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A systematic review update of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists

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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.

Glossary

Absolute relative risk (ARR) The difference between the event rates in the two groups; where the adverse event rate is less in the intervention group this suggests the intervention is beneficial.

Activated partial thromboplastin time (aPTT) Control measure in treatment with heparin.

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 Surgery of blood vessels during which a balloon is passed into the artery and inflated to enlarge it and increase blood flow; also: percutaneous transluminal angioplasty (PTCA).

Antagonist A drug that nullifies the effect of another drug.

Anticoagulant A pharmaceutical that helps to stop the blood from clotting.

Arteriogram A radiographic technique where a radiopaque (shows up on X-ray) contrast material 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 known as 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).

Cardiac catheterisation A procedure involving the introduction of a catheter into the right side or the 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 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.

Central tendency The degree of clustering of the values of a statistical distribution that is usually measured by the arithmetic mean, mode or median.

continued

Glossary *contd*

Cerebral vascular disease Damage to the blood vessels in the brain, resulting in a stroke.

Coagulation Clotting of the blood. A complex reaction depending 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.

Confidence interval (CI) A measure of precision of statistical estimates.

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.

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

Coronary artery disease (CAD) Gradual blockage of the coronary arteries.

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 involves measuring individuals' 'willingness to pay' for given outcomes, and can be quite difficult.

Cost-effectiveness The consequences of the alternatives are measured in natural units, such as years of life gained. The consequences are not given a monetary value.

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

Cost–utility analysis 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.

Creatine kinase myocardial band (CK-MB) A cardiac enzyme, marker of damage to heart muscles, which becomes raised in serum.

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.

Diastolic Pressure during the relaxing of the heart.

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.

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

End-point A clearly defined outcome or event associated with an individual in a

continued

Glossary *contd*

medical investigation. A simple example is the death of a patient.

Exercise stress test A treadmill or cycle-ergometer test that delivers 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; this identifies the individual's maximal oxygen uptake. The test allows the prescription of exercise to 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 this experiment to a larger population.

Forest plot The way in which results from a meta-analysis are often presented. Results are displayed graphically as horizontal lines representing the 95% confidence intervals of the effect of each trial (strictly the 95% CIs of the relative risk of the intervention group compared with the control group). The results of the meta-analysis are also shown in forest plots.

GI-bleeding This describes any bleeding that may occur along the course of the gastrointestinal tract.

GU-bleeding This describes any bleeding that may occur as a result of gastric ulcer bleeding.

Haematemesis The vomiting of blood.

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 bleeding in the brain.

Haemostasis The arrest of bleeding, either by the physiological properties of vaso-constriction 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 of time while the patient records their symptoms and activities in a diary. A small portable ECG device is worn in a pouch around the neck. 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.

Intention-to-treat analysis method 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 part-way through a study.

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

International normalised ratio The test used to monitor warfarin anticoagulant therapy.

Intravenous Fluid injected into a vein.

continued

Glossary *contd*

Ischaemia A low oxygen state usually due to obstruction of the arterial blood supply or inadequate blood flow leading to hypoxia in the tissue.

Kaplan–Meier curves (also product limit method) A non-parametric method of compiling life or survival tables, developed by Kaplan and Meier in 1958. This 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, withdrawal) occurs and are therefore unequal.

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

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

Mitral regurgitation (MR) The back flow of blood from the left ventricle to the left atrium through a defective mitral bicuspid valve.

Monoclonal antibody A biological response modifier with unique 'homing device' properties.

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

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

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

Number needed to treat (NNT) 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/(risk difference).

Percutaneous revascularisation The surgical restoration of blood supply (e.g. by a procedure, through a skin incision into an artery).

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

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, the safety of the new drug is tested. Early effectiveness data are also collected for varying 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, the drug is tested against a placebo or alternative treatment.

Placebo A 'dummy' treatment administered to the reference 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 reduce bleeding and physical obstruction by inducing clotting.

Proportional hazards model Regression method for modelling survival times. The outcome variable is whether or not the event of interest has occurred, and, if so, after what period of time; if not, the duration of follow-up. The model predicts the hazard or risk of the event in question at any given time.

***p*-value** In the context of significance tests, the *p*-value represents the probability that a given difference is 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.

continued

Glossary *contd*

Quality-adjusted life-years (QALYs) 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 electrocardiogram. An abnormal Q-wave is one that 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 reference 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.

Randomised controlled trial (RCT) (also randomised clinical trial) These are 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, where 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 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.

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. This should be used in those cohort studies where those with and without disease are followed to observe which individuals become diseased.

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

ST-elevation Elevation of the ST part in an ECG.

Stent In cardiology, a tube placed into an artery to maintain its patency.

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

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

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; used in therapy of myocardial infarction.

Thrombus An aggregation of blood factors, primarily platelets and fibrin with entrapment of cellular elements, frequently causing 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.

Unstable angina Angina pectoris in which the cardiac pain has changed in pattern, or occurs at rest.

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

Vasospasm The 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. Also used as a rat poison.

List of abbreviations

ACE	angiotensin-converting enzyme
ACS	acute coronary syndrome
AMI	acute myocardial infarction
aPTT	activated partial thromboplastin time
ARR	absolute relative risk
BCIS	British Cardiovascular Intervention Society
CABG	coronary artery bypass graft
CAD	coronary artery disease
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
CK-MB	creatine kinase myocardial band fraction
CNS	central nervous system
CPK	creatine phosphokinase
CVD	cerebral vascular disease
DBP	diastolic blood pressure
DM	diabetes mellitus
ECG	electrocardiogram
GI	gastrointestinal
GPA	glycoprotein antagonist
GU	genitourinary
ICER	incremental cost-effectiveness ratio
IVUS	intravascular ultrasound
LBBB	left bundle branch block
LYG	life-year gained
MACE	major adverse cardiac effects
MI	myocardial infarction
NICE	National Institute for Clinical Excellence
NNT	number needed to treat
OR	odds ratio
PCI	percutaneous coronary intervention
PTCA	percutaneous transluminal coronary angioplasty
QALY	quality-adjusted life-year
RBC	red blood cells
RCT	randomised controlled trial
RD	risk difference
RI	refractory ischaemia
RR	relative risk
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
ST-T	ST-troponin
TNK	tenecteplase
t-PA	tissue plasminogen activator
TVR	target-vessel revascularisation
UAP	unstable angina pectoris

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

Executive summary

Background

Most of the morbidity and mortality due to coronary heart disease arises from disruption to atheromatous plaques, followed by platelet aggregation and thrombus formation. Glycoprotein IIb/IIIa antagonists (GPAs) inhibit the final common pathway of platelet aggregation, and so offer a means to limit the adverse effects of plaque disruption, over and above that of other pharmacological or physical approaches.

This systematic review focuses on the use of GPAs in three indications:

- as part of the medical management of non-ST-elevation acute coronary syndrome (ACS) in conjunction with aspirin and heparin
- as an adjunct to percutaneous coronary intervention (PCI) in various groups of patients
- as a supplement to thrombolytic therapy in patients with acute myocardial infarction (AMI).

Reviews of the effectiveness and cost-effectiveness of GPAs for the first two indications are an update on those undertaken for the National Institute for Clinical Excellence (NICE) in 2000.

The first of these reviews considered seven trials concerned with the intravenous use of tirofiban, eptifibatide or lamifiban, four trials concerned with oral GPAs, and seven economic studies – two of which were unpublished company submissions. The main findings were:

- intravenous use of the drugs showed only small benefits (risk differences (RDs) for composite outcome at 30 days ranging from 1.0% to 3.8%), but this appeared to be greater in troponin-positive subgroup analyses (RD about 8%); major bleeding was more common in the treatment arms by 1.0–1.5%
- oral use was consistently negative
- cost-effectiveness was uncertain, but one unpublished analysis suggested that eptifibatide was dominant to placebo in costs per life-years gained (LYG) at 30 days.

The second review considered 12 trials on the intravenous use of abciximab, tirofiban or eptifibatide, and one trial of an oral agent. A total of 17 published economics studies and one company submission were also included. The main findings were:

- a consistent benefit of the use of GPAs during PCI (RD for composite outcome at 30 days and 6 months about 5%)
- an increased risk of major bleeding of about 5%, less with low molecular weight heparin (LMWH)
- major limitations to estimates of cost-effectiveness, with values for the incremental cost per LYG ranging from £1700 to £10,000.

Specification for update/objectives

- Oral agents excluded.
- Update on medical management (indication 1) restricted to drugs licensed in the UK (abciximab, tirofiban and eptifibatide).
- Update on adjunctive use with PCI (indication 2) and *de novo* review for adjunctive use with thrombolytics (indication 3) similarly restricted to UK drugs; at present only abciximab is licensed for indication 2 and none of the drugs is licensed for indication 3.

Methods

The search strategy, trial validity assessment, and data abstraction and analysis were in general unchanged from the previous reviews. In light of the importance assigned to high-risk subgroups in NICE's guidance to the NHS, papers reporting such subgroup analysis were considered together with equivalent results from the main reports.

Results

Indication 1

The previous review considered seven trials of intravenous use, three of which have been excluded here because the drug involved (lamifiban) is not licensed in the UK. One additional study (GUSTO IV-ACS) was discovered from the update searches.

