relative to the whole trial. If this difference in PCI rates is real, then eptifibatide may indeed be dominant to placebo. However, the smaller sample size and the fact that the PURSUIT study did not find a difference in

PCI rates suggest that this result should be interpreted with caution.

No cost-effectiveness analyses of lamifiban were identified.

Conclusions

Generalisability

While patients with acute coronary syndrome are very high risk in general, the generalisability of this review's findings is limited by the characteristics of the patients enrolled. For example, the mean ages of the patients enrolled in these trials (range, 59–67 years) were notably lower than the ages of patients generally seen in clinical practice. Furthermore, there may be subgroups of clinically homogeneous patients in whom these drugs are more or less effective. The results for the overall group may then underestimate or overestimate the effect for these subgroups. The trials also restricted the use of coronary interventions during the period of drug infusion, except for patients requiring emergency procedures. Because this restriction would not be in place in clinical practice, the results may not be generalisable.

Recommendations for research

Further research into the clinical effectiveness and cost-effectiveness of these drugs, including testing the troponins T and I as markers of patients who will benefit, is recommended.

Two additional trials, TACTICS TIMI-18 and GUSTO IV ACS, are reported to have completed enrolment. TACTICS TIMI-18 is a trial of tirofiban, and GUSTO IV ACS is a trial of abciximab. When data from these trials are available, this review will need to be updated.

Chapter 1

Aim and background

Aim of the review

The purpose of this report is to answer the following question: what is the clinical effectiveness and cost-effectiveness of the glycoprotein IIb/IIIa antagonists in the treatment of unstable angina and non-Q-wave myocardial infarction (MI)?

The glycoprotein antagonists that are currently licensed in the UK (abciximab, eptifibatide, and tirofiban) are reviewed in this report. In addition, any other non-licensed glycoprotein antagonists identified through the literature search are reviewed, because these drugs may possibly be licensed in the future. **The use of the glycoprotein antagonists as a part of a percutaneous coronary intervention (PCI) procedure was explicitly excluded**.

Background

Acute coronary syndrome (ACS) is a term that covers a range of patients with a broadly similar underlying pathology. At one end of the spectrum are those patients with evidence of ST elevation in a resting electrocardiogram (ECG) who are eligible for treatment with thrombolysis and who may subsequently develop a Q wave in their ECG. The remaining patients are classified as having either unstable angina or non-Q-wave MI.

Unstable angina itself represents a spectrum of clinical states that fall between stable angina and acute MI. It includes angina at rest (typically lasting more than 20 minutes), new-onset angina (within 2 months of onset), increasing angina (e.g. increasing frequency, longer duration and at lower thresholds), variant angina (ST-segment elevation) and angina occurring more than 24 hours post-MI. Unstable angina typically indicates significant coronary artery disease (CAD), although this is not always the case.

Non-Q-wave MI is the term used when the cardiac enzymes are elevated to the range indicating that MI has occurred, but a Q wave does not develop on ECG tracings. This condition is thought to indicate a subendocardial infarction, in which the damage does not extend through the full thickness of the myocardium.

At the time patients present, it is difficult to distinguish those patients with non-ST-elevation ACS who will or will not go on to develop acute MI. It is only possible to differentiate between the two conditions after 4–16 hours (at the earliest), when the cardiac enzymes can be tested. A definite diagnosis is often not possible until 2–3 days after the event, when the full pattern of enzyme elevation becomes known. However, the first clinical decision that must be made is whether the patient's chest pain is due to CAD or other causes. Information required to determine the cause of chest pain includes a careful medical history, assessment of the patient for evidence of prior MI, other indicators of CAD, patient age and gender, and a number of other risk factors for atherosclerosis.

The risk of death or ischaemic complications from unstable angina is significant. A recent study of men aged 51–59 years showed that the 16-year survival rate was 34% for those with a history of MI, 53% for those with a history of angina and 72% for those with no history of coronary disease.[1] The risk is highest in the early stages of symptom presentation but returns to baseline levels (i.e. the risk level of stable angina) within 2 months. The prognosis of a patient with an ACS depends on the nature of the recent clinical course, the extent of underlying CAD and other factors that determine his or her general condition, which in turn determine the likelihood that the patient would survive an acute ischaemic event. The frequency and severity of angina leading up to the ACS are particularly important factors in predicting the subsequent clinical course. Indicators of poor prognosis on physical examination include heart failure, mitral regurgitation murmur or hypotension (particularly during pain). ECG findings that help identify high-risk patients include ST-segment changes of 1 mm or more, or T-wave inversion that resolves with symptom resolution. Patient age and the concentration of troponins (serum markers of heart muscle damage) have been found to be important prognostic factors.

Patients who experience angina post-MI have a higher risk than those who have not had a recent MI, and this risk is increased if there are ST-T changes during symptoms.

Rizik and co-workers have proposed a stratification system for patients with unstable angina.[2] Class IA includes patients with increasing exertional angina but without ECG changes, Class IB includes patients with increasing exertional angina who also show ECG changes, Class II includes patients with new-onset exertional angina, Class III includes those with new-onset rest angina, and Class IV includes those with protracted rest angina with ECG changes. These classes exclude patients with post-MI angina, variant angina or non-Q-wave MI. However, these authors found an increasing incidence of cardiac events as the class designation increased, with the exception of classes IB and II.

The definition and exact operationalisation of unstable angina that is chosen for use in a clinical trial can greatly influence the event rates that are found. For example, even in studies that used 'pain at rest' as the definition of unstable angina, the 1-month incidence proportions of death varied between 2% and 60%.[3–6] Those studies using a definition of 'increasing angina' showed 1-month incidence proportions of death between 16% and 50%.[7–11] It must be recognised that the participants in many of these trials are expected to be healthier than typical patients with unstable angina and that many studies use a definitive diagnosis of unstable angina (i.e. after the results from the cardiac enzymes tests are fully available). Both of these factors could result in reported mortality figures that underestimate the figure for the entire population of patients with unstable angina.

Not only is unstable angina an unspecific diagnostic category, but patients present with varying degrees of atherosclerosis (e.g. stenosis size, plaque location and plaque fragility), thrombus formation (with low or high platelet content) and vasospasm. Each of these variables contributes to the morbidity and mortality of the disease. Each therefore represents a potential target for intervention with medical therapy. Aspirin and heparin (unfractionated or low molecular weight) are currently used to reduce thrombus formation, and nitrates are used to help reduce vasospasm and cardiac oxygen requirements. In addition, beta-adrenergic antagonists and calcium channel blockers are used. Interventional therapy typically involves PCI or coronary artery bypass surgery.

Current service provision and costs

Estimating the current service provision and current costs of unstable angina is quite difficult because the International Classification of Diseases, 9th revision, coding system does not differentiate between stable and unstable angina. The number of people coded as having an acute MI, but who were admitted with unstable angina, is also not known. The incidence of new cases of 'angina pectoris' in the UK is conservatively estimated to be about 22,600 patients per year.[12] The 1999 NHS Executive data show that at least 129,458 patients with angina were seen by consultants, with the cost per 'finished consultant episode' ranging from £156 to £1123.[13] The 1998 mortality statistics indicate that ischaemic heart disease was the cause of 4421 deaths per million population, and an additional 2224 deaths per million population were due to acute MI.[14] According to UK Hospital Episode Statistics, there are about 1000 admissions for unstable angina per million population per year, but other estimates in the UK and the US are 2–3 times greater, being similar to the reported rates for acute MI.[15,16] These latter figures would indicate that between 60,000 and 180,000 new cases occur in the UK annually.

The glycoprotein IIb/IIIa antagonists are new drugs that may be given in addition to the current medical therapies. While the provision of other services may potentially be reduced by using these drugs, their cost would be additive to the initial treatment costs. For each of the three licensed drugs, the cost of the drug alone (not including infusion costs) for treating a person weighing 70 kg is shown in *Table 1*. The maintenance dose ranges reflect the **total** amount of drug required for the duration of the maintenance phase (e.g. 12–36 hours for abciximab). The doses and treatment duration ranges are based on the November 1999 *Monthly Index of Medical Specialties* (*MIMS*).[17] Prices for tirofiban and eptifibatide are taken from the September 1999 British National Formulary,[18] and the price for abciximab is from the November 1999 *MIMS*.[17]

Several randomised clinical trials of oral glycoprotein IIb/IIIa antagonists are ongoing, have been completed or were prematurely stopped. If found effective, these drugs might be used following an episode of unstable angina. The optimal duration of treatment has not yet been established.

TABLE 1 *Doses and costs of glycoprotein IIb/IIIa antagonists currently licensed in the UK*

Drug	Bolus dose (mg per 70 kg)	Maintenance dose range (mg per 70 kg)	Maintenance duration range (hours)	Drug cost range* (£)
Abciximab	17.5	23.8–36.4	12–36	666.40–1019.20
Eptifibatide	12.6	604.8–806.4	72–96	436.36–578.29
Tirofiban	0.84	20.16–45.36	48–108	253.78–558.32

** Cost of bolus dose plus range of maintenance dose*

Description of technology

The formation of the thrombus results from a complex interaction of the coagulation system and platelet homeostasis. Endogenous agonists and inhibitors in these systems maintain the normal balance between haemostasis and haemorrhage. Via the enzyme acetylating cyclooxygenase, aspirin inhibits formation of thromboxane (a platelet aggregator and vasoconstrictor), thus inhibiting platelet aggregation. By inhibiting adenosine 5'-diphosphate from binding to the platelet, ticlopidine and clopidogrel also act as antiplatelet drugs. Heparin increases anticoagulation and helps to limit the extension of an existing clot by binding to the natural anticoagulant antithrombin III and by reducing platelet function. Low-molecular-weight heparins work in a similar way, but because they are more selective in their binding, they provide a greater antithrombotic effect and reduced haemorrhagic complications. However, none of these drugs inhibit all the stimuli for platelet aggregation.

The glycoprotein IIb/IIIa receptor on the platelet surface is thought to be the final common pathway of platelet aggregation. The glycoprotein IIb/IIIa antagonists are a new class of drugs that may be more effective in preventing platelet aggregation. Abciximab is a monoclonal antibody targeted at the receptor, while the other drugs being considered here (e.g. eptifibatide and tirofiban) are more conventional pharmacological receptor antagonists.

Chapter 2

Methods

Search strategy and bibliographic databases used

The databases listed below were searched for reviews and studies of glycoprotein IIb/IIIa antagonists in relation to the treatment of unstable angina, using a range of keywords (see appendix 1 for details).

Internet resources

- Database of Abstracts of Reviews of Effectiveness (DARE) http://www.york.ac.uk/inst/crd/
- Development and Evaluation Committee (DEC) Reports http://cochrane.epi.bris.ac.uk/rd/
- Internet Database of Evidence-Based Abstracts and Articles (IDEA) Topic List http://www.ohsu.edu/bicc-informatics/ebm/ebm_topics/
- International Network of Agencies for Health Technology Assessment (INAHTA) published reports and ongoing reviews http://www.hta.nhsweb.nhs.uk/
- National Co-ordinating Centre for Health Technology Assessment http://www.hta.nhsweb.nhs.uk/
- National Guideline Clearinghouse http://www.ahcpr.gov/clinic/assess.htm
- NHS Economic Evaluations Database (NHSEED) http://www.york.ac.uk/inst/crd/
- School of Health and Related Research (ScHARR) Lock's Guide to the Evidence http://www.shef.ac.uk/uni/academic/R-Z/scharr/ir/scebm.html
- Scottish Health Purchasing Information Centre (SHPIC) Reports http://www.nhsconfed.net/shpic/
- Scottish Intercollegiate Guidelines Network (SIGN) Guidelines http://www.sign.ac.uk/
- Turning Research Into Practice (TRIP) Index (index to reviews, guidelines and evidence summaries) http://www.ceres.uwcm.ac.uk/frameset.cfm?section=trip

Paper resources

- Godlee F, editor. Clinical evidence: a compendium of the best available evidence for effective health care. Issue 2. London: *BMJ* Publishing Group; Dec 1999.

CD-ROM resources

- Cochrane Library (Version 2000, Issue 2)
- EMBASE (1980–2000/04)
- MEDLINE (1966–2000/05)
- National Research Register (Version 2000, Issue 2).

Online resources

- Conference Papers Index (CPI) (1973 onwards).

A general Internet search was also carried out. The National Institute for Clinical Excellence (NICE) approached the manufacturers (Lilly, Merck Sharp & Dohme, and Schering-Plough) to encourage them to submit any additional or unpublished data.

The Cochrane Heart Group and researchers, who were known to have published economic analyses in the area of coronary artery diseases, were contacted for further information.

Reference checking was accomplished by reviewing the bibliographies of all included studies to identify any further relevant data.

Inclusion and exclusion criteria

Interventions

The review included studies of glycoprotein IIb/IIIa antagonists that were not used in close association with angioplasty.

The intravenous drugs included:

- abciximab (ReoPro®, Eli Lilly and Company, USA)
- eptifibatide (Integrilin®, COR Therapeutics Inc. and Schering-Plough Corporation, USA)
- tirofiban (Aggrastat®, Merck & Company Inc., USA)
- lamifiban.

The oral drugs included:

- sibrafiban
- orbofiban
- lefradafiban.

Other interventions

In the included studies, the direct comparator to the glycoprotein IIb/IIIa antagonists was placebo, aspirin or heparin. Aspirin and unfractionated heparin are the standard treatment, and were generally given in addition to the glycoprotein IIb/IIIa antagonist.

Participants

The participants in the included studies were patients presenting with unstable angina or ACS, defined as increasing angina, rest angina, new-onset angina, variant angina (ST elevation), non-Q-wave MI and post-MI angina (> 24 hours after MI).

Outcomes

The outcomes in the included studies were:

- acute MI
- severe recurrent angina
- overall mortality
- haemorrhagic stroke
- fatal bleeding episode
- major bleeding episode
- minor bleeding episode
- any bleeding
- thrombocytopenia
- cost-effectiveness ratios, cost–utility ratios, cost–benefit ratios and cost differences.

Design

Only studies with the following designs were included:

- randomised clinical trials
- economic analyses (i.e. cost-effectiveness, cost-minimisation, cost–utility or cost–benefit analyses).

Data extraction strategy

Two reviewers assessed all the titles and abstracts found by the searches in order to identify all potentially eligible studies using an over-inclusive approach, so as not to miss potentially relevant reports. An efficacy paper was deemed potentially relevant if it met all the following criteria:

- was a randomised trial
- reported on the use of a glycoprotein IIb/IIIa antagonist as primary treatment
- studied patients with unstable angina or ACS (based on any definition).

It should be noted that studies in which glycoprotein IIb/IIIa antagonists were investigated as adjunctive drugs in planned angioplasty procedures were excluded. In case of uncertainty, the full papers were obtained.

An economic evaluation was eligible for inclusion if it reported on one of the following:

- cost-effectiveness analysis (including cost-minimisation analysis)
- cost–utility analysis
- cost–benefit analysis of the use of one or more glycoprotein IIb/IIIa antagonists in patients with unstable angina or ACS, but not as an adjunct in planned angioplasty procedures.

After the full papers were obtained, two reviewers independently assessed them against the inclusion criteria. Disagreements were registered and then resolved by discussion.

The data of all included studies were extracted into tables independently by two reviewers. A third reviewer resolved any discrepancies.

Quality assessment strategy

All trials included in the review were assessed using a list of items indicating components of internal validity in a standardised fashion. This list was pretested on a small sample of excluded studies addressing the appraisal topic. In addition, details on treatment, patients in-cluded and outcome phenomena were registered. Finally, more descriptive information was collected, such as the year of publication and language. Two reviewers independently scored the internal validity items. Discordant scores resulting from obvious reading errors were corrected. Discordant scores resulting from real differences in interpretation were resolved through consensus. A third reviewer resolved any remaining discrepancies. The reviewers were not blinded for names of authors, institutions, journals or the outcomes of the trials.

All economic analyses were assessed in a similar fashion by one reviewer, who used an established checklist for evaluating the methods of various types of economic analysis.[19] Three trained economists checked a sample of the assessments, and any discrepancies were discussed.

Synthesis and analysis

For efficacy and economic papers, the results of the data extraction and assessment of study validity are presented in structured tables and as a narrative description. For efficacy papers, the results are also presented as forest plots. Both beneficial and adverse effects are discussed in the light of study quality.

Heterogeneity of studies has been assessed by clinical judgements of differences regarding:

- patients enrolled
- interventions
- outcome phenomena
- study quality
- costs.

Chapter 3

Search results

Literature searches

The literature searches identified 871 articles relating to glycoprotein IIb/IIIa antagonists and unstable angina. After independent assessment against the inclusion criteria by two reviewers, it was agreed that 123 full papers would be obtained. Of these papers, 79 were background articles, 18 were economic papers, and 27 appeared to be reports of relevant randomised trials of efficacy. On closer examination, an additional 13 of the economic papers and five of the randomised trials of efficacy papers were rejected (see appendix 2), leaving five economic papers and 22 efficacy papers.

The total number of 22 efficacy papers includes duplicate publications and subgroup analyses (*Table 2*). For abciximab, no randomised trials were found regarding its use in conjunction with PCI only. Papers addressing glycoprotein IIb/IIIa antagonists in conjunction with PCI were excluded (see *Inclusion and exclusion criteria* in chapter 2).

TABLE 2 *Efficacy papers on intravenous and oral glycoprotein IIb/IIIa antagonists*

Drug	Number of papers	Number of trials
Abciximab	0	0
Eptifibatide	8	2
Tirofiban	5	2
Lamifiban	4	3
Sibrafiban	3	2
Orbofiban	1	1
Lefradafiban	1	1
Total	22	11

Chapter 4

Efficacy of intravenous glycoprotein IIb/IIIa antagonists

Seventeen papers were identified that evaluated the effectiveness of **intravenous** glycoprotein IIb/IIIa antagonists for the treatment of unstable angina and ACSs. These papers pertained to seven randomised clinical trials (two Phase II, one Phase II/III and four Phase III):

- Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM)[20]
- PRISM in Patients Limited to Very Unstable Signs and Symptoms (PRISM-PLUS)[21]
- Multicentre trial of Integrilin by Schulman and co-workers[22]
- Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT)[23–27]
- Canadian Lamifiban Study by Théroux and co-workers[28]
- Platelet IIb/IIIa Antagonist for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON)[29]
- PARAGON B.[30]

For clarification, the first PARAGON study will be referred to as PARAGON A. The two PRISM studies evaluated tirofiban. The Schulman and PURSUIT studies evaluated eptifibatide (Integrilin), and the Théroux and PARAGON studies evaluated lamifiban. No Phase II studies of tirofiban were located.

All seven of these studies were randomised controlled trials (*Table 3*). All the trials included patients with unstable angina or non-Q-wave MI. However, there was variation in the definition of unstable angina used. Exclusion criteria primarily attempted to remove patients with evolving or completed MI or at risk of serious bleeding. The Schulman and Théroux studies were Phase II studies exploring safety and dosing, while the PURSUIT, PRISM, PRISM-PLUS and PARAGON studies were Phase III studies. PARAGON A was intended to be a dose-finding study that led to PARAGON B, which was a Phase III efficacy study.

Follow-up duration varied between the trials, ranging from 24 hours to 1 year (*Table 3*). However, there was also variation in the primary end-point of the trials: 24 hours (Schulman and co-workers), 48 hours (PRISM), 96 hours (PURSUIT), 7 days (PRISM-PLUS) and 30 days (PARAGON A and B). The length of follow-up for the Théroux study was the infusion time for the study drug, which was at least 72 hours. The length of follow-up in the Schulman trial was reported to be 24 hours for recurrent ischaemia. The time-point for other outcomes was assumed to be 24 hours but was not stated. The inclusion and exclusion criteria, as defined by each trial, are reported in *Table 4*.

Interventions

The randomised study interventions are described in *Table 5*. Schulman and co-workers' Phase II study of eptifibatide used much lower doses than the Phase III PURSUIT study. The Schulman study[22] compared 'high'-dose eptifibatide, 'low'-dose eptifibatide and aspirin (325 mg daily). The patients assigned to the study drug were also given placebo aspirin capsules daily. All participants received unfractionated intravenous heparin. In the PURSUIT trial,[23–27] 'high' and 'low' doses of eptifibatide were also used, but the bolus dose in the 'low'-dose group was twice that of the 'high' dose in the Schulman trial. The control group in the PURSUIT trial was given placebo eptifibatide, and all other treatments (i.e. aspirin and heparin) were left to the discretion of the physician treating the patient. The 'low'-dose group, which was used only for establishing safety, was dropped after 3218 patients had been randomly assigned and the safety of the 'high' dose had been established.

The two trials of tirofiban (PRISM[20] and PRISM-PLUS[21]) compared tirofiban with heparin. The PRISM-PLUS study also included a tirofiban-plus-heparin arm, at a lower dose of tirofiban. The tirofiban-only arm of PRISM-PLUS was stopped early by the Data and Safety Monitoring Board, due to greater numbers of deaths and composite end-points. However, the data up to the discontinuation of this arm are presented here.

TABLE 3 *Designs of included studies of intravenous glycoprotein IIb/IIIa antagonists*

Study	Design/phase	Treatment arms	Number of participants	Follow-up time-points
Schulman *et al.*, 1996[22]	RCT Phase II	Low-dose eptifibatide High-dose eptifibatide Aspirin	77 76 74	24 hours
PURSUIT, 1998[23–27]	RCT Phase III	Eptifibatide Placebo (± aspirin or heparin)	4722 4739	96 hours 7 days 30 days
PRISM, 1998[20]	RCT Phase III	Tirofiban Heparin	1616 1616	48 hours 7 days 30 days
PRISM-PLUS, 1998[21]	RCT Phase III	Tirofiban Tirofiban + heparin Heparin	345 773 797	48 hours 7 days 30 days 6 months
Théroux *et al.*, 1996[28]	RCT Phase II	Lamifiban, 1 µg/minute Lamifiban, 2 µg/minute Lamifiban, 4 µg/minute Lamifiban, 5 µg/minute Placebo	40 41 120 41 123	During infusion 1 month
PARAGON A, 1998[29]	RCT Phase II/III	Low-dose lamifiban Low-dose lamifiban + heparin High-dose lamifiban High-dose lamifiban + heparin Placebo + heparin	378 377 396 373 758	30 days 6 months 1 year
PARAGON B, 1999[30]	RCT Phase III	Lamifiban Placebo	2628 2597	30 days 6 months

RCT, randomised controlled trial

The Théroux,[28] PARAGON A[29] and PARAGON B[30] studies used bolus doses of lamifiban ranging from 150 µg (Théroux) to 750 µg (PARAGON A) and infusions ranging from 1 µg/minute to 5 µg/minute (Théroux and PARAGON A). The final bolus dose chosen for PARAGON B was 500 µg, and the infusion dosage range was 1–2 µg/minute.

Baseline characteristics

Table 6 presents the baseline characteristics of the participants in each study, including the mean age and the proportion of patients with prognostic indicators. The mean age was very similar across the seven trials and was substantially lower than in routine clinical practice, ranging from 61 to 67 years. The Schulman study had more patients with a history of a prior MI, PCI or CABG than any of the other trials, with the exception of previous MIs in the Théroux study. The PURSUIT and PARAGON A studies had the least numbers of participants who had experienced these events.

Secondary drugs

Heparin and aspirin

The studies differ in the use of the secondary drugs, heparin and aspirin (*Table 7*). The use

of heparin and aspirin both before and after randomisation could also be important in determining outcome. Although heparin and aspirin were often required by the study protocols after randomisation, some protocols left the decision of their use up to the treating physicians. In the Schulman trial, all the patients received intravenous heparin (non-adjusted dose) but were randomised to aspirin or eptifibatide. In the PURSUIT study, all the patients received aspirin but heparin use was left to the discretion of the treating physicians. If heparin was used, the protocol stipulated that the dose be adjusted to produce an aPTT of 50–70 seconds. Both PRISM and PRISM-PLUS required adjusted-dose intravenous heparin and initially aspirin therapy. The PRISM study required aspirin only for the first 48 hours, after which its administration was left to the treating physician's judgement. In all three of the lamifiban studies, all the patients received aspirin but doses varied. The Théroux study and PARAGON B allowed heparin use to be specified by the treating physicians, while the PARAGON A study randomised the patients to heparin or no-heparin conditions. The reported rates of aspirin and heparin use, both before and after randomisation, in each of the trials are listed in *Table 7*.

The proportion of patients receiving aspirin prior to enrolment was reported to be 86–100%, while the proportion with prior use of heparin was 18–26%. However, four studies did not report this information. The use of aspirin after randomisation ranged from 93% to 100%, although the studies that required aspirin use did not report the rate of compliance (Schulman, PRISM and PRISM-PLUS). The range and variation in the proportions of patients receiving heparin after enrolment were broad and difficult to interpret. The Théroux study reported the lowest rates, ranging from 18% to 22%, plus "an additional 6% were given intravenous heparin together with the study medication. This was evenly distributed among the treatment arms." In the PURSUIT study, further variation was reported based on geographical location, in that the North American study sites reported the use of heparin in 97% of patients, compared with 77% reported by the South American sites.

Anti-anginal medications

Anti-anginal medications used prior to randomisation may be used to identify the severity of pre-existing disease, and their use after randomisation could have an effect on outcomes. In large, properly randomised trials, one may assume comparable use of anti-anginal medications at baseline. Therefore, the presentation of data on their use during the trial is more important than the baseline data. Imbalances occurring during the trial may be due to chance, treatment side-effects or problems with blinding. However, non-occurrence of imbalances does not of course rule out these phenomena.

The three drug classes considered to be anti-anginal medications are nitrates, calcium channel blockers and beta-adrenergic blockers. There was fairly wide variation in their use across the studies. No data on previous use of these medications was presented in the PURSUIT or PARAGON A studies, although data on their use during the PARAGON A trial were presented. No information on the use of these drugs was presented in the abstract on the PARAGON B study. *Table 8* presents the proportions of participants in each study arm that reported taking each of the three identified anti-anginal medications at baseline.

In one of the various subgroup analyses, the PRISM-PLUS study found that the effect of tirofiban appeared to be modified by previous use of beta blockers. More specifically, tirofiban appeared to have no effect on the composite end-point at 7 days among patients who had not been taking beta blockers prior to study ntry. The PRISM researchers did not present such an analysis.

The use of anti-anginal drugs **after** randomisation is reported in *Table 9*. Only the PRISM, PRISM-PLUS and PARAGON A studies reported the rates of use of the three drug classes after randomisation. The other four studies did not report on anti-anginal medication use after randomisation.

Definition of outcomes

For the studies reviewed here, the definition of outcomes may be critical. While new ST-T changes were required for the diagnosis of a new MI in four of the studies, the timing and other indicators of MI differed (*Table 10*). The PURSUIT study in particular has been criticised for using a definition of MI that is considered too loose. This issue is further explored below (see *PURSUIT study, Myocardial infarction*).

A composite end-point was considered in all the studies. In viewing stable angina, unstable angina, MI and death as points on a continuum, a composite end-point may be an acceptable way to evaluate the drugs. The definitions of the composite end-points, however, were not consistent across the studies.

Internal validity

The assessment of the internal validity of these studies is presented in *Table 11*. Many items were assigned a question mark, which may reflect poor reporting only and does not necessarily indicate poor study design or study conduct.

The validity assessment of the trials reveals three areas that were consistently not addressed in the published articles. The selection of prognostically homogeneous subpopulations and prestratification based on prognostically relevant variables attempt both to avoid heterogeneity of groups and to make very clear to which group of patients these data pertain. Although tables of baseline characteristics of patients enrolled were included in all the trial reports, it is difficult to determine if the groups were truly homogeneous. Prestratification based on variables known to be prognostically important would involve stratifying at randomisation in smaller trials or stratifying by centre in multicentre trials.

The extent to which blinding was successful was not reported in any of the trials. This may be an important factor, particularly in trials involving randomisation to and blinding of heparin administration. Inadvertent unblinding through the reporting of unblinded aPTT values, for example, could have an impact on the evaluation of outcomes. Although one trial did attempt to improve the concealment of randomisation by using a bedside device to monitor aPTT (PARAGON A), the success of this approach was not reported.

The lack of description of how missing values were handled is cause for concern. Among large multicentre trials, it is difficult to accept that there were no missing values. The description of the number of missing values as well as how they were dealt with in the analysis could have a significant impact on the interpretation of the results.

Compliance with the intravenous therapies (i.e. the number of missed doses) was not reported in the trials. The numbers of participants who dropped out or were lost to follow-up were not reported in any of the trials, except PARAGON A. All the other analyses were conducted as if there were no participants lost to follow-up. In the PARAGON A study, 3.2% of the participants were lost to follow-up at 6 months, and 6.7% at 1 year. The numbers lost in each treatment group were not specified. Those 'lost to follow-up' at 6 months were defined as participants who were removed from the analysis because they had not had an event and had a follow-up time of less than 120 days.

Differences between trials

The differences between the trials with regard to drugs studied, dosages used, type of patients enrolled, co-treatment strategies, end-point definitions, composite end-point composition, timing of end-point assessment and study validity probably make any pooling of study results inappropriate or hazardous. For example, the PRISM study enrolled patients with symptoms in the previous 24 hours, whereas the PRISM-PLUS study enrolled patients with symptoms in the previous 12 hours. Short-term cohort effects may easily cause great prognostic differences between the two control (heparin-treated) groups in the trials. The introduction of patients who survived an extra 12 hours before entering the PRISM study may have improved overall prognosis in that study. Furthermore, in the PRISM study, it was recommended that treatment with tirofiban be stopped if revascularisation was performed, whereas the PRISM-PLUS study stipulated continued administration of the study drugs.

In general, more details on study methods and fewer details on study outcomes would greatly enhance the studies' utility for decision-making. With the exception of the Schulman trial, all the studies used blinded end-point committees to determine outcomes. However, in the PURSUIT study, the local investigators assessed the outcomes at 6 months. Therefore, measurement bias does not seem to be an issue in the outcome measurement before 6 months in these trials.

The validity assessment of individual trials is discussed in *Results of trials* below.