GUSTO IV-ACS was designed specifically to address the issue of whether GPAs were of benefit in the absence of early revascularisation. Only 2% of patients underwent revascularisation within the first 48 hours of study, as opposed to much higher rates in previous trials. Although recruits were required to have a positive troponin test or ST-depression, implying that they would be at high risk of adverse outcome, the observed rates of death or MI at 30 days in the placebo arm (8%) was lower than observed in previous trials (about 11%). Both regimes of abciximab were ineffective: the 30-day rate of death or MI being 0.2% greater than placebo with 24-hour treatment duration, and 1.1% greater with 48-hour duration. Major bleeding was slightly more common in the treatment arms in line with previous studies.

Indication 2

The previous review considered 10 trials with abciximab, one trial with tirofiban and two with eptifibatide, all against placebo.

The update search discovered five further trials, including two that were head-to-head comparisons of two separate agents, and one in which both arms received a GPA.

ADMIRAL, a placebo-controlled trial of abciximab, showed a reduction of 8.6% in the combined 30-day composite outcome of death, re-infarction or urgent revascularisation in patients with AMI intended for stent insertion.

ESPRIT assessed eptifibatide versus placebo in patients undergoing stenting who were not considered eligible for routine GPA support for the procedure. A novel dosage of eptifibatide was employed with the aim of achieving greater inhibition than previous trials with this agent. A significant reduction of 3.9% was observed in the primary composite outcome at 48 hours.

PRICE was a concurrent trial that compared abciximab and eptifibatide for non-urgent stent insertion. Similar clinical outcomes and slightly lower hospital costs were demonstrated for eptifibatide.

TARGET was designed to demonstrate the non-inferiority of tirofiban compared with abciximab; in practice a 1.6% increase in the 30-day composite end-point in the tirofiban group was observed, with no difference in major bleeding.

TACTICS, in which all patients received tirofiban, has also been included in the review because it is frequently referred to in the relevant company submission (and was also identified in the update searches). A lower 30-day rate of death/MI was observed than in previous trials, suggesting that early GPA treatment might offer particular benefit when PCI was planned.

Indication 3

The searches discovered a total of six randomised controlled trials, one of which was excluded because it was a pilot for another. Three of the remaining studies were small studies powered on intermediate outcomes. The other two studies both compared abciximab plus a reduced dose of thrombolytic versus a full dose of the thrombolytic.

In GUSTO V, the primary end-point of death at 30 days was observed in 5.6% of the abciximab group as opposed to 5.9% of the control group ($p = 0.43$), but at the expense of an increase in all grades of severity of bleeding except intracranial haemorrhage. In ASSENT-3, there was a 4.3% reduction in a composite outcome of death, re-infarction or refractory ischaemia in the abciximab group compared with the control group. A third arm of the trial using LMWH instead of abciximab was almost as effective (RD 4.0% compared with control), with much lower rates of major (RD 1.3%) and minor (RD 12.0%) bleeding.

Cost-effectiveness

Relating to the use of GPAs in the medical management of ACS, a total of seven studies were included in the 2000 rapid review, and no additional studies were identified in this update. For the use of the agents alongside PCI, 18 studies were identified in the 2000 review, and a further six were found in this update. For the new indication of the use of GPAs alongside thrombolysis in AMI, no economic studies were located. Those studies that have been reviewed to date (including company submissions) exhibited a number of important limitations. These include short-term time horizons; the use of condition-specific measures of effectiveness rather than generic measures of health gain such as quality-adjusted life-years or life-years; and the estimation of costs and effects using data from clinical trials that are largely or wholly undertaken outside the UK. Particularly in the case of the use of GP IIb/IIIa antagonists in ACS, studies also include an incomplete set of comparative options, which do not reflect the various ways in which the agents can be used in the NHS.

For ACS, the estimates of cost per LYG which seem most relevant to UK practice come in the Schering-

Plough submission for eptifibatide on the basis of Western European patients in the PURSUIT trial. These estimates range from £8179 to £11,079 per LYG depending on the discount rate used for future survival. A new cost-effectiveness model for use of GP IIb/IIIa antagonists in ACS in a UK setting has been produced, and will be reported separately.

In the case of the use of GPAs alongside PCI, the estimates most relevant to UK decision-making are again contained in the company submission, this time from Eli Lilly for abciximab. It should be noted that their estimates are only UK-specific in terms of costs, with estimates of effectiveness taken directly from the EPIC, EPISTENT and EPILOG trials. The submission estimates cost per LYG to range between £3554 and £13,191 depending on the trial from which effectiveness data are taken and assumptions made.

The absence of any economic studies looking at the cost-effectiveness of GPAs alongside thrombolysis in AMI patients represents a limitation of this review.

Conclusions

Most of the trials described in this report were conducted wholly or mainly in the USA. Although there are always uncertainties about the extrapolation of results from trials to routine practice, because these trials have been conducted outside the UK this is likely to increase this uncertainty. In particular:

- early invasive management strategies are much less commonly applied in the UK than elsewhere; it has been suggested that the effectiveness of GPAs may be related to the frequency of PCI, and this is supported by the results from the one international trial (PURSUIT) where a geographical subgroup analysis of this type has been published, and by the results from GUSTO IV-ACS
- age – the mean age of individuals enrolled in these trials (range 59–67 years) is notably lower than is generally seen in clinical practice.

The following conclusions may be drawn from the update:

- the effectiveness of GPAs as adjuncts to PCI is further confirmed by additional large studies showing similar effect sizes and bleeding rates
- there is no evidence for the clinical superiority of tirofiban or eptifibatide over abciximab; drug costs of the newer agents are somewhat lower, however
- the evidence that GPAs are effective in non-ST-elevation ACS in situations when PCI is not undertaken is weakened by the publication of the GUSTO IV-ACS study; however, a recent meta-analysis of individual patient data from all major trials including GUSTO IV-ACS showed a small overall effect in such patients
- based on current evidence, it may be considered that the extra benefits of GPAs adjunctive to thrombolysis in AMI are not justified by the risks of extra bleeding.

Recommendations for further research

Further research is desirable to:

- assess the benefits, if any, of GPAs in non-ST-elevation ACS, in particular in subgroups such as women and those not scheduled for PCI
- assess the benefits, if any, of GPAs in similar troponin-negative patient subgroups
- assess the benefits of GPAs as an adjunctive to PCI in urgent and elective patients already receiving clopidogrel or starting clopidogrel at the time of randomisation, and the optimal timing in conjunction with urgent PCI
- assess the cost-effectiveness of GPAs used with thrombolytics in selected patients with AMI, preferably in a revised formulation that reduces unwanted bleeding.

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 (GP IIb/IIIa) antagonists in three indications: (i) the acute treatment of non-ST-elevation acute coronary syndromes (ACSs); (ii) as an adjunct to percutaneous coronary interventions (PCIs); and (iii) for acute myocardial infarction (AMI), alongside treatment with thrombolytics (where thrombolysis is indicated)? The reviews of the effectiveness and cost-effectiveness of GP IIb/IIIa antagonists for the first two indications are an update on those undertaken for the National Institute for Clinical Excellence (NICE) in 2000.

The three GP IIb/IIIa antagonists that are currently licensed in the UK (abciximab, eptifibatide and tirofiban) are included in the review. In addition, any other non-licensed glycoprotein antagonists (GPAs) identified through the literature search are reviewed, excluding oral agents and agents for which no licence applications are expected in the foreseeable future. As in the previous reviews, it was not considered appropriate to pool results from separate trials, given the variations between trials in terms of patients' enrolled settings and concurrent interventions. A Cochrane Review that does pool results has recently been published,[1] along with a recent meta-analysis of individual patient data from all major trials including GUSTO IV-ACS.[2]

Background

In 2000, two rapid reviews were undertaken for NICE on the use of GP IIb/IIIa antagonists in cardiology. The first of these[3] focused on the role of these drugs in ACS and the second[4] looked at the use of GP IIb/IIIa antagonists alongside PCIs such as coronary angioplasty.

This report relates to an update of these reviews. In addition to the two clinical uses of GP IIb/IIIa antagonists referred to above, a third application will be covered in the review: the use of GP IIb/IIIa antagonists alongside thrombolytic therapy in patients with AMI.

Description of the underlying health problem

Coronary heart disease

The general health problem covered by this review is coronary heart disease (CHD). CHD is an important health problem; it is a leading cause of mortality, with over 110,000 deaths in England in 1998, including more than 41,000 individuals under the age of 75 years.[5] The overall prevalence of CHD in England in 1998 was estimated to be 7.1% in men and 4.6% in women, with prevalence increasingly sharply with age.[6]

Although age-standardised mortality rates are falling by about 4% per annum in the UK, these reductions are lower than in other countries. Furthermore, improvements in death rates have not been experienced symmetrically across the social classes, and death rates from heart disease among unskilled men are now three times greater than those among professional men.[5] There remains a clear difference in mortality from CHD between the sexes, with lower rates in women.[7]

The three indications covered in this report relate to several underlying health problems. The first indication relates to ACS, which itself includes a range of patient groups. The second relates to PCI, which is a procedure rather than a health problem and is used to manage a number of different patient groups. The third is AMI.

ACS is a term that includes a range of patients with a broadly similar underlying pathology. At one end of the spectrum are those patients with evidence of ST-elevation on a resting electrocardiogram (ECG) who are eligible for treatment with thrombolysis and who may subsequently develop Q-wave on their ECG. Non-ST-elevation ACS includes a spectrum of patients who may also be labelled as unstable angina or non-Q-wave AMI. There are approximately 130,000 such episodes in the UK per year and this incidence may be rising. Despite the use of standard anti-platelet and anti-thrombotic therapy, there is a substantial risk of death, non-fatal MI or re-infarction of about 10% within 30 days. Intravenous thrombolytic therapy, a major therapeutic advance for ST-elevation ACS, is not effective for non-ST-elevation cases. **Unstable angina** itself represents a spectrum of

clinical states that fall between stable angina and AMI. It includes angina at rest (typically lasting > 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 > 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 is thought to indicate a sub-endocardial infarction, where the damage does not extend through the full thickness of the myocardium.

At the time the patient presents, it is difficult to distinguish those patients with non-ST-elevation ACS that will or will not go on to develop AMI. It is only possible to differentiate between the two 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 taking a careful medical history, assessing the patient for evidence of prior MI, other indicators of CAD, patient age and gender, and 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.[8]

The risk is highest in the early stages of symptom presentation, but returns to baseline levels (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 subsequent clinical course. Indicators of poor prognosis on physical examination include heart failure, mitral regurgitation murmur, or hypertension (particularly during pain). ECG findings that help identify high-risk patients include ST-segment changes of ≥ 1 mm or T-wave inversion that resolves with symptom resolution. Patient age and 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-troponin (ST-T) changes during symptoms. Rizik and colleagues have proposed a stratification system of unstable angina.[9] Class IA are patients with increasing exertional angina, without ECG changes; Class IB are the same patients with ECG changes; Class II are patients with new-onset exertional angina; Class III are those with new-onset rest angina; and Class IV are those with protracted rest angina with ECG changes. These classes exclude patients with post-MI angina, variant angina, and 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 use 'pain at rest' as the definition of unstable angina the 1-month incidence proportions of death varied between 2% and 60%.[10–13] Those studies using a definition of increasing angina showed 1-month incidence proportions of death between 16% and 50%.[14–18] 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 could result in the mortality figures reported to 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 (stenosis size, location and plaque fragility), thrombus formation (low or high platelet content) and vasospasm. Each of these 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.

Patients undergoing PCI

PCI represents a key element of the therapeutic armamentarium available for the management of CHD. First used in the 1970s, percutaneous transluminal coronary angioplasty (PTCA) represented a less invasive way to revascularise occluded coronary arteries than coronary artery bypass surgery, although the overall relative effectiveness and cost-effectiveness of these two forms of revascularisation is less clear.[19,20] The development of new interventional coronary techniques as an addition or alternative to PTCA – particularly coronary stents[20] – has led to increasing indications for PCI. The procedure has traditionally been seen mainly as a way of managing the symptoms of stable angina, particularly in single- or double-vessel disease, which are resistant to medical management. However, the development of the technique has resulted in PCI having an important role in revascularising the occluded arteries of other types of patient with CHD, such as those with ACS and AMI.

For all patients undergoing PCI, there is a risk of acute complications such as death and MI, as well as longer-term restenosis. The incidence of these events has been reduced by the use of coronary stents,[21] but these complications remain an increasing consideration in clinical decision-making.

Patients undergoing thrombolysis

In patients with AMI, intravenous thrombolytic therapy to achieve myocardial reperfusion has become a mainstay of management since the late 1980s.[22] The effectiveness of thrombolysis was established in large randomised controlled trials (RCTs) such as GISSI and ISIS-2, which showed that mortality could be reduced by up to 50% depending on how quickly the drugs were administered.[23,24] Subsequent trials, such as GUSTO-1, sought to identify whether the use of newer generation thrombolysis could increase vessel patency and hence increase survival. GUSTO-1 found that accelerated tissue plasminogen activator (t-PA) resulted in a 15% relative risk (RR) reduction in mortality at 30 days compared with streptokinase.[25] More recent trials have used accelerated t-PA as the 'gold standard' form of intravenous thrombolysis, and a new generation of plasminogen activators has been evaluated in 15,000–17,000 patients.[22] Three new agents have emerged – reteplase (r-PA), tenecteplase (TNK) and lanoteplase (n-PA) – but none has yet been shown to offer superior mortality outcomes to t-PA although they generate a more rapid or complete vessel patency.[22]

Despite refinements to the approach, only 50–55% of vessels are reperfused by thrombolytic therapy alone. This is less than the approximately 75% of AMI patients who obtain equivalent flow after primary PCI.[26] Another limitation of thrombolysis in achieving reperfusion is the importance of how platelets react to the plaque fissure or rupture of the diseased coronary artery. There is a risk that platelet-thrombus will embolise to the microcirculation. Moreover, plasminogen activators can stimulate platelet aggregation through their ability to lyse fibrin from the fibrin-thrombin clot.[25] This has led to research into the effectiveness of combining thrombolysis with agents that can inhibit platelet aggregation such as GP IIb/IIIa antagonists.

Current service provision

Estimating the current service provision and current costs in the areas relevant to this review is difficult owing to a dearth of routine data. Regarding treatment of ACS, 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 AMI, but who were admitted with unstable angina is also not known. In addition, deaths due to ACS will often be classified as AMI. The incidence of new cases of angina pectoris in the UK is conservatively estimated to be around 22,600 patients per annum.[27] The 1999 NHS Executive data show that at least 129,458 cases of angina were seen by consultants, with cost per 'finished consultant episode' ranging from £156 to £1,123.[28] According to UK Hospital Episode Statistics, there is about one admission for unstable angina per 1000 total population per year but other estimates in the UK and in the USA are two to three times greater, similar to the reported rates for AMI.[29] NICE guidance estimated a total of 115,000 admissions per year in England and Wales with the condition.

There is a similar dearth of routine statistics on the use of thrombolytic therapy following AMI. In an audit of 3714 patients in 15 UK hospitals between 1993 and 1997, there was an increase in the proportion of patients receiving thrombolysis within 90 minutes of the call for help from 28.2% to 39.1%.[30]

The British Cardiovascular Intervention Society (BCIS) provides valuable data on the use of PCI

in the UK. BCIS audit returns go back to 1991 and, for the latest returns, data were collected in all UK interventional cardiology centres (although not every centre provided complete data).[31] *Table 1* shows the numbers of PCIs, rates per million and year-on-year increase between 1991 and 2000, as reported by BCIS. The table shows a rapid increase in the use of PCI in this country. The BCIS returns do not, however, break down PCI rates between different patient groups.

Internationally, PCI rates in the UK are now higher than in some European countries (e.g. Spain, Italy and Finland), but remain lower than countries such as Germany, France and the USA.[31]

Over the last 10 years, the proportion of PCIs in which a coronary stent is implanted has increased markedly. In the 2000 BCIS returns, stents were used in 84% of PCI procedures.

Description of new intervention

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 are also antiplatelet drugs. Heparin increases anticoagulation and helps to limit the extension of an existing clot by binding to the natural anticoagulant antithrombin III and reducing platelet functioning. Low molecular weight heparins work in a similar way, but because they are more selective in their binding, provide a greater antithrombotic effect and reduced haemorrhagic complications. However, none of these drugs inhibit all of the stimuli for platelet aggregation. The GP IIb/IIIa receptor on the platelet surface is thought to be the final common pathway of platelet aggregation. The GP IIb/IIIa antagonists are a class of drugs that may be more effective in preventing platelet aggregation than previous agents. Abciximab is a monoclonal antibody targeted at the receptor, while eptifibatide and tirofiban are more conventional pharmacological receptor antagonists.

Abciximab differs from the other GP IIb/IIIa antagonists in that it not only binds to the platelet receptor but also to other integrins such as the vitronectin receptor. Vitronectin is involved in the processes of cell adhesion, migration and neointimal proliferation.[32] Thus abciximab may have wider effects than the small molecule GPAs. Abciximab also differs in its pharmacokinetics, in that its clearance from plasma is much slower. It binds to platelets for up to 2 weeks after infusion, and produces a reduction in platelet aggregation for up to 1 week.[33]

Tirofiban and eptifibatide, the other two GP IIb/IIIa antagonists licensed for use in the UK, are much more similar to each other. Inhibition of platelet aggregation lasts only 2–4 hours after the end of an infusion.[33] The characteristics of GP IIb/IIIa antagonists have resulted in these agents being increasingly used in the management of various groups of patients with CHD. In patients presenting with ACS, initial rupture of plaque in the diseased artery is followed by platelet adhesion at the site of the injury and subsequent thrombosis. In unstable angina, there is typically intermittent thrombus formation and dissolution at the injury site. In AMI, a stabilised clot at the site of the

TABLE 1 *PCI rates in the UK, 1991–2000*

Year	Centres	Total procedures	Rate per million	% increase
1991	52	9,933	174	–
1992	52	11,575	203	16.5
1993	53	12,937	227	11.8
1994	54	14,624	256	13.0
1995	54	17,344	304	18.6
1996	53	20,511	359	18.1
1997	58	22,902	402	11.7
1998	61	24,899	437	8.7
1999	63	28,133	494	13.0
2000	66	33,652	590	20.0

Source: BCIS audit returns (http://www.bcis.org.uk/audit/oct01.html[31])

injury causes occlusion. In PCI patients, there is a risk of iatrogenic plaque rupture followed by ischaemic complications due to platelet aggregation, and this is not fully removed by standard anti-thrombotic therapies such as heparin. GP IIb/IIIa antagonists are now used in each of these areas as a way of repressing platelet aggregation.

Animal models first showed the potential of GPAs to enhance reperfusion in conjunction with intravenous thrombolytics in the 1980s.[34] The first clinical studies used a sequential approach, where abciximab was given after the thrombolytic.[35] The usual approach to using the two drug types together has been to reduce the dose of the thrombolytic agent, to lessen the risk of unwanted effects, in particular haemorrhage.