TABLE 4 *Inclusion and exclusion criteria from published texts*

Study/drug	Inclusion criteria	Exclusion criteria
Schulman *et al.*, 1996[22] Eptifibatide	Men and women with unstable angina (age range, 21–80 years). Unstable angina was defined as the recent onset of a changing pattern of cardiac ischaemic symptoms at rest, with one episode lasting at least 10 minutes and occurring within 24 hours of randomisation. In addition, all participants had transient ST-segment depression or elevation in two or more ECG leads during an episode of pain, or if an ECG was not obtained during an episode of ischaemic pain, they had known CAD on the basis of previous MI or cardiac catheterisation	Suspected MI in evolution, prior CABG surgery within 6 months, coronary angioplasty within 72 hours, thrombolytic therapy within 7 days, major surgery within 6 weeks, a history of cerebrovascular disease, major GI or GU bleeding within 30 days, significant thrombocytopenia (platelet count < 100,000/mm^3), coagulopathy (receiving warfarin or bleeding time > 20 minutes), and if they presented with severe hypertension (systolic blood pressure > 180 mmHg or diastolic blood pressure > 120 mmHg) or had renal insufficiency with a creatinine level > 4 mg/dl
PURSUIT, 1998[23–27] Eptifibatide	Symptoms of ischaemic chest pain at rest, lasting 10 minutes or longer, within the previous 24 hours. Must also have transient ST-segment elevation of > 0.5 mm, transient or persistent ST-segment depression of > 0.5 mm, T-wave inversion of > 1 mm within 12 hours before or after chest pain, or a serum concentration of CK-MB isoenzyme that was above the upper limit of normal for the hospitals where they were evaluated	Persistent ST-segment elevation of > 1 mm, active bleeding or a history of bleeding diathesis, GI or GU bleeding within 30 days before enrolment, systolic blood pressure > 200 mmHg or diastolic blood pressure > 110 mmHg, a history of major surgery within the previous 6 weeks, a history of non-haemorrhagic stroke within the previous 30 days or any history of haemorrhagic stroke, renal failure, pregnancy, the planned administration of a platelet glycoprotein IIb/IIIa inhibitor or thrombolytic agent, or the receipt of thrombolytic therapy within the previous 24 hours
PRISM, 1998[20] Tirofiban	Patients who had their most recent episode of chest pain at rest or accelerating chest pain within 24 hours of randomisation. CAD was defined as one of the following: (1) electrocardiographic evidence of myocardial ischaemia in two contiguous leads during an episode of chest pain with new, persistent or transient ST-segment elevation (lasting < 20 minutes) of 0.1 mV or more; (2) elevated cardiac enzyme levels consistent with the occurrence of non-Q-wave MI; or (3) a history of MI, percutaneous revascularisation > 6 months earlier, coronary surgery > 1 month earlier, a positive exercise stress test or dipyridamole (or adenosine) nuclear stress test, or narrowing of at least 50% of the luminal diameter of a major coronary artery on a previous arteriogram	Patients were excluded if they had received thrombolytic therapy within the previous 48 hours or had allergy to or intolerance of heparin; a serum creatinine level > 2.5 mg/dl (221 µmol/l); an active bleeding disorder; a history of GI bleeding; haematuria; a positive faecal occult-blood test; known coagulopathy; a platelet disorder or a history of thrombocytopenia; persistent systolic blood pressure > 180 mmHg, diastolic blood pressure > 110 mmHg or both at the time of enrolment; a history of haemorrhagic cerebrovascular disease or an active intracranial pathological process; a history of cerebrovascular disease or transient ischaemic attack within the previous year; a major surgical procedure within the previous month; active peptic ulceration within the previous 3 months; or an invasive procedure within 14 days before enrolment that would substantially increase the risk of haemorrhage
PRISM-PLUS, 1998[21] Tirofiban	Prolonged anginal pain or repetitive episodes of angina at rest or during minimal exercise in the previous 12 hours and new transient or persistent ST-T ischaemic changes on the ECG (ST-segment elevation or depression of 0.1 mV or more, T-wave inversion of 0.3 mV or more in three or more limb leads or four or more precordial leads excluding V1, or pseudonormalisation of 0.1 mV or more) or an elevation of plasma levels of CK and the CK-MB fraction	ST-segment elevation lasting > 20 minutes, thrombolysis in the previous 48 hours, coronary angioplasty within the previous 6 months or bypass surgery within the previous month, angina caused by identifiable factors, a history of platelet disorder or thrombocytopenia, active bleeding or a high risk of bleeding, or stroke within the previous year. Patients who had serum creatinine values > 2.5 mg/dl or a platelet count < 150,000/mm^3 were also excluded

continued

TABLE 4 contd *Inclusion and exclusion criteria from published texts*

Study/drug	Inclusion criteria	Exclusion criteria
Théroux *et al.*, 1996[28] Lamifiban	Chest pain at rest or upon minimal exercise, ≥ 5 minutes in duration in the 24 hours preceding randomisation as well as evidence of CAD by either ECG ST-T changes, documentation of a previous MI, a thallium-201 exercise test or coronary angiography	Age > 75 years; unstable angina precipitated by identifiable factors or occurring within 6 months of coronary angioplasty or 2 months after bypass surgery; a previous stroke; a high bleeding risk, including trauma, surgery or active bleeding within the previous month, and shock; CHF; LBBB; uncontrolled hypertension (systolic blood pressure > 200 mmHg); a life-threatening concomitant illness; platelet count < 100,00/mm^3; the use of oral anticoagulants or of an investigational drug; the potential for pregnancy; or the inability to obtain informed consent
PARAGON A, 1998[29] Lamifiban	Chest discomfort associated with transient or persistent ST-segment depression (≥ 0.5 mm) or T-wave inversion, or transient (30 minutes) ST-segment elevation (≥ 0.5 mm)*	Receiving oral anticoagulants and an international normalised ratio > 1.5 x control; received thrombolytic therapy within 24 hours; had active significant bleeding; contraindications to aspirin or heparin; systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 100 mmHg despite treatment; serum creatinine level > 2.0 mg/dl (177 mmol/l); platelet count < 100,00/mm^3; cerebrovascular accident within the past year; any history of haemorrhagic stroke, tumour or intracranial aneurysm; angioplasty within the previous week; or GI bleeding, major surgery or trauma within 1 month. Women of childbearing potential were excluded unless the pregnancy test was negative. During the study, patients were discontinued if their serum creatinine was ≥ 2.0 mg/dl, the platelet count decreased by one-third and was < 100,000/mm^3, or important bleeding occurred
PARAGON B, 1999[30] Lamifiban	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	Not stated (abstract)

CABG, coronary artery bypass graft; GI, gastrointestinal; GU, genitourinary; CK-MB, creatine kinase, myocardial band; CHF, congestive heart failure; LBBB, left bundle branch block

* *10 mm = 1 mV (ECG)*

TABLE 5 *Interventions specified by study protocols*

Study	Intervention 1	Intervention 2	Control
Schulman *et al.*, 1996[22]	High-dose eptifibatide,* bolus of 90 µg/kg, followed by 1.0 µg/kg/minute, plus placebo aspirin	Low-dose eptifibatide, bolus of 45 µg/kg over 3 minutes, followed by 0.5 µg/kg/minute continuous infusion, plus placebo aspirin	Aspirin, 325 mg/day, initiated immediately upon randomisation, plus placebo eptifibatide
	Study drug was given for 24–72 hours, but it was discontinued if cardiac catheterisation, angioplasty or cardiac bypass was performed. After termination of study drug, all patients received oral aspirin, 325 mg. All patients also received standard medical therapy, including heparin, 5000-unit bolus, followed by continuous infusion, with dose adjusted to maintain the aPTT between 1.5 and 2.5 times the control value		
PURSUIT, 1998[23–27]	Eptifibatide, bolus of 180 µg/kg, followed by infusion of 2.0 µg/kg/minute	Eptifibatide, bolus of 180 µg/kg, followed by infusion of 1.3 µg/kg/minute†	Placebo bolus and infusion
	Study drug was given for 72 hours or until discharge, if earlier. The duration of infusion was extended to 96 hours if PCI was performed. Subcutaneous or intravenous adjusted-dose heparin was recommended but not required. Aspirin, 80–325mg/day, was given at the discretion of the treating physicians. If contraindicated or if the patient was intolerant to aspirin, ticlopidine could be given		
PRISM, 1998[20]	Tirofiban, 0.6 µg/kg/minute, for 30 minutes, followed by 0.15 µg/kg/minute for 47.5 hours, plus placebo heparin (5% dextrose). Random alterations were made in the placebo heparin administration rate	Adjusted-dose heparin plus placebo tirofiban (normal saline) for 48 hours. Heparin dose regimen: 5000-unit bolus, followed by 1000 units/hour, adjusted at 6 and 24 hours to maintain the aPTT at twice the control value	
	Aspirin, 325 mg/day, was administered to all patients before randomisation and daily for 48 hours, and thereafter at the discretion of the physician. Other medication, except NSAIDs, ticlopidine or warfarin, could be prescribed		
PRISM-PLUS, 1998[21]	Tirofiban, 0.6 µg/kg/minute for 30 minutes, followed by 0.15 µg/kg/minute, plus placebo heparin	Tirofiban, 0.4 µg/kg/minute for 30 minutes, followed by 0.1 µg/kg/minute, plus adjusted-dose heparin	Adjusted-dose heparin plus placebo tirofiban
	The drugs were infused for a minimum of 48 hours. Heparin dose regimen: 5000-unit bolus, followed by 1000 units/hour, adjusted after 6, 12, 24, 36 and 48 hours, and thereafter as needed, to maintain the aPTT at twice the control value. Random alterations were made in the placebo heparin administration rate. Aspirin, 325 mg, was administered to all patients at the time of randomisation and daily thereafter		
Théroux *et al.*, 1996[28]	Lamifiban, bolus of 150 µg, followed by 1 µg/minute	Lamifiban, bolus of 300 µg, followed by 2 µg/minute	Lamifiban, bolus of 600 µg, followed by 4 µg/minute	Lamifiban, bolus of 750 µg, followed by 5 µg/minute	Placebo
	Study drug was infused for 72–120 hours. Dose was reduced by 10% for patients < 70 kg, 20% if < 60 kg or 30% if < 50 kg. Aspirin, 325 mg, was administered to all patients at the time of randomisation and daily thereafter. Use of intravenous heparin was left to the discretion of the treating physician, but the decision had to be made prior to randomisation. Heparin dose was adjusted to maintain the aPTT at twice the control value. Anti-anginal drugs were recommended but not required		

continued

TABLE 5 contd *Interventions specified by study protocols*

Study	Intervention 1		Intervention 2		Control
PARAGON A, 1998[29]	Low-dose lamifiban, bolus of 300 µg, followed by 1 µg/minute	Low-dose lamifiban plus heparin	High-dose lamifiban, bolus of 750 µg, followed by 5 µg/minute	High-dose lamifiban plus heparin	Adjusted-dose heparin plus placebo lamifiban
	Study drugs were infused for a minimum of 3 days and a maximum of 5 days. If PCI was performed on day 5, an additional 12–24 hours was allowed. Heparin dose regimen: for patients > 80 kg, bolus of 5000 units, followed by infusion of 1000 units/hour; for patients < 80 kg, bolus of 60 units/kg, followed by infusion of 12 units/kg. A bedside aPTT-monitoring device was used to maintain blinding. Coded values obtained at the bedside were entered into a centralised computer by telephone. The computer decoded the aPTT and the randomisation of the patient, and returned instructions for adjusting the heparin/placebo infusion. The aPTT values were maintained within 60–85 seconds. Bedside aPTT monitoring was performed at intervals of 6–12 hours until therapeutic range was reached, then at least daily. All patients received aspirin, 80–325 mg, at enrolment and daily thereafter				
PARAGON B, 1999[30]	Lamifiban, bolus of 500 µg, followed by infusion, with dose adjusted based on renal function (range, 1–2 µg/minute, depending on creatinine clearance)				Placebo
	Study drug infused for 72 hours. All patients received aspirin and heparin (either unfractionated or low-molecular-weight heparin). Low-molecular-weight heparin was used in over one-third of the total cohort				

aPTT, activated partial thromboplastin time; NSAID, non-steroidal anti-inflammatory drug

[*] *The study drug was referred to as Integrilin in the Schulman study but will be referred to as eptifibatide here*

[†] *Patients receiving low-dose eptifibatide stopped treatment early, so data for the high-dose group only were presented and analysed*

TABLE 6 *Baseline characteristics of participants in studies of intravenous drugs*

Study	Prognostic indicators	Intervention 1	Intervention 2	Control
Schulman *et al.*, 1996[22]	Mean age (years)	64	61	61
	Previous MI (%)	59	53	53
	Previous PCI (%)	37	40	34
	Previous CABG (%)	37	22	28
	CHF (%)	15	12	12
PURSUIT, 1998[23–27]	Mean age (years)	64		64
	Previous MI (%)	32		33
	Previous PCI (%)	13		13
	Previous CABG (%)	12		12
	CHF (%)	11		11
	Angina at rest (%)	65		64
PRISM, 1998[20]	Mean age (years)	63	62	
	Previous MI (%)	47	47	
	Previous CABG (%)	17	18	
	Previous angioplasty (%)	14	16	
	Previous heart failure (%)	12	13	
PRISM-PLUS, 1998[21]	Mean age (years)	63	63	63
	Previous MI (%)	46	45	39
	Previous CABG (%)	17	16	13
	Previous angioplasty (%)	13	9	9
	Previous heart failure (%)	11	11	8
	ST-segment elevation (%)	15	15	13
	ST-segment depression (%)	57	57	60
	T-wave changes (%)	58	52	52

Théroux *et al.*, 1996[28]	Lamifiban infusion dose	1 µg/minute	2 µg/minute	4 µg/minute	5 µg/minute	Placebo
	Mean age (years)	59	63	61	61	59
	Previous MI (%)	58	41	50	54	63
	Ischaemic ECG (%)	60	68	67	59	67

PARAGON A, 1998[29]	Lamifiban dose, with or without heparin	Low dose only	Low dose + heparin	High dose only	High dose + heparin	Heparin only
	Mean age (years)	65	66	66	67	66
	Previous MI (%)	37	31	36	35	35
	Previous CABG (%)	10	11	11	10	11
	Previous angioplasty (%)	11	7	8	9	9
	Killip class I (%)	92	91	92	88	89
	Killip class II (%)	8	7	8	11	10
	Killip class III (%)	< 1	2	< 1	1	1

PARAGON B, 1999[30]	Few details reported. Nearly 60% of the patients had history of MI at study enrolment. Qualifying ECG showed ST depression in approximately 44% of patients in both groups and ST elevation in 15%

TABLE 7 *Rates of the administration of aspirin and heparin (by treatment arm)*

Study/drug	Before randomisation		After randomisation	
	Aspirin	**Heparin**	**Aspirin**	**Heparin**
Schulman *et al.*, 1996[22] Eptifibatide	88% (aspirin) 88% (low-dose eptifibatide) 86% (high-dose eptifibatide)	NS	Patients assigned by protocol to aspirin or placebo for 72 hours, then 100% to receive aspirin	100%
PURSUIT, 1998[23–27] Eptifibatide	NS	NS	92.7% (eptifibatide) 93.2% (placebo)	89.7% (eptifibatide) 89.9% (placebo)
PRISM, 1998[20] Tirofiban	94.9% (tirofiban) 94.3% (heparin)	25.4% (tirofiban) 25.7% (heparin)	100% assigned by protocol to aspirin for 48 hours. After 48 hours: NS	Patients assigned by protocol to heparin or placebo
PRISM-PLUS, 1998[21] Tirofiban	NS	NS	100% (by protocol)	Patients assigned by protocol to heparin or placebo for 48 hours. After 48 hours: 31.4% (tirofiban) 32.6% (heparin)
Théroux *et al.*, 1996[28] Lamifiban	100% (all groups)	20% (placebo) 20% (1 μg/minute) 22% (2 μg/minute) 18% (4 μg/minute) 22% (5 μg/minute)	100%	"An additional 6%, evenly distributed among the groups"
PARAGON A, 1998[29] Lamifiban	NS	NS	99–100% (all groups)	Patients assigned by protocol to heparin or placebo
PARAGON B, 1999[30] Lamifiban	NS	NS	"Ubiquitous"	90%

NS, not specified

TABLE 8 *Rates of the use of anti-anginal medications at baseline*

Study	Treatment arm	Nitrates (%)	Calcium channel blocker (%)	Beta blocker (%)
Schulman *et al.*, 1996[22]	High-dose eptifibatide	60	40	33
	Low-dose eptifibatide	64	46	38
	Placebo	57	38	40
PURSUIT, 1998[23–27]	–	–	–	–
PRISM, 1998[20]	Tirofiban	78	52	45
	Heparin	77	53	46
PRISM-PLUS, 1998[21]	Tirofiban	95	50	75
	Tirofiban + heparin	95	49	78
	Heparin	94	43	81
Théroux *et al.*, 1996[28]	Lamifiban, 1 µg/minute	88	70	70
	Lamifiban, 2 µg/minute	93	71	81
	Lamifiban, 4 µg/minute	87	58	81
	Lamifiban, 5 µg/minute	93	73	78
	Placebo	96	66	82
PARAGON A, 1998[29]	–	–	–	–
PARAGON B, 1999[30]	–	–	–	–

TABLE 9 *Rates of the use of anti-anginal medications after randomisation*

Study	Treatment arm	Nitrates (%)	Calcium channel blocker (%)	Beta blocker (%)
Schulman *et al.*, 1996[22]	–	–	–	–
PURSUIT, 1998[23–27]	–	–	–	–
PRISM, 1998[20]	Tirofiban	88	46	71
	Heparin	89	48	72
PRISM-PLUS, 1998[21]	Tirofiban	95	50	75
	Tirofiban + heparin	95	49	78
	Heparin	94	43	81
Théroux *et al.*, 1996[28]	–	–	–	–
PARAGON A, 1998[29] *	Low-dose lamifiban	75/67	42	69/5
	Low-dose lamifiban + heparin	73/70	42	73/6
	High-dose lamifiban	74/61	42	75/6
	High-dose lamifiban + heparin	74/68	42	71/7
	Placebo + heparin	76/67	45	73/7
PARAGON B, 1999[30]	–	–	–	–

* *Oral or topical/intravenous administration of nitrates or beta blocker*

TABLE 10 *Definitions of outcomes in trials of intravenous drugs*

Study	Acute MI	Severe recurrent angina/ refractory ischaemia	Composite end-point
Schulman *et al*., 1996[22]	Not defined	Ischaemic pain unresponsive to standard anti-ischaemic therapy and requiring intra-aortic blood counterpulsation, emergency catheterisation and angioplasty, or morphine sulphate	Not defined
PURSUIT, 1998[23–27]	***< 18 hours after enrolment*** Chest pain with ST-T changes (depression or elevation) in two continuous leads for > 30 minutes ***> 18 hours after enrolment*** CK-MB fraction above the upper limit of normal, total CK more than twice the upper limit or new Q waves	Not defined	Death from any cause and new MI
PRISM, 1998[20]	New episode of chest pain with: 1. new ST-T changes 2. new pathological Q waves > 0.03 seconds 3. changes 1 and 2 (above) with serum CK more than twice the upper limit Patients with non-Q-wave MI at enrolment: increase of total CK by 50% or more between two blood samples and more than twice the normal value Non-Q-wave MI was classified after enrolment when: CK exceeded twice the normal value or the CK-MB fraction was above the upper limit in first 24 hours	1. Recurrent anginal chest pain with ischaemic ST-T changes (new ST-segment depression or elevation of at least 0.1 mV or T-wave inversion in two contiguous leads) lasting 20 minutes or more, or two episodes lasting at least 10 minutes, each within a 1-hour period, despite full medical therapy 2. Haemodynamic instability attributed to ischaemia, as evidenced by pulmonary oedema (new rales over one-third of the lung fields or tachypnoea lasting > 30 minutes), systolic blood pressure < 95 mmHg that was not related to medication, or a need for inotropic agents	Death from any cause, and new MI and refractory ischaemia
PRISM-PLUS, 1998[21]	A new episode of chest pain at least 20 minutes in duration with new ST-T changes, or both a rise n serum CK level to two times the upper limit of normal or higher (three times the upper limit of normal when infarction was related to coronary angioplasty) and elevated CK-MB values. An evolving MI at study entry was defined as a new increase in CK and CK-MB levels to > 50% above the previous value after an initial peak. A perioperative MI was defined as new Q waves	1. Chest pain 20 minutes or more in duration or two episodes of chest pain, each lasting 10 or more minutes within a 1-hour period, with transient ST-T changes while the patient was receiving medical therapy adjusted according to heart rate and blood pressure 2. Recurrent ischaemia with pulmonary oedema or hypotension 3. Repetitive chest pain (three or more episodes, each lasting 5 minutes or more) necessitating intra-aortic counterpulsation, urgent intervention or both within 12 hours	Death from any cause, new MI or refractory ischaemia within 7 days after randomisation. Rehospitalisation for unstable angina was included at 7 days, 30 days and 6 months

continued

TABLE 10 contd *Definitions of outcomes in trials of intravenous drugs*

Study	Acute MI	Severe recurrent angina/ refractory ischaemia	Composite end-point
Théroux *et al.*, 1996[28]	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	Ischaemia at rest or minimal exercise, with objective documentation of ischaemic ST changes	Death, MI or ischaemia requiring intervention (PCI or CABG)
PARAGON A, 1998[29]	Not defined	Not a reported end-point in this trial	All-cause mortality and non-fatal MI (or re-infarction)
PARAGON B, 1999[30]	Not reported separate to composite end-point	Not a reported end-point in this trial	Death and MI

TABLE 11 *Assessment of internal validity*

	Schulman, 1996[22]	PURSUIT, 1998[23–27]	PRISM, 1998[20]	PRISM-PLUS, 1998[21]	Théroux, 1996[28]	PARAGON A, 1998[29]	PARAGON B, 1999[30]
Internal validity							
Selection of prognostically homogeneous study population	?	?	?	?	?	?	?
Pre-stratification based on prognostically relevant variables	?	?	?	?	?	?	?
Random allocation: random sequence generation	?	+	?	±	+	?	?
Random allocation: concealment of allocation	±	+	±	±	+	?	?
Registration of loss to follow-up	±	+	±	+	+	–	?
Blinding of patients	±	±	+	±	±	±	?
Blinding of persons implementing interventions	±	±	±	±	±	±	?
Registration of co-interventions that affect outcome for each group	±	?	+	+	±	+	?
Blinding of persons assessing treatment effects	?	+	+	?	+	+	+
Checking to what extent blinding was successful	?	?	?	?	?	?	?
Data description and analysis							
Measures of central tendency and their CIs (or dispersion)	+	+	+	+	+	+	+
Statistical methods	+	+	+	+	+	+	±
Method of dealing with missing values	?	?	?	?	?	?	?
Intention-to-treat analysis	+	+	+	+	+	–	?
Distributions of baseline characteristics	+	+	+	+	±	±	?
Method of accounting for any imbalances in prognostic variables	±	±	+	+	–	±	?

CI, confidence interval

+, item properly addressed; ±, item partially addressed; –, item not properly addressed; ?, unknown

Results of trials

The results of the drug trials are presented below by drug (eptifibatide, tirofiban and lamifiban). In *Tables 12* and *13*, the bold data indicate the primary outcome for that trial. In the plots of risk difference, the vertical line (at 0) indicates the 'no-effect' line. For the study results illustrated in a plot, a rectangle represents the 95% CI around the mean. The 95% CI is the interval which one is 95% certain contains the true population value, as it might be estimated from a much larger study. If a rectangle crosses the 'no-effect' line, the difference is not statistically significant. The scale specifies the percentage risk difference (absolute risk difference multiplied by 100). The rectangles are shaded (by time-point) if they are from Phase III studies and clear if from Phase II studies. The different time-points assessed are represented by the distinct shading of the boxes.

It is impossible to estimate the extent or even the direction of bias that may be present in the estimates; however, considering the validity assessment of these trials, bias could exist. Clinically relevant effect sizes and their precision are therefore emphasised, and statistical significance at the 5% level is de-emphasised. In this report, the risk difference estimates at 30 days and later were considered more relevant than those at 48 and 96 hours and at 7 days.

Eptifibatide

Schulman study

The Schulman study[22] (*Table 12*) refers to the study drug as Integrilin, which is now the brand name of eptifibatide. This Phase II study appeared to have lower internal validity than the Phase III studies reviewed because, in addition to the items that were not addressed in all studies, random sequence allocation and blinding of persons assessing outcomes were not addressed (*Table 11*). The Schulman study also had a number of items that were only partially addressed, such as registration of co-interventions that affect outcome for each group (e.g. anti-anginal drugs). However, this study did describe in detail the numbers of and reasons for patients not being included in the primary end-point analysis.

The primary end-point for this study was ischaemia identified by Holter monitoring. The number of participants evaluable by Holter monitoring was

TABLE 12 *Results of study by Schulman* et al., *1996[22] (the trial's primary outcome is shown in* ***bold****)*

Treatment arm	Time-point	MI		Recurrent ischaemia		Death		Composite end-point	
		n	%	*n*	%	*n*	%	*n*	%
Low-dose eptifibatide (*n* = 77)	**24 hours**	1	0.8	**1**	**0.8**	0	0.0	2	1.5
High-dose eptifibatide (*n* = 76)	**24 hours**	0	0.0	**1**	**0.8**	0	0.0	1	0.8
Placebo (*n* = 74)	**24 hours**	1	0.7	**4**	**3.0**	0	0.0	4	3.0

TABLE 13 *Results of PURSUIT study, 1998[23–27] (the trial's primary outcome is shown in* ***bold****)*

Treatment arm	Time-point	MI		Death		Composite end-point	
		n	%	*n*	%	*n*	%
Eptifibatide (*n* = 4722)	**96 hours**	**335**	**7.1**	42	0.9	**359**	**7.6**
	7 days	439	9.3	71	1.5	476	10.1
	30 days	595	12.6	16	3.5	670	14.2
	6 months					836	17.7
Placebo (*n* = 4739)	**96 hours**	**393**	**8.3**	57	1.2	**431**	**9.1**
	7 days	493	10.4	95	2.0	550	11.6
	30 days	640	13.5	17	3.7	744	15.7
	6 months					896	18.9

57 in the aspirin group, 54 in the low-dose eptifibatide group and 58 in the high-dose eptifibatide group. There were 58 patients who were not evaluable by Holter monitoring for the following reasons (*n*): study drug not received by patient (4), missing data (2), abnormal baseline ST segment on Holter monitoring (27), malfunction of Holter monitoring (13), wrong study drug received by patient (3), wrong infusion rate (4), and eligibility violation such as MI (4) or anaemia (1). The absolute risk difference for ischaemic events in the high-dose eptifibatide group versus the aspirin group was –1.1 (95% CI, –2.5 to 2.8). The absolute risk difference for the low-dose eptifibatide group versus the aspirin group was –0.68 (95% CI, –16.0 to 14.8).

While other end-points are reported (*Table 12*), they were not the primary outcome measures. The composite end-point reported here refers to any outcome: refractory ischaemia; MI; need for morphine, intra-aortic balloon pump, emergency cardiac catheterisation or percutaneous transluminal angioplasty (PTCA); or death.

PURSUIT study

The PURSUIT study[23–27] (*Table 13*) evaluated eptifibatide versus placebo while recommending intravenous or subcutaneous heparin for all patients. Additionally, all patients received aspirin (80–325 mg/day). The primary end-point was MI, death or composite endpoint at 96 hours. The validity assessment of the PURSUIT study indicates that it is one of the better studies in terms of the methodological quality. Registration of co-interventions, however, was also not addressed in this study. Because heparin and aspirin were given at the discretion of the treating physicians, these data could have been important; the authors, in response to letters to the journals editors, later reported these data. Data on the use of anti-anginal medications, before or after enrolment, were not reported. Also unclear was the success of blinding of patients and of persons assessing treatment effects.

Death from any cause

The effect of eptifibatide on death is presented in *Figure 1*. The Schulman study did not have any deaths in any group in the 24-hour period reported. In the PURSUIT trial, the risk difference for death from any cause at 30 days was –0.2% (95% CI, –1.0% to 0.6%).

Myocardial infarction

The effect of eptifibatide on MI is presented in *Figure 2*. The incidence of MI reported here includes fatal and non-fatal MI. The risk difference for new MI at 30 days was –0.9% (95% CI, –2.3% to 0.5%).

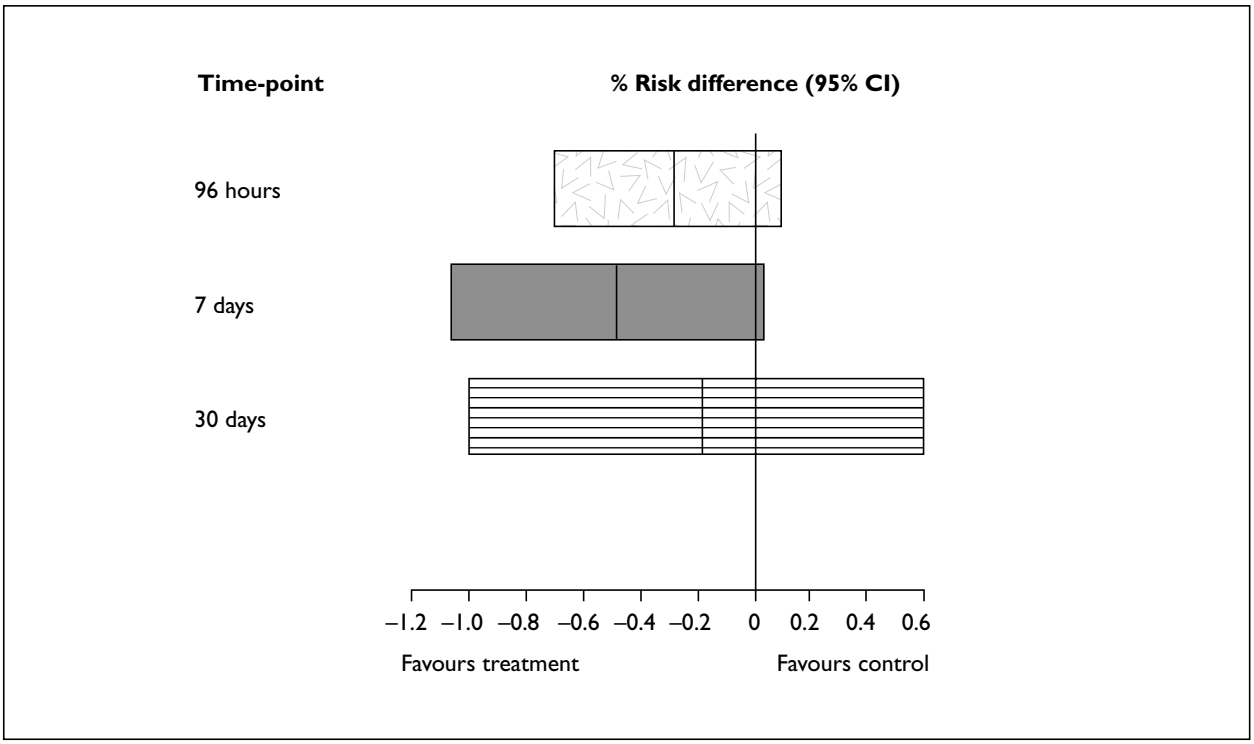

FIGURE 1 *PURSUIT trial[23–27] of eptifibatide versus placebo: mean risk differences for outcome of death*

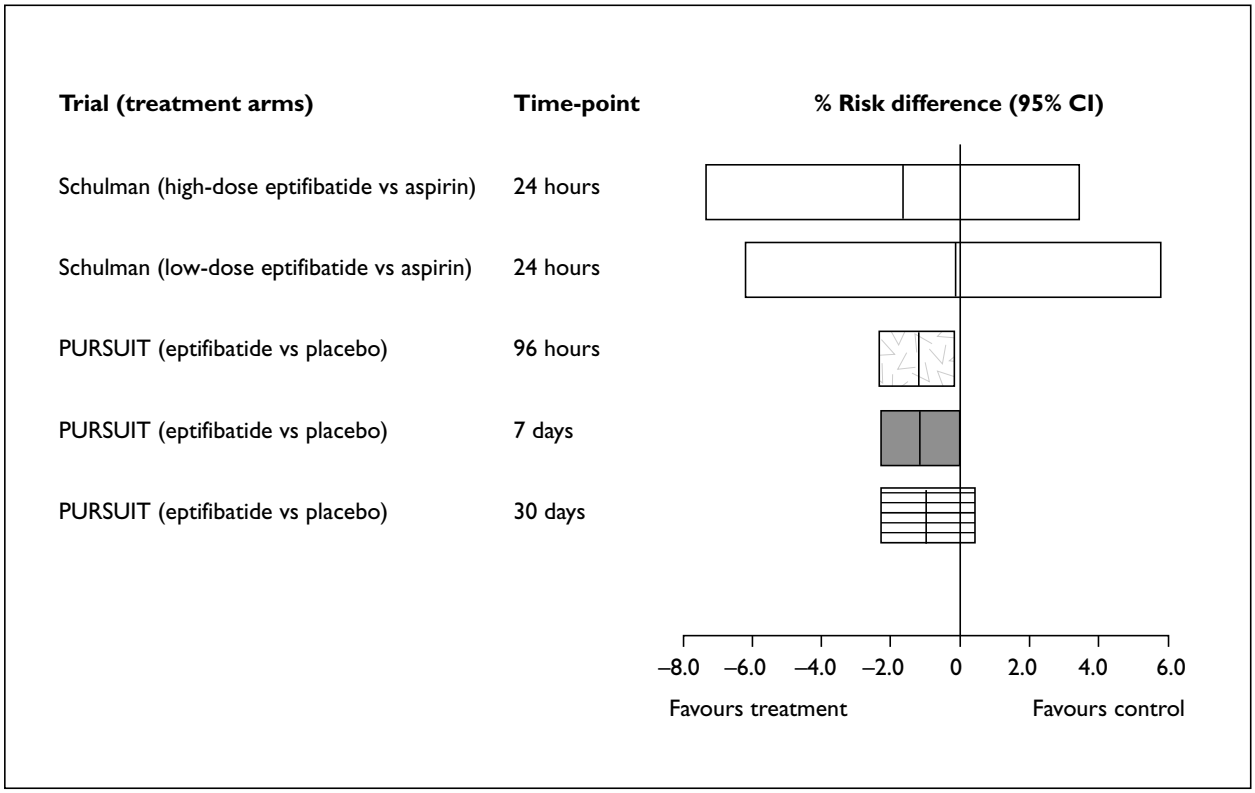

FIGURE 2 *Schulman[22] and PURSUIT[23–27] trials of eptifibatide: mean risk differences for outcome of MI*

In the PURSUIT study, eptifibatide was not significantly better than placebo in preventing MI at 7 or 30 days. A blinded Clinical Events Committee judged MIs in this study at 48 hours, 7 days and 30 days. The local investigators at the study sites determined the MIs at the 6-month time-point. The CK-MB portion of the definition of MI occurring 18 hours or more after randomisation (CK-MB fraction above normal limit) is considered controversial because, in clinical practice and in other studies, a CK-MB fraction greater than double or triple the normal limit is required.

Composite end-point

Death or non-fatal MI was the composite end-point identified in the PURSUIT study. The Kaplan–Meier survival curves of the combined end-points of death or non-fatal MI up to day 30 showed a statistically significantly difference (log-rank test, $p = 0.03$). The effect of eptifibatide on this composite end-point is presented in *Figure 3*. The risk difference at 30 days was –1.5% (95% CI, –2.9% to –0.1%), with a number needed to treat (NNT) of 68 (95% CI, 35 to 1919).

A re-analysis of the 96-hour data for **death and non-fatal MI** using other definitions of MI (as defined in *Table 14*) was reported by Simoons.[25] The plot of the resulting risk differences is presented in *Figure 4*. Data for MI alone were not presented.