The GP IIb/IIIa antagonists are given in addition to other 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. The cost of drug alone (not including infusion costs) for treating a 70-kg person is given in *Table 2* for each of the three drugs, together with details of their licensed indications. The information is taken from the *British National Formulary*.[29]

GP IIb/IIIa antagonists have been licensed for some years in the UK and experience of their use is developing. In the BCIS audit returns, about 6% of PCI procedures were undertaken using abciximab in 1997, but this had increased to 22% in 2000.[31] Despite not being formally licensed in this indication, eptifibatide or tirofiban was reported as being used in 50 cases in 2000 (about 0.2%). Although no formal data have been identified to indicate the use of GP IIb/IIIa antagonists in the other two indications considered in this review, it is clear that this class of drugs is now being widely used in the NHS.

TABLE 2 *GP IIb/IIIa antagonists: indications, doses and prices*

Drug name	Indication	Bolus dose/ 70 kg	Maintenance dose range/70 kg	Maintenance duration	Cost
Abciximab (ReoPro®, Lilly)	Prevention of ischaemic cardiac complications in patients undergoing PCI; short-term prevention of MI in patients with unstable angina not responding to conventional treatment and who are scheduled for PCI	17.5 mg	6.3–18.9 mg	12–36 hours	£840–£1120
Eptifibatide (Integrilin®, Schering-Plough)	Prevention of early MI in patients with unstable angina or non-Q-wave MI and with last episode of chest pain within 24 hours	12.6 mg	604.8–806.4 mg	72–96 hours	£455.10–£552.78
Tirofiban (Aggrastat®, MSD)	Prevention of early MI in patients with unstable angina or non-Q-wave MI and with last episode of chest pain within 12 hours	840 µg	20.16–45.36 mg	48–108 hours	£292.22–£584.44

Chapter 2

Clinical effectiveness

Methods for reviewing effectiveness*

Search strategy

See appendix 1 for full details of the search strategies.

Search results were de-duplicated against previous results obtained for the HTA review[3] and the Leeds update project. The Leeds update project is secondary research funded by the HTA Programme, which focuses on the use of GP IIb/IIIa antagonists in non-ST-elevation ACS patients.

For the two clinical indications covered in the earlier rapid reviews (the acute use of GP IIb/IIIa antagonists in non-ST-elevation ACS and alongside PCI) and for the third indication (the use of GP IIb/IIIa antagonists alongside thrombolytic therapy in AMI), the searching and review period went back to the date from which the medical management review commenced (i.e. the start of CD-ROM resources). See appendix 2 for the original search strategy.

The authors of trials identified in the National Research Register were contacted by email initially and then by a follow-up telephone call for further information about their studies. Other contacts included the Cochrane Heart Group and researchers known to have published economic analyses in the area of CADs. Six possible relevant trials were identified. The lead person in all of the cases was contacted for more information: only one replied (trial of abciximab, lead person Dr Rodney Foale). This trial has been discontinued due to recruitment difficulties.

The bibliographies of all included studies were reviewed to identify further relevant studies.

Any information from consultees submitting to NICE was also searched for relevant data, conforming to the inclusion criteria of the review.

Inclusion and exclusion criteria

Interventions

1. GP IIb/IIIa antagonists: abciximab (ReoPro®); eptifibatide (Integrilin®); and tirofiban (Aggrastat®).
2. Thrombolytics: GP IIb/IIIa antagonists listed above, when used alongside one of the following thrombolytics: alteplase (Actilyse®), reteplase (Rapilysin®), streptokinase (non-proprietary) and tenecteplase (TNKase, Metalyse®).

Comparators

The direct comparator to the GP IIb/IIIa antagonists was typically placebo in all indications. Depending on the indication, patients would also typically be taking a range of standard medical treatments such as aspirin and unfractionated heparin in unstable angina. In respect of the use of GP IIb/IIIa antagonists alongside thrombolytics, thrombolytic therapy alone was the relevant comparator.

Participants

For the three patient types listed below:

1. patients who presented 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. 'ACS' means any constellation of clinical signs or symptoms suggestive of AMI or unstable angina without ST-elevation on resting ECG
2. patients who were undergoing acute or elective PCI
3. patients who had confirmed AMI and were undergoing thrombolytic therapy.

Outcomes

- AMI/recurrent AMI
- cardiovascular death
- overall mortality
- composite outcomes
- severe recurrent angina
- haemorrhagic stroke
- fatal bleeding episode
- major bleeding episode
- minor bleeding episode
- revascularisation
- other adverse events
- quality of life
- cost and cost-effectiveness.

* According to the explicit Quality Standards agreed by InterTASC.

Study designs

1. RCTs.
2. Subgroup analysis of previously reported trials concerning one or more recognised high-risk groups: the elderly, diabetics, patients with positive troponins, patients with ST-depression on initial ECG.
3. Full economic evaluations where both cost and effects have been considered (including cost-effectiveness, cost-minimisation, cost–utility, cost–benefit or cost–consequences analyses).

Pilot studies for other studies were excluded.

Data extraction strategy

Two reviewers independently assessed all obtained titles and abstracts for inclusion. Data were extracted into tables independently by one reviewer and checked by a second. A third reviewer was consulted to resolve any discrepancies. Authors were contacted in an attempt to gather missing information.

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 pre-tested on a small sample of excluded studies addressing the appraisal topic. In addition, details of treatment, patients included and outcome phenomena were recorded. Finally, more descriptive information, such as year of publication and language, was noted. The validity assessment tool can be seen in appendix 3.

Two reviewers independently scored the internal and external validity of each included study. Discordant scores based on obvious reading errors were corrected. Discordant scores based on real differences in interpretation were resolved through consensus. A third party was sought if necessary. The reviewers were not blinded for names of authors, institutions, journals or the outcomes of the trials.

Synthesis and analysis

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 RR forest plots. These were intended only as a graphical representation of results. As no pooling of results was undertaken the line of effect depicted for each study does not reflect the weight of each trial. Both beneficial and adverse events 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.

Search results

Quantity and quality of research available

A total of 2974 hits were derived from the update searches and stored in an Endnote library. Duplicates were then excluded and 2851 records remained. These records were transferred to a Microsoft Access database. Two reviewers then independently assessed titles and abstracts against the inclusion criteria. Discrepancies were resolved by discussion. A total of 156 full papers were then obtained for closer examination. Of these, six economic studies and 22 efficacy papers were selected for inclusion in the review. A list of included and excluded papers can be seen in appendix 4.

Studies included in the review

Table 3 shows the number of completed trials (efficacy) and studies (economics) featured in the current review.

Ongoing and late-breaking trials

To ensure that the update literature searches did not miss any important late-breaking or ongoing clinical trials, additional searches of the following web-based registries were carried out on 1 October 2001:

- American College of Cardiology, annual conference 2001, late-breaking clinical trials

TABLE 3 *Numbers of studies identified in the original review and in the update*

	Update search	McDonagh *et al.*, 2000[3]	Fischer *et al.*, 2000[4*,†]
Clinical efficacy	22	4	12
Economics	6	5	12

* *EXCITE excluded because xemilofiban does not have a current UK licence for this indication*
† *Papers on lamifiban were excluded because the drug does not have a current UK licence*

- American Heart Association, late-breaking clinical trials 2001
- British Cardiac Society, annual conference 2001
- Cardiosource, ongoing and unpublished trials.

In addition to the six trials identified by the National Research Register, for which no details on status were available, the following ongoing trial was also identified: A–Z trial – this study has evaluated the safety of tirofiban and the low molecular weight heparin enoxaparin, and results are expected to be available late 2002.

Use of glycoproteins in the medical management of ACS

Efficacy of intravenous GP IIb/IIIa antagonists

In addition to the four relevant trials identified in the previous NICE review (McDonagh and colleagues 2000[3]), one additional trial was identified in the update searches, GUSTO IV-ACS.[36] This has now been extracted and discussed alongside the previously reported studies. Two papers relating to subgroup analysis of previously reported trials (PURSUIT and PRISM-PLUS) were identified in the update searches; these have been extracted and discussed in the sections pertaining to high-risk subgroups.

General details

The five trials all took place between 1996 and 2001 (*Table 4*), with four conducted in an international setting and one in the USA (Schulman and colleagues 1996[37]). All studies were classified as RCTs, and included unstable angina or non-Q-wave MI patients. The Schulman study was a Phase II study exploring safety and dosing, while the PURSUIT,[38–41] PRISM,[42] PRISM-PLUS[43] and GUSTO IV-ACS[36] studies were Phase III studies looking at efficacy.

PRISM[42] and PRISM-PLUS[43] studies evaluated the effectiveness of tirofiban, Schulman[37] and PURSUIT[38–41] looked at eptifibatide, and GUSTO IV-ACS[36] looked at abciximab. The intervention studied can be seen in *Table 5*. Duration of follow-up varied from 24 hours (Schulman) to 6 months (PRISM-PLUS).

PRISM differed from the other trials in that GP IIb/IIIa antagonists were given without heparin. PRISM-PLUS also initially contained an arm with GP IIb/IIIa antagonists without heparin but this was stopped early due to a disproportionate number of deaths.

The number of participants in each trial varied quite significantly: PURSUIT was the largest trial with 9461 participants and Schulman the smallest trial with 227 participants.

Patient characteristics and inclusion criteria

Although all trials included unstable and non-Q-wave MI patients, the definition of these patients varied (see inclusion criteria in *Table 6*). Schulman was the only study to define the

TABLE 4 *Designs of included studies of intravenous GP IIb/IIIa antagonists in ACSs*

Study	Setting	Design/phase	Treatment arms	Number of participants	Follow-up time-points
Schulman *et al.*, 1996[37]	USA	RCT Phase II	Low-dose eptifibatide	77	24 hours
			High-dose eptifibatide	76	
			Aspirin	74	
PURSUIT[38–41*]	International	RCT Phase III	Eptifibatide	4722	96 hours, 7 days, 30 days
			Placebo	4739	
PRISM, 1998[42]	International	RCT Phase III	Tirofiban	1616	48 hours, 7 days, 30 days
			Heparin	1616	
PRISM-PLUS: Bazzino *et al.*, 1998[43]	International	RCT Phase III	Tirofiban	345	48 hours, 7 days, 30 days, 6 months
			Tirofiban + heparin	773	
			Heparin	797	
GUSTO IV-ACS: Simoons, 2001[36]	International	RCT Phase III	24 hours abciximab	2590	48 hours, 7 days, 30 days
			48 hours abciximab	2612	
			Placebo	2598	

* *Harrington, 1997[38]; PURSUIT Trial Investigators, 1997[38A]; Simoons, 1999[39]; Mahaffey* et al., *1999[40]; PURSUIT Trial Investigators, 1998[41]*

TABLE 5 *Interventions specified by study protocols*

Study	Intervention 1	Intervention 2	Control
Schulman *et al.*, 1996[37]	High-dose eptifibatide bolus of 90 µg/kg, followed by 1.0 µg/kg per minute, plus placebo	Low-dose eptifibatide bolus of 45 µg/kg over 3 minutes, followed by 0.5 µg/kg per 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[38–41]*	Eptifibatide bolus of 180 µg/kg followed by infusion of 2.0 µg/kg per minute	† Eptifibatide bolus of 180 µg/kg followed by infusion of 1.3 µg/kg per minute	Placebo bolus and infusion
	Study drugs given for 72 hours or until discharge if earlier. Extended to 96 hours if PCI performed. Subcutaneous or intravenous adjusted dose heparin was recommended, but not required. Aspirin (80–325 mg/day) was given at the discretion of the treating physicians. If contraindicated or if intolerant to aspirin, ticlopidine could be given		
PRISM, 1998[42]	Tirofiban 0.6 µg/kg per minute for 30 minutes, followed by 0.15 µg/kg per minute for 47.5 hours plus placebo heparin (5% dextrose)	Adjusted dose heparin plus placebo tirofiban (normal saline) for 48 hours. Heparin dosing: 5000-unit bolus followed by 1000 units/hour, adjusted at 6 and 24 hours to twice the aPTT	–
	Random alterations were made in the placebo heparin administration rate. Aspirin (325 mg daily) was administered to all patients before randomisation, and daily for 48 hours, and thereafter at the discretion of the physician. Other medications, except non-steroidal anti-inflammatory drugs, ticlopidine or warfarin, could be prescribed		
PRISM-PLUS: Bazzino *et al.*, 1998[43]	Tirofiban 0.6 µg/kg per minute for 30 minutes, followed by 0.15 µg/kg per minute plus placebo heparin	Tirofiban 0.4 µg/kg per minute for 30 minutes, followed by 0.1 µg/kg per minute plus adjusted dose heparin	Adjusted dose heparin plus placebo tirofiban
	The drugs were infused for a minimum of 48 hours. Heparin dosing: 5000-unit bolus followed by 1000 units/hour, adjusted after 6, 12, 24, 36 and 48 hours and thereafter as needed to twice the aPTT. 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		
GUSTO IV-ACS: Simoons, 2001[36]	Abciximab therapy for 24 hours (0.25 mg/kg bolus followed by a 0.125 µg/kg per minute infusion up to a maximum of 10 µg/kg for 24 hours) followed by 24 hours of placebo infusion	Abciximab therapy for 48 hours (same bolus and infusion for total duration of 48 hours)	Matching placebo (bolus and 24-hour infusion)
	All patients were to receive 150–325 mg non-enteric coated aspirin orally (or 250–300 mg intravenously) as soon as possible after randomisation, and 75–325 mg daily for at least 30 days if not contraindicated. All patients were to receive a 70-unit/kg unfractionated heparin bolus (to maximum of 5000 units) followed by a continuous infusion of 10 units/kg per hour (to a maximum of 800 units/kg). Coronary angiography was not to be done during or within 12 hours after completion of infusion		

* *Harrington, 1997[38]; PURSUIT Trial Investigators, 1997[38A]; Simoons, 1999[39]; Mahaffey* et al., *1999[40]; PURSUIT Trial Investigators, 1998[41]*
† *Low-dose group stopped early; data for high-dose group only presented and analysed*

TABLE 6 *Inclusion and exclusion criteria from published texts*

Study and drug	Inclusion criteria	Exclusion criteria
Schulman *et al.*, 1996[37] Eptifibatide	Men and women aged 21–80 years old with unstable angina. 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 CVD, major GI- or GU-bleeding within 30 days, significant thrombocytopenia (< 100,000/mm^3), coagulopathy (receiving coumadin or bleeding time > 20 minutes), and if they presented with severe hypertension (SBP > 180 mmHg or DBP > 120 mmHg) or had renal insufficiency with a creatinine level > 4 mg/dl
PURSUIT[38–41*] 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 more than 0.5 mm, transient or persistent ST-segment depression of more than 0.5 mm, T-wave inversion of more than 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 more than 1 mm, active bleeding or a history of bleeding diathesis, GI- or GU-bleeding within 30 days before enrolment, SBP above 200 mmHg or DBP above 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 GP IIb/IIIa inhibitor or thrombolytic agent or the receipt of thrombolytic therapy within the previous 24 hours
PRISM, 1998[42] 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 less than 20 minutes) of 0.1 mV or more; (2) elevated cardiac enzyme levels consistent with the occurrence of non-Q wave MI; (3) a history of MI, percutaneous revascularisation more than 6 months earlier, coronary surgery more than 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 enrolment on a previous arteriogram	Patients were excluded if they had received thrombolytic therapy within the previous 48 hours or had an allergy to or intolerance of heparin, a serum creatinine level above 2.5 mg/dl (221 mmol/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 SBP above 180 mmHg, DBP above 110 mmHg or both at the time of enrolment, a history of haemorrhagic CVD or an active intracranial pathologic process, a history of CVD 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: Bazzino *et al.*, 1998[43] 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 pseudo-normalisation of 0.1 mV or more) or an elevation of plasma levels of CK and of the CK-MB fraction	ST-segment elevation lasting more than 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, and stroke within the previous year. Patients who had serum creatinine values above 2.5 mg/dl or a platelet count below 150,000/mm^3 were also excluded

continued

***TABLE 6* contd** *Inclusion and exclusion criteria from published texts*

Study and drug	Inclusion criteria	Exclusion criteria
GUSTO IV-ACS: Simoons, 2001[36] Abciximab	Patients with ACS, without persistent ST-segment elevation, aged 21 years or over with more than one episode of angina lasting at least 5 minutes within the preceding 24 hours. Either a positive troponin T or I test or at least 0.5 mm of transient or persistent ST-segment depression not known to be pre-existing and not attributable to coexisting disorders or medication. Patients with a history of MI were required to have new ST-segment depression and CK-MB concentrations below the upper limit of normal	Myocardial ischaemia precipitated by a disorder other than atherosclerotic CAD, persistant ST-segment-elevation MI, or new left-bundle branch block; PCI within previous 14 days; planned PCI or CABG within 30 days after enrolment; active internal bleeding or history of haemorrhagic diathesis; major surgery, serious trauma or GI- or GU-bleeding of clinical significance within the previous 6 weeks; intracranial neoplasm or aneurysm, arterioventricular malformation, history of stroke within 2 years, or prior stroke with a residual neurological deficit; oral anticoagulation within the previous 7 days unless the international normalised ratio was 1:4 or less. Platelet count of < 100 000/µl, confirmed hypertension, history of vasculitis, puncture of the non-compressible vessel within 24 hours before enrolment, allergy to abciximab or other murine proteins, weight more than 120 kg, a coexisting disorder associated with limited life expectancy

* *Harrington, 1997[38]; PURSUIT Trial Investigators, 1997[38A]; Simoons, 1999[39]; Mahaffey* et al., *1999[40]; PURSUIT Trial Investigators, 1998[41]*

presence of unstable angina explicitly, defining it as "the recent onset of a changing pattern of cardiac ischaemic symptoms at rest, with one episode lasting ≥ 10 minutes and occurring within 24 hours of randomisation". Inclusion and exclusion criteria used in each trial can be seen in *Table 6*.

The baseline characteristics of participants can be seen in *Table 7*. The mean age of participants was approximately the same between trials, ranging from 63 to 65 years; this was, however, substantially lower than reported in UK routine practice (PRAIS-UK). Prognostic information collected in each trial shows that participants did not differ significantly with respect to previous interventions and co-morbidities between the arms within each trial. There were some important differences between trials, for example the proportion of patients with ST-depression varied from 31.5% in PRISM to 80% in GUSTO IV-ACS. Troponin status was only known for all participants in GUSTO IV-ACS (60% were positive). The comparable figure in the subgroup of PRISM in whom troponin was measured was 29%.