Recurrent ischaemia

The effect of eptifibatide on recurrent ischaemia is presented in *Figure 5* (see *Table 10* for the definition of recurrent ischaemia used in the Schulman study). The PURSUIT study did not report refractory ischaemia as a separate end-point.

Revascularisation

Table 15 specifies the rates of revascularisation in the trials of eptifibatide. As shown in *Figure 6*, the risk difference for PTCA at 30 days in the PURSUIT study was –1.5% (95% CI, –3.2% to 0.2%).

Adverse events

Adverse effects from eptifibatide were related to an extension of the pharmacological effect: bleeding, thrombocytopenia and complications of these (e.g. haemorrhagic strokes).

Bleeding

Table 16 details the definitions of major and minor bleeding used in each of the trials of eptifibatide. The PURSUIT trial used laboratory definitions of bleeding based on the Thrombolysis in Myocardial

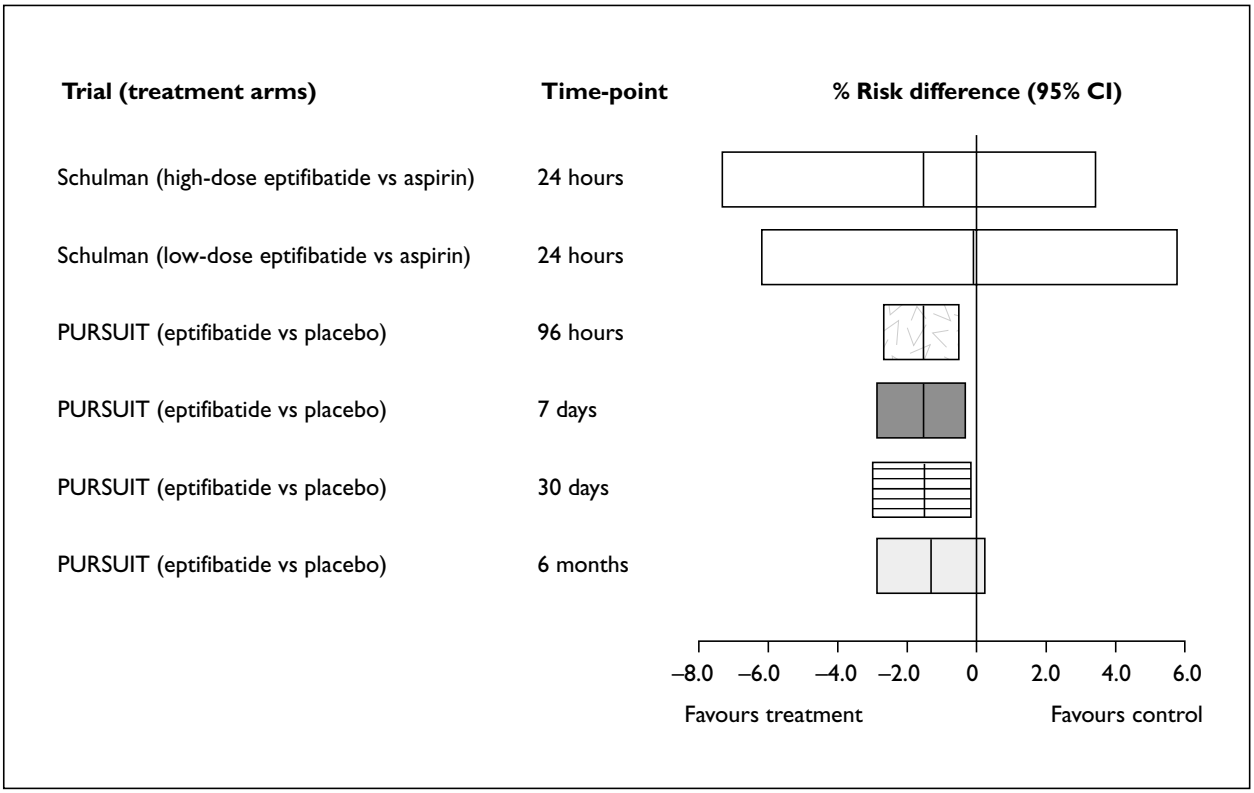

FIGURE 3 *Schulman[22] and PURSUIT[23–27] trials of eptifibatide: mean risk differences for composite end-points*

TABLE 14 *Various definitions of MI used by Simoons[25] in a re-analysis of PURSUIT study data for death and non-fatal MI*

Definition 1 (Clinical Events Committee)	Definition 2	Definition 3	Definition 4	Definition 5
< 18 hours after enrolment Chest pain with ST-T changes (depression or elevation) in two continuous leads for > 30 minutes ***> 18 hours after enrolment*** CK-MB fraction above the upper limit of normal, total CK more than twice the upper limit or new Q waves	CK-MB more than twice the upper limit of normal	CK-MB more than three times the upper limit of normal	CK-MB more than five times the upper limit of normal	Local investigator's decision

Infarction (TIMI) trial criteria,[31] as well as clinical definitions assigned by the local investigators and based on the Global Use of Strategies to Open Occluded Arteries (GUSTO) trial criteria.[32]

The rates reported in *Table 17* are those that correspond to the TIMI definition.There were no cases of major bleeding in any of the groups in the Schulman study. The PURSUIT study used the definitions of major and minor bleeding from the TIMI trial[31] as a primary end-point and the definitions from the GUSTO trial[32] as a secondary end-point. However, by either definition, the risk of a major bleed was significantly greater with eptifibatide (*Figure 7*). The bleeding events were those reported during hospitalisation. Using the TIMI definition, the risk difference was 1.7% (95% CI, 0.3% to 2.7%), with a number needed to harm (NNH) of 59 (95% CI, 51 to 67).

Thrombocytopenia

Thrombocytopenia has been suggested as a potential adverse effect associated with glycoprotein IIb/IIIa antagonists. Thrombocytopenia was not reported in the Schulman study.

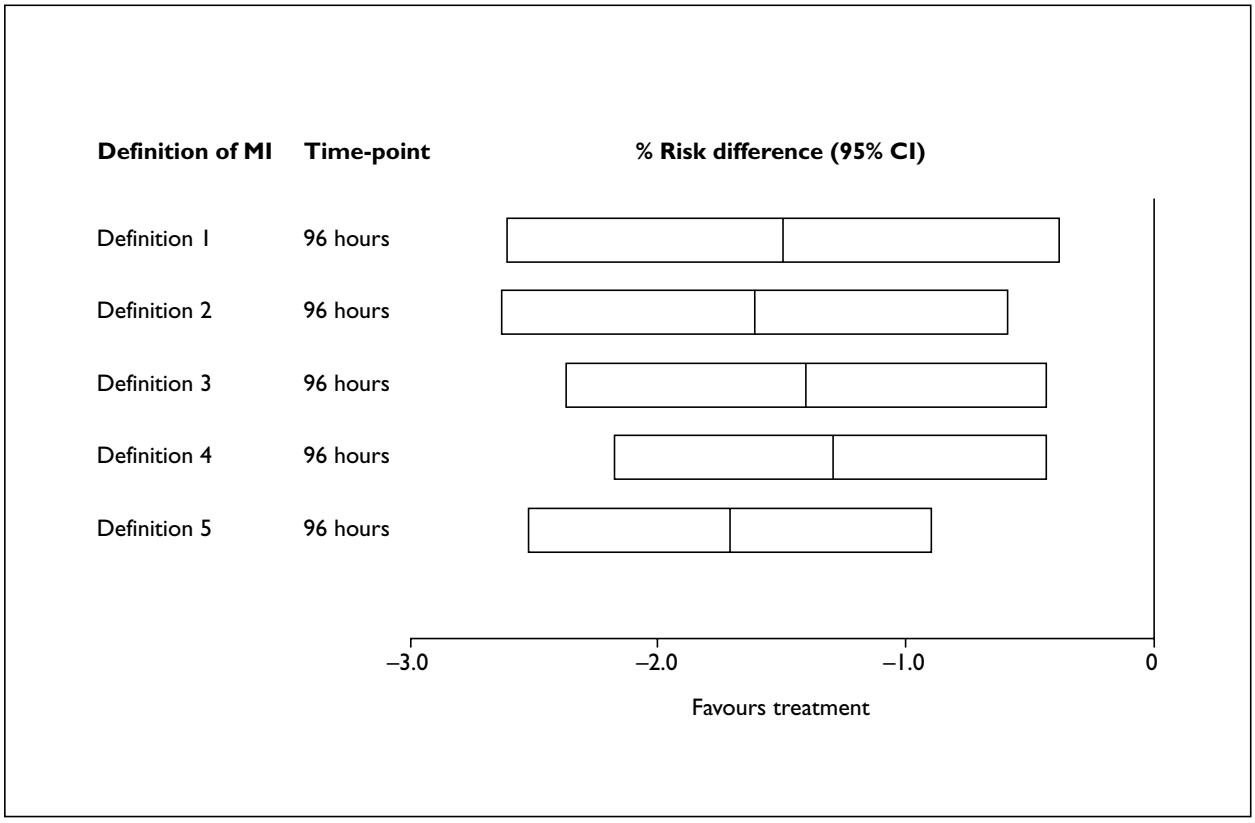

FIGURE 4 *PURSUIT trial[23–27] of eptifibatide versus placebo: mean risk differences for outcomes of death and non-fatal MI, based on other definitions of MI specified in* Table 14

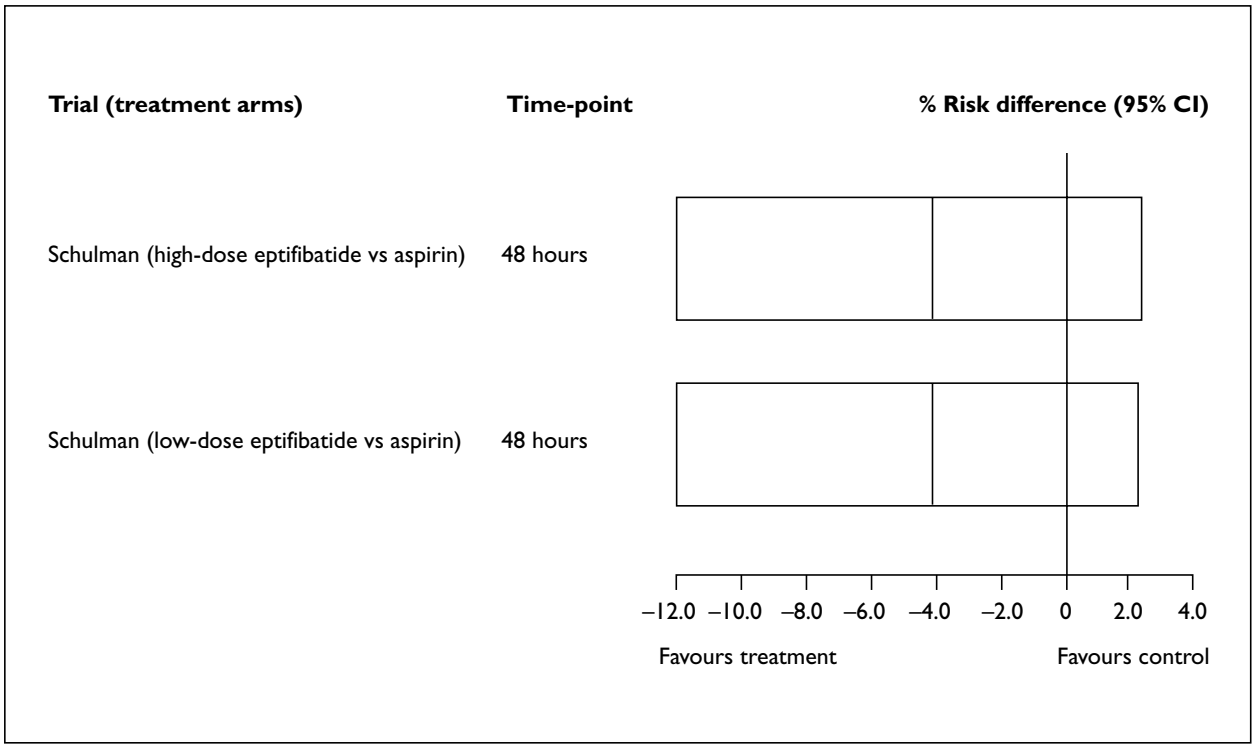

FIGURE 5 *Schulman trial[22] of eptifibatide: mean risk differences for outcome of recurrent angina/refractory ischaemia*

TABLE 15 *Revascularisation rates in trials of eptifibatide*

Study	Treatment arm	Time-point	Cardiac catheterisation (%)	Coronary angioplasty (%)	Cardiac bypass (%)
Schulman *et al.*, 1996[22]	High-dose eptifibatide	24 hours	1.3*	0.0*	–
	Low-dose eptifibatide		0.0*	0.0*	–
	Placebo		2.7*	1.4*	–
PURSUIT, 1998[23–27]	Eptifibatide	30 days	59.0	23.3	13.9
	Placebo		59.9	24.8	14.3

**Emergency procedures only*

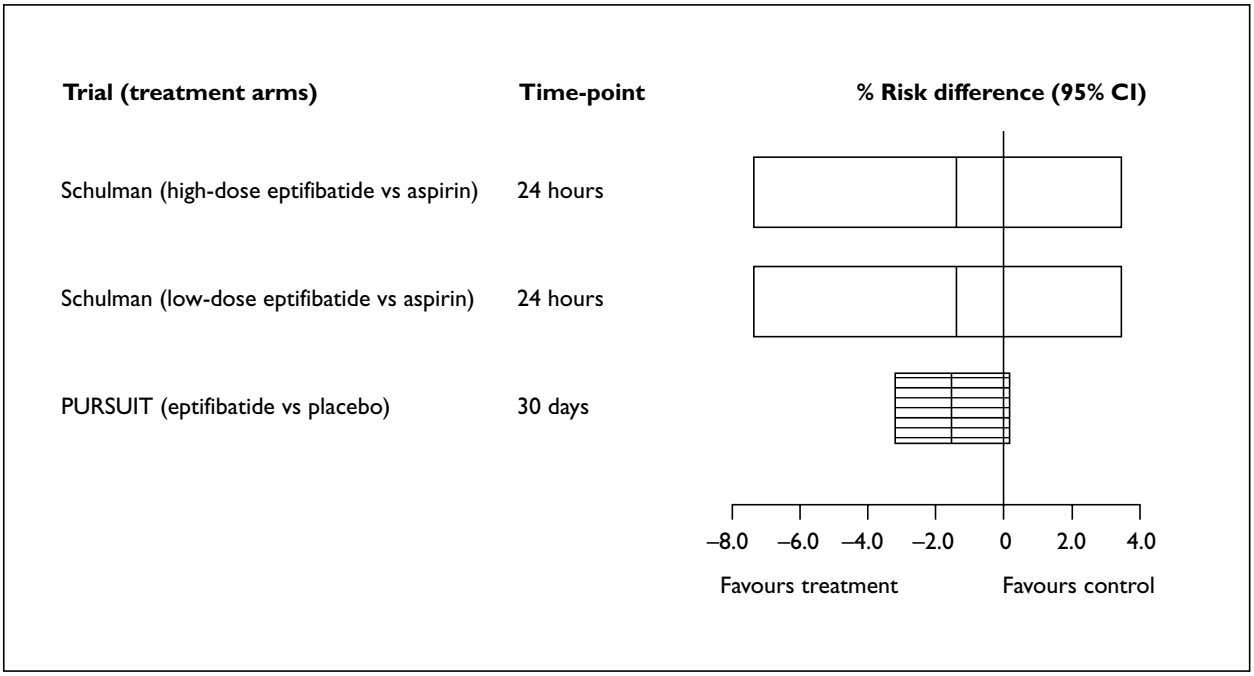

FIGURE 6 *Schulman[22] and PURSUIT[23–27] trials of eptifibatide: mean risk differences for outcome of PTCA*

TABLE 16 *Definitions of bleeding in trials of eptifibatide*

Study	Major/minor bleeding
Schulman *et al.*, 1996[22]	Not defined, but petechiae, ecchymoses, haematomas, haemoptysis, haematemesis, haematuria and rectal bleeding were reported and included here as minor bleeding. Blood transfusions given within 24 hours of stopping the study drug and haemoglobin levels recorded at 24 hours were reported
PURSUIT, 1998[23–27]	***TIMI trial criteria[31]*** Major bleeding: intracranial haemorrhage or bleeding associated with a drop of 15% or more in the haematocrit, or of 5 g/dl or more in the haemoglobin level Minor bleeding: (a) observed blood loss and a drop of > 10% in the haematocrit or of 3 g/dl or more in the haemoglobin level, or (b) no observed blood loss and a drop of 12% or more in the haematocrit or of 4 g/dl or more in the haemoglobin level ***GUSTO trial criteria[32]*** Severe or life-threatening bleeding: intracranial haemorrhage or bleeding that caused haemodynamic compromise and required intervention Moderate bleeding: bleeding that required blood transfusion without causing haemodynamic compromise

TABLE 17 *Rates of the occurrence of bleeding episodes in trials of eptifibatide*

Study	Treatment arm	Time-point	Stroke	Major bleeding episode (%)	Minor bleeding episode (%)	Any bleeding episode (%)
Schulman *et al*., 1996[22]	Low-dose eptifibatide (*n* = 77)	72 hours	–	0	9	11
	High-dose eptifibatide (*n* = 76)		–	0	14	14
	Placebo (*n* = 74)		–	0	8	10
PURSUIT, 1998[23–27]	Eptifibatide (*n* = 4722)	During hospitalisation	–	10.6	12.9	25.2
	Placebo (*n* = 4739)		–	9.1	7.4	19.0

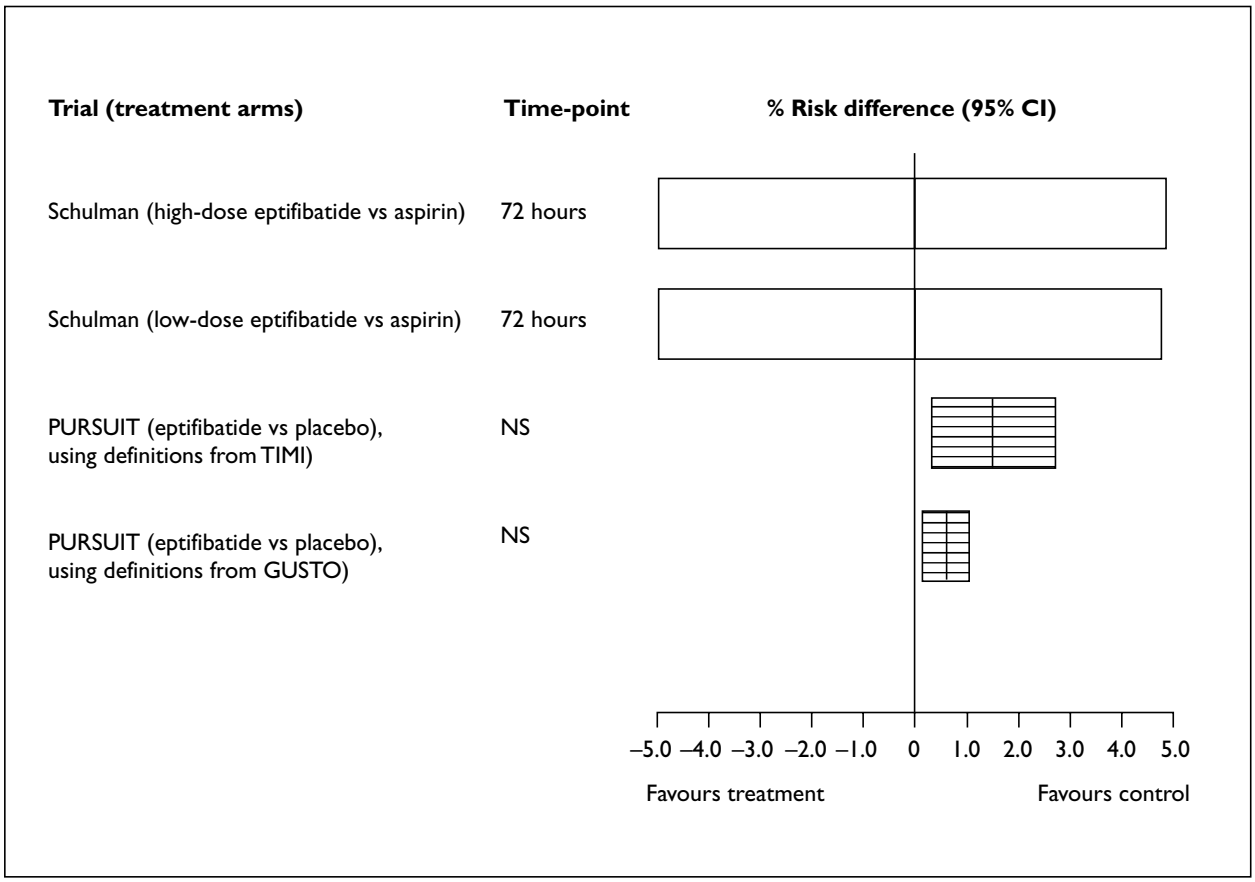

FIGURE 7 *Schulman[22] and PURSUIT[23–27] trials of eptifibatide: mean risk differences for adverse events of major bleeding (NS, not specified)*

In the PURSUIT study, the rate of thrombocytopenia was very similar in both groups (*Table 18*), with a risk difference of –0.1% (95% CI, –1.1% to 0.9%). However, the rate of profound thrombocytopenia (i.e. platelet count < 20,000/mm^3) was 0.2% versus 0.1% in the eptifibatide and placebo groups, respectively. While the absolute difference and numbers of patients affected were very small, the difference was statistically significant, with a risk difference of 0.15% (95% CI, 0.01% to 0.30%) and an NNH of 667 (95% CI, 333 to 10,000).

TABLE 18 *Incidence of thrombocytopenia in trials of eptifibatide*

Study	Definition of thrombocytopenia	Treatment arm (total *n* reported)	Incidence (%)
Schulman *et al.*, 1996[22]	Not reported		
PURSUIT, 1998[23–27]	Platelet count < 100,000/mm^3 or < 50% of baseline	Eptifibatide (4603) Placebo (4614)	6.8 6.9

TABLE 19 *Results of PRISM study, 1998[20] (the trial's primary outcome is shown in* ***bold****)*

Treatment arm	Time-point	MI		Recurrent ischaemia		Death		Composite end-point	
		n	%	*n*	%	*n*	%	*n*	%
Tirofiban	**48 hours**	**15**	**0.9**	**57**	**3.5**	**6**	**0.4**	**61**	**3.8**
(*n* = 1616)	7 days	42	2.6	147	9.1	16	1.0	166	10.3
	30 days	66	4.1	171	10.6	37	2.3	257	15.9
Heparin	**48 hours**	**23**	**1.4**	**86**	**5.3**	**3**	**0.2**	**90**	**5.6**
(*n* = 1616)	7 days	50	3.1	160	9.9	26	1.6	181	11.2
	30 days	69	4.3	176	10.8	58	3.6	276	17.1

Tirofiban

PRISM study

The PRISM study[20] compared treatment with tirofiban to treatment with heparin. The quality assessment used in the PRISM study was very similar to that of the PURSUIT study (*Table 11*). The random allocation of participants (i.e. information on the randomisation process) was not stated. Concealment of randomisation, blinding of persons who implemented interventions and loss to follow-up were only partially addressed.

In the PRISM study, the primary end-points were MI, refractory ischaemia, death and the composite end-point at 48 hours (*Table 19*). Kaplan–Meier curves for cumulative mortality up to 30 days were presented, with an absolute difference of 1.3% ($p = 0.02$) in favour of tirofiban. At 48 hours, the hazard ratio for the composite end-point was 0.67 (95% CI, 0.48 to 0.92) and that for refractory ischaemia was 0.65 (95% CI, 0.46 to 0.91). None of the other outcomes were significant at any time-point.

PRISM-PLUS study

The PRISM-PLUS study[21] examined tirofiban alone, tirofiban plus heparin and heparin alone. The validity assessment of this study differed from that of the PRISM study in that blinding of persons assessing treatment effects was not discussed (*Table 11*). Items that were only partially addressed involved the randomisation procedure and blinding of persons implementing interventions. While data on anti-anginal medication use before and after randomisation were reported, the rates of aspirin use were not.

Kaplan–Meier curves for MI or death and the composite end-point were presented for tirofiban plus heparin and for heparin alone; the tirofiban alone group stopped treatment early. The PRISM-PLUS study results (*Table 20*) showed a non-significant benefit from treatment with tirofiban plus heparin at 6 months, with an absolute reduction in risk for death or MI of 3.0% (95% CI, –0.4% to 6.4%; NNT, 33). The absolute reduction in risk for the composite end-point was 4.4% (95% CI, 0.0% to 9.0%; NNT, 23).

Death from any cause

Multiple comparisons are presented for the studies with more than two study arms. The most striking feature is the opposite effect of tirofiban versus heparin in the PRISM-PLUS study at all time-points (risk difference for death at 7 days, 2.8%; NNH, 36) compared with the PRISM study (risk difference for death at 30 days, –1.3%; NNT, 77). The risk differences for the outcome of death are presented in *Figure 8*.

Myocardial infarction

The risk differences for new MI at the various time-points reported are presented in *Figure 9*.

TABLE 20 *Results of PRISM-PLUS study, 1998[21] (the trial's primary outcome is shown in **bold**)*

Treatment arm	Time-point	MI		Recurrent ischaemia		Death		Composite end-point		MI/death		Re-admission due to unstable angina	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Tirofiban	**48 hours**	**2**	**0.6**			**2**	**0.6**	**26**	**7.5**	**6**	**1.7**		
(*n* = 345)	7 days	16	4.6	–	–	16	4.6	59	17.1	36	10.4	–	–
	30 days	21	6.1			21	6.1	81	23.5	47	13.6		
	6 months	25	7.2			25	7.2	105	30.4	55	15.9		
Tirofiban + heparin	**48 hours**	**6**	**0.8**	**37**	**4.8**	**1**	**0.1**	**44**	**5.7**	**7**	**0.9**		
(*n* = 773)	7 days	30	3.9	72	9.3	15	1.9	100	12.9	38	4.9		
	30 days	51	6.6	82	10.6	28	3.6	143	18.5	67	8.7	16	2.1
	6 months	64	8.3	82	10.6	53	6.9	214	27.7	95	12.3	84	10.9
Heparin	**48 hours**	**19**	**2.4**	**47**	**5.9**	**2**	**0.3**	**62**	**7.8**	**21**	**2.6**		
(*n* = 797)	7 days	56	7.0	101	12.7	15	1.9	143	17.9	66	8.3		
	30 days	73	9.2	107	13.4	36	4.5	178	22.3	95	11.9	11	1.4
	6 months	84	10.5	107	13.4	56	7.0	256	32.1	122	15.3	85	10.7

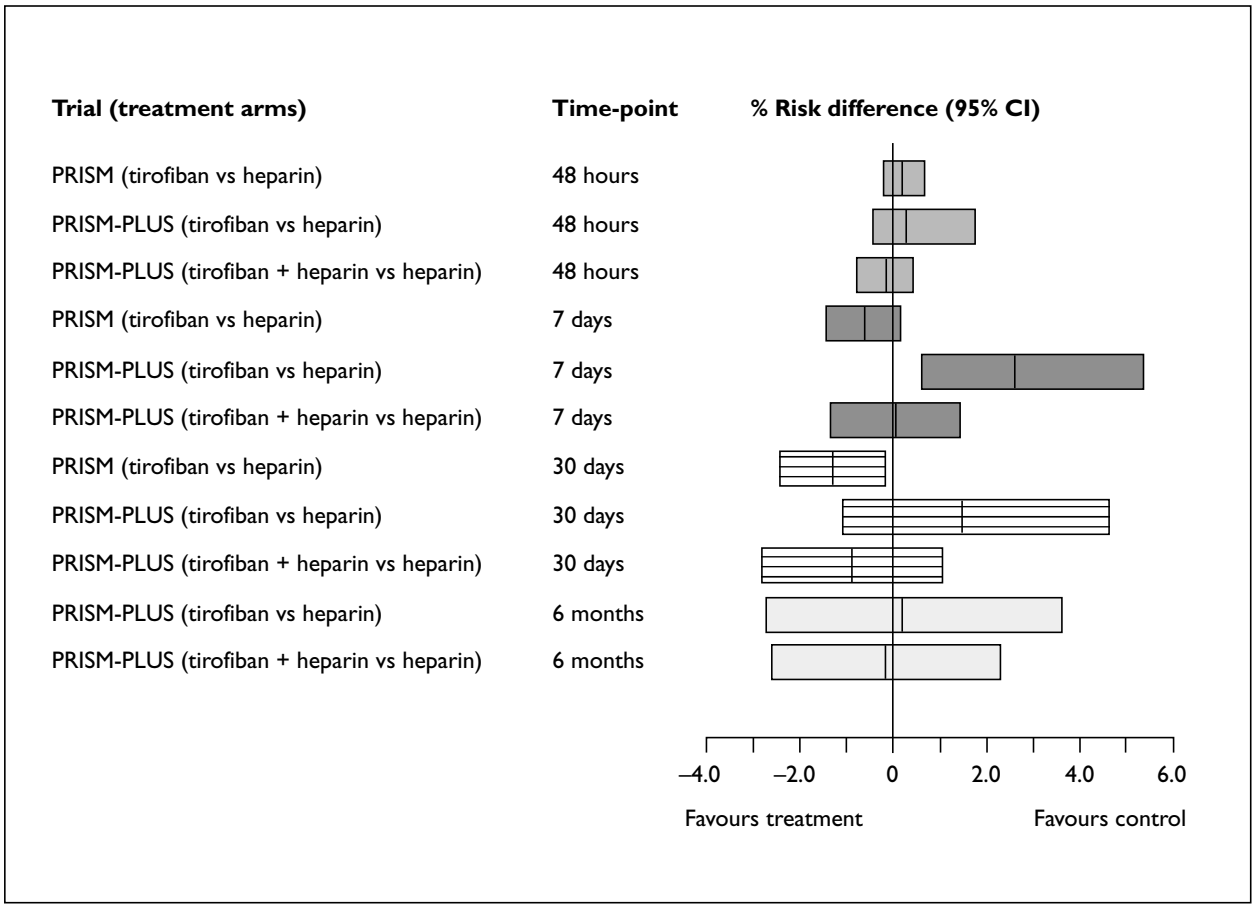

FIGURE 8 *PRISM[20] and PRISM-PLUS[21] trials of tirofiban: mean risk differences for outcome of death*

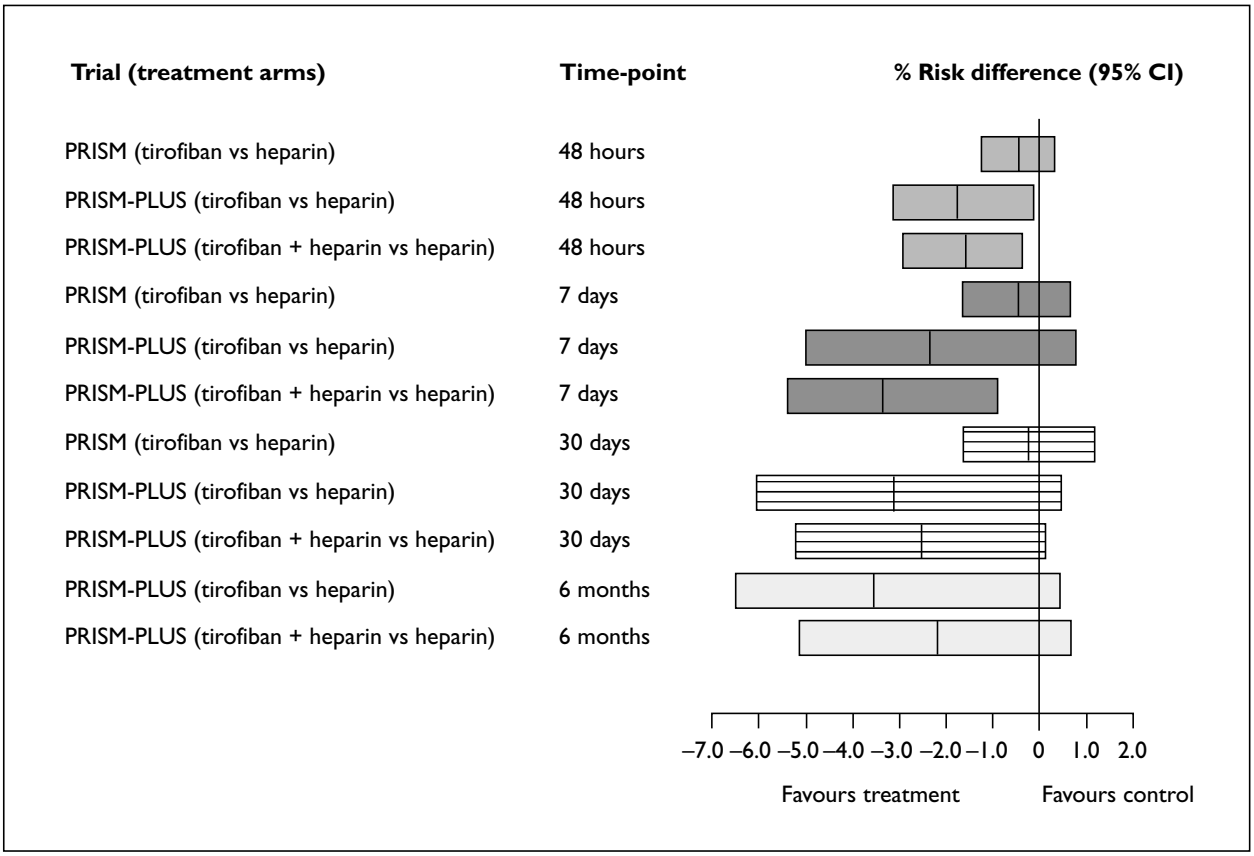

FIGURE 9 *PRISM[20] and PRISM-PLUS[21] trials of tirofiban: mean risk differences for outcome of MI*

At 48 hours and 7 days, there were fewer infarctions in patients receiving tirofiban plus heparin in the PRISM-PLUS study than in patients receiving heparin alone, but the difference was not statistically significant at 30 days or 6 months. In the PRISM trial, tirofiban was not significantly better than the control (heparin), although many of the point estimates favoured treatment.