Concomitant medication

Table 8 details the use of concomitant medications. Use of concomitant medication before and after randomisation differed between studies. Study protocols often required that aspirin and heparin were given after randomisation. However, the decision to prescribe these medications was often left to the discretion of the treating physician. Schulman randomised patients to receive placebo or 325 mg aspirin, with all patients given heparin. On termination, placebo patients were then also given 325 mg aspirin in conjunction with heparin. PRISM randomised patients to heparin or placebo, all patients received aspirin. GUSTO IV-ACS administered aspirin and heparin to the majority of patients, beta-blockers, dalteparin, calcium antagonists IV nitrates and ACE inhibitors were also administered to varying percentages of patients.

Outcomes recorded and definition of outcomes

Table 9 details the definitions of outcomes in the trials. All studies reported death and MI; all except Schulman at 7 and 30 days, and all except Schulman and PURSUIT at 48 hours. However, there were important differences in the definition of MI. In particular, PURSUIT recognised MI based on a single measurement of creatine kinase (CK) above the upper limit of normal, whereas most other trials required twice the upper limit of normal. GUSTO IV-ACS required the CK myocardial band fraction (CK-MB) to be greater than the upper limit of normal in two samples, of which one was more than three times the upper limit of normal. All the studies also defined a composite outcome; however, this did not include the same types of events in each trial. PURSUIT and GUSTO IV-ACS only considered death or MI events. Schulman

TABLE 7 *Baseline characteristics of participants in studies of intravenous drugs*

Study	Prognostic indicators	Intervention 1	Intervention 2	Control
Schulman *et al.*, 1996[37]	Mean age	64	61	61
	Diabetes (%)	–	–	–
	Previous MI (%)	59	53	53
	Previous PCI (%)	37	40	34
	Previous CABG (%)	37	22	28
	CHF (%)	15	12	12
	ST-depression (%)	–	–	–
	Troponin I/T positive (%)	–	–	–
PURSUIT[38–41]*	Mean age	64	–	64
	Diabetes (%)	22	–	23
	Previous MI (%)	32	–	33
	Previous PCI (%)	13	–	13
	Previous CABG (%)	12	–	12
	CHF (%)	11	–	11
	ST-depression (%)	50	–	50
	T-wave inversion (%)	52	–	50
PRISM, 1998[42]	Mean age	63	62	–
	Diabetes (%)	20	22	–
	Previous MI (%)	47	47	–
	Previous CABG (%)	17	18	–
	Previous PCI (%)	14	16	–
	Previous heart failure (%)	12	13	–
	ST-depression (%)	–	–	–
	Troponin I/T positive (%)	–	–	–
PRISM-PLUS: Bazzino *et al.*, 1998[43]	Mean age	63	63	63
	Diabetes (%)	25	22	24
	Previous MI (%)	46	45	39
	Previous PCI (%)	13	9	9
	Previous CABG (%)	17	16	13
	Previous heart failure (%)	11	11	8
	ST-depression (%)	57	57	60
	T-wave changes (%)	58	52	52
GUSTO IV-ACS: Simoons, 2001[36]	Mean age	65	65	65
	Diabetes (%)	21	22	22
	Previous MI (%)	30	27	28
	Previous PCI (%)	11	10	9
	Previous CABG (%)	10	9	9
	Previous heart failure (%)	8	8	7
	ST-depression (%)	81	80	80
	Troponin I/T positive (%)	60	59	58

* *Harrington, 1997[38]; PURSUIT Trial Investigators, 1997[38A]; Simoons, 1999[39]; Mahaffey* et al., *1999[40]; PURSUIT Trial Investigators, 1998[41]*

recorded refractory ischaemia (RI), MI, need for morphine, intra-aortic balloon pump, emergency catheterisation or PTCA, or death. PRISM and PRISM-PLUS looked at death, MI or recurrent ischaemia for the 48-hour and 30-day follow-up, and included readmission for unstable angina in the 30-day composite outcome (PRISM-PLUS also looked at this outcome at the 6-month follow-up).

Outcomes for high-risk patients

Four additional papers were found that looked at pre-defined high-risk groups (diabetics, elderly patients, troponin-positive and ST-depression). General details on these subgroup papers can be seen in *Table 10*.

Heeschen and colleagues (1999)[44] looked at outcomes in the PRISM trial by troponin-I status; an indication of high risk. Theroux and colleagues (2000)[45] looked at patients with a diagnosis of diabetes mellitus (DM) at enrolment. Hasdai and colleagues (2000)[46] and Boersma and colleagues (2000)[47] looked at the impact of age, ST-depression and diabetes on the outcomes of patients in

TABLE 8 *Use of concomitant medication*

Study	Treatment arm	Aspirin (%)	Heparin (%)	Nitrates (%)	Calcium channel blocker (%)	Beta blocker (%)
Schulman *et al.*, 1996[37]	High-dose eptifibatide	86	–	60	40	33
	Low-dose eptifibatide	88	–	64	46	38
	Aspirin	88	–	57	38	40
PURSUIT[38–41*]	–	–	–	–	–	–
PRISM, 1998[42]	Tirofiban	94.9	25.4	78	52	45
	Heparin	94.3	25.7	77	53	46
PRISM-PLUS: Bazzino *et al.*, 1998[43]	Tirofiban	–	–	95	50	75
	Tirofiban + heparin	–	–	95	49	78
	Heparin	–	–	94	43	81
GUSTO IV-ACS: Simoons, 2001[36]	24 hours of abciximab	–	–	59	22	78
	48 hours of abciximab	–	–	60	23	76
	Placebo	–	–	61	22	76

* *Harrington, 1997[38]; PURSUIT Trial Investigators, 1997[38A]; Simoons, 1999[39]; Mahaffey* et al., *1999[40]; PURSUIT Trial Investigators, 1998[41]*

PURSUIT. Full data extraction for the high-risk studies can be seen in appendix 5.

In addition to this, some of the main reports of trials reported data on high-risk groups, although this was primarily restricted to reporting of the composite outcome. The results reported in each trial can be seen in *Table 11*. Only Schulman[37] did not undertake any analysis on high-risk subgroups.

Assessment of internal validity

The assessment of the internal validity of the studies included in the review is presented in *Table 12*. Many items were assigned a question mark. This may reflect poor reporting only and does not necessarily indicate bad study design or study conduct.

The validity assessment of the trials reveals three areas that are consistently not addressed in the published articles.

1. Although tables of baseline characteristics of patients enrolled are included in all of the trials, it is difficult to determine if the groups are truly homogeneous. Prestratification on variables known to be prognostically important would involve stratifying at randomisation in smaller trials, or stratifying by centre in multicentre trials. This was not reported in any of the trials.
2. 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. Inadvertent unblinding through reporting of unblinded activated partial thromboplastin time (aPTT) values, for example, could have an impact on evaluation of outcomes.
3. The lack of description of how missing values were handled is concerning. Among large, multicentre trials it is difficult to accept that there were no missing values. The description of how many missing values there were, as well as how they were dealt with in the analysis could have a significant impact on the interpretation of the results. Compliance (i.e. number of missed doses) to these intravenous therapies was not reported in the trials. The numbers lost in each treatment group were not specified.

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 makes any pooling of study results inappropriate or hazardous. For example, PRISM enrolled patients with symptoms in the previous 24 hours, whereas PRISM-PLUS enrolled patients with symptoms in the previous 12 hours. Short-term cohort effects may easily cause great prognostic differences observed between the two reference (heparin-treated) groups in the trials. The introduction of patients who survived an extra 12 hours before entering PRISM may have improved overall prognosis in that study. Furthermore, in PRISM it was recommended that treatment with tirofiban be stopped if revascularisation was performed, whereas PRISM-PLUS stipulated continued administration of the study drugs.

With the exception of the Schulman trial all studies used blinded end-points committees

TABLE 9 *Definitions of outcomes in trials of intravenous drugs*

Study	Acute MI	Severe recurrent angina/RI	Composite end-point
Schulman *et al.*, 1996[37]	Not defined	Ischaemic pain unresponsive to standard anti-ischaemic therapy and requiring intra-aortic blood counter-pulsation, emergency catheterisation and angioplasty or morphine sulphate	RI, MI, need for morphine, intra-aortic balloon pump, emergency cardiac catheterisation or PTCA, or death
PURSUIT[38–41]*	***< 18 hours after enrolment***: Chest pain with ST-T changes (depression or elevation) in two continuous leads for more than 30 minutes ***> 18 hours after enrolment***: CK or 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[42]	New episode of chest pain with: 1. new ST-T changes 2. new pathologic Q-waves > 0.03 seconds 3. 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 after enrolment classified when CK exceeded twice the normal value, or the CK-MB fraction went above the upper limit in the 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 two episodes lasting ≥ 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), SBP < 95 mmHg not related to medication, or a need for inotropic agents	Primary: death, MI or RI at 48 hours Secondary: death, MI or RI at 7 days Composite at 30 days: death, MI, RI or re-admission for unstable angina
PRISM-PLUS: Bazzino *et al.*, 1998[43]	A new episode of chest pain at least 20 minutes in duration with new ST-T changes, or both a rise in serum CK level to twice 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 more than 50% above the previous value after an initial peak. A peri-operative 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 counter-pulsation, urgent intervention or both within 12 hours	Death from any cause, new MI or RI within 7 days after randomisation. Rehospitalisation for unstable angina was included at 7 days, 30 days and 6 months

continued

***TABLE 9* contd** *Definitions of outcomes in trials of intravenous drugs*

Study	Acute MI	Severe recurrent angina/RI	Composite end-point
GUSTO IV-ACS: Simoons, 2001[36]	New Q-wave > 0.04 seconds or 1/4 R 2 leads or, CK-MB > upper limit of normal in two samples of which ≥ three times upper limit of normal in one sample. MI post-PCI: as above; post CABG MI: Q-wave only	Not defined	Death or MI at 30 days