As shown in *Figure 9*, the risk difference for new MI at 30 days for tirofiban alone in the PRISM study was –0.2% (95% CI, –1.7% to 1.2%); in the PRISM-PLUS study, it was –3.1% (95% CI, –6.1% to 0.4%). For tirofiban plus heparin in the PRISM-PLUS study, the risk difference at 30 days was –2.6% (95% CI, –5.3% to 0.1%).

Composite end-points

The composite end-point used in the PRISM and PRISM-PLUS studies was death from any cause, non-fatal MI and refractory ischaemia. Rehospitalisation for unstable angina was also included at 7 days, 30 days and 6 months in the PRISM-PLUS trial.

Figure 10 illustrates the risk differences at various time-points. The risk differences and NNT values at 30 days and 6 months are presented in *Table 21*. In the PRISM-PLUS study, the risk difference at 30 days for tirofiban versus heparin resulted in a negative NNT, which should be interpreted as an NNH (i.e. for every 87 patients treated with tirofiban rather than heparin, one additional patient will die or experience a non-fatal MI).

Recurrent ischaemia

The risk differences for recurrent ischaemia are presented in *Figure 11*. While the point estimates are consistently less than zero for all the studies, the differences are significant only for tirofiban versus heparin at 48 hours (PRISM study) and tirofiban plus heparin versus heparin at 7 days (PRISM-PLUS study).

Revascularisation

Table 22 presents the data regarding the need for revascularisation in each trial. The rates of both angioplasty and CABG were higher in the PRISM-PLUS study than in the PRISM study.

The risk differences are presented in *Figure 12*. The risk difference for PTCA for tirofiban at

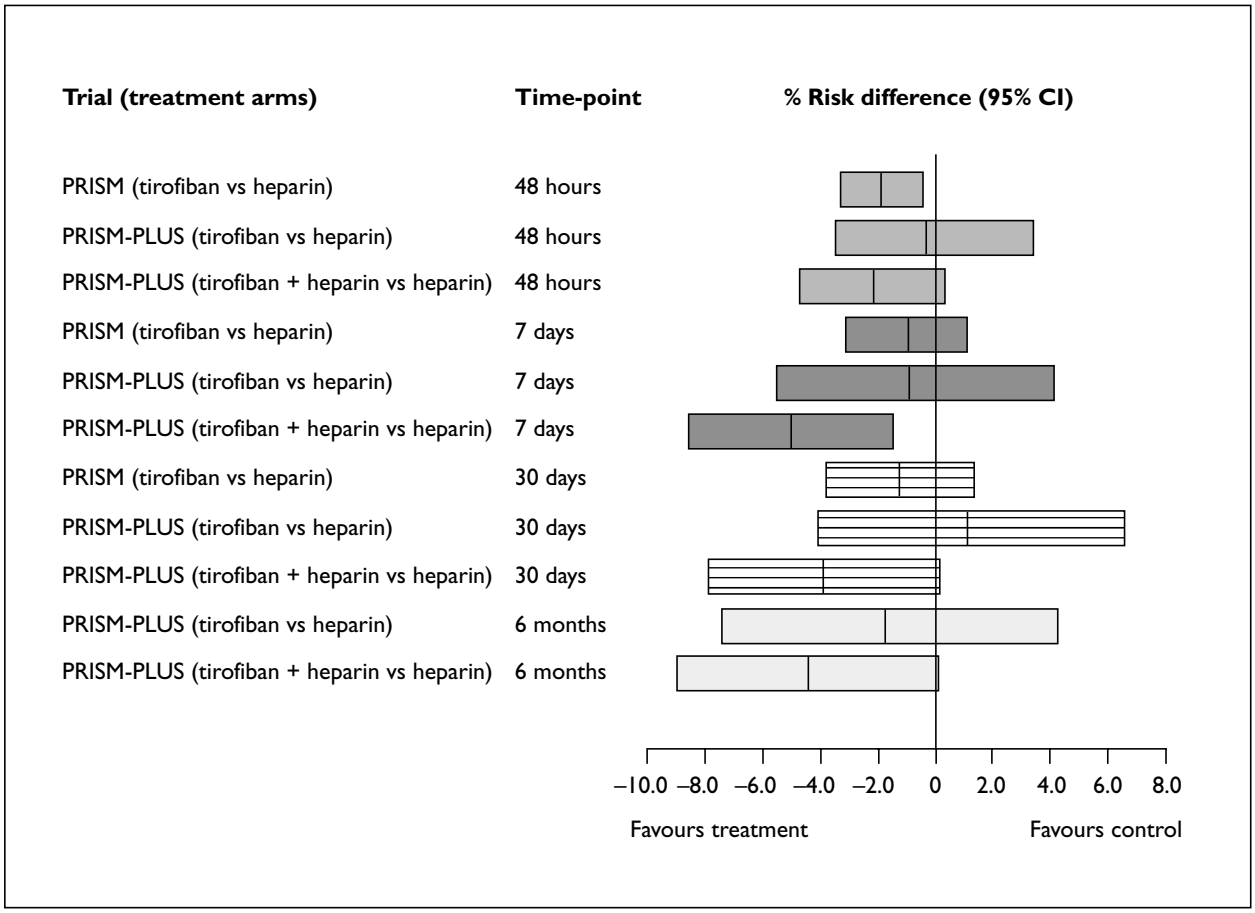

FIGURE 10 *PRISM[20] and PRISM-PLUS[21] trials of tirofiban: mean risk differences for composite end-points*

TABLE 21 *Composite end-points at 30 days and 6 months in trials of tirofiban*

Study	Treatment	Time-point	% RD	95% CI	NNT	95% CI
PRISM, 1998[20]	Tirofiban vs heparin	30 days	–1.2	–3.7 to 1.4	85	27 to infinity
PRISM-PLUS, 1998[21]	Tirofiban vs heparin	30 days	1.1	–4.0 to 6.6	–87*	– infinity to –15
	Tirofiban + heparin vs heparin	30 days	–3.8	–7.8 to 0.2	27	13 to infinity
	Tirofiban vs heparin	6 months	–1.7	–7.4 to 4.3	60	14 to infinity
	Tirofiban + heparin vs heparin	6 months	–4.4	–8.9 to 0.1	23	12 to infinity

RD, risk difference

* *Represents an NNH of 87 (i.e. for every 87 patients treated, one additional patient will experience an unfavourable outcome), rather than the NNT*

30 days in the PRISM study was –0.3% (95% CI, –3.0% to 2.5%), with an NNT of 333; for tirofiban plus heparin in the PRISM-PLUS study, the risk difference was 1.3% (95% CI, –3.3% to 5.8%), with an NNH of 77. While the point estimates for these two studies are on opposing sides of the 'no-effect' line, the difference in the number of procedures required was very small.

Adverse events

The main concerns about the adverse effects of tirofiban were related to an extension of the pharmacological effect: bleeding,

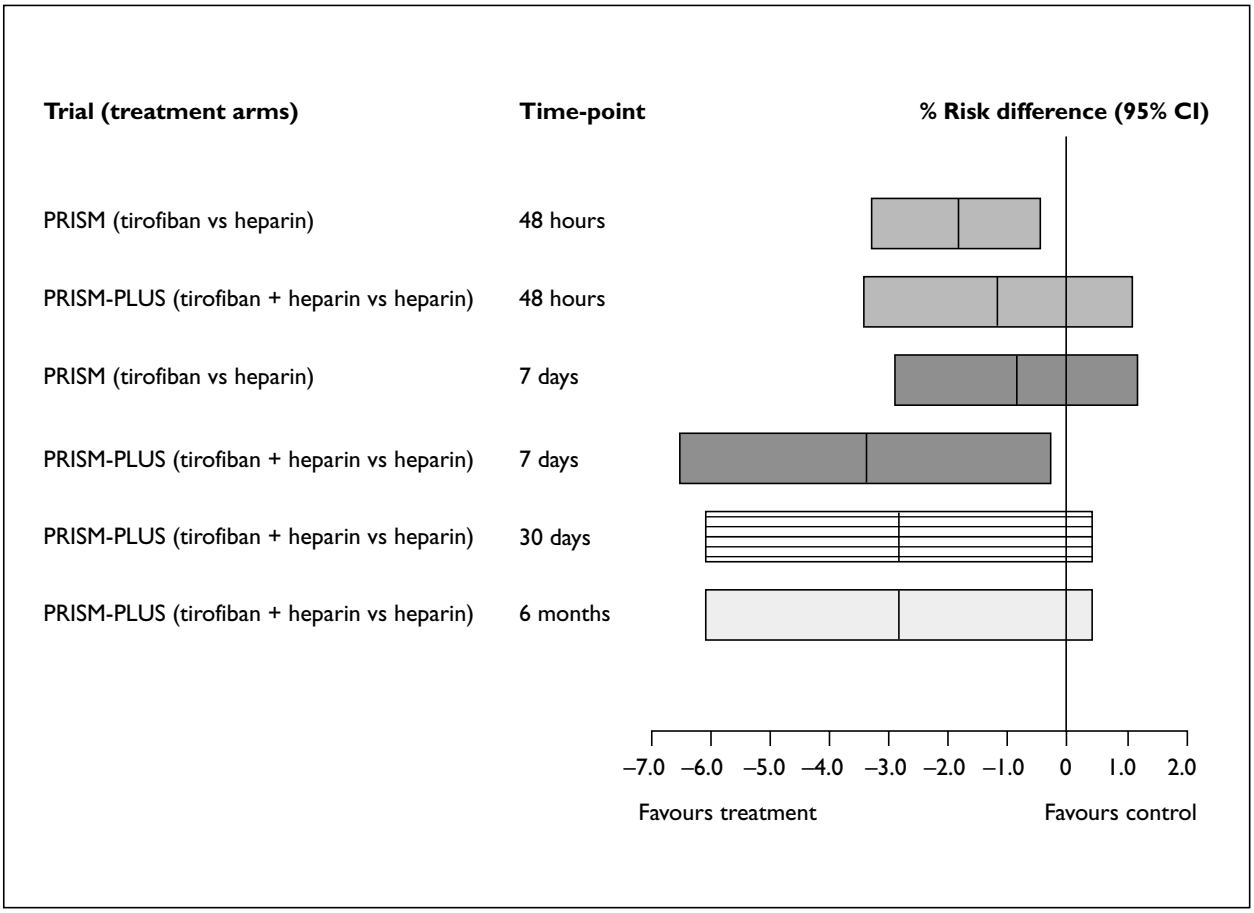

FIGURE 11 *PRISM[20] and PRISM-PLUS[21] trials of tirofiban: mean risk differences for outcome of recurrent ischaemia*

TABLE 22 *Revascularisation rates in trials of tirofiban*

Study	Treatment arm	Time-point	Cardiac catheterisation (%)	Coronary angioplasty (%)	Cardiac bypass (%)
PRISM, 1998[20]	Tirofiban Heparin	30 days	–	21.3 21.6	18.1 16.5
PRISM-PLUS, 1998[21]	Tirofiban Tirofiban + heparin Heparin	30 days	–	NR 30.9 29.6	NR 23 (3.4)* 23 (2.5)*

NR, not reported (because tirofiban arm was discontinued)

* *Values in parentheses represent urgent procedures*

thrombocytopenia and complications of these (e.g. haemorrhagic strokes).

Bleeding

Table 23 details the definitions of major and minor bleeding used in each of the trials. The PRISM study used the TIMI trial criteria for bleeding.[31] The PRISM-PLUS study used an independent definition but also evaluated bleeding based on the TIMI criteria.

The bleeding rates observed in each trial and the occurrence of stroke are listed in *Table 24*. Minor bleeding events were not reported in the PRISM-PLUS trial. *Figure 13* shows the risk difference for major bleeding, as defined by each trial. The risk difference in the PRISM trial was zero. Based on the investigator's criteria for bleeding in the PRISM-PLUS study, the risk difference was 0.99% (95% CI, –0.84% to 2.90%), with an NNH of 101. Based on the somewhat less conservative TIMI

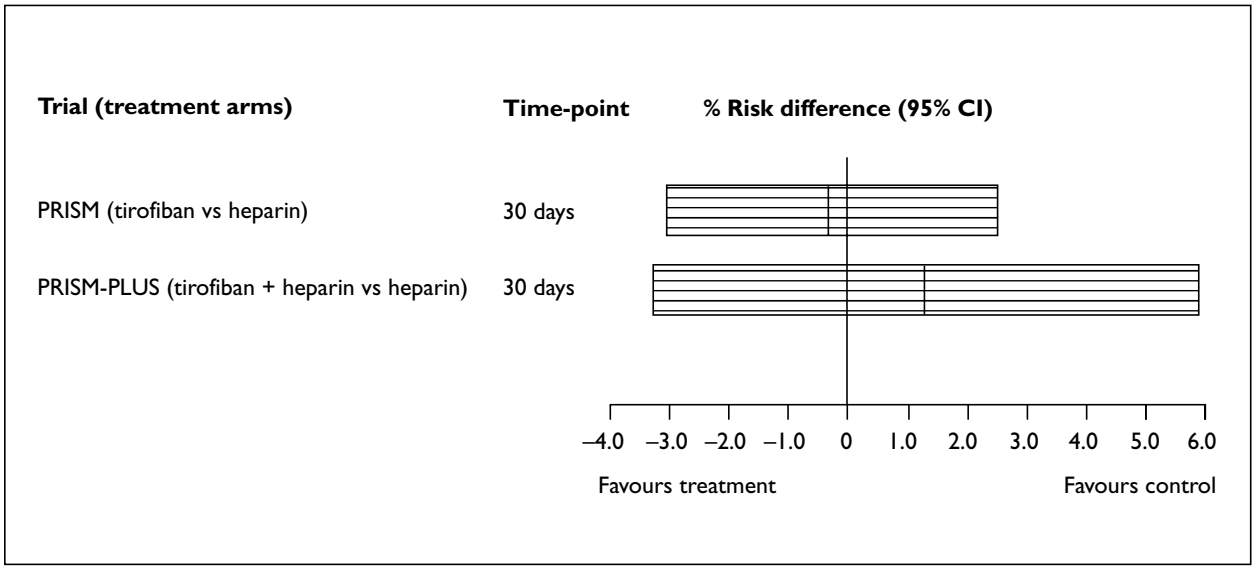

FIGURE 12 *PRISM[20] and PRISM-PLUS[21] trials of tirofiban: mean risk differences for outcome of PTCA*

TABLE 23 *Definitions of bleeding in trials of tirofiban*

Study	Major/minor bleeding
PRISM, 1998[20]	***TIMI trial criteria[31]*** Major bleeding: a decrease in the haemoglobin level of 50 g/l, intracranial haemorrhage or cardiac tamponade Minor bleeding: observed blood loss and a decrease in the haemoglobin level of > 30 g/l due to bleeding from an identified site, spontaneous gross haematuria, haematemesis or haemoptysis
PRISM-PLUS, 1998[21]	Decrease in the blood haemoglobin level of > 4.0 g/dl, the need for the transfusion of two or more units of blood, the need for corrective surgery, the occurrence of an intracranial or retroperitoneal haemorrhage, or any combination of these events. Bleeding was also assessed using the TIMI trial criteria (defined above)

TABLE 24 *Rates of the occurrence of bleeding episodes in trials of tirofiban*

Study	Treatment arm	Time-point	Stroke (%)	Major bleeding episode (%)	Minor bleeding episode (%)	Any bleeding episode (%)
PRISM, 1998[20]	Tirofiban (*n* = 1616)	72 hours	0.1	0.4	2.0	–
	Heparin (*n* = 1616)		0.1	0.4	1.9	–
PRISM-PLUS, 1998[21]	Tirofiban (*n* = 345)	Not stated	–	4.0	–	3.5
	Tirofiban + heparin (*n* = 773)		–	3.0	–	1.3
	Heparin (*n* = 797)		–	–	–	–

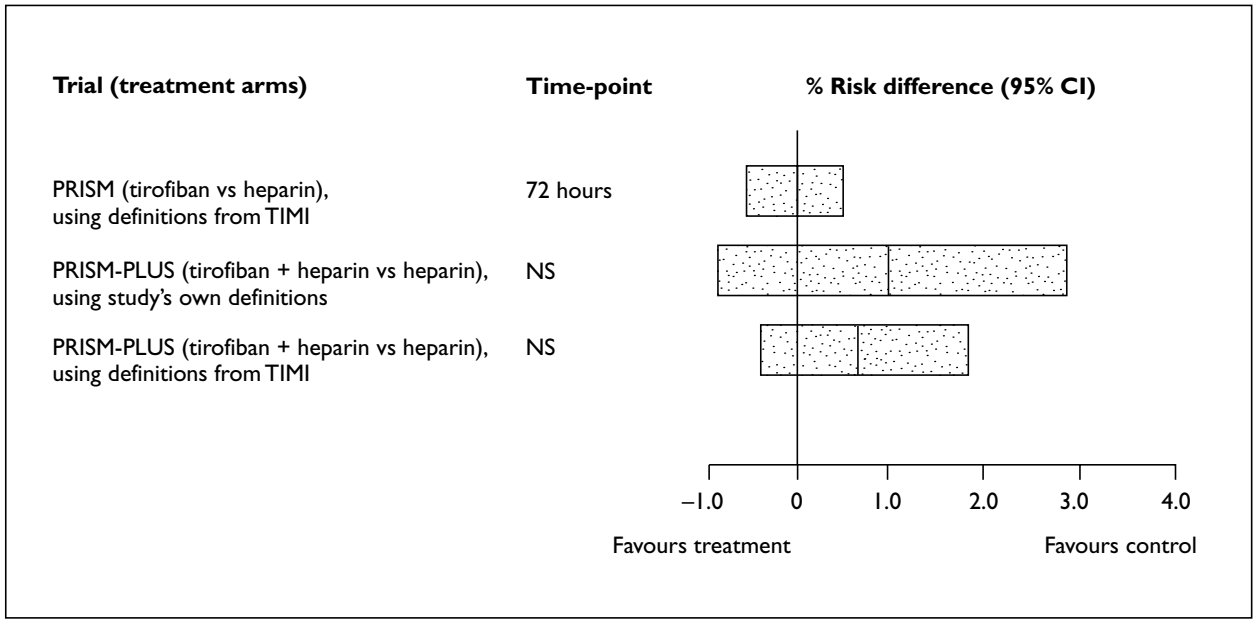

FIGURE 13 *PRISM[20] and PRISM-PLUS[21] trials of tirofiban: mean risk differences for adverse events of major bleeding (NS, not specified)*

criteria, the risk difference was 0.67% (95% CI, –0.39% to 1.86%), with an NNH of 149.

Thrombocytopenia

Both studies showed an increased rate of thrombocytopenia in the treatment groups (*Table 25*). As shown in *Figure 14*, the risk difference found with tirofiban versus heparin in the PRISM study was 0.7% (NNH, 143), and with tirofiban plus heparin versus heparin was 1.2% (NNH, 83). As heparin can also cause thrombocytopenia, the increased rate found with the combination treatment in the PRISM-PLUS study may be expected.

Lamifiban

Théroux study

Three studies evaluated the use of lamifiban in unstable angina and ACSs. The 1996 Théroux study,[28] subtitled 'The Canadian Lamifiban Study', was a Phase II dose-finding study in preparation for the PARAGON studies. This study had a slightly lower validity assessment than the Phase III studies (PURSUIT, PRISM and PRISM-PLUS). 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 that were not fully addressed were blinding (patients and persons implementing interventions) and registration of co-interventions, such as anti-anginal medications (*Table 11*).

Four dose levels (two low and two high) were tested against placebo in the Théroux study. The results are presented separately, but they were analysed based on groups receiving low-dose (1 and 2 µg/minute combined) and high-dose (4 and 5 µg/minute combined) lamifiban (*Table 26*). A primary end-point was not stated. There were very few deaths or MIs during study drug infusion. Survival analysis for participants surviving without MI showed that the benefit seen in the high-dose groups was sustained at 30 days (odds ratio [OR], 0.29; 95% CI, 0.09 to 0.94), but not with the low dose.

TABLE 25 *Incidence of thrombocytopenia in trials of tirofiban*

Study	Definition of thrombocytopenia	Treatment arm	Incidence (%)
PRISM, 1998[20]	Platelet count < 90,000/mm^3	Tirofiban Heparin	1.1 0.4
PRISM-PLUS, 1998[21]	Platelet count ≤ 90,000/mm^3	Tirofiban + heparin Heparin	1.9 0.8

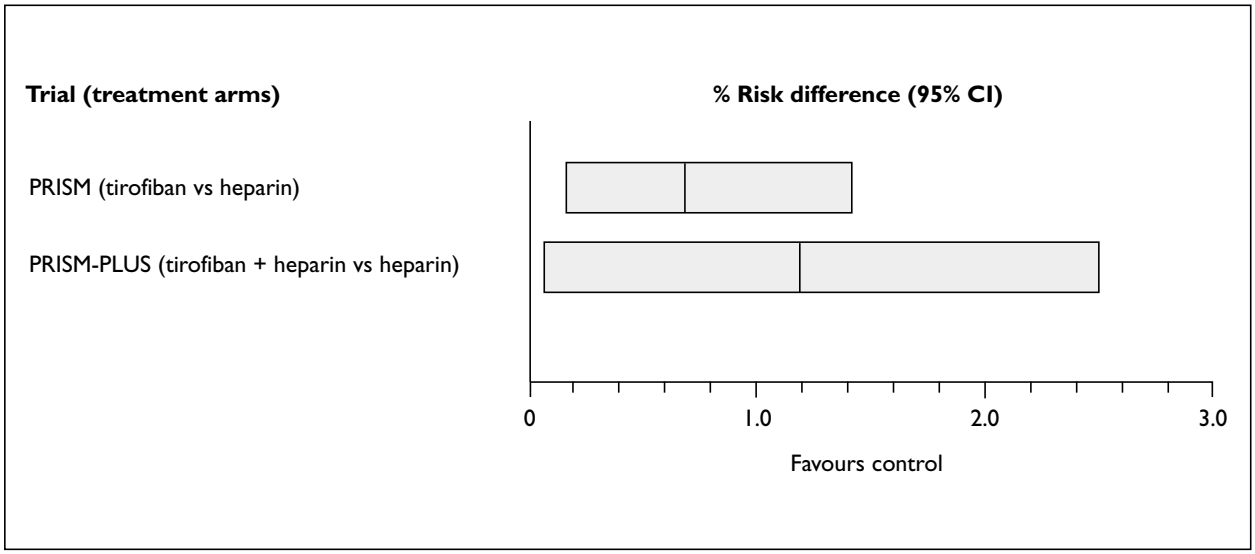

FIGURE 14 *PRISM[20] and PRISM-PLUS[21] trials of tirofiban: mean risk differences for adverse event of thrombocytopenia*

TABLE 26 *Results of study by Théroux* et al.*, 1996[28]*

Treatment arm	Time-point	MI		Recurrent ischaemia		Death		Composite end-point	
		n	%	*n*	%	*n*	%	*n*	%
Lamifiban, 1 µg/minute	Infusion	0	0	3	7	0	0	1	3
(*n* = 40)	30 days	1	2	6	15	0	0	3	7
Lamifiban, 2 µg/minute	Infusion	1	3	5	13	0	0	2	5
(*n* = 41)	30 days	3	8	9	23	2	5	7	18
Lamifiban, 4 µg/minute	Infusion	0	0	18	15	0	0	4	3
(*n* = 120)	30 days	3	3	22	18	0	0	12	10
Lamifiban, 5 µg/minute	Infusion	0	0	2	5	0	0	1	2
(*n* = 40)	30 days	0	0	3	7	1	2	3	7
Placebo	Infusion	2	2	15	12	1	1	10	8
(*n* = 128)	30 days	7	5	19	15	5	4	19	15

PARAGON A study

The PARAGON A study[29] compared heparin alone with two doses of lamifiban (high and low) with or without heparin (*Table 27*). This dose-finding Phase II/III study 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 studies (PURSUIT, PRISM and PRISM-PLUS). The procedures of randomisation were not described, and the blinding of patients and persons implementing interventions was not clear (*Table 11*). It was noted that 2.0% of the patients assigned to lamifiban and 0.9% of the patients assigned to placebo did not receive the study drug.

Overall, 3.0% and 6.7% of the patients were lost to follow-up at 6 months and 1 year, respectively. The numbers lost in each treatment group were not stated. Additionally, 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. **Because the number of patients in each group at 6 months was not known, risk**

TABLE 27 *Results of PARAGON A study, 1998[29] (the trial's primary outcome is shown in* ***bold****)*

Treatment arm	Time-point	MI		Death		Composite end-point	
		n	%	*n*	%	*n*	%
Low-dose lamifiban (*n* = 378)	**30 days**	36	10	12	3	**41**	11
	6 months	NS	11	NS	6	NS	15
Low-dose lamifiban + heparin (*n* = 377)	**30 days**	35	9	11	3	**39**	10
	6 months	NS	11	NS	5	NS	13
High-dose lamifiban (*n* = 396)	**30 days**	42	11	14	4	**46**	12
	6 months	NS	12	NS	6	NS	15
High-dose lamifiban + heparin (*n* = 373)	**30 days**	43	11	14	4	**46**	12
	6 months	NS	14	NS	8	NS	18
Heparin (*n* = 758)	**30 days**	80	11	22	3	**89**	12
	6 months	102	14	51	7	131	18

NS, not specified

TABLE 28 *Results of PARAGON B study, 1999[30] (the trial's primary outcome is shown in* ***bold****)*

Treatment arm	Time-point	Death or MI		Composite end-point	
		n	%	*n*	%
Lamifiban (*n* = 2628)	**30 days**	279	11	**310**	**12**
Placebo (*n* = 2597)	**30 days**	299	12	**332**	**13**

differences could not be calculated and therefore are not presented in the figures.

Kaplan–Meier survival curves were presented for the composite end-point, MI and death over 6 months. The alternate-dose lamifiban groups (with or without heparin) were combined in the survival analysis. There was no difference between the control group and any of the lamifiban groups at 30 days for the composite end-point. However, at 6 months, differences were seen. The difference between heparin only and either low-dose lamifiban group was 23% (OR, 0.73; 95% CI, 0.55 to 0.97). The difference between heparin only and either high-dose group was 8% (OR, 0.90; 95% CI, 0.69 to 1.18). The difference in death at 1 year was minimal: 8.7% in the heparin only group, 7.3% in the low-dose lamifiban groups and 8.9% in the high-dose lamifiban groups.

PARAGON B study

To date, the PARAGON B study[30] results have been reported in abstract form only. The results for 30 days post-randomisation are available (*Table 28*). 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 µg/minute or 2 µg/minute were given, depending on the calculated creatinine clearance rate. The cut-off for dose adjustment or the proportion of patients requiring the lower dose was not stated in the abstract. Survival analysis curves were not presented, but the abstract stated that there was no survival benefit with lamifiban at 6 months. Validity assessment based on an abstract was not reliable.

Death from any cause

The risk difference for death from any cause is presented in *Figure 15*. The PARAGON B study did not report death (alone) as an end-point. Multiple comparisons are presented for the Théroux and PARAGON A studies. The risk differences reported ranged from –0.8% in the Théroux study (for lamifiban dose of 1, 2 or 5 µg/minute) to 5.0% (for lamifiban dose of 4 µg/minute).

Myocardial infarction

The risk differences for new MI at 30 days and 6 months are presented in *Figure 16*. In the Théroux and PARAGON A trials, the study drugs were not significantly better than the control, although many of the point estimates favour treatment.

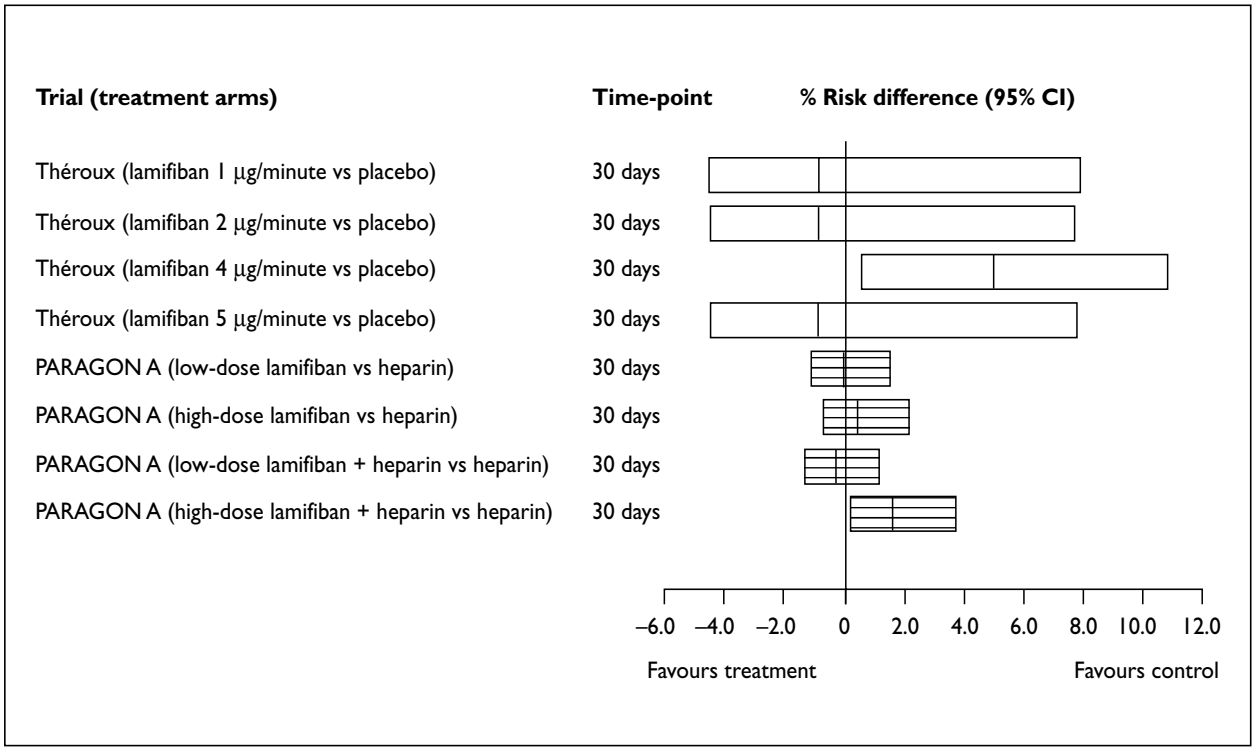

FIGURE 15 *Théroux[28] and PARAGON A[29] trials of lamifiban: mean risk differences for outcome of death*

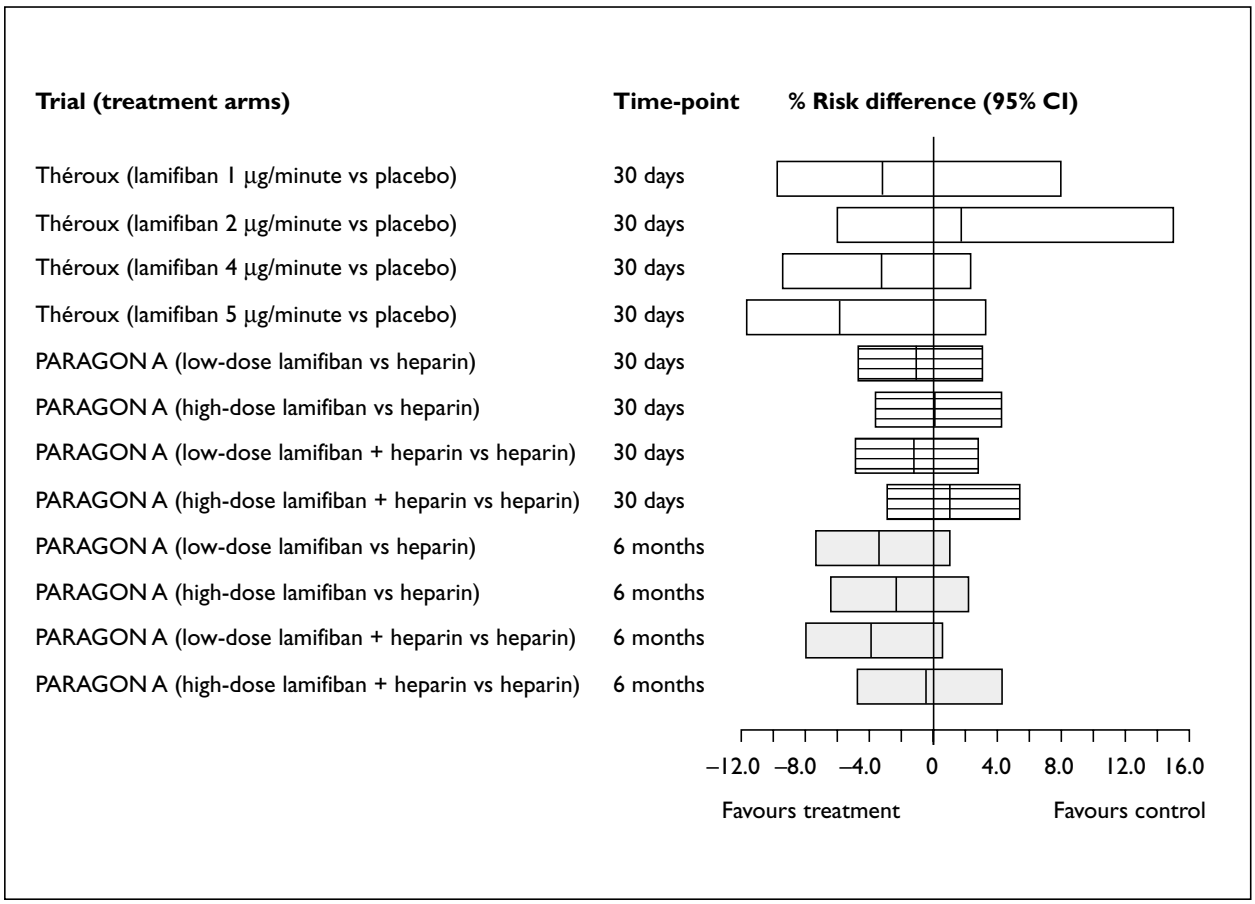

FIGURE 16 *Théroux[28] and PARAGON A[29] trials of lamifiban: mean risk differences for outcome of MI*

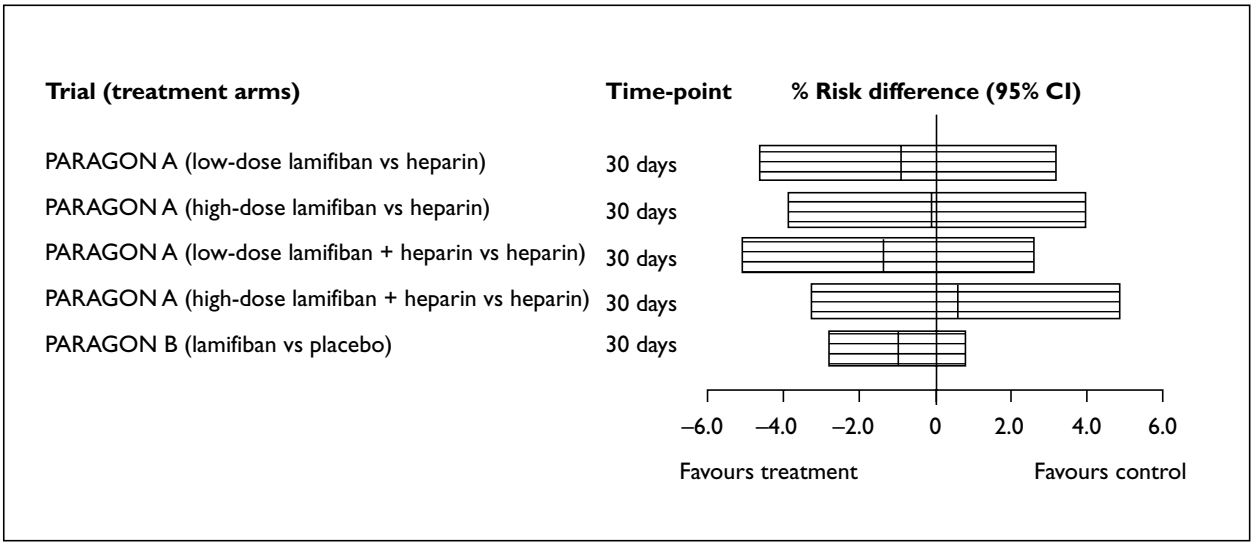

FIGURE 17 *PARAGON A[29] and B[30] trials of lamifiban: mean risk differences for composite end-points*

TABLE 29 *Composite end-points at 30 days in trials of lamifiban*

Study	Treatment	% RD	95% CI	NNT	95% CI
PARAGON A, 1998[29]	Low-dose lamifiban vs heparin	–0.9	–4.6 to 3.2	112	22 to infinity
	High-dose lamifiban vs heparin	–0.1	–3.8 to 3.9	799	26 to infinity
	Low-dose lamifiban + heparin vs heparin	–1.3	–5.1 to 2.6	72	20 to infinity
	High-dose lamifiban + heparin vs heparin	0.6	–3.3 to 4.9	–169*	– infinity to –21
PARAGON B, 1999[30]	Lamifiban vs placebo	–1.0	–2.8 to 0.8	102	37 to infinity

* *Represents an NNH of 169 (i.e. for every 169 patients treated, one additional patient will experience an unfavourable outcome), rather than the NNT*

Composite end-points

The results for the composite end-points used in the trials (all-cause mortality and non-fatal MI) are illustrated in *Figure 17*. The risk differences and NNT or NNH for lamifiban compared with placebo at 30 days are presented in *Table 29*. High-dose lamifiban (combined with heparin) versus heparin alone results in an NNH of 169 patients treated for each additional patient to experience all-cause mortality, non-fatal MI or re-infarction. For all other combinations and doses, the resulting NNT values ranged from 72 to 799, with the 95% CIs including infinity.

Recurrent ischaemia

Refractory ischaemia was reported as an outcome only in the Théroux trial. Risk differences during drug infusion and at 30 days are shown in *Figure 18*. CIs for all the point estimates are wide, reflecting the small sample size.

Revascularisation

Table 30 presents the data regarding the need for revascularisation in each lamifiban trial. The PARAGON B study reported only combined results (treatment and control arms together) for cardiac catheterisation and angioplasty.

Figure 19 shows the risk differences for PCI during hospitalisation in the PARAGON A study. The risk difference for PTCA for low-dose lamifiban alone versus heparin was –3.4% (95% CI, –7.7% to 1.3%), with an NNT of 29 (however, the 95% CI includes infinity). The risk difference for high-dose lamifiban plus heparin versus heparin was –6.0% (95% CI, –10.3% to –1.7%), with an NNT of 16.

Adverse events

The main concerns about the adverse effects of lamifiban were related to an extension of the pharmacological effect: bleeding, thrombocytopenia and complications of these (e.g. haemorrhagic strokes).

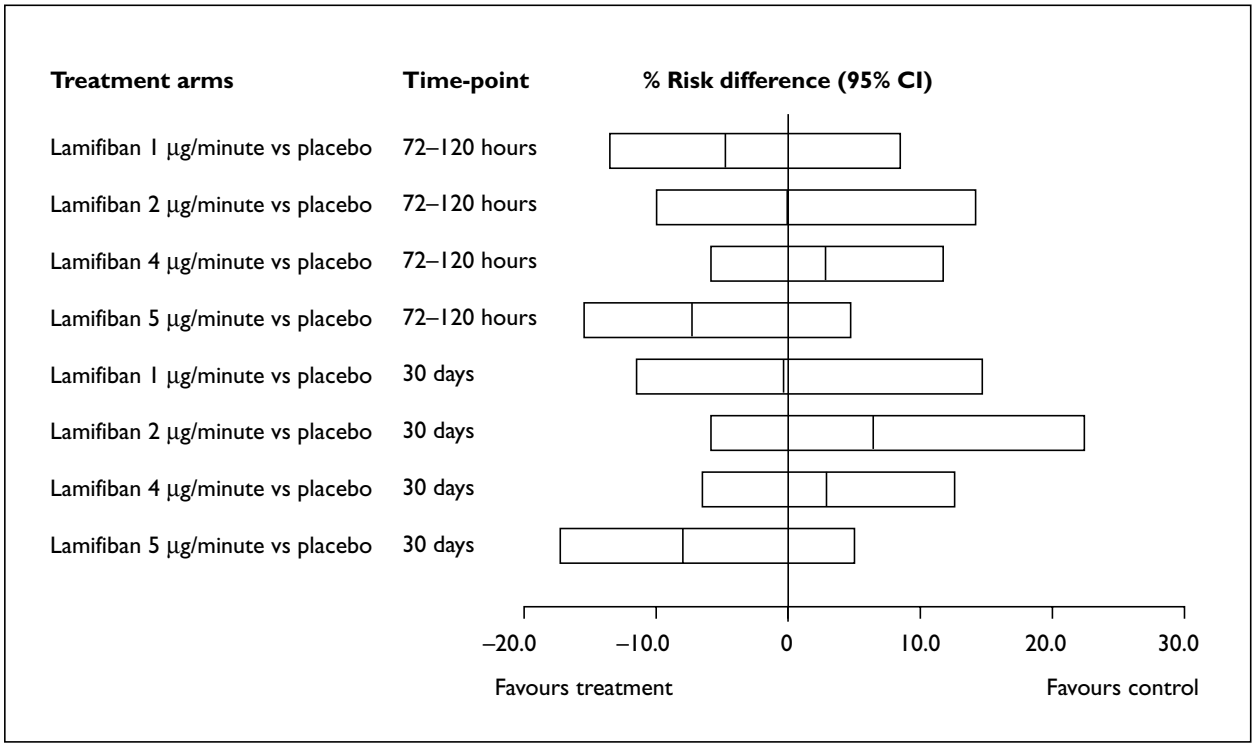

FIGURE 18 *Théroux trial[28] of lamifiban: mean risk differences for outcome of recurrent ischaemia*

TABLE 30 *Revascularisation rates in trials of lamifiban*

Study	Treatment arm	Time-point	Cardiac catheterisation (%)	Coronary angioplasty (%)	Cardiac bypass (%)
PARAGON A, 1998[29]	High-dose lamifiban + heparin	During hospitalisation	51	12 (1.6)*	12
	High-dose lamifiban		47	13 (1.5)*	10
	Low-dose lamifiban + heparin		50	13 (2.1)*	12
	Low-dose lamifiban		50	15 (1.6)*	10
	Heparin		53	17 (2.4)*	11
PARAGON B, 1999[30]	Lamifiban	30 days	65†	27–28†	~15
	Placebo				~15

* *Rates of emergency procedures appear in parentheses*
† *Rates reported only for combined groups (treatment and control arms)*

Bleeding
Table 31 details the definitions of major and minor bleeding used in each of the trials. The definition of major bleeding in the Théroux trial is very similar to the TIMI criteria. The bleeding rates observed in each of the three studies are reported in *Table 32*.

Figure 20 shows the risk differences for major bleeding, as defined by each trial. The risk difference for bleeding for high-dose lamifiban plus heparin versus heparin at 30 days in the PARAGON A study was 1.6% (95% CI, 0.2% to 3.8%), with an NNT of 63 (95% CI, 26 to 500). However, the bleeding rates for low-dose lamifiban and high-dose lamifiban alone were close to those of heparin alone.

Thrombocytopenia
Thrombocytopenia was reported in the PARAGON A study and mentioned in the PARAGON B abstract. The reported data are

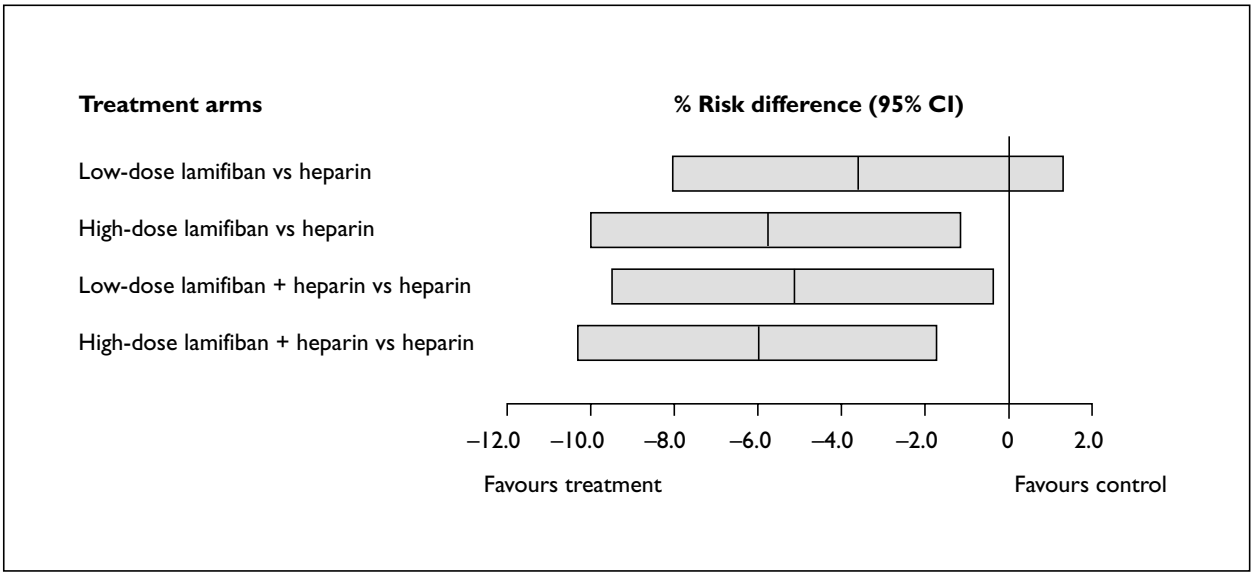

FIGURE 19 *PARAGON A trial[29] of lamifiban: mean risk differences for outcome of PTCA during hospitalisation*

TABLE 31 *Definitions of bleeding in trials of lamifiban*

Study	Major/minor bleeding
Théroux *et al.*, 1996[28]	Major bleeding: intracranial haemorrhage, cardiac tamponade, a decrease in blood haemoglobin of ≥ 5 g/dl or the need for blood transfusion Minor bleeding: all bleeding affecting the patients' daily activities Other types of bleeding, such as minor bruises or self-limiting mucosal bleeding, were classified as insignificant
PARAGON A, 1998[29]	Major bleeding: not defined Intermediate bleeding: bleeding necessitating a red blood cell transfusion or causing a drop in blood haemoglobin of > 5 g/dl without haemodynamic compromise
PARAGON B, 1999[30]	Not defined

presented in *Table 33*. The risk differences for the incidence of thrombocytopenia in the PARAGON A study are illustrated in *Figure 21*. While the point estimates for lamifiban alone indicate harm and the estimates for lamifiban plus heparin indicate reduced risk, the CIs overlap, suggesting caution in interpretation.

Troponin levels and outcome

Troponin T and I are markers of MI and may be useful in stratifying cardiac risk to a greater extent than is possible with current routine clinical methods.

PRISM study and troponin

To investigate the ability of troponin levels to predict response to tirofiban, the PRISM investigators attempted to measure troponin levels at baseline (mean, 8.4 hours after onset of symptoms) in all patients enrolled. Of the 3232 patients enrolled in the PRISM study, troponin levels were available for 2222 (69%). Missing samples were due to insufficient volume or haemolysis. The authors stated that the characteristics of this subset of patients did not differ from those of the overall PRISM study population.

The diagnostic threshold of troponin I for MI is 2.0 µg/l or more. The diagnostic threshold used to define patients with ACS (troponin I-positive) in the PRISM study was greater than 1.0 µg/l. The lower detection limit of the troponin T assay is 0.01 µg/l, and the diagnostic threshold used to define patients with ACS (troponin T-positive) in this study was greater than 0.1 µg/l.

The presented data on the outcomes of death, MI, recurrent ischaemia and death or MI were stratified by troponin I-positive (+) or -negative

TABLE 32 *Rates of the occurrence of bleeding episodes in trials of lamifiban*

Study	Treatment arm	Time-point	Stroke (%)	Major bleeding episode (%)	Minor bleeding episode (%)
Théroux *et al.*, 1996[28]	Lamifiban, 1 μg/minute (*n* = 40)	Drug infusion + 24 hours		0.0	0.0
	Lamifiban, 2 μg/minute (*n* = 41)			0.0	14.6
	Lamifiban, 4 μg/minute (*n* = 120)		–	5.8	11.7
	Lamifiban, 5 μg/minute (*n* = 40)			0.0	17.1
	Placebo (*n* = 128)			0.8	1.6
PARAGON A, 1998[29]	Low-dose lamifiban (*n* = 378)	30 days	1.1	0.8	2.9
	Low-dose lamifiban + heparin (*n* = 377)		1.1	0.5	5.8
	High-dose lamifiban (*n* = 396)		0.8	1.3	8.4
	High-dose lamifiban + heparin (*n* = 373)		0.5	2.4	9.2
	Heparin (*n* = 758)		0.4	0.8	4.4
PARAGON B, 1999[30]	Lamifiban (*n* = 2628)	30 days	1.1	–	14*
	Placebo (*n* = 2597)		0.6	–	12*

* *Intermediate bleeding in PARAGON B study*

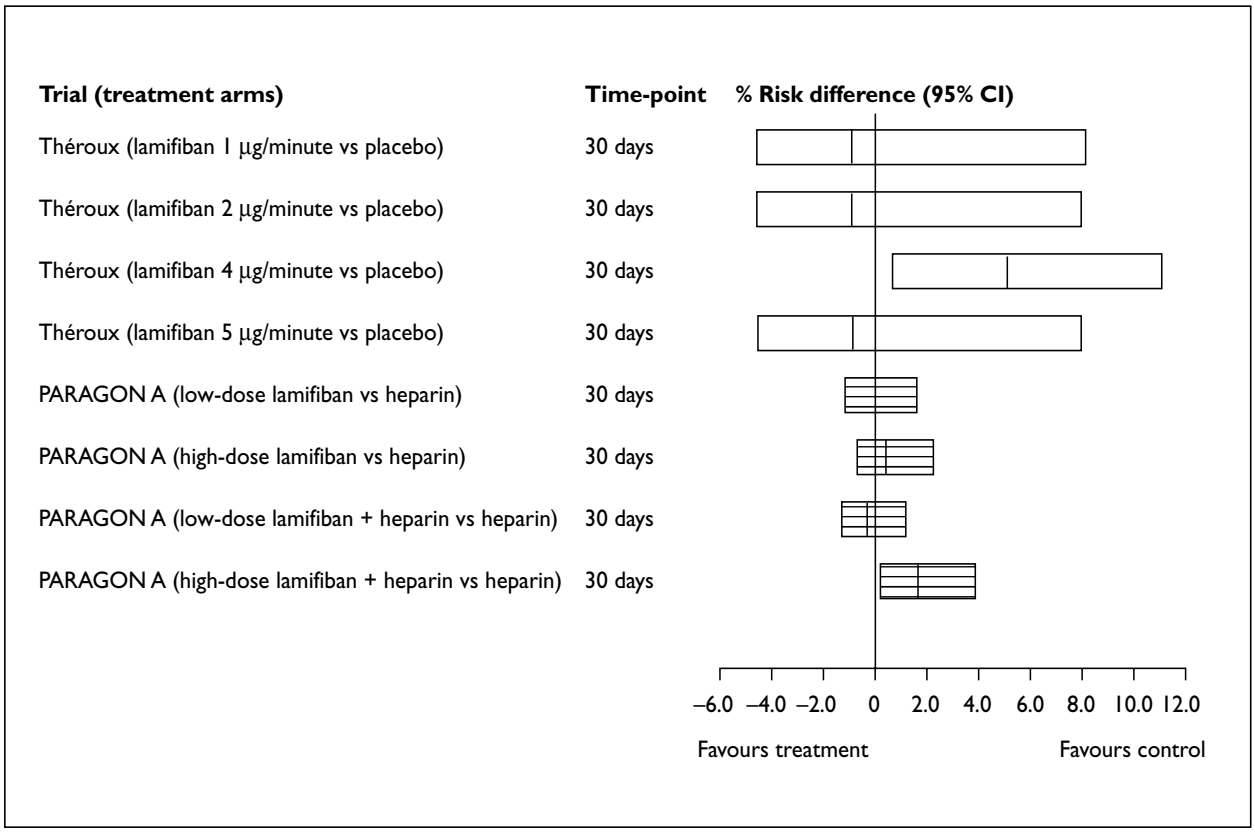

FIGURE 20 *Théroux[28] and PARAGON A[29] trials of lamifiban: mean risk differences for adverse events of major bleeding*

TABLE 33 *Incidence of thrombocytopenia in trials of lamifiban*

Study	Definition of thrombocytopenia	Treatment arm	Incidence (%)
Théroux *et al.*, 1996[28]	Not reported	–	–
PARAGON A, 1998[29]	Not defined	Low-dose lamifiban	2.1
		Low-dose lamifiban + heparin	0.8
		High-dose lamifiban	1.8
		High-dose lamifiban + heparin	0.8
		Heparin	1.1
PARAGON B, 1999[30]	Not defined	Lamifiban Placebo	Incidence of 'severe' thrombocytopenia was low but slightly higher in lamifiban group; however, this difference was not statistically significant

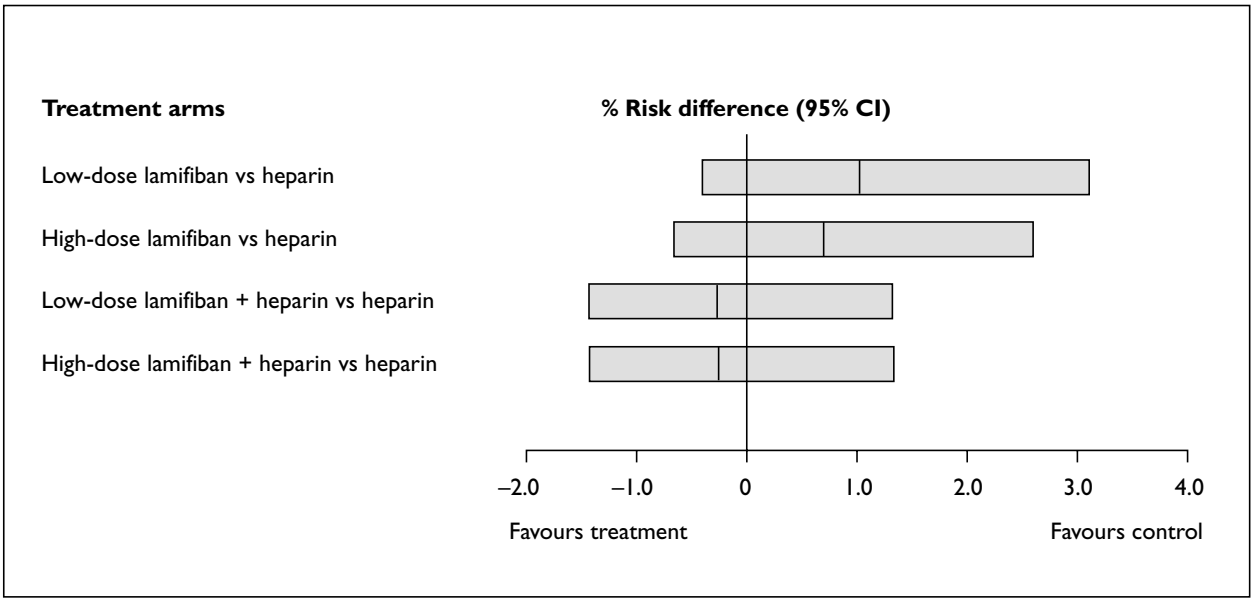

FIGURE 21 *PARAGON A trial[29] of lamifiban: mean risk differences for adverse event of thrombocytopenia*

(–) for both the heparin and tirofiban groups. *Figure 22* shows the risk differences plotted for 48 hours, 7 days and 30 days. Patients with elevated troponin I appeared to respond to tirofiban, whereas those with non-elevated troponin I did not. At 7 and 30 days, the risk difference was significant for death, with values of –3.0% (95% CI, –5.8% to –0.9%) and –4.5% (95% CI, –7.9% to –1.6%), respectively; while the difference for recurrent ischaemia was significant at 48 hours and 7 days, with values of –6.0% (95% CI, –10.0% to –2.3%) and –6.0% (95% CI, –11.0% to –1.0%), respectively. The data for troponin T were not presented in a way that permitted forest plots to be made. However, the results reported (adjusted hazard ratios) showed a similar pattern. Regression analysis with interaction terms for troponin T and randomised treatment showed that there was no significant difference in the event rates between heparin and tirofiban in troponin T-negative patients. For troponin T-positive patients, the rate of recurrent ischaemia was lower in the tirofiban group at 48 hours (3.1% versus 8.8%) and at 30 days (9.1% versus 15.2%; relative risk, 0.56; 95% CI, 0.34 to 0.91). The event rate of death or MI at 30 days was lower in the tirofiban group (3.5% versus 13.7%; relative risk, 0.23; 95% CI, 0.12 to 0.45).

Composite end-point (death or MI)

As illustrated in *Figure 22*, the risk difference for troponin I-positive patients at 30 days was –8.7%

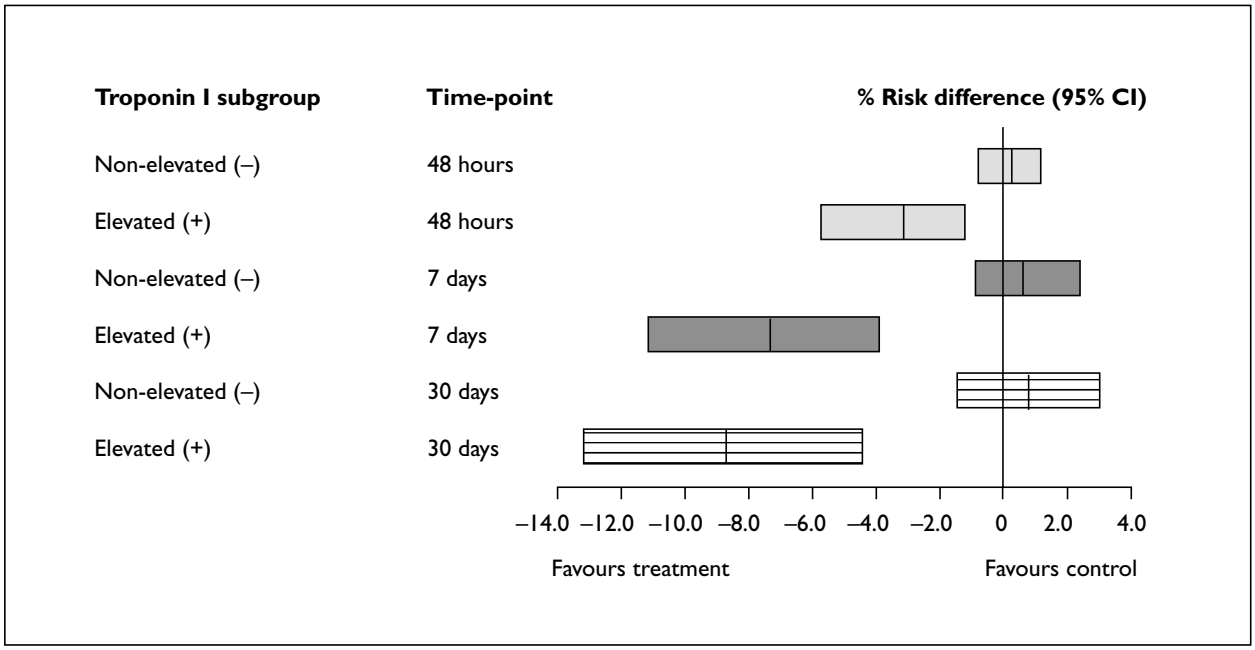

FIGURE 22 *PRISM trial[20] of tirofiban: mean risk differences for composite end-point by troponin I subgroup*

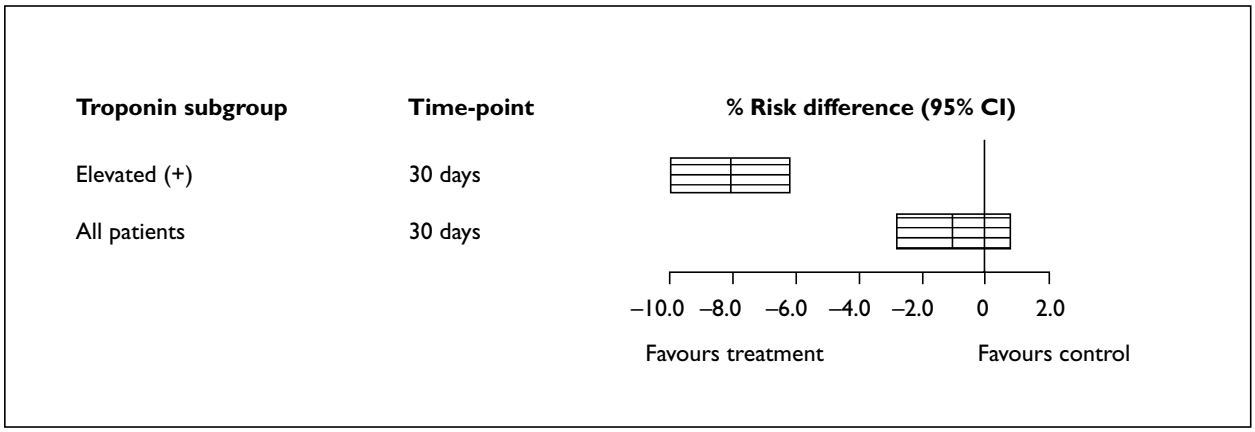

FIGURE 23 *PARAGON B trial[30] of lamifiban: mean risk differences for composite end-point by troponin subgroup*

(95% CI, –13.2% to –4.4%), with a calculated NNT of 12 (95% CI, 8 to 23). The risk difference for troponin I-negative patients at 30 days was 0.8% (95% CI, –1.4% to 3.1%), with a calculated NNH of 123 (95% CI, 31 to infinity).

PARAGON B study and troponin

The cut-off for troponin-positive/negative was not described in the abstract of the PARAGON B study, and the specific type of troponin measured and found elevated (I or T) was also not discussed.

As shown in *Figure 23*, the risk difference for troponin-positive patients in the PARAGON B study was –8.0% (95% CI, –9.9% to –6.1%), with a calculated NNT of 13 (95% CI, 11 to 17). For comparison, the risk difference for all patients was –1.0% (95% CI, –2.8% to 0.8%), with a calculated NNT of 102 (95% CI, 37 to infinity).

Chapter 5

Efficacy of oral glycoprotein IIb/IIIa antagonists

Several **oral** glycoprotein IIb/IIIa antagonists are currently being evaluated. Four randomised controlled trials of three oral glycoprotein antagonists (sibrafiban, orbofiban and lefradafiban)[33–35] used to treat unstable angina and ACSs (not in association with PCI) were identified by the current review's search strategy and met the inclusion criteria:

- Sibrafiban versus Aspirin to Yield Maximum Protection from Ischemic Heart Events Post-acute Coronary Syndromes (SYMPHONY)
- SYMPHONY 2
- Orbofiban in Patients with Unstable Coronary Syndromes, Thrombolysis in Myocardial Infarction (OPUS-TIMI) 16
- Fibrinogen Receptor Occupancy STudy (FROST), a dose-escalation trial of lefradafiban in patients with ACSs.

Three studies were published in abstract form only (FROST, SYMPHONY 2 and OPUS-TIMI 16). A Phase II study of sibrafiban (TIMI-12)[36] was excluded from the review, because patients with Q-wave MI were included in this study. For clarification, the SYMPHONY trial will be referred to as SYMPHONY 1.

Interventions

The SYMPHONY 1 and SYMPHONY 2 studies[33,34] examined the effect of different doses of sibrafiban with or without aspirin (*Table 34*). The OPUS-TIMI 16 trial[35] considered the effect of administering orbofiban plus aspirin for 30 days. The FROST study[35] considered the effect of treatment with lefradafiban plus aspirin and heparin for 1 month.