* *Harrington, 1997[38]; PURSUIT Trial Investigators, 1997[38A]; Simoons, 1999[39]; Mahaffey* et al., *1999[40]; PURSUIT Trial Investigators, 1998[41]*

TABLE 10 *Separate subgroup analysis undertaken on medical management trials*

Study	Trial	High-risk group	Patients enrolled	Outcomes reported
Heeschen *et al.*, 1999[44]	PRISM	Troponin-positive patients	2222 patients in PRISM of which 629 had troponin concentrations higher than 1.0 μg/l and 644 higher than 0.1 μg/l	Death, MI, death/MI and RI reported for troponin-positive versus troponin-negative patients
Theroux *et al.*, 2000[45]	PRISM-PLUS	Diabetics	1570 patients in PRISM-PLUS of which 362 were diabetic	Composite and MI reported for diabetics versus non-diabetics. Adverse events reported for diabetic patients according to treatment arm
Hasdai *et al.*, 2000[46]	PURSUIT	Elderly	9722 patients in PURSUIT were divided into five age groups	Looked at the impact of age on all patients and high-risk groups on death or re-infarction
Boersma *et al.*, 2000[47]	PURSUIT	Age, ST-depression and diabetics	9461 patients enrolled in the PURSUIT trial	Analysed the relation between baseline characteristics and the 30-day incidence of death and the composite of death or MI. Risk of events in subgroups calculated

TABLE 11 *Outcomes of high-risk groups reported in trials*

Trial	Diabetics	Troponin T positive	ST-depression	Elderly patients
Schulman *et al.*, 1996[37]	–	–	–	–
PURSUIT[38–41*]	ORs reported for death/MI	–	ORs reported for death/MI	ORs reported for death/MI
PRISM, 1998[42]	Risk ratios reported for composite of death/MI/RI within 48 hours	–	Risk ratios reported for composite of death/MI/RI within 48 hours	Risk ratios reported for composite of death/MI/RI within 48 hours
PRISM-PLUS: Bazzino *et al.*, 1998[43]	Numbers of patients reported in tirofiban + heparin or heparin only group experiencing composite outcomes at 7 days	–	–	Numbers of patients reported in tirofiban + heparin or heparin only group experiencing composite outcomes at 7 days
GUSTO IV-ACS: Simoons, 2001[36]	Death or MI up to 30 days reported	Death or MI up to 30 days reported	Death or MI up to 30 days reported	Death or MI up to 30 days reported

* *Harrington, 1997[38]; PURSUIT Trial Investigators, 1997[38A]; Simoons, 1999[39]; Mahaffey* et al., *1999[40]; PURSUIT Trial Investigators, 1998[41]*

TABLE 12 *Assessment of internal validity*

Study	Schulman *et al.*, 1996[37]	PURSUIT[38–41*]	PRISM, 1998[42]	PRISM-PLUS[43†]	GUSTO IV-ACS[36‡]
Internal validity					
Selection of prognostically homogeneous study population	?	?	?	?	+
Pre-stratification 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 who implement interventions	±	±	±	±	+
Registration of co-interventions that affect the outcome for each group	±	?	+	+	+
Blinding of persons assessing treatment effects	?	+	+	?	+
Check 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	±	±	+	+	+

+, Item properly addressed; –, item not properly addressed or not stated; ?, unclear; ±, item partially addressed

* *Harrington, 1997[38]; PURSUIT Trial Investigators, 1997[38A]; Simoons, 1999[39]; Mahaffey* et al., *1999[40]; PURSUIT Trial Investigators, 1998[41]*

† *Bazzino* et al., *1998[43]*

‡ *Simoons, 2001[36]*

to determine outcomes. However, in PURSUIT the local investigators assessed the outcomes at 6 months. This means that measurement bias is unlikely to be an issue in the outcome measurement before 6 months in these trials.

Results of trials

The results of the trials are presented below by drug. In the plots of RR, the vertical line (at 1) indicates the 'no-difference' line. 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. In this report, the RR estimates at 30 days and later were considered more relevant than those at 48 and 96 hours and at 7 days.

Eptifibatide

The Schulman trial[37] (*Table 13*) refers to the study drug as Integrilin, which is now the brand name of

TABLE 13 *Results from the Schulman* et al. *study (1996[37]): outcomes at 24 hours*

Treatment arm	MI		Recurrent ischaemia		Death		Composite	
	n	%	*n*	%	*n*	%	*n*	%
Low-dose eptifibatide (*n* = 77)	1	1.3	1	1.3	0	0.0	1	1.3
High-dose eptifibatide (*n* = 76)	0	0.0	0	0.0	0	0.0	2	2.6
Placebo (*n* = 74)	1	1.4	1	1.4	0	0.0	4	5.4

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 undertaken. This study also had a number of items that were only partially addressed, such as registration of co-interventions that bear on outcomes for each group (e.g. anti-anginal drugs). However, this study did describe in detail the numbers of, and reasons for, individuals not included in the primary end-point.

The primary end-point for this study was ischaemia identified by Holter monitoring. The number of participants evaluable by Holter monitoring was 57 in the aspirin group, 54 in the low-dose group and 58 in the high-dose group. There were 58 patients who were not evaluable by Holter monitoring for the following reasons: did not receive study drug (four), missing data (two), abnormal baseline ST-segment on Holter (27), Holter malfunction (13), received wrong study drug (three), wrong infusion rate (four), and eligibility violation, such as MI (four) or anaemia (one).

The RR for ischaemic events in the high-dose group versus the aspirin group was 0.48 (95% CI, 0.09 to 2.25). The RR for the low-dose group versus the aspirin group was 0.24 (95% CI, 0.03 to 2.13). While other end-points are reported they were not the primary outcome measures. The composite end-point reported here refers to any outcome (RI, MI, requiring morphine, intra-aortic balloon pump, emergency cardiac catheterisation or PTCA, or death).

PURSUIT evaluated eptifibatide versus placebo while recommending intravenous or subcutaneous heparin for all patients. All patients received aspirin (80–325 mg/day). The primary end-point was MI, death or composite end-point (death or MI) at 96 hours. The validity assessment of PURSUIT indicates that it is one of the better studies in terms of the methodological quality. Registration of co-interventions was, however, 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 journal's editors, later reported these). Use of anti-anginal medications before or after enrolment was not reported. The degree of blinding of patients and persons making assessments of treatment effects were also not clear. The results of the PURSUIT study are shown in *Table 14*. This showed that fewer events occurred in eptifibatide patients compared with those that received placebo; this occurred at all time-points.

Death from any cause

The effect of eptifibatide on death can be seen in the forest plot *Figure 1*. No deaths occurred in the Schulman study, so this figure relates to the PURSUIT study only. PURSUIT showed a significant effect of eptifibatide on death at 48 hours and 7 days.

Myocardial infarction

The effect of eptifibatide on MI can be seen in the forest plot in *Figure 2*. The incidence of MI reported here includes fatal and non-fatal MI. The effect of eptifibatide on MI reported in the Schulman study, although large was not statistically significant. PURSUIT did show a statistically significant effect at 7 days.

Recurrent ischaemia

Schulman reported on the effect of eptifibatide on recurrent ischaemia at 24 hours; see *Figure 3*. PURSUIT did not report RI as a separate end-point.

TABLE 14 *Results from the PURSUIT[38–41*] study*

Treatment arm	Time-point	MI		Death		PTCA		CABG		Composite	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%
Eptifibatide	96 hours	335	7.1	42	0.9	–	–	–	–	359	7.6
(*n* = 4722)	7 days	439	9.3	71	1.5	–	–	–	–	476	10.1
	30 days	595	12.6	16	0.34	1100	23	656	14	670	14.2
	6 months	–	–	–	–	–	–	–	–	836	17.7
Placebo	96 hours	393	8.3	57	1.2	–	–	–	–	431	9.1
(*n* = 4739)	7 days	493	10.4	95	2.0	–	–	–	–	550	11.6
	30 days	640	13.5	17	0.36	1175	25	678	14	744	15.7
	6 months	–	–	–	–	–	–	–	–	896	18.9

[*] *Harrington, 1997[38]; PURSUIT Trial Investigators, 1997[38A]; Simoons, 1999[39]; Mahaffey* et al., *1999[40]; PURSUIT Trial Investigators, 1998[41]*

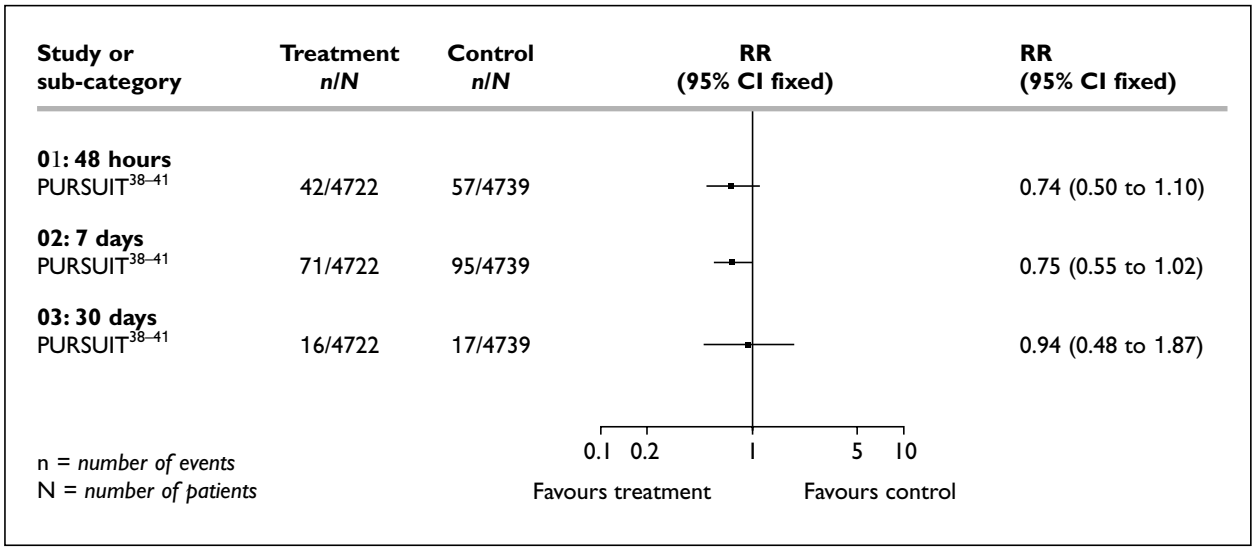

FIGURE 1 *Effect of eptifibatide on death for patients receiving glycoproteins as part of medical management*