The length of follow-up varied between the trials. The SYMPHONY 1 study measured primary end-points over 90 days; secondary end-points were also analysed at 6 and 12 months. The SYMPHONY 2 trial was stopped early when the results of SYMPHONY 1 were published, therefore the

TABLE 34 *Design of included studies of oral glycoprotein IIb/IIIa antagonists*

Study	Design	Treatment arms	Number of participants	Number lost to follow-up	Follow-up time-points
SYMPHONY 1, 2000[33]	RCT	Low-dose sibrafiban	3105	25	90 days
		High-dose sibrafiban	3039	24	Then at 6 and 12 months for secondary end-points only
		Aspirin	3089	15	
SYMPHONY 2, 2000[34]	RCT	Low-dose sibrafiban + aspirin	2133*	NS	NS
		High-dose sibrafiban	2133*	NS	
		Aspirin	2133*	NS	
OPUS-TIMI 16, 1999[35]	RCT	High-dose orbofiban	3434*	NS	30 days
		Tapering-dose orbofiban	3434*	NS	Then at subsequent
		Placebo	3434*	NS	follow-up (mean, 7 months)
FROST, 1999[35]	RCT	Low-dose lefradafiban	132*	NS	NS
		Medium-dose lefradafiban	132*	NS	
		High-dose lefradafiban	132*	NS	
		Placebo	132*	NS	

NS, not specified

* *Abstract states the total number of patients randomised; the number in each group is estimated only*

length of follow-up was not reported. The OPUS-TIMI 16 study followed participants for a mean duration of 7 months. However, enrolment was stopped early because of excess 30-day mortality in one treatment group. The FROST study failed to report the length of follow-up. Participants receiving high-dose lefradafiban discontinued treatment early as a consequence of excessively high bleeding rates. The data compiled up until the point of discontinuation in the SYMPHONY 2, OPUS-TIMI 16 and FROST studies are presented.

All the trials included patients with unstable angina and ACSs. Specific inclusion and exclusion criteria varied between trials (*Table 35*).

The SYMPHONY 1 study investigated two different doses of sibrafiban (*Table 36*) versus aspirin. The experimental group did not receive aspirin as additional therapy, and the placebo group received only aspirin. The SYMPHONY 2 study also compared the effect of high and low doses of sibrafiban. The low-dose group received aspirin as additional therapy. In the OPUS-TIMI 16 trial, the participants received different doses of orbofiban or an unknown placebo. It was not possible to determine the duration of treatment with orbofiban after 50 mg was administered twice daily for 30 days.[35] The FROST study assessed the use of different doses of lefradafiban versus placebo.[35] All the participants also received a combination of aspirin and heparin.

Baseline characteristics

The mean age of participants was 60 years in the SYMPHONY 1 and SYMPHONY 2 studies (*Table 37*). From the data presented, it was not possible to determine the age of participants in the OPUS-TIMI 16 or FROST trial,[35] nor was it possible to determine cardiac prognostic indicators, such as previous ischaemic episodes and heart failure, in any of the included trials.

TABLE 35 *Inclusion and exclusion criteria used in trials of oral drugs*

Study/drug	Inclusion criteria	Exclusion criteria
SYMPHONY 1, 2000[33] Sibrafiban	Chest pain or anginal-equivalent symptoms for ≥ 20 minutes **and** at least one of the following criteria: CK-MB level above the upper limit of normal Total CK level twice the upper limit of normal Troponin I or T concentration above the upper limit of normal ST-segment elevation or depression of 0.5 mV New LBBB Clinically stable for 12 hours pre-enrolment Killip class II or lower No continuing ischaemia	Serious illness Predisposition to bleeding Major surgery Previous stroke or intracranial haemorrhage Poor dentition History of nose bleeds Packed-cell volume < 30% Platelet count < 1 x 10^{11}/l Prothrombin time (international normalised ratio) > 1.5 Serum creatinine level > 133 µmol/l Treatment with other antiplatelet agents, warfarin or other investigational agents Need for long-term treatment with NSAIDs or steroids Previous sibrafiban treatment
SYMPHONY 2, 2000[34] Sibrafiban	ACS of 7 days duration Initially stabilised (without CHF, ongoing chest pain or haemodynamic instability at time of enrolment)	Serum creatinine level > 1.5 mg/dl Propensity for bleeding Haematocrit < 30% or platelet count < 100,000/mm^3 CNS pathology Long-term requirement for warfarin, aspirin or NSAIDs
OPUS-TIMI 16, 1999[35] Orbofiban	ACS Unstable angina (pain at rest within 72 hours of enrolment) Most patients had documented ECG and/or enzyme changes	NS
FROST, 1999[35] Lefradafiban	ACS Chest pain during past 24 hours Documented ECG changes	NS

NS, not specified

TABLE 36 *Interventions specified by study protocols*

Study	Intervention 1	Intervention 2	Intervention 3	Control
SYMPHONY 1, 2000[33]	***Low-dose sibrafiban*** Creatinine ≤ 0.8 mg/dl • Weight ≤ 70 kg: 3.0 mg every 12 hours • Weight > 70 to ≤ 100 kg: 4.5 mg every 12 hours • Weight > 100 kg: 4.5 mg every 12 hours Creatinine > 0.8 to 1.1 mg/dl • Weight ≤ 70 kg: 3.0 mg every 12 hours • Weight > 70 kg to ≤ 100 kg: 3.0 mg every 12 hours • Weight >100 kg: 4.5 mg every 12 hours Creatinine > 1.1 to 1.5 mg/dl • Weight ≤ 70 kg: 3.0 mg every 12 hours • Weight > 70 to ≤ 100 kg: 3.0 mg every 12 hours • Weight > 100 kg: 3.0 mg every 12 hours	***High-dose sibrafiban*** Creatinine ≤ 0.8 mg/dl • Weight ≤ 70 kg: 4.5 mg every 12 hours • Weight > 70 to ≤ 100 kg: 6.0 mg every 12 hours • Weight > 100 kg: 6.0 mg every 12 hours Creatinine > 0.8 to 1.1 mg/dl • Weight ≤ 70 kg: 4.5 mg every 12 hours • Weight > 70 to ≤ 100 kg: 6.0 mg every 12 hours • Weight > 100 kg: 6.0 mg every 12 hours Creatinine > 1.1 to 1.5 mg/dl • Weight ≤ 70 kg: 3.0 mg every 12 hours • Weight > 70 to ≤ 100 kg: 4.5 mg every 12 hours • Weight > 100 kg: 6.0 mg every 12 hours	NA	• Aspirin: 80 mg every 12 hours
SYMPHONY 2, 2000[34]	***Low-dose sibrafiban + aspirin*** • Sibrafiban: dose based on patient weight and renal function • Plus aspirin: 80 mg every 12 hours	***High-dose sibrafiban*** • Sibrafiban: dose based on patient weight and renal function	NA	• Aspirin: 80 mg every 12 hours
OPUS-TIMI 16, 1999[35]	***High-dose orbofiban*** • Orbofiban: 50 mg twice daily for 30 days • Plus aspirin: 150–162 mg daily	***Tapering-dose orbofiban*** • Orbofiban: 50 mg twice daily for 30 days • Then orbofiban: 30 mg twice daily • Plus aspirin: 150–162 mg daily	NA	• Placebo • Plus aspirin: 150–162 mg daily
FROST, 1999[35]	***Low-dose lefradafiban*** • Lefradafiban: 20 mg three times daily • Plus aspirin and heparin	***Medium-dose lefradafiban*** • Lefradafiban: 30 mg three times daily • Plus aspirin and heparin	***High-dose lefradafiban*** • Lefradafiban: 45 mg three times daily • Plus aspirin and heparin	• Placebo • Plus aspirin and heparin

Secondary drugs

No data on the use of other anti-anginal medications (i.e. nitrates, calcium channel blockers or beta-adrenergic blockers) used pre- or post-intervention were presented in the SYMPHONY 1, SYMPHONY 2, OPUS-TIMI 16 and FROST trial reports.

Definition of outcomes

A composite end-point was considered the primary outcome measure in all studies. All-cause mortality, new non-fatal MI, re-infarction or severe recurrent ischaemia were considered in both of the SYMPHONY studies. The definitions of end-points for SYMPHONY 1 are shown in *Table 38*.

TABLE 37 *Baseline characteristics of participants in trials of oral drugs*

Study	Intervention	Median age (years)	Prognostic indicators	*n* (%)
SYMPHONY 1, 2000[33]	Low-dose sibrafiban	60	MI	599 (19)
			CABG	293 (9)
			PTCA	332 (11)
			Heart failure	142 (5)
	High-dose sibrafiban	60	MI	559 (18)
			CABG	270 (9)
			PTCA	303 (10)
			Heart failure	136 (5)
	Control: aspirin	60	MI	609 (20)
			CABG	244 (8)
			PTCA	312 (10)
			Heart failure	148 (5)
SYMPHONY 2, 2000[34]	Low-dose sibrafiban + aspirin	60	NS	NS NS
	High-dose sibrafiban	60	NS	NS NS
	Control: aspirin	60	NS	NS NS
OPUS-TIMI 16, 1999[35]	High-dose orbofiban	NS	NS	NS NS
	Tapering-dose orbofiban	NS	NS	NS NS
	Control: placebo	NS	NS	NS NS
FROST, 1999[35]	Low-dose lefradafiban	NS	NS	NS NS
	Medium-dose lefradafiban	NS	NS	NS NS
	High-dose lefradafiban	NS	NS	NS NS
	Control: placebo	NS	NS	NS NS

NS, not specified

The OPUS-TIMI 16 study considered death, MI, recurrent ischaemia leading to hospitalisation, urgent revascularisation and stroke to be end-points, whereas FROST considered death, MI and severe recurrent angina leading to revascularisation to be end-points. Neither the OPUS-TIMI 16 nor FROST trial provided definitions of the outcome measures used.

Internal validity

The assessment of the internal validity of these studies is presented in *Table 39*.

Results of trials

Given the substantial heterogeneity of interventions studied, doses used and outcome measures evaluated across studies, it would not be sensible to use meta-analysis to pool the results of these studies. Instead, the results of the included studies have been presented in tabular form (*Table 40*).

Myocardial Infarction

The risk of new MI and re-infarction showed no significant difference between groups in the SYMPHONY 1 study (*Table 40*). No other data were available

Refractory ischaemia (severe recurrent angina)

In the SYMPHONY 1 study, the rates of recurrent ischaemia were not significantly different in the sibrafiban and aspirin groups (*Table 40*).

Death from any cause

Results from the SYMPHONY 1 study suggest a higher rate of mortality in the sibrafiban treatment arms compared with controls, but this difference was not statistically significant. The SYMPHONY 2 study also observed an excess of deaths in participants treated with high-dose sibrafiban compared with low-dose sibrafiban or aspirin

TABLE 38 *Definitions of outcomes in trials of oral drugs*

Study	Acute MI	Severe recurrent ischaemia	Composite end-point
SYMPHONY 1, 2000[33]	1. (Re)elevation of CK-MB level to above the upper limit of the reference range **or** an increase in CK-MB level by ≥ 50% or CK level ≥ two times the upper reference limit **or** new significant Q waves in two or more leads on an ECG or elevation in troponin I or T level above the upper reference limit ***Within 18 hours*** 2. Severe ischaemic pain lasting at least 20 minutes or recurrent ST elevation (> 0.5 mm) for at least 20 minutes 3. Periprocedural CK-MB (or CK) level ≥ three times the upper reference limit or new significant Q waves in at least two leads on an ECG 4. Perioperative CK-MB (or CK) level ≥ five times the upper reference limit or new Q waves in at least two leads on an ECG	Recurrent chest discomfort or other equivalent ischaemic symptoms lasting at least 20 minutes and leading to unplanned or unscheduled revascularisation	Death, non-fatal MI or re-infarction, or severe recurrent ischaemia
SYMPHONY 2, 2000[34]	NS	NS	Death, MI or severe recurrent ischaemia
OPUS-TIMI 16, 1999[35]	NS	NS	Death, MI, recurrent ischaemia leading to rehospitalisation or urgent revascularisation, or stroke
FROST, 1999[35]	NS	NS	Death, MI or recurrent angina leading to revascularisation

NS, not specified

(*Table 40*). The OPUS-TIMI 16 trial reported that the use of orbofiban may be associated with a small early excess in mortality.

Revascularisation

The SYMPHONY 1 study presented data on the numbers of participants requiring any revascularisation and those requiring readmission to hospital regardless of cause. The data reported showed no significant difference between groups (*Table 41*). The rates of all-cause readmission were generally found to track rates of revascularisation. The type of revascularisation (PTCA, stenting or CABG) was not reported for each intervention group. The SYMPHONY 2 study reported no significant difference in the rate of revascularisation between treatment arms. A reduction in the rate of revascularisation was observed in those treated with orbofiban compared with placebo in the OPUS-TIMI 16 trial.

Adverse events

The main adverse effects of oral glycoprotein IIb/IIIa antagonists consisted of bleeding, thrombocytopenia and complications of these (e.g. haemorrhagic strokes).

Bleeding

Table 42 shows the bleeding event rates in the various groups. The SYMPHONY 1 study reported "significant gradients, from aspirin to low-dose sibrafiban to high-dose sibrafiban, in the rates of major, minor bleeding and their composite." The SYMPHONY 2 study reported

TABLE 39 *Assessment of internal validity*

	SYMPHONY 1, 2000[33]	SYMPHONY 2, 2000[34]	OPUS-TIMI 16, 1999[35]	FROST, 1999[35]
Internal validity				
Selection of prognostically homogeneous study population	+	?	?	?
Blinding of persons assessing inclusion criteria	+	?	?	?
Pre-stratification based on prognostically relevant variables	+	?	?	?
Random allocation: description of procedure	+	?	?	?
Registration of loss to follow-up	+	?	?	?
Blinding of patients	+	?	?	?
Blinding of persons implementing interventions	?	?	?	?
Registration of co-interventions that affect outcome for each group	–	?	?	?
Blinding of persons assessing treatment effects	+	?	?	?
Checking to what extent blinding was successful	?	?	?	?
Data description and analysis				
Measures of central tendency and their CIs	+	?	–	–
Statistical methods	+	?	?	?
Methods of dealing with missing values	?	?	?	?
Intention-to-treat analysis	+	?	?	?
Distributions of baseline characteristics	+	?	?	?
Method of accounting for any unbalances in prognostic variables	+	?	?	?

+, item properly addressed; –, item not properly addressed or not specified; ?, unknown

TABLE 40 *Results of studies of oral glycoprotein IIb/IIIa antagonists (each trial's primary outcome is shown in* ***bold****)*

Study	Treatment arm	*n*	MI	Recurrent ischaemia	Death	Composite end-point
			n (%)	*n* (%)	*n* (%)	*n* (%)
SYMPHONY 1, 2000[33]	Low-dose sibrafiban	3039	179 (5.8)	86 (2.8)	63 (2.0)	**310 (10.1)**
	High-dose sibrafiban	3089	195 (6.5)	75 (2.5)	59 (2.0)	**303 (10.1)**
	Aspirin	3105	171 (5.6)	97 (3.2)	54 (1.8)	**302 (9.8)**
SYMPHONY 2, 2000[34]	Low-dose sibrafiban + aspirin	2133*	NS	NS	(1.7)	**(9.2)**
	High-dose sibrafiban	2133*	NS	NS	(2.4)	**(10.5)**
	Aspirin	2133*	NS	NS	(1.3)	**(9.3)**
OPUS-TIMI 16, 1999[35]	High-dose orbofiban	3434*	NS	(3.3)	(1.6)	**(9.3)**
	Tapering-dose orbofiban	3434*	NS	(2.9)	(2.3)	**(9.7)**
	Placebo	3434*	NS	(5.3)	(1.4)	**(10.7)**
FROST, 1999[35]	Low-dose lefradafiban	132*	NS	NS	NS	NS
	Medium-dose lefradafiban	132*	NS	NS	NS	NS
	High-dose lefradafiban	132*	NS	NS	NS	NS
	Placebo	132*	NS	NS	NS	NS

NS, not specified

* *Only total numbers randomised were specified; an equal breakdown was assumed*

TABLE 41 *Revascularisation rates in trials of oral glycoprotein IIb/IIIa antagonists*

Study	Treatment arm	Any revascularisation (%)
SYMPHONY 1, 2000[33]	Low-dose sibrafiban	23.3
	High-dose sibrafiban	22.2
	Aspirin	23.3
SYMPHONY 2, 2000[34]	Low-dose sibrafiban + aspirin	NS
	High-dose sibrafiban	NS
	Aspirin	NS
OPUS-TIMI 16, 1999[35]	High-dose orbofiban	NS
	Tapering-dose orbofiban	NS
	Placebo	NS
FROST, 1999[35]	Low-dose lefradafiban	NS
	Medium-dose lefradafiban	NS
	High-dose lefradafiban	NS
	Placebo	NS

NS, not specified

TABLE 42 *Rates of the occurrence of bleeding episodes in trials of oral drugs*

Study	Treatment arm	Stroke (*n*)	Major bleeding episode (%)	Minor bleeding episode (%)	Any bleeding episode (%)
SYMPHONY 1, 2000[33]	Low-dose sibrafiban	26	5	18	27
	High-dose sibrafiban	17	6	25	36
	Aspirin	25	4	13	19
SYMPHONY 2, 2000[34]	Low-dose sibrafiban + aspirin	NS	NS	NS	NS
	High-dose sibrafiban	NS	NS	NS	NS
	Aspirin	NS	NS	NS	NS
OPUS-TIMI 16, 1999[35]	High-dose orbofiban	NS	3.7	NS	NS
	Tapering-dose orbofiban	NS	3.3	NS	NS
	Placebo	NS	1.9	NS	NS
FROST, 1999[35]	Low-dose lefradafiban	NS	NS	NS	3
	Medium-dose lefradafiban	NS	NS	NS	3
	High-dose lefradafiban	NS	NS	NS	11
	Placebo	NS	NS	NS	1

NS, not specified

that the sibrafiban groups had approximately twice the amount of major bleeding episodes, compared with the aspirin treatment arm. The OPUS-TIMI 16 trial reported that episodes of severe or major bleeding were "slightly, but significantly, increased" in patients treated with orbofiban. The FROST study did not present data on bleeding episodes, although participants treated with high-dose lefradafiban stopped treatment early as a consequence of excessively high bleeding rates.

Both SYMPHONY studies found no statistically significant difference in the incidence of stroke. The FROST study reported a "trend toward fewer recurrent ischaemic events."

Thrombocytopenia

Table 43 shows the incidence of thrombocytopenia. The SYMPHONY 1 and SYMPHONY 2 studies reported a low incidence of thrombocytopenia and reported no significant differences between groups. The OPUS-TIMI 16 trial stated that the incidence of thrombocytopenia was "rare, but slightly more frequent" in the orbofiban treatment arm. The FROST study reported an incidence of 0.5% in the arms treated with lefradafiban; however, the incidence in the placebo group was not specified.

Summary

Four randomised controlled trials evaluating the effect of oral glycoprotein IIb/IIIa antagonists met inclusion criteria. It was not possible to determine the quality of these studies because insufficient data were reported in three studies (SYMPHONY 2, OPUS-TIMI 16 and FROST). The reported data from the SYMPHONY 1 study suggest that sibrafiban offers no additional benefit when compared with aspirin. Treatment with either sibrafiban or orbofiban leads to an increase in clinical events and adverse outcomes, according to results from the SYMPHONY 2 and OPUS-TIMI 16 trials. The FROST study reported a trend towards fewer clinical events but also reported problems with the safety of lefradafiban.

TABLE 43 *Incidence of thrombocytopenia in trials of oral drugs*

Study	Treatment arm	Minor	Moderate	Severe
		n (%)	*n* (%)	*n* (%)
SYMPHONY 1, 2000[33]	Low-dose sibrafiban	83 (2.0)	10 (0.3)	9 (0.3)
	High-dose sibrafiban	66 (2.2)	8 (0.3)	8 (0.3)
	Aspirin	60 (2.0)	5 (0.2)	9 (0.3)
SYMPHONY 2, 2000[34]	Low-dose sibrafiban + aspirin	NS	NS	NS
	High-dose sibrafiban	NS	NS	NS
	Aspirin	NS	NS	NS
OPUS-TIMI 16, 1999[35]	High-dose orbofiban	NS	NS	NS
	Tapering-dose orbofiban	NS	NS	NS
	Placebo	NS	NS	NS
FROST, 1999[35]	Low-dose lefradafiban	NS	NS	NS
	Medium-dose lefradafiban	NS	NS	NS
	High-dose lefradafiban	NS	NS	NS
	Placebo	NS	NS	NS

NS, not specified

Chapter 6

Economic evaluations

Five economic evaluations of the glycoprotein IIb/IIIa antagonists in unstable angina and ACSs, excluding use closely associated with PCI, were found through literature searches. An additional two unpublished evaluations (of tirofiban[37] and eptifibatide[38]) were submitted by pharmaceutical companies; however, these evaluations pertain only to the intravenous use of these drugs.

Of these seven economic evaluations, only the two unpublished evaluations examine the cost-effectiveness of these drugs in the NHS. A paper by Szucs and co-workers[39] evaluates tirofiban, based on Swiss resource and cost data converted to European currency units. The four other analyses examine the cost-effectiveness using US cost and resource data.[40–43] Application of the findings of the foreign papers to the UK healthcare system is difficult or impossible and has not been attempted. While the other studies are considered briefly, the main focus of the discussion is on the two analyses relating to the UK.

Structured extractions from each of these papers are shown in *Tables 44–57*. An overview of the validity of the studies is presented in *Table 58*.

The number of different options for calculating cost-effectiveness ratios may reach 20 or more. This is due to the great choice in cost numerators (e.g. direct, indirect, short-term, long-term, UK, Western Europe and all countries) and effect denominators (e.g. 48 hours, 96 hours, 7 days, 30 days, 6 months and life-long), as well as the many possible ways of combining these choices.

Only the PURSUIT study of eptifibatide was planned with a prospective economic analysis. In a carefully conducted study, Mark and co-workers[40] calculated that the use of eptifibatide would cost US$16,491 per life-year gained or US$19,693 per quality-adjusted life-year (QALY) (*Tables 44* and *45*). These figures are based on the risk difference of 3.5% found in the North American subgroup. Using the overall 1.5% risk difference found in the PURSUIT study, the cost per life-year gained was US$33,619. It should be noted that the risk difference for the Western European patients was smaller (1.0%). It is difficult to translate the US findings to the UK. Further sensitivity analyses resulted in a cost of US$23,449 per QALY using a more conservative QALY rating scale outcome.

Analyses relating to UK

The submission by Merck Sharp & Dohme used the results of the PRISM-PLUS study to estimate the effectiveness of tirofiban (*Table 54*).[37] The PRAIS-UK study[44] was used to estimate UK-specific resource consumption. Finally, the CHKS Ltd (Alcester, UK) national comparative database of hospital activity was used to estimate costs of resources used. At 6 months, the calculated costs to prevent the occurrence of one composite end-point event (death, MI, refractory ischaemia or readmission for unstable angina/non-Q-wave MI) was £9955 (*Table 55*). The lower 95% confidence limit for this estimate was £4889. The upper 95% confidence limit could not be calculated because it involved a risk difference of zero, indicating additional costs with no added benefits. In a cost-offset analysis for the first 7 days, it was calculated that £97 of the £438 drug costs could be offset due to the reduction of event rates in the tirofiban-treated patients.

The submission by Schering-Plough used the results of the PURSUIT study to estimate the effectiveness of eptifibatide (*Table 56*).[38] This analysis seems to be thorough and was in part based on the methods developed by Mark and co-workers.[40] A cost-effectiveness analysis was presented using the effectiveness estimate based on the Western European patients of the PURSUIT study (a 0.37% risk difference for survival and a 1.01% risk difference for MI-free survival at 6 months favouring eptifibatide). Only the 429 UK patients in the PURSUIT study were used to estimate cost. Using a modelling approach and life expectancy data from the Duke Cardiovascular Disease Database, years of life gained were calculated. Depending on the discounting rate, the life expectancy difference between patients treated with eptifibatide and those receiving control treatment (not standardised in the PURSUIT study) was between

8 and 11 days (*Table 57*). The life-years gained analysis shows that treatment with eptifibatide is 'dominant', that is, the costs for eptifibatide are lower and the effects more favourable. Analysis at 30 days showed a cost-effectiveness ratio of £213 per death or MI avoided. When all Western European PURSUIT study patients were used to calculate cost, the cost-effectiveness ratios varied from £8179 to £11,079 per life-year gained, depending on the discount rate used for survival.

TABLE 44 *Description of study by Mark* et al.*, 2000*[40]

Country/ currency	Diagnosis definition	Drugs, doses and response rates	Source of efficacy data	Source of cost data	Methods
USA US$ (1996)	As defined in the PURSUIT study[23–27]	Eptifibatide, as used in the PURSUIT study	The results from the US subpopulation in the PURSUIT study were used The overall results from PURSUIT were used in a sensitivity analysis	Empirical resource use in the US Hospital charges were converted into costs using the department-specific correction factors	Cost analysis to 6 months Cost-effectiveness analysis (lifetime): US$ required to add 1 life-year, assuming no incremental cost difference between the treatment groups after 6 months Cost–utility analysis (time trade-off): US$ per QALY All analyses were performed prospectively alongside PURSUIT The perspective was societal, but inpatient consultations, non-medical cost, outpatient care (other than catheterisation) and productivity costs were omitted Discounting was done at 3%

TABLE 45 *Results of study by Mark* et al.*, 2000*[40]

Costs	Benefits	Synthesis	Sensitivity analysis	Author's conclusions
First 6 months: US$18,456 for eptifibatide vs US$18,828 for placebo ($p$ = 0.78) US$372 advantage for eptifibatide after 6 months was exclusive of drug costs Drug costs: US$1217 ± 574	0.111 undiscounted life-years	US$16,491 per life-year gained US$19,693 per QALY Discounted at 3%	Extensively used US$33,619 per life-year gained, if the overall PURSUIT results were used (i.e. non-US patients added to the analysis) US$23,449 per QALY, using a more conservative QALY rating scale outcome	Based on the US patients in the PURSUIT trial, the routine addition of eptifibatide to the usual care for patients with non-ST elevation ACS is economically attractive by conventional standards

TABLE 46 *Description of study by McElwee and Johnson, 1997*[41]

Country/ currency	Diagnosis definition	Drugs, doses and response rates	Source of efficacy data	Source of cost data	Methods
USA US$ (1996)	Unstable angina Non-Q-wave MI	Generalisation to all glycoprotein blockers was based on the effects of abciximab Bolus: 0.25 mg/kg Infusion: 0.6 mg/hour Doses were calculated for an 82-kg patient Infusion length: 60 hours for primary treatment or 24 hours for PTCA/stent only	IMPACT II, EPIC and CAPTURE studies: an extrapolation of the results from these trials was used for stents because no real data were available References 8–12 were used for frequency of death and MI post-CABG Data from the GUSTO trial[32] were used to estimate lifetime survival	IMPACT II All cost assumptions were based on a price of US$450 for 10 mg of abciximab	Cost-effectiveness analysis was based on a literature review (all patients vs PTCA/stent only vs standard care, which was not defined) The study took the perspective of the treating hospital Survival was discounted at 5% per year

IMPACT, Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis; EPIC, Evaluation of 7E3 for the Prevention of Ischemic Complications; CAPTURE, Chimeric 7E3 Antiplatelet Therapy in Unstable Angina Refractory to Standard Treatment

TABLE 47 *Results of study by McElwee and Johnson, 1997*[41]

Costs	Benefits	Synthesis	Sensitivity analysis	Author's conclusions
Urgent CABG: US$19,000 Elective CABG: US$14,000 Urgent PTCA: US$6500 Elective PTCA: US$3300 Stent: US$5500 Catheterisation: US$1500 Non-fatal MI: US$5000 Baseline costs of hospitalisation only: US$7500 Average total cost per patient: US$10,000, US$20,000 or US$41,000, depending on the use of RRR estimates of 20%, 30% or 40%, respectively	Life-years saved	Depending on the rate of revascularisation and RRR estimates, the costs per life-year saved varied from US$0 to about US$45,000	For treatment effects of primary therapy with glycoprotein blockers, RRR estimates of 20%, 30% and 40% vs revascularisation rates of 25–65% were used Death and MI rates after stenting were varied	For patients with acute ischaemic coronary syndromes, adjunctive or primary therapy with glycoprotein blockers would appear to yield good value for money relative to the present standard of care. Primary therapy [with glycoprotein blockers] is wise in patients with unstable angina

RRR, relative risk reduction

TABLE 48 *Description of study by Bell, 1999*[42]

Country/ currency	Diagnosis definition	Drugs, doses and response rates	Source of efficacy data	Source of cost data	Methods
USA US$ (1998)	As defined in the PURSUIT[23–27] and PRISM-PLUS[21] studies	Eptifibatide and tirofiban, according to the regimens used in the PURSUIT (testing eptifibatide vs placebo) and PRISM-PLUS (testing tirofiban vs placebo) studies Doses were calculated for an 85-kg patient	PURSUIT and PRISM-PLUS studies, including all patients who underwent early PCI. For medically managed patients, only the North American cohort was used because differences in concomitant treatment may affect the risk differences (and NNT values)	Wholesale acquisition cost	Cost-effectiveness analysis from the provider's perspective, based on a literature review: "cost to prevent one death or MI at 30 days" Note that two trials (PURSUIT and PRISM-PLUS) were compared (i.e. not a head-to-head comparison in one trial with randomised groups)

TABLE 49 *Results of study by Bell, 1999*[42]

Costs	Benefits	Synthesis	Sensitivity analysis	Author's conclusions
Eptifibatide PURSUIT (North American subpopulation) In patients who underwent early PCI: US$1078.60 In patients not receiving PCI: US$1078.60	Based on PURSUIT: NNT of 20 for patients undergoing early PCI and NNT of 37 for the North American subpopulation of patients not receiving PCI	To prevent one death or MI in patients who underwent early PCI, eptifibatide cost US$11,217 less than tirofiban	The 95% CIs of the risk differences were used. In addition, the wholesale acquisition costs were varied, but it was not stated how. These variables were not simultaneously modelled	Tirofiban and eptifibatide have the potential to be cost-effective if administered to populations at high risk for adverse outcomes of ACS
Tirofiban PRISM-PLUS (North American subpopulation) In patients who underwent early PCI: US$1082.76 In patients not receiving PCI: US$1037.07	Based on PRISM-PLUS: NNT of 23 for patients undergoing early PCI and NNT of 44 for the North American subpopulation of patients not receiving PCI	To prevent one death or MI in patients who were medically managed, eptifibatide cost US$5723 less than tirofiban		

TABLE 50 *Description of study by Hillegass* et al.*, 1999*[43]

Country/ currency	Diagnosis definition	Drugs, doses and response rates	Source of efficacy data	Source of cost data	Methods
USA US$ (year not stated)	ACS, as defined in the PRISM,[20] PRISM-PLUS[21] and PURSUIT[23–27] studies	Eptifibatide and tirofiban, according to the regimens used in the PRISM, PRISM-PLUS and PURSUIT studies	Outcomes at 30 days of the PRISM, PRISM-PLUS and PURSUIT studies	The paper only specifies the use of "data from Merck and Cor Pharmaceuticals and Premier Purchasing Partners"	Cost-effectiveness analysis based on a review of the literature

TABLE 51 *Results of study by Hillegass* et al.*, 1999*[43]

Costs	Benefits	Synthesis	Sensitivity analysis	Author's conclusions
Drug procurement costs (price providers pay to the manufacturers): US$1050–1223	Composite end-point of death or MI prevented at 30 days (expressed as NNT) PURSUIT: NNT, 67 PURSUIT (North American patients only): NNT, 30 PRISM: NNT, 77 PRISM-PLUS: NNT, 31	The cost per death or MI prevented at 30 days Eptifibatide (based on the complete PURSUIT study): US$81,941 Eptifibatide (based on the North American subpopulation in PURSUIT): US$36,690 Tirofiban (based on PRISM): US$53,900 Tirofiban (based on PRISM-PLUS): US$32,550	Not performed	It is likely that only the very-high-risk patients (such as patients with elevated troponin or unstable angina refractory to maximal traditional medical therapy, or the PRISM-PLUS trial population) will have cost-effectiveness ratios that most Western health-care systems can afford

TABLE 52 *Description of study by Szucs* et al.*, 1999*[39]

Country/ currency	Diagnosis definition	Drugs, doses and response rates	Source of efficacy data	Source of cost data	Methods
Switzerland Swiss francs (1998) ECU at a rate of 1 ECU to 1.6428 Swiss francs	As defined in the PRISM-PLUS study[21]	Tirofiban, as used in PRISM-PLUS study	PRISM-PLUS study	Typical clinical practice patterns (probability and quantity of additional days on the normal ward and in ICUs, and probability of revascularisation) in Swiss hospitals were estimated using structured interviews of six cardiologists representing university and smaller hospitals Costs per day on the normal ward and in the ICU were taken from a publication of the Association of Swiss Hospitals Revascularisation costs were taken from published secondary sources[29] ***Drug costs*** Tirofiban: 821 Swiss francs Heparin: 10 Swiss francs per day Additional days were weighted by average costs per day	Cost–benefit analysis The perspective of an average Swiss admitting hospital was taken, and a 7-day time-horizon was used

ECU, European currency unit; ICU, intensive care unit

TABLE 53 *Results of study by Szucs* et al.*, 1999*[39]

Costs	Benefits	Synthesis	Sensitivity analysis	Author's conclusions
Based on additional hospital days required to treat refractory ischaemic conditions and MI, potentially in the ICU, taking into account the need for revascularisation	The number of refractory ischaemic complications and MIs prevented in the first 7 days were costed	Savings of 549 Swiss francs per patient	Univariate analyses were performed using: • unit resource cost ± 50% • threshold analysis for drug costs • 95% CI for risk difference in the PRISM-PLUS study	Primary therapy with tirofiban is an economically justified intervention in the initial management of patients with acute coronary ischaemic syndrome in the Swiss hospital setting

TABLE 54 *Description of study by Merck Sharp & Dohme (tirofiban submission)*[37]

Country/ currency	Diagnosis definition	Drugs, doses and response rates	Source of efficacy data	Source of cost data	Methods
UK £ (year not stated)	As defined for the PRISM-PLUS study population[21]	Tirofiban, at doses used in PRISM-PLUS study	The primary end-point of the PRISM-PLUS study was used (death, MI, refractory ischaemia or readmission for unstable angina/ non-Q-wave MI) at 7 days and 180 days	Company data were used for drug costs The PRAIS-UK study[44] was used to estimate treatment patterns for UK patients with unstable angina/non-Q-wave MI who were receiving heparin Costs were estimated using the CHKS Ltd national comparative database of hospital activity	A cost-efficacy analysis and a cost-offset analysis were conducted

TABLE 55 *Results of study by Merck Sharp & Dohme (tirofiban submission)*[37]

Costs	Benefits	Synthesis	Sensitivity analysis	Author's conclusions
Drug costs: £438 (at £146 per vial) for 71-hour treatment, which was the average treatment duration in the PRISM-PLUS study Costs of events during the initial hospitalisation were estimated for the cost-offset analysis. Death: £2803 MI: £2737 Refractory ischaemia: £4807 Unstable angina/non-Q-wave MI: £1470	The 5% benefit at 7 days in the incidence of the composite end-point from PRISM-PLUS was used (risk difference). This end-point consisted of death, MI, refractory ischaemia or readmission for unstable angina/non-Q-wave MI. In addition, the 4.4% benefit at 180 days was used for the cost-efficacy analysis only Using the PRISM-PLUS outcome data at 7 days and taking into account only the most serious clinical outcome for each patient (to avoid double counting), the average cost saved per patient was £97	Incremental cost-effectiveness ratios: • at 7 days, £8760 • at 180 days, £9955 Cost-offset analysis: at 7 days, 22% (£97/£438, where £438 – £341 = £97) of the costs for tirofiban can be offset due to the reduction of events in the tirofiban-treated patients	The 95% CI limits of the risk difference were used Incremental cost-effectiveness ratios: • at 7 days, £5112 to £30,358 • at 180 days, £4889 to infinity Note that, at 180 days, the risk difference was zero, precluding the calculation of the upper 95% CI limit Cost-offset analysis at 7 days: £243 to £439, corresponding to 44% and 100%, respectively	Considered within the context of (a) the high clinical, economic and humanistic costs associated with CHD, as well as (b) the cost-effectiveness ratios for other glycoprotein IIb/IIIa antagonists and chronic CHD medications such as cholesterol reducers, the cost per event avoided ratios for tirofiban are comparable

CHD, coronary heart disease

TABLE 56 *Description of study by Schering-Plough (eptifibatide submission)*[38]

Country/ currency	Diagnosis definition	Drugs, doses and response rates	Source of efficacy data	Source of cost data	Methods
UK £ (1996)	As defined in the PURSUIT study[23–27]	Eptifibatide, as used in the PURSUIT study	The 3697 Western European patients from the PURSUIT study	Data on the resource consumption of the 429 UK patients in the PURSUIT study were collected prospectively. Resource unit costs were obtained from the UK hospitals' financial or contracts departments, or from the published literature	Cost-effectiveness analysis: • life-years gained, determined using a modelling approach employing data from the Western European patients in the PURSUIT study and data from the Western European PURSUIT-eligible subgroup of the Duke Cardiovascular Disease Database to estimate survival, assuming that resource use beyond 6 months was equal in both treatment groups • cost per death and MI prevented at 30 days Only direct medical costs were included in the analysis. Because all costs were occurred within 1 year, no discounting was applied on costs

TABLE 57 *Results of study by Schering-Plough (eptifibatide submission)*[38]

Costs	Benefits	Synthesis	Sensitivity analysis	Author's conclusions
Cost-effectiveness analysis at 30 days produced average total costs per patient (initial and rehospitalisation) Eptifibatide: £4666 Placebo: £4880	Incremental 6-month survival: 0.37% 6-month MI-free survival: 1.01% Life expectancy difference (undiscounted, discounted 1.5% and discounted 3%): 0.029, 0.025 and 0.022 years (i.e. 11, 9 and 8 days), respectively Risk difference for composite end-point at 30 days: 1%	Cost per life-years gained analysis, based on the UK data to estimate treatment cost: for the average eptifibatide-treated patient, the costs were lower and the effects better (eptifibatide was dominant) Cost-effectiveness analysis at 30 days: on average per patient, £213 can be saved per death or MI avoided by using eptifibatide	Cost per life-years gained analysis, based on the Western European data to estimate treatment cost: the costs per life-year gained varied from £8179 to £11,079, depending on the discount rate for survival at 0%, 1.5% and 3% Several (one-way) analyses were performed, with the resource consumption or the dose of the drug varied. Decreasing the dose increased savings for UK patients, whereas a fairly extreme scenario resulted in an estimate of £13,422 per life-year gained	The likely finding is that wide adoption of eptifibatide treatment will be nearly cost neutral but improve patient outcomes. The cost per life-year gained is likely to be between 'cost saving' and up to £11,079 per life-year gained, depending on the rate of discounting, source of resource consumption and sensitivity analysis. Assuming that 50% of the annual 125,000 UK patients with unstable angina/non-Q-wave MI would be treated with eptifibatide, this economic evaluation suggests that the NHS could save £9.6 million annually and reduce the number of deaths or MIs by 625

TABLE 58 *Validity assessment of economic evaluations*

	Mark, 2000[40]	McElwee, 1997[41]	Bell, 1999[42]	Hillegass, 1999[43]	Szucs, 1999[39]	MSD, 2000[37]	S-P, 2000[38]
Well-defined question	+	+	+	±	+	+	+
Comprehensive description of alternatives	+	–	+	+	+	+	+
Effectiveness established	+	±	+	±	+	+	+
All important and relevant costs and consequences for each alternative identified	+	±	–	–	–	–	±
Costs and consequences measured accurately	+	?	–	–	±	± PRAIS-UK[44]	±
Costs and consequences valued credibly	+	?	–	–	+	± CHKS Ltd	±
Costs and consequences adjusted for differential timing	+	±	NA	NA	NA	NA	+
Incremental analysis of costs and consequences	+	+	+	–	+	+	+
Sensitivity analyses to allow for uncertainty in estimates of cost or consequences	+	±	±	–	+	–	±
Study results/discussion include all issues of concern to users	+	–	+	–	+	±	±

MSD, Merck Sharp & Dohme; S-P, Schering-Plough; +, item properly addressed; ±, item partially addressed, –, item not properly addressed; ?, unknown

Chapter 7
Discussion

Efficacy of intravenous glycoprotein IIb/IIIa antagonists

Seven studies of three intravenous glycoprotein IIb/IIIa antagonists were found. Among these were two Phase II, one Phase II/III and four Phase III studies. The three drugs examined were eptifibatide, tirofiban and lamifiban. The validity assessment of these studies indicates that, in general, they were of good methodological quality. However, the current review identified reporting problems, particularly with the blinding of patients or persons providing care, a lack of details on randomisation methods, measuring and dealing with imbalances in the enrolment of participants with various prognoses, patients lost to follow-up and missing values. These problems could bias the results in an unknown direction and to an unknown extent. Therefore, caution is recommended in interpreting the estimates of effect. Longer-term outcomes (30 days and 6 months) are emphasised because short-term differences in effect may be transient. The heterogeneity of study populations and interventions precluded the use of statistical pooling.

Death from all causes

The effect of the drugs in reducing death from all causes is small, and in some cases, an increased risk of death was seen (tirofiban alone). With eptifibatide, the point estimates all suggested a small treatment effect (risk difference at 30 days, –0.2%; 95% CI, –1.0% to 0.6%; NNT, 504). For tirofiban alone, the estimates suggested an increased risk of death at 48 hours in both the PRISM (risk difference, 0.2%; 95% CI, –0.2% to 0.7%) and PRISM-PLUS (risk difference, 0.3%; 95% CI, –0.4% to 1.8%) studies. The PRISM-PLUS study continued to show a small increase in deaths with tirofiban alone at 7 days, 30 days and 6 months (risk differences, 2.8%, 1.6% and 0.2%, respectively). However, the PRISM study showed a benefit for tirofiban alone at 7 and 30 days, with risk differences of –0.6% (95% CI, –1.5% to 0.2%) and –1.3% (95% CI, –2.5% to –0.1%), respectively. The tirofiban plus heparin combination showed a risk difference that was close to zero at 48 hours (–0.1%) and 7 days (0.1%), but an increased benefit at 30 days, although the CI also became wider (risk difference, –0.9%; 95% CI, –2.9% to 1.1%; NNT, 112).

Myocardial Infarction

The effects on MI were also small in terms of the absolute reduction in risk. For instance, the results of the PURSUIT study suggest that eptifibatide reduced the risk of MI (risk difference at 30 days, –0.9%; 95% CI, –2.3% to 0.5%; NNT, 112). While the point estimates for eptifibatide at 96 hours, 7 days and 30 days were surrounded by CIs narrower than those seen with estimates for the other drugs, the reduction was very small. With tirofiban, the estimates of the effect on MI also favoured the treatment arms. For tirofiban alone at 30 days in the PRISM study, the risk difference estimate was –0.2% (95% CI, –1.7% to 1.2%), with an NNT of 404; and in the PRISM-PLUS study, the risk difference was –3.1% (95% CI, –6.1% to 0.4%), with an NNT of 33.

While the results of the PRISM study remained stable at 48 hours, 7 days and 30 days (risk differences, –0.5%, –0.5% and –0.2%, respectively), the PRISM-PLUS study estimates appeared to improve over time for the tirofiban alone group (risk differences, –1.8%, –2.4% and –3.1%, respectively). Again, the CIs were wide, and the results could shift with a more precise estimate. The combination of heparin and tirofiban in the PRISM-PLUS study resulted in risk differences of –1.6%, –3.1%, –2.6% and –2.3% at 48 hours, 7 days, 30 days, and 6 months, respectively. The NNT for the 6-month estimate was 44, but the 95% CI included the possibility of infinity.

The data for lamifiban indicated a small treatment effect at 30 days, with the exception of high-dose lamifiban plus heparin, which produced data slightly on the side of increasing MI occurrence (range of risk differences, –1.2% to 0.9%). The data at 6 months were slightly better (range of risk differences, –3.6% to –0.3%), but because of the exclusion of patients with no events and less than 120 days of follow-up from the analysis, these results particularly should be interpreted cautiously.

Composite end-points

The composite end-points used in the Phase III trials were similar for eptifibatide and lamifiban

(all-cause death and non-fatal MI); however, the PRISM and PRISM-PLUS studies also included refractory ischaemia (and rehospitalisation for unstable angina). In the PURSUIT study, the estimate of risk difference at 30 days for eptifibatide was –1.5% (95% CI, –2.9% to 0.1%), with an NNT of 67. In the PARAGON B study, the similar risk difference for lamifiban was –1.0% (95% CI, –2.8% to 0.8%), with an NNT of 102. These differences in risk are very small. The inclusion of refractory ischaemia improves the estimate of risk difference for tirofiban. At 30 days, the risk reduction for tirofiban plus heparin was –3.8% (95% CI, –7.8% to 0.2%), with an NNT of 27. However, for tirofiban alone at 30 days, the risk difference in the PRISM-PLUS study was an increase of 1.1% (95% CI, –4.0% to 6.6%), and in the PRISM study, a risk reduction of –1.2% (95% CI, –3.7% to 1.4%).

Revascularisation

The PCI rates in the Phase III trials ranged from 21.3% (for the tirofiban group in the PRISM study) to 30.9% (for the tirofiban plus heparin group in the PRISM-PLUS study), and were not meaningfully different between treatment and control groups. However, the rates of intervention quoted could have occurred at any time during follow-up, and the use of other glycoprotein IIb/IIIa antagonists during PTCA procedures occurring outside the study drug infusion time was not reported in any of the Phase III studies.

Adverse effects

The adverse effects monitored included bleeding and thrombocytopenia. The incidence of major bleeding was slightly higher in the groups treated with eptifibatide (10.6% versus 9.1%), the two tirofiban groups in the PRISM-PLUS study (4.0% and 3.0%, versus none in the heparin only group) and the two high-dose lamifiban groups in the PARAGON A trial (2.4% and 1.3%, versus 0.8%). It is striking that the PURSUIT and PRISM studies used the TIMI criteria for defining major bleeding and that the rates of bleeding were greatly different. The absolute difference in major bleeding events in the PURSUIT study was 69 additional patients in the eptifibatide arm with major bleeding (NNH, 59), and in the PRISM-PLUS study, the difference was 7 patients (NNH, 101). The low-dose lamifiban groups in the PARAGON A trial had bleeding rates equal to or lower than those of the control group. This low dose was used in PARAGON B. The PARAGON B trial reported that major bleeding was not higher in the lamifiban group. Major bleeding was equal in the two groups in the PRISM study (0.4%).

Most of the definitions of major bleeding included intracranial haemorrhage; however, the incidence of overall stroke was not reported in most studies. The trials of eptifibatide and tirofiban reported rates of stroke that were similar in both the treatment and control groups. The rate with eptifibatide was 0.8%, compared with 0.6% in patients receiving placebo. A sub-analysis of the cases of stroke revealed that most of the strokes were non-haemorrhagic (83.5% of all strokes), and the rates were not higher in the eptifibatide-treated patients.[26] In both the PARAGON studies, the rate of stroke was higher in all treatment arms than in patients receiving heparin alone. In the PARAGON B study, the rates of non-haemorrhagic strokes were 1.1% with lamifiban and 0.6% with heparin alone.

The rates of thrombocytopenia were very similar for eptifibatide and placebo in the PURSUIT study (6.8% versus 6.9%, respectively). The rates for tirofiban were higher in the treatment groups in both the PRISM and PRISM-PLUS studies (1.1% versus 0.4% and 1.9% versus 0.8%, respectively). In the PARAGON A trial, the rates for lamifiban ranged from 0.8% to 2.1%, compared with 1.1% for heparin alone. Strangely, adding heparin to either lamifiban group appeared to reduce the rate of thrombocytopenia to 0.8%, compared with 1.1% for heparin alone. The PARAGON B trial reported that thrombocytopenia was slightly higher in the lamifiban group.

The definitions of thrombocytopenia varied and may help explain the difference in rates observed between PURSUIT and the two PRISM studies. The PURSUIT trial defined thrombocytopenia as a platelet count of less than 100,000/m^3, while the PRISM and PRISM-PLUS studies defined it as less than 90,000/m^3. Definitions were not given for the PARAGON studies.

Economic analyses of intravenous glycoprotein IIb/IIIa antagonists

The economic analyses that were found varied significantly in methods, time-horizon studied, perspective and country. Only two analyses based on UK resource use and efficacy were found. There were five analyses from other countries, which are summarised below.

The McElwee and Johnson study[41] used data from trials of abciximab to estimate cost-effectiveness in

"all-comers" and PTCA/stent-only subgroups (*Tables 46* and *47*). Because there were no data on abciximab use outside of PCI, this analysis is not relevant.

Szucs and co-workers[39] performed a cost–benefit analysis of tirofiban at 7 days based on the findings of the PRISM-PLUS study (*Table 52*). The result was a net saving of 549 Swiss francs per patient, based on the costs of treating recurrent ischaemia or MI (*Table 53*).

Mark[40] found the cost of eptifibatide per life-year gained to be US$16,491 and the cost per QALY to be US$19,693 at 6 months (*Table 45*). Sensitivity analyses, using a lower efficacy rate and a more conservative QALY rating scale, resulted in costs of US$33,619 per life-year gained and US$23,449 per QALY, respectively.

Two economic analyses compared the cost-effectiveness of eptifibatide versus tirofiban, per death or MI prevented at 30 days (*Tables 48–51*).[42,43] Bell[42] found that eptifibatide was US$5723 less expensive than tirofiban per death or MI avoided (*Table 49*). Hillegass and co-workers[43] found that the lower ends of the ranges of estimated cost per death or MI avoided were similar for tirofiban and eptifibatide (US$32,550 to US$36,690, respectively) (*Table 51*). The upper limit of cost per death or MI avoided was higher for eptifibatide than tirofiban (US$81,941 and US$53,900, respectively). Cost-effectiveness ratios were not calculated.

The unpublished economic analysis of tirofiban in the UK reported cost-effectiveness ratios of £8760 at 7 days and £9955 at 6 months per composite end-point (*Table 55*).[37] In a further cost-offset analysis, 22% of the costs of tirofiban could be offset by the reduction of events (MI and recurrent ischaemia). A sensitivity analysis using the 95% confidence limits of the risk difference resulted in incremental cost-effectiveness ratios ranging from £5112 to £30,358 at 7 days and £4889 to infinity at 6 months. The risk difference at 6 months was zero, precluding the calculation of the upper 95% confidence limit.

The unpublished economic analysis of eptifibatide in the UK reported that eptifibatide was dominant to placebo in costs per life-years gained at 30 days (*Table 57*).[38] The cost-effectiveness analysis at 30 days resulted in an estimated saving of £213 per death or MI avoided by using eptifibatide. The sensitivity analysis for the cost-effectiveness of eptifibatide using Western European data, rather than the UK data, to estimate costs resulted in the cost per life-year gained ranging from £8179 to £11,079, by varying the discount rate for survival from 0% to 1.5% to 3.0%.

Efficacy of oral glycoprotein IIb/IIIa antagonists

Four randomised controlled trials evaluating the effect of glycoprotein IIb/IIIa antagonists met inclusion criteria. The drugs evaluated were sibrafiban, orbofiban and lefradafiban. There were two studies of sibrafiban. The data reported in the first of these two studies (SYMPHONY 1) suggest that sibrafiban offered no additional benefit when compared with aspirin.[33] In the second study (SYMPHONY 2), treatment with sibrafiban led to an increase in clinical events and adverse outcomes. The OPUS-TIMI 16 trial reported similar results for orbofiban.[35,45] The FROST study reported a trend towards fewer clinical events with lefradafiban but was stopped early due to safety concerns.

Adverse effects

The bleeding rates of the oral glycoprotein antagonists were difficult to assess, because the abstracts of the SYMPHONY 2 and FROST studies did not report rates of major bleeding. Compared with the control groups, there were higher rates of bleeding with sibrafiban in the SYMPHONY 1 study (5–6% versus 4%) and orbofiban in the OPUS-TIMI 16 trial (3.3% to 3.7%, versus 1.9%) The rates of stroke were similar in the sibrafiban and control groups.

Economic evaluation

No economic evaluations of oral glycoprotein IIb/IIIa antagonists were found. Considering the lack of efficacy data and suggestion of harm, economic analysis is not likely to be necessary.

Assumptions, limitations and uncertainties

Efficacy analysis

While there are some validity issues that were unsatisfactorily addressed in the published reports of these studies, they were in general well-conducted trials. Issues that could substantially alter the results were the lack of adequate information on patients lost to follow-up, missing values, success of blinding (particularly with heparin) and possible heterogeneity of the enrolled patients with regard to baseline risk.

Given the overall high quality of the Phase III studies, it seems unlikely that the results are biased.

The use of composite end-points may be a concern if, although the risk differences between treatment and control groups for the components of the composite end-point (i.e. MI and death) are very small, when added together, the effect becomes clinically important. With the intravenous glycoprotein IIb/IIIa antagonists, this appears to be the case. The survival analyses presented in the studies suggest a significant benefit that is consistent over time, when using composite end-points. In examining the forest plots of the risk differences, it is clear that the estimate of effect is shifted towards a larger treatment effect when adding the outcomes together, but the effect size is still small.

Differences between the baseline characteristics of patients enrolled in the PRISM and PRISM-PLUS studies may partially explain the opposing findings with tirofiban alone. In the PRISM-PLUS study, more than 90% of the patients had baseline ST-T ECG changes, whereas only 39% of the patients in the PRISM study were reported to have these changes. These changes are highly prognostic of a poor outcome and suggest more severe disease. Chesebro and Badimon[46] propose that a higher dose or the addition of heparin may be required to produce an effect in these patients. The tirofiban plus heparin arm of the PRISM-PLUS study did report positive results, although small differences.

The difference between the two PRISM trials is again reflected in the rates of PCI, as more patients required intervention in PRISM-PLUS than in PRISM. Both the PRISM and PRISM-PLUS trials allowed intervention during the 48-hour drug infusion only if deemed necessary. The PURSUIT study left PCI decisions up to the treating physician. When PCI was deemed necessary in the PRISM, PRISM-PLUS and PURSUIT trials, the study drug (active or placebo) was continued. The PARAGON B study abstract did not state the protocol stipulations regarding PCI.

If early use of the glycoprotein IIb/IIIa antagonists was effective, their use would also be expected to reduce the rate of revascularisation required, particularly within the time frames considered in these trials. While the rates of revascularisation in patients treated with tirofiban in the PRISM study were slightly smaller compared with placebo, treatment with tirofiban plus heparin was associated with slightly more interventions in the PRISM-PLUS study.

If the use of these drugs in combination with PCI is effective in reducing these same end-points and patients could have received an intervention (possibly in combination with a glycoprotein IIb/IIIa antagonist) during these studies, then the result would be an underestimate of the real effects of the glycoprotein IIb/IIIa antagonists. The treatment effect may also be understated if the patients who are already receiving study drug and require PCI have more severe disease than those receiving PCI in the control group.

The variation in rates of PCI in different geographical locations is well recognised and was reported in the PURSUIT trial. The PURSUIT and PRISM studies indicated that patients in North America had better response rates than patients from other areas. The PRISM-PLUS trial did not report results by location, but commented that both US and non-US patients benefited from tirofiban. If the effect seen in these studies is modified by the benefit of these drugs used in association with PCI, the effect modification would be stronger in North America, where PCI rates are much higher. The real effect of glycoprotein IIb/IIIa antagonists among patients not going on to receive PCI may be much smaller than is reported in these trials.

Because of the nature of unstable angina and ACS, it would be very difficult, if not impossible, to design a study that would avoid this confounding related to PCI and still include the patients of interest. If data were provided on when PCI occurred and what other interventions were received (i.e. other glycoprotein antagonists), it might be possible to establish the effect of the study drugs in treating unstable angina and ACS without PCI. Registration and reporting of co-interventions are very important in trying to evaluate the added benefit of using these drugs early, not in association with PCI. While a solution may not be possible, this issue complicates the interpretation of these results.

The effects seen with eptifibatide for the composite end-point were slightly less at 6 months compared with at 96 hours, but the CIs overlap (*Figure 3*). The effects seen with tirofiban plus heparin for the composite end-point appeared to be the greatest at 7 days and were slightly less at 6 months (*Figure 10*). However, the CIs again overlap. The Phase III trial of lamifiban presented data for the composite end-point at 30 days only (*Figure 17*), so no comparison of the potential loss of effect over time could be assessed.

The precision of the estimates of effect is relatively low, with wide CIs for all trials except for PURSUIT. Many of the CIs cross the no-effect mark.

Economic analyses

The lack of standardised economic outcomes (e.g. QALYs gained) used in the majority of the located economic analyses made comparing and contrasting very difficult. The time-horizons analysed also varied from 7 days to 6 months. The US and Swiss analyses are difficult to translate to the NHS situation in the UK, and none of the analyses took a societal perspective. For these reasons, only the two analyses based on UK data are discussed here.

In the tirofiban analysis,[37] the authors argue that the analysis is conservative because many savings may accrue after the first week (e.g. savings in cardiac rehabilitation and additional physician office visits). This point may be valid, but it would have been appropriate to demonstrate this more quantitatively. The authors point out that their analysis is strictly a cost-efficacy analysis, as distinct from a cost-effectiveness analysis, because the clinical outcomes were derived from a randomised trial, not from a real-world-type study. Because compliance seems to be a non-issue with this intravenously administered drug, the main difference between the PRISM-PLUS study and the real world appears to be the patient mix. This analysis does not incorporate cost-efficacy ratios stratified by cardiac risk, therefore it is doubtful whether the findings presented are really conservative from an NHS point of view.

There are other issues that make a proper assessment of the cost-effectiveness difficult.

1. Bleeding events have not been analysed.
2. The overall findings of the largely North American PRISM-PLUS study may not be applicable to the UK.
3. Details were not provided on how the PRAIS-UK study was used to estimate resource consumption.
4. A cost-offset analysis at 180 days would have been more informative than at 7 days.
5. The finding in the PRISM study that tirofiban had an effect only in patients with a high troponin level has not been taken into account. The cost-effectiveness ratio may be more favourable in the troponin-positive patients but notably more negative in the troponin-negative patients.

In the analysis of eptifibatide, a potential source of uncertainty is the translation of US life expectancy data to the UK population via the use of the effectiveness data from the Western European subcohort of the PURSUIT study. However, the main issue that severely limits the interpretation of the findings is the omission of a sensitivity analysis using the lower CI limit of the small and statistically insignificant effectiveness estimate found in the Western European subcohort of the PURSUIT study. It is likely that this particular sensitivity analysis would have a major impact on the findings presented.

It is concerning that the US-based analysis[40] found a cost per life-year gained of over US$16,000, while the UK-based analysis found that eptifibatide is dominant (i.e. is more effective and costs less). This difference is particularly a concern because the efficacy rate for the composite end-point assumed in the US-based study was 3.5%, while it was only 1% in the UK-based study, making it even more unlikely to find eptifibatide dominant. The most likely reason for the apparent discordant cost-effectiveness estimates is that the costs of managing outcomes (e.g. recurrent ischaemia or MI) are much higher in the UK than in the US, or in the placebo arm than in the treatment arm.

The UK-based analysis appropriately used a subset of data from the PURSUIT study to estimate resource use among UK patients in the trial, and used the efficacy rate found among the Western European subset to estimate benefits. While the PCI rate is lower in the UK than in the US, there was no difference in the rate of PCI between the treatment and placebo groups in the PURSUIT study. This was also true when comparing PCI rates in treatment and placebo groups in the Western European data from the PURSUIT study. However, the number of PTCA or stent procedures in the placebo arm in the UK patient data was 1.8 times that of the eptifibatide group. The sizes of the groups from whom UK resource use data were obtained were small (215 and 214 patients in the UK eptifibatide and UK placebo groups, respectively) relative to the whole trial population. If this difference in PCI rates is real, then eptifibatide may indeed be dominant to placebo. However, the smaller sample size as well as the fact that the Western European data and North American data did not show a difference suggest that this result should be interpreted with caution.

Chapter 8
Conclusions

Treatment efficacy

Overall, the best evidence suggests a small beneficial treatment effect resulting from intravenous glycoprotein IIb/IIIa antagonists. For the most relevant outcomes at 30 days and 6 months, however, this effect cannot be differentiated from the effects of the PCI–glycoprotein IIb/IIIa antagonist combination. It is difficult to say if there is a class effect for glycoprotein IIb/IIIa antagonists, because of the differences in patient populations enrolled, outcome definitions used and combinations with other drugs such as heparin. However, there are broadly similar findings across the drug class of glycoprotein IIb/IIIa antagonists.

Cost-effectiveness

US economic analysis of eptifibatide indicates that the cost of eptifibatide per life-year gained is US$16,491 and the cost per QALY is US$19,693 at 6 months. UK economic analysis of eptifibatide indicates that the drug is more effective and less expensive than placebo, and may save a small amount per death or MI avoided at 30 days. UK economic analysis of tirofiban indicates that the incremental cost-effectiveness ratio is approximately £9000. However, all these estimates have drawbacks, which make it impossible to provide a range of cost-effectiveness ratios to compare these drugs with each other and with other technologies.

Recommendations for research

Further research into the clinical effectiveness and cost-effectiveness of these drugs, including testing the troponins T and I as markers of patients who will benefit, is recommended.

Two additional trials, Treat Angina with Aggrastat (tirofiban) and Determine Cost of Therapy with Invasive or Conservative Strategy (TACTICS) TIMI-18 and Global Use of Strategies to Open Occluded Arteries (GUSTO) IV ACS, are reported to have completed enrolment. TACTICS TIMI-18 is a trial of tirofiban, and GUSTO IV ACS is a trial of abciximab. When data from these trials are available, this review will need to be updated.

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The views expressed in this report are those of the authors, who are also responsible for any errors.

References

1. Rosengren A, Wilhelmsen L, Hagman M, Wedel H. Natural history of myocardial infarction and angina pectoris in a general population sample of middle-aged men: a 16-year follow-up of the Primary Prevention Study, Göteborg, Sweden. *J Intern Med* 1998;**244**:495–505.

2. Rizik DG, Healy S, Margulis A, Vandam D, Bakalyar D, Timmis G, *et al.* A new clinical classification for hospital prognosis of unstable angina pectoris. *Am J Cardiol* 1995;**75**:993–7.

3. Muller JE, Turi ZG, Pearle DL, Schneider JF, Serfas DH, Morrison J, *et al.* Nifedipine and conventional therapy for unstable angina pectoris: a randomised, double-blind comparison. *Circulation* 1984;**69**:728–39.

4. Nyman I, Areskog M, Areskog NH, Swahn E, Wallentin L. Very early risk stratification by electrocardiogram at rest in men with suspected unstable coronary heart disease. The RISC Study Group. *J Intern Med* 1993;**234**:293–301.

5. Wilcox I, Freedman SB, McCredie RJ, Carter GS, Kelly DT, Harris PJ. Risk of adverse outcome in patients admitted to the coronary care unit with suspected unstable angina pectoris. *Am J Cardiol* 1989;**64**:845–8.

6. Cairns JA, Singer J, Gent M, Holder DA, Rogers D, Sackett DL, *et al.* One year mortality outcomes of all coronary and intensive care unit patients with acute myocardial infarction, unstable angina or other chest pain in Hamilton, Ontario, a city of 375,000 people. *Can J Cardiol* 1989;**5**:239–46.

7. Théroux P, Waters D, Lam J, Juneau M, McCans J. Reactivation of unstable angina after the discontinuation of heparin. *N Engl J Med* 1992;**327**:141–5.

8. Théroux P, Taeymans Y, Morissette D, Bosch X, Pelletier GB, Waters DD. A randomised study comparing propranolol and diltiazem in the treatment of unstable angina. *J Am Coll Cardiol* 1985;**5**:717–22.

9. Théroux P, Waters D, Qiu S, McCans J, De Guise P, Juneau M. Aspirin versus heparin to prevent myocardial infarction during the acute phase of unstable angina. *Circulation* 1993;**88**:2045–8.

10. White LD, Lee TH, Cook EF, Weisberg MC, Rouan GW, Brand DA, *et al.* Comparison of the natural history of new onset and exacerbated chronic ischemic heart disease. *J Am Coll Cardiol* 1990;**16**:304–10.

11. Karlson BW, Herlitz J, Pettersson P, Hallgren P, Strombom U, Hjalmarson A. One-year prognosis in patients hospitalized with a history of unstable angina pectoris. *Clin Cardiol* 1993;**16**:397–402.

12. Gandhi MM, Lampe FC, Wood DA. Incidence, clinical characteristics, and short-term prognosis of angina pectoris. *Br Heart J* 1995;**73**:193–8.

13. NHS Executive. The new NHS 1999 reference costs. London: Department of Health (UK); 1999.

14. Office of National Statistics. Mortality statistics: cause. London: The Stationary Office; 1998.

15. Purcell H. The epidemiology of unstable angina. *Br J Cardiol* 1998;**2**:S3–S4.

16. Government Statistics Service. Hospital Episode Statistics. Finished consultant episodes by diagnosis and operative procedure; injury/poisoning by external causes. England: financial year 1995–96. London: Department of Health (UK); 1997.

17. Monthly Index of Medical Specialties (MIMS). London: Haymarket Business Publications; 1999.

18. British Medical Association and Royal Pharmaceutical Society of Great Britain. British National Formulary. London: *BMJ* Books; 1999.

19. Drummond M, O'Brien B, Stoddart G, Torrance G. Methods for the economic evaluation of health care programmes. 2nd ed. Oxford: Oxford University Press; 1997.

20. Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. *N Engl J Med* 1998;**338**:1498–505.

21. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction [published erratum appears in *N Engl J Med* 1998;**339**:415]. *N Engl J Med* 1998;**338**:1488–97.

22. Schulman SP, Goldschmidt-Clermont PJ, Topol EJ, Califf RM, Navetta FI, Willerson JT, *et al.* Effects of integrilin, a platelet glycoprotein IIb/IIIa receptor antagonist, in unstable angina. A randomised multicenter trial. *Circulation* 1996;**94**:2083–9.

23. Harrington RA. Design and methodology of the PURSUIT trial: evaluating eptifibatide for acute ischemic coronary syndromes. Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy. *Am J Cardiol* 1997; **80**:34b–38b.

24. The PURSUIT Trial Investigators. PURSUIT (Platelet IIb/IIIa in unstable angina: receptor suppression using Integrilin™ therapy). *Clin Cardiol* 1997;**20**:967.

25. Simoons ML. New findings from the PURSUIT study. *Eur Heart J Suppl* 1999;**1**:N30–4.

26. Mahaffey KW, Harrington RA, Simoons ML, Granger CB, Graffagnino C, Alberts MJ, *et al.* Stroke in patients with acute coronary syndromes: incidence and outcomes in the platelet glycoprotein IIb/IIIa in unstable angina. Receptor suppression using integrilin therapy (PURSUIT) trial. The PURSUIT Investigators. *Circulation* 1999;**99**:2371–7.

27. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy. *N Engl J Med* 1998;**339**:436–43.

28. Théroux P, Kouz S, Roy L, Knudtson ML, Diodati JG, Marquis JF, *et al.* Platelet membrane receptor glycoprotein IIb/IIIa antagonism in unstable angina. The Canadian Lamifiban Study. *Circulation* 1996;**94**:899–905.

29. The PARAGON Investigators. International, randomised, controlled trial of lamifiban (a platelet glycoprotein IIb/IIIa inhibitor), heparin, or both in unstable angina. Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network. *Circulation* 1998;**97**:2386–95.

30. Harrington R. Optimal dosing of a platelet glycoprotein IIb/IIIa antagonist, lamifiban, using renal-based algorithms, in patients with acute coronary syndromes: results from the PARAGON B (the Platelet IIb/IIIa Antagonist for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network) study. Proceedings of the American College of Cardiology 49th Annual Scientific Session; 2000 Mar 12–15; Anaheim (CA), USA. 2000.

31. Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, *et al.* Thrombolysis in myocardial infarction (TIMI) trial, phase I. *Circulation* 1987;**76**:142–54.

32. The GUSTO Investigators. An international randomised trial comparing four thrombolytic strategies for acute myocardial infarction. *N Eng J Med* 1993;**329**:673–82.

33. The SYMPHONY Investigators. Comparison of sibrafiban with aspirin for prevention of cardiovascular events after acute coronary syndromes: a randomised trial. Sibrafiban versus Aspirin to Yield Maximum Protection from Ischemic Heart Events Post-acute Coronary Syndromes. *Lancet* 2000;**355**:337–45.

34. Robert M, Califf R. A randomised comparison of sibrafiban, an oral glycoprotein (GP) IIb/IIIa receptor antagonist, with and without aspirin vs. aspirin after acute coronary syndromes: results of the second SYMPHONY trial. Proceedings of the American College of Cardiology 49th Annual Scientific Session; 2000 Mar 12–15; Anaheim (CA), USA. 2000.

35. Ferguson J. Meeting highlights. Highlights of the 48th scientific sessions of the American College of Cardiology. *Circulation* 1999;**100**:570–5.

36. Ault KA, Cannon CP, Mitchell J, McCahan J, Tracy RP, Novotny WF, *et al.* Platelet activation in patients after an acute coronary syndrome: results from the TIMI-12 trial. *J Am Coll Cardiol* 1999;**33**:634–9.

37. Merck Sharp & Dohme. AGGRASTAT (tirofiban) in the treatment of unstable angina and coronary syndromes. Sponsor submission to the National Institute for Clinical Excellence. 2000. p. 27–32.

38. Schering-Plough. Eptifibatide in treating acute coronary syndromes in the United Kingdom. A submission to the National Institute for Clinical Excellence. 2000.

39. Szucs TD, Meyer BJ, Kiowski W. Economic assessment of tirofiban in the management of acute coronary syndromes in the hospital setting. An analysis based on the PRISM-PLUS trial. *Eur Heart J* 1999;**20**:1253–60.

40. Mark D, Harrington R, Lincoff M, Califf R, Nelson C, Tsiatis A, *et al.* Cost-effectiveness of platelet glycoprotein IIb/IIIa inhibition with eptifibatide in patients with non-ST-elevation acute coronary syndromes. *Circulation* 2000;**101**:366–71.

41. McElwee NE, Johnson ER. Potential economic impact of glycoprotein IIb-IIIa inhibitors in improving outcomes of patients with acute ischemic coronary syndromes. *Am J Cardiol* 1997;**80**:39b–43b.

42. Bell DM. Analysis of number needed to treat and cost of platelet glycoprotein IIb/IIIa inhibitors in percutaneous coronary interventions and acute coronary syndromes. *Pharmacotherapy* 1999;**19**:1086–93.

43. Hillegass WB, Newman AR, Raco DL. Economic issues in glycoprotein IIb/IIIa receptor therapy. *Am Heart J* 1999;**138**(1 Pt 2):S24–32.

44. Collinson J, Flather MD, Fox KA, Findlay I, Rodrigues E, Dooley P, *et al.* Clinical outcomes, risk stratification and practice patterns of unstable angina and myocardial infarction without ST elevation: prospective registry of acute ischaemic syndromes in the UK (PRAIS-UK). *Eur Heart J* 2000;**21**:1450–7.

45. Cannon CP, McCabe CH, Borzak S, Henry TD, Tischler MD, Mueller HS, *et al.* Randomised trial of an oral platelet glycoprotein IIb/IIIa antagonist, sibrafiban, in patients after an acute coronary syndrome: results of the TIMI 12 trial. Thrombolysis in Myocardial Infarction. *Circulation* 1998; **97**:340–9.

46. Chesebro J, Badimon J. Platelet glycoprotein IIb/IIIa receptor blockade in unstable coronary disease. *N Engl J Med* 1998;**338**:1539–41.

Appendix 1

Search strategies

Internet resources

All the Internet sites listed in chapter 2 (see *Search strategy and bibliographic databases used*) were searched on 14 January 2000 and again on 17 May 2000. The Internet sites that contained only a few references were simply browsed for relevant papers. Other Internet sites were searched using a search engine/search form. The search interfaces for most resources on the web allow only single-word searches or very simple combinations. Therefore, searches involved several stages with printouts of the results. Most web interfaces do not offer date restriction, and thus none of the searches were limited by date. The search terms used were as follows (not all the terms used produced hits):

ABCIXIMAB	REOPRO	AGGRASTAT
EPTIFIBATIDE	INTRIFIBAN	INTEGRELIN
INTEGRILIN	TIROFIBAN	AGGRASTAT
GP	GLYCOPROTEIN	GLYCOPROTEINS
INTEGRIN	LAMIFIBAN	RO 44-9883
SIBRAFIBAN	XUBIX	RO 48-3657
FRADAFIBAN	BIBU 52	LEFRADADIBAN
BIBU 104	XEMILOFIBAN	SC-54701A
SC-54684A	ORBOFIBAN	SC-57099B

CD-ROM resources

The Cochrane Library (Version 2000, Issue 2)

The Cochrane Database of Systematic Reviews (CDSR) and the Cochrane Controlled Trials Register (CCTR) were searched via the Cochrane Library. The NHSEED, DARE and HTA databases were searched via the Internet (http://www.york.ac.uk/inst/crd/), which provides versions of the databases that are more up to date than those found in the Cochrane Library.

Search strategy for licensed glycoprotein antagonists

The first search undertaken was limited to the three glycoprotein antagonists currently licensed in the UK (abciximab, eptifibatide and tirofiban). The use of these drug names and their corresponding trade names yielded 150 hits. Limiting the search further with terms relating to unstable angina was therefore felt to be unnecessary. The first strategy used was as follows:

1. ((GLYCOPROTEIN* or GP*) near IIB*)
2. GPIIB*
3. (ABCIXIMAB or REOPRO)
4. (((EPTIFIBATIDE or INTRIFIBAN) or INTEGRELIN) or INTEGRILIN)
5. (TIROFIBAN or AGGRASTAT)
6. ((((#1 or #2) or #3) or #4) or #5)

Search strategy for unlicensed glycoprotein antagonists

After it was decided that the review should include unlicensed glycoprotein antagonists, a second search was conducted. This search strategy was designed to exclude all papers already retrieved and yielded two additional hits. The numerical drug identities are excluded from the search strategy because the Cochrane Library search software ignores all numbers.

1. ((GLYCOPROTEIN* or GP*) near IIB*)
2. GPIIB*
3. (ABCIXIMAB or REOPRO)
4. (((EPTIFIBATIDE or INTRIFIBAN) or INTEGRELIN) or INTEGRILIN)
5. (TIROFIBAN or AGGRASTAT)
6. ((((#1 or #2) or #3) or #4) or #5)
7. (((LAMIFIBAN or SIBRAFIBAN) or XUBIX) or FRADAFIBAN)
8. (((LEFRADAFIABN or BIBU*) or XEMILOFIBAN) or ORBOFIBAN)
9. (#7 or #8)
10. (#9 not #6)

The above searches were updated when the new issues of the Cochrane Library were released. The last search was carried out on 19 May 2000 using Version 2000, Issue 2. For the entire search, there were four hits on CDSR and 173 hits on CCTR.

EMBASE: SilverPlatter® (Version 1980–2000/04)

Search strategy for licensed glycoprotein antagonists

The first set of searches were divided into two areas (cost-effectiveness studies and clinical effectiveness studies) and limited to the three glycoprotein antagonists currently

licensed in the UK (abciximab, eptifibatide and tirofiban). Both search strategies were designed to find references relating to unstable angina in conjunction with glycoprotein antagonists.

Cost-effectiveness search strategy
The search strategy used to find references to cost-effectiveness studies on licensed glycoprotein antagonists was as follows:

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. explode "angina-pectoris"/ all subheadings
17. angina in ti ab
18. explode "heart-infarction"/ all subheadings
19. myocard* infarct*
20. heart attack*
21. coronary syndrome*
22. crescendo
23. explode "economic-evaluation"/ all subheadings
24. cost effect*
25. cost benefit*
26. economic evaluation*
27. technology assessment*
28. pharmacoeconomic*
29. cost util*
30. #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
31. #16 or #17 or #18 or #19 or #20 or #21 or #22
32. #23 or #24 or #25 or #26 or #27 or #28 or #29
33. #30 and #31 and #32
34. explode "animal"/ all subheadings
35. explode "human"/ all subheadings
36. #34 not (#34 and #35)
37. #33 not #36

Clinical effectiveness search strategy
The search strategy used to find references to clinical trials relating to licensed glycoprotein antagonists was as follows:

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. explode "angina-pectoris"/ all subheadings
17. angina in ti ab
18. explode "heart-infarction"/ all subheadings
19. myocard* infarct*
20. heart attack*
21. coronary syndrome*
22. crescendo
23. explode "Clinical-Trials"/ all subheadings
24. (clin* near trial*) in ti ab
25. ((singl* or doubl* or trebl* or tripl*) near (blind* or mask*)) in ti ab
26. Placebos
27. placebo* in ti ab
28. random in ti ab
29. "randomised-controlled-trial"/ all subheadings
30. #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
31. #16 or #17 or #18 or #19 or #20 or #21 or #22
32. #23 or #24 or #25 or #26 or #27 or #28 or #29
33. #30 and #31 and #32
34. explode "animal"/ all subheadings
35. explode "human"/ all subheadings
36. #34 not (#34 and #35)
37. #33 not #36

Search strategy for unlicensed glycoprotein antagonists
It was subsequently decided that the review should include unlicensed glycoprotein antagonists, and a second set of searches was therefore conducted. These search strategies were designed to exclude all the papers already retrieved.

Cost-effectiveness search strategy
The search strategy used to find references to cost-effectiveness studies on unlicensed glycoprotein antagonists was as follows:

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. explode "angina-pectoris"/ all subheadings
17. angina in ti ab
18. explode "heart-infarction"/ all subheadings
19. myocard* infarct*
20. heart attack*
21. coronary syndrome*
22. crescendo
23. explode "economic-evaluation"/ all subheadings
24. cost effect*
25. cost benefit*
26. economic evaluation*
27. technology assessment*
28. pharmacoeconomic*
29. cost util*
30. #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
31. #16 or #17 or #18 or #19 or #20 or #21 or #22
32. #23 or #24 or #25 or #26 or #27 or #28 or #29
33. #30 and #31 and #32
34. explode "animal"/ all subheadings
35. explode "human"/ all subheadings
36. #34 not (#34 and #35)
37. #33 not #36
38. lamifiban or ro 44-9883
39. sibrafiban or xubix or ro 44-3888 or ro 48-3657
40. fradafiban or bibu
41. lefradafiban
42. xemilofiban or sc-54701a or sc-54684a
43. orbofiban or sc-57099b
44. #38 or #39 or #40 or #41 or #42 or #43
45. #31 and #32 and #44
46. #45 not #36
47. #46 not #37

Clinical effectiveness search strategy

The search strategy used to find references to clinical trials relating to unlicensed glycoprotein antagonists was as follows:

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. explode "angina-pectoris"/ all subheadings
17. angina in ti ab
18. explode "heart-infarction"/ all subheadings
19. myocard* infarct*
20. heart attack*
21. coronary syndrome*
22. crescendo
23. explode "Clinical-Trials"/ all subheadings
24. (clin* near trial*) in ti ab
25. ((singl* or doubl* or trebl* or tripl*) near (blind* or mask*)) in ti ab
26. Placebos
27. placebo* in ti ab
28. random in ti ab
29. "randomised-controlled-trial"/ all subheadings
30. #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
31. #16 or #17 or #18 or #19 or #20 or #21 or #22
32. #23 or #24 or #25 or #26 or #27 or #28 or #29
33. #30 and #31 and #32
34. explode "animal"/ all subheadings
35. explode "human"/ all subheadings
36. #34 not (#34 and #35)
37. #33 not #36
38. lamifiban or ro 44-9883
39. sibrafiban or xubix or ro 44-3888 or ro 48-3657
40. fradafiban or bibu
41. lefradafiban
42. xemilofiban or sc-54701a or sc-54684a
43. orbofiban or sc-57099b
44. #38 or #39 or #40 or #41 or #42 or #43
45. #31 and #32 and #44
46. #45 not #36
47. #46 not #37

The above searches were updated regularly, and the last search was carried out on 19 May 2000 using Version 1980–2000/04. The searches in total yielded 110 cost-effectiveness references and 595 clinical effectiveness references.

MEDLINE: SilverPlatter (Version 1966–2000/05)

Search strategy for licensed glycoprotein antagonists

The first set of searches was divided into two areas (cost-effectiveness studies and clinical effectiveness studies) and limited to the three glycoprotein antagonists currently licensed in the UK (abciximab, eptifibatide and tirofiban). Both search strategies were designed to find references relating to unstable angina in conjunction with glycoprotein antagonists.

Cost-effectiveness search strategy

The search strategy used to find references to cost-effectiveness studies on licensed glycoprotein antagonists was as follows:

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. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
12. explode "Angina-Pectoris"/ all subheadings
13. angina
14. explode "Myocardial-Infarction"/ all subheadings
15. myocard* infarct*
16. heart attack*
17. coronary syndrome*
18. crescendo
19. #12 or #13 or #14 or #15 or #16 or #17 or #18
20. #11 and #19
21. cost effect*
22. cost benefit*
23. economic evaluation*
24. technology assessment*
25. pharmacoeconomic*
26. cost util*
27. explode "Economics"/ all subheadings
28. #21 or #22 or #23 or #24 or #25 or #26 or #27
29. #20 and #28

Clinical effectiveness search strategy

The search strategy used to find references to clinical trials relating to licensed glycoprotein antagonists was as follows:

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. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
12. explode "Angina-Pectoris"/ all subheadings
13. angina
14. explode "Myocardial-Infarction"/ all subheadings
15. myocard* infarct*
16. heart attack*
17. coronary syndrome*
18. crescendo
19. #12 or #13 or #14 or #15 or #16 or #17 or #18
20. #11 and #19
21. explode "Clinical-Trials"/ all subheadings
22. (clin* near trial*) in ti ab
23. ((singl* or doubl* or treble* or tripl*) near (blind* or mask*)) in ti ab
24. "Placebos"/ all subheadings
25. random* in ti ab
26. placebo* in ti ab
27. #21 or #22 or #23 or #24 or #25 or #26
28. #20 and #27

Search strategy for unlicensed glycoprotein antagonists

It was subsequently decided that the review should include unlicensed glycoprotein antagonists, and a second set of searches was therefore conducted. These search strategies were designed to exclude all papers already retrieved.

Cost-effectiveness search strategy

The search strategy used to find references to cost-effectiveness studies on unlicensed glycoprotein antagonists was as follows:

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. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
12. explode "Angina-Pectoris"/ all subheadings
13. angina
14. explode "Myocardial-Infarction"/ all subheadings
15. myocard* infarct*
16. heart attack*
17. coronary syndrome*
18. crescendo
19. #12 or #13 or #14 or #15 or #16 or #17 or #18
20. #11 and #19
21. cost effect*
22. cost benefit*
23. economic evaluation*
24. technology assessment*
25. pharmacoeconomic*
26. cost util*
27. explode "Economics"/ all subheadings
28. #21 or #22 or #23 or #24 or #25 or #26 or #27
29. #20 and #28
30. lamifiban or ro 44-9883
31. sibrafiban or ro 44-3888 or ro 48-3657 or xubix
32. fradafiban or bibu
33. lefradafiban
34. xemilofiabn or sc-54701A or sc-54684A
35. orbofiban or sc-57099B
36. #30 or #31 or #32 or #33 or #34 or #35
37. #19 and #28 and #38
38. #37 not #29

Clinical effectiveness search strategy

The search strategy used to find references to clinical trials relating to unlicensed glycoprotein antagonists was as follows:

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. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
12. explode "Angina-Pectoris"/ all subheadings
13. angina
14. explode "Myocardial-Infarction"/ all subheadings
15. myocard* infarct*
16. heart attack*
17. coronary syndrome*
18. crescendo
19. #12 or #13 or #14 or #15 or #16 or #17 or #18
20. #11 and #19
21. explode "Clinical-Trials"/ all subheadings
22. (clin* near trial*) in ti ab
23. ((singl* or doubl* or treble* or tripl*) near (blind* or mask*)) in ti ab
24. "Placebos"/ all subheadings
25. random* in ti ab
26. placebo* in ti ab
27. #21 or #22 or #23 or #24 or #25 or #26
28. #20 and #27
29. lamifiban or ro 44-9883
30. sibrafiban or xubix or ro 44-3888 or ro 48 3657
31. fradafiban or bibu
32. lefradafiban
33. xemilofiban or sc-54701A or sc-54684A
34. orbofiban or sc-57099b
35. #29 or #30 or #31 or #32 or #33 or #34
36. #19 and #27 and #35
37. #36 not #28

The above searches were updated regularly, and the last search was carried out on 19 May 2000 using Version 1966–2000/05. A total of 35 cost-effectiveness references and 264 clinical effectiveness references were identified.

National Research Register CD-ROM (Version 2000, Issue 2)

Search strategy for licensed glycoprotein antagonists

The first search was limited to the three glycoprotein antagonists currently licensed in the UK (abciximab, eptifibatide and tirofiban). The use of these drug names and their corresponding trade names yielded 25 hits. Limiting the search further with terms relating to unstable angina was therefore felt to be unnecessary. The first strategy used was as follows:

1. ((GLYCOPROTEIN* or GP*) near IIB*)
2. GPIIB*
3. (ABCIXIMAB or REOPRO)
4. (((EPTIFIBATIDE or INTRIFIBAN) or INTEGRELIN) or INTEGRILIN)
5. (TIROFIBAN or AGGRASTAT)
6. ((((#1 or #2) or #3) or #4) or #5)

Search strategy for unlicensed glycoprotein antagonists

This search strategy was designed to exclude all the papers already retrieved, and the search performed on 5 April 2000 yielded an additional 26 hits. The numerical drug identities were excluded from the search strategy because all

numbers are ignored by the National Research Register search software.

1. ((GLYCOPROTEIN* or GP*) near IIB*)
2. GPIIB*
3. (ABCIXIMAB or REOPRO)
4. (((EPTIFIBATIDE or INTRIFIBAN) or INTEGRELIN) or INTEGRILIN)
5. (TIROFIBAN or AGGRASTAT)
6. ((((#1 or #2) or #3) or #4) or #5)
7. (((LAMIFIBAN or SIBRAFIBAN) or XUBIX) or FRADAFIBAN)
8. (((LEFRADAFIABN or BIBU*) or XEMILOFIBAN) or ORBOFIBAN)
9. (#7 or #8)
10. (#9 not #6)

The above searches were carried out on both Issue 1 and Issue 2 of the National Research Register Version 2000. The results from Issue 2 were limited to 'new this issue'. The searches yielded a total of 73 references to ongoing or completed reviews or studies.

Online resources

Conference Papers Index (CPI) on DIALOG (1973–present)

Search strategy for licensed glycoprotein antagonists

The first search was limited to the three glycoprotein antagonists currently licensed in the UK (abciximab, eptifibatide and tirofiban). The use of theses drug names and their corresponding trade names yielded 111 hits. Limiting the search further with terms relating to unstable angina was therefore felt to be unnecessary, and the results were sifted by hand. The first strategy used was as follows:

Set	Description
1.	ABCIXIMAB?
2.	REOPRO?
3.	AGGRASTAT?
4.	EPTIFIBATIDE?
5.	INTRIFIBAN?
6.	INTEGRELIN? OR INTEGRILIN?
7.	TIROFIBAN? OR AGGRASTAT?
8.	(GP? OR GLYCOPROTEIN?) (2W) (IIB?(W)IIIA?)
9.	INTEGRIN? (W) (IIB? (W) IIIA?)
10.	S1:S9

Search strategy for unlicensed glycoprotein antagonists

This search strategy was designed to exclude all the papers already retrieved and yielded an extra seven hits.

Set	Description
1.	ABCIXIMAB?
2.	REOPRO?
3.	AGGRASTAT?
4.	EPTIFIBATIDE?
5.	INTRIFIBAN?
6.	INTEGRELIN? OR INTEGRILIN?
7.	TIROFIBAN? OR AGGRASTAT?
8.	(GP? OR GLYCOPROTEIN?) (2W) (IIB?(W)IIIA?)
9.	INTEGRIN? (W) (IIB? (W) IIIA?)
10.	S1:S9
11.	LAMIFIBAN? OR RO(W)44(W)9883 OR RO(W)44(W)9883 OR RO449883
12.	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
13.	FRADAFIBAN? OR BIBU(W)52
14.	LEFRADADIBAN? OR BIBU(W)104
15.	XEMILOFIBAN? OR SC-54701A OR SC-54684A OR SC(W)54701A OR SC54701A OR SC(W)54684A OR SC54684A
16.	ORBOFIBAN? OR SC-57099B OR SC(W)57099B OR SC57099B
17.	S11:S16
18.	S17 not S10

The above strategies were last run on 19 May 2000. This database yielded a total of 118 references to conference papers.

All the search results from the CD-ROM and online databases were downloaded into an Endnote library, and duplicate references were then deleted.

Appendix 2

Included and excluded papers

Included papers

Alexander JH. Relationship of outcomes to treatment with lamifiban in patients. Proceedings of the 46th Annual Scientific Session of the American College of Cardiology; 1997 Mar 16–19; Anaheim (CA), USA.

Bell DM. Analysis of number needed to treat and cost of platelet glycoprotein IIb/IIIa inhibitors in percutaneous coronary interventions and acute coronary syndromes. *Pharmacotherapy* 1999;**19**:1086–93.

Califf R. Lamifiban in acute coronary syndromes: comparison of different dosing [abstract]. Proceedings of the 18th Congress of the European Society of Cardiology; 1996 Aug 25–29; Birmingham, UK. *Eur Heart J* 1996;**17**(Suppl).

Goldschmidt Clermont PJ, Schulman SP, Bray PF, Chandra NC, Grigoryev D, Dise KR, *et al.* Refining the treatment of women with unstable angina – a randomised, double-blind, comparative safety and efficacy evaluation of Integrelin versus aspirin in the management of unstable angina. *Clin Cardiol* 1996;**19**:869–74.

Harrington RA. Design and methodology of the PURSUIT trial: evaluating eptifibatide for acute ischemic coronary syndromes. Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy. *Am J Cardiol* 1997;**80**:34b–38b.

Heeschen C, Hamm CW, Goldmann B, Deu A, Langenbrink L, White HD. Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. *Lancet* 1999;**354**:1757–62.

Henderson RA, Brown R. The costs of routine eptifibatide use in acute coronary syndromes in Western Europe: an economic sub-study of the PURSUIT trial. *Eur Heart J Suppl* 1999;**1**:N35–41.

Hillegass WB, Newman AR, Raco DL. Economic issues in glycoprotein IIb/IIIa receptor therapy. *Am Heart J* 1999;**138**(1 Pt 2):S24–32.

Mahaffey KW, Harrington RA, Simoons ML, Granger CB, Graffagnino C, Alberts MJ, *et al.* Stroke in patients with acute coronary syndromes: incidence and outcomes in the platelet glycoprotein IIb/IIIa in unstable angina. Receptor suppression using integrilin therapy (PURSUIT) trial. The PURSUIT Investigators. *Circulation* 1999;**99**:2371–7.

Mark D, Harrington R, Lincoff M, Califf R, Nelson C, Tsiatis A, *et al.* Cost-effectiveness of platelet glycoprotein IIb/IIIa inhibition with eptifibatide in patients with non-ST-elevation acute coronary syndromes. *Circulation* 2000;**101**:366–71.

Mattsson E, Martinsson A, Nyqvist O, Rasmanis G, Sylven C, Karlberg KE. The glycoprotein IIb/IIIa platelet receptor blocker tirofiban, but not heparin, counteracts platelet aggregation in unstable angina pectoris. *Am J Cardiol* 1997;**80**:938–40.

McClure MW, Berkowitz SD, Sparapani R, Tuttle R, Kleiman NS, Berdan LG, *et al.* Clinical significance of thrombocytopenia during a non-ST-elevation acute coronary syndrome: the platelet glycoprotein IIb/IIIa in unstable angina: receptor suppression using integrilin therapy (PURSUIT) trial experience. *Circulation* 1999;**99**:2892–900.

McElwee NE, Johnson ER. Potential economic impact of glycoprotein IIb-IIIa inhibitors in improving outcomes of patients with acute ischemic coronary syndromes. *Am J Cardiol* 1997;**80**:39b–43b.

Moliterno DJ. Delaying and preventing ischemic events in patients with acute coronary syndromes using the platelet glycoprotein IIb/IIIa inhibitor lamifiban. Proceedings of the 46th Annual Scientific Session of the American College of Cardiology; 1997 Mar 16–19; Anaheim (CA), USA.

Newby LK. Long-term oral platelet glycoprotein IIb/IIIa receptor antagonism with sibrafiban after acute coronary syndromes: study design of the sibrafiban versus aspirin to yield maximum protection from ischemic heart events post-acute coronary syndromes (SYMPHONY) trial. Symphony Steering Committee. *Am Heart J* 1999;**138** (2 Pt 1):210–18.

The PARAGON Investigators. International, randomised, controlled trial of lamifiban (a platelet glycoprotein IIb/IIIa inhibitor), heparin, or both in unstable angina. Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network. *Circulation* 1998;**97**:2386–95.

Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. *N Engl J Med* 1998;**338**:1488–97.

Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. *N Engl J Med* 1998;**338**:1498–505.

PURSUIT (Platelet IIb/IIIa in unstable angina: receptor suppression using Integrilin™ therapy). *Clin Cardiol* 1997;**20**:967.

The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy. *N Engl J Med* 1998;**339**:436–43.

Schulman SP, Goldschmidt-Clermont PJ, Topol EJ, Califf RM, Navetta FI, Willerson JT, *et al.* Effects of integrelin, a platelet glycoprotein IIb/IIIa receptor antagonist, in unstable angina. A randomised multicenter trial. *Circulation* 1996;**94**:2083–9.

Simoons ML. New findings from the PURSUIT study. *Eur Heart J Suppl* 1999;**1**:N30–4.

The SYMPHONY Investigators. Comparison of sibrafiban with aspirin for prevention of cardiovascular events after acute coronary syndromes: a randomised trial. Sibrafiban versus Aspirin to Yield Maximum Protection from Ischemic Heart Events Post-acute Coronary Syndromes. *Lancet* 2000;**355**:337–45.

Szucs TD, Meyer BJ, Kiowski W. Economic assessment of tirofiban in the management of acute coronary syndromes in the hospital setting. An analysis based on the PRISM-PLUS trial. *Eur Heart J* 1999;**20**:1253–60.

Zhao XQ, Théroux P, Snapinn SM, Sax FL. Intracoronary thrombus and platelet glycoprotein IIb/IIIa receptor blockade with tirofiban in unstable angina or non-Q-wave myocardial infarction: angiographic results from the PRISM-PLUS trial (platelet receptor inhibition for ischemic syndrome management in patients limited by unstable signs and symptoms). *Circulation* 1999;**100**:1609–15.

Excluded papers

Abernathy GB, Hewitt KK. Cost and outcomes analysis of abciximab use in a community teaching hospital. *Am J Health Syst Pharm* 1998;**55**(24 Suppl 4):S35–7.

Anderson KM, Bala MV, Weisman HF. Economics and cost-effectiveness in evaluating the value of cardiovascular therapies. An industry perspective on health economics studies. *Am Heart J* 1999;**137**:S129–32.

Califf RM, Mark DB. Issues of cost-effectiveness in the use of antithrombotic therapy for ischemic heart disease. *Am Heart J* 1997;**134**:S88–96.

Cohen M, Théroux P, Weber S, Laramee P, Huynh T, Borzak S, *et al.* Combination therapy with tirofiban and enoxaparin in acute coronary syndromes. *Int J Cardiol* 1999;**71**:273–81.

Colombo A. Different benefits, different risks, equal cost. *Eur Heart J* 1999;**20**:1531–2.

Economic constraints should not inhibit use of effective therapies for acute coronary syndromes [news and notes]. *Am J Managed Care* 1998;**4**:127–8.

Eisenstein EL, Peterson ED, Jollis JG, Tardiff BE, Califf RM, Knight JD, *et al.* Assessing the value of newer pharmacologic agents in non-ST elevation patients: a decision support system application. *Proc AMIA Annu Fall Symp* 1997:273–7.

European Society of Cardiology. First reports: new study aims to improve treatment of acute coronary syndromes. *Br J Cardiol* 1999;**6**:485.

Klein WW. Cost-effective treatment of acute coronary syndromes: IIB or not IIB? *Eur Heart J* 1999;**20**:1217–19.

Klepzig H, Krobot K, Flettner R, Winten G, Zeiher AM. Determinants of treatment costs for unstable angina. *Zeitschrift fur Kardiologie* 1999;**88**:261–9.

Klootwijk P, Meij S, Melkert R, Lenderink T, Simoons ML. Reduction of recurrent ischemia with abciximab during continuous ECG–ischemia monitoring in patients with unstable angina refractory to standard treatment (CAPTURE). *Circulation* 1998;**98**:1358–64.

Mark D, Peterson E. Health economics of acute coronary syndromes. *J Thrombosis Thrombolysis* 1998;**5**:S161–8.

Muhlestein JB. Antiplatelet agents in clinical practice: an economic perspective. *Fibrinolysis Proteolysis* 1997;**11**(Suppl 2):133–6.

Noveck RJ, McMahon FG, Karim A, Toole J. Pharmacodynamic effects of xemilofiban, and orally active IIb/IIIa. Proceedings of the 98th Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics; 1997 Mar 5–8; San Diego (CA), USA.

Smith PF, Morton S, Bouchard P, Levin S, Nicholson N, Milton M, *et al.* Safety assessment of SC-54684A (SC), the ester prodrug of a potent glycoprotein IIb/IIIa antagonist. Proceedings of the 34th Annual Meeting of the Society of Toxicology; 1995 Mar 5–9; Baltimore (MD), USA.

Topol EJ, Califf RM, Weisman HF, Ellis SG, Tcheng JE, Worley S, *et al.* Randomised trial of coronary intervention with antibody against platelet IIb/IIIa integrin for reduction of clinical restenosis: results at six months. *Lancet* 1994;**343**:881–6.

Weintraub WS, Culler SD, Kosinski A, Becker ER, Mahoney E, Burnette J, *et al.* Economics, health-related quality of life, and cost-effectiveness methods for the TACTICS (Treat Angina with Aggrastat [tirofiban] and Determine Cost of Therapy with Invasive or Conservative Strategy)-TIMI 18 trial. *Am J Cardiol* 1999;**83**:317–22.

Zed PJ, Frighetto L, Sunderji R, Marra CA. Cost-effectiveness analysis of abciximab: a Canadian hospital perspective. *Ann Pharmacother* 1998;**32**:536–42.

Appendix 3

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