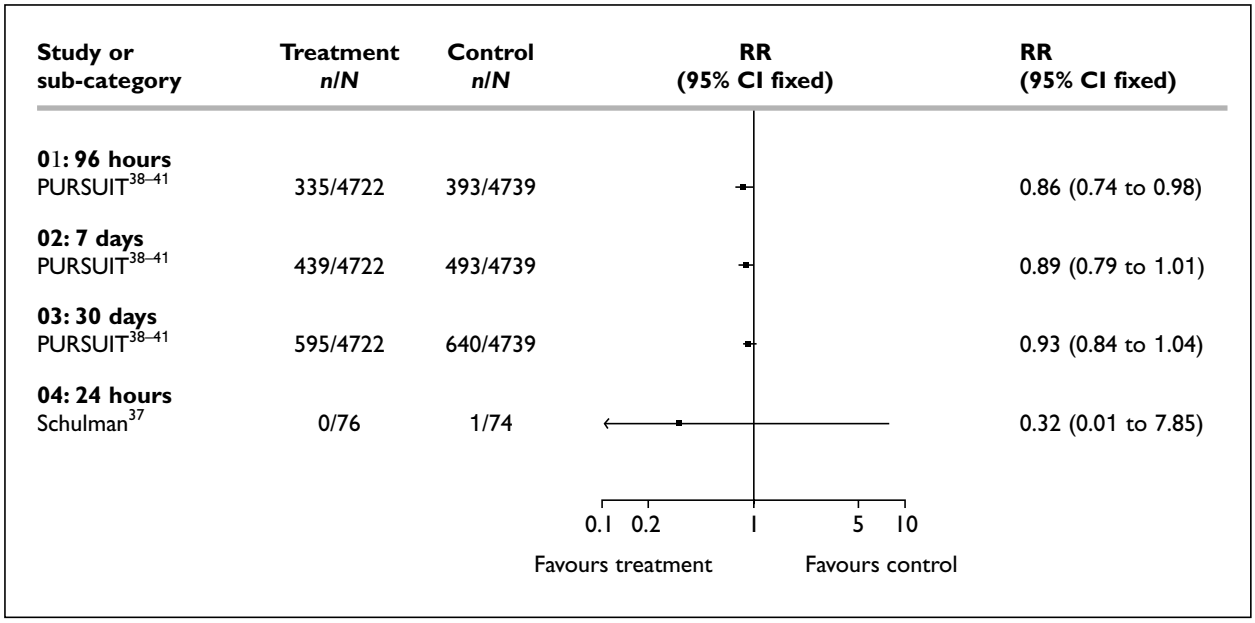

FIGURE 2 *Effect of eptifibatide on MI for patients receiving glycoproteins as part of medical management*

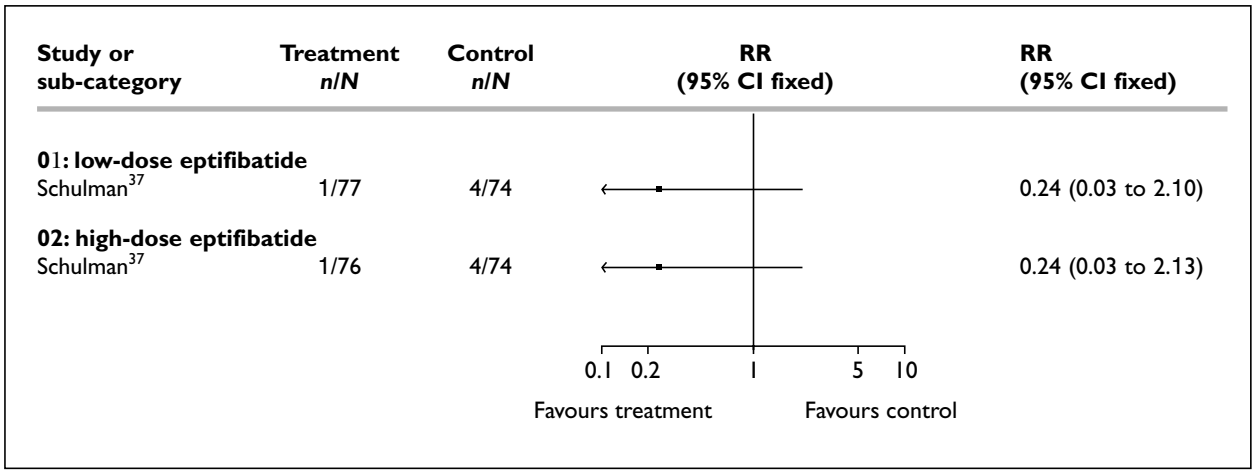

FIGURE 3 *Effect of eptifibatide on recurrent ischaemia at 24 hours for patients receiving glycoproteins as part of medical management*

Revascularisation
The effect of eptifibatide on revascularisation (PTCA and coronary artery bypass graft (CABG)) can be seen in the forest plots in *Figures 4* and *5*.

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
The effect of eptifibatide on major and minor bleeding can be seen in *Figures 6* and *7*.

There were no cases of major bleeding in any of the groups in the Schulman study. PURSUIT used the definitions for major and minor bleeding from the TIMI[48] trial as a primary end-point, and the definitions from the GUSTO-I[25,48] trial as a secondary end-point. However, by either definition, the risk of a major or minor bleed was significantly greater with eptifibatide. The bleeding events were those reported during hospitalisation.

The definitions of bleeding used in the trials can be seen in *Table 15*.

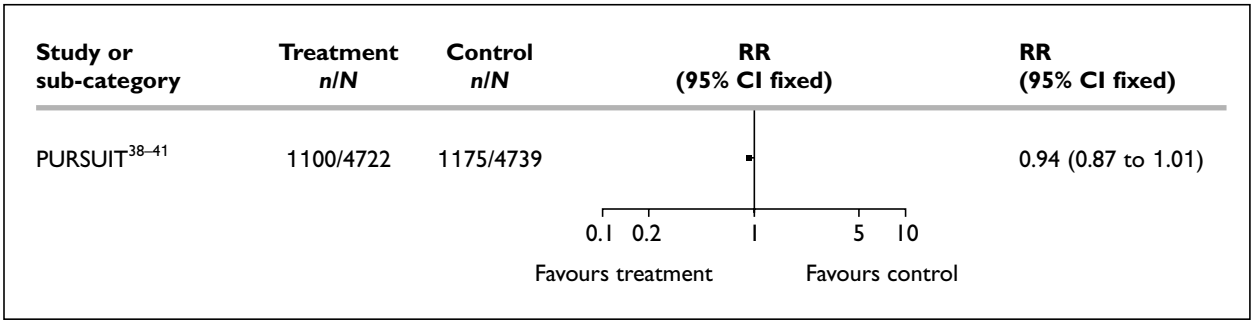

FIGURE 4 *Effect of eptifibatide on rates of PTCA at 30 days for patients receiving glycoproteins as part of medical management*

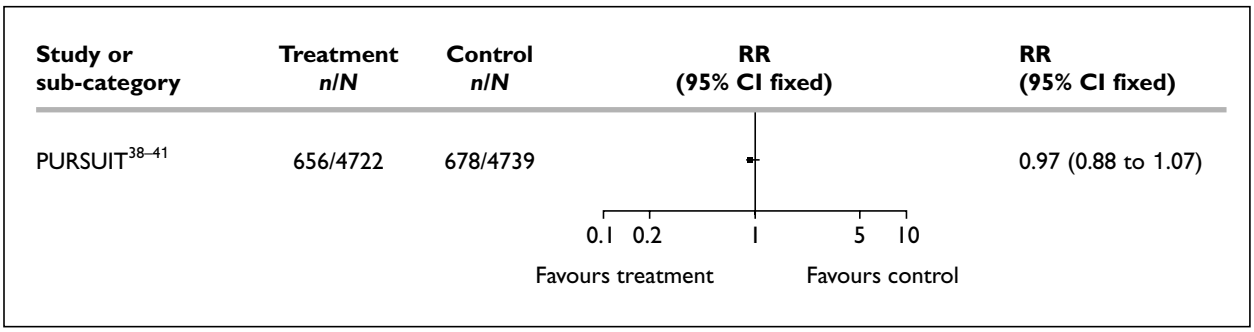

FIGURE 5 *Effect of eptifibatide on rates of CABG at 30 days for patients receiving glycoproteins as part of medical management*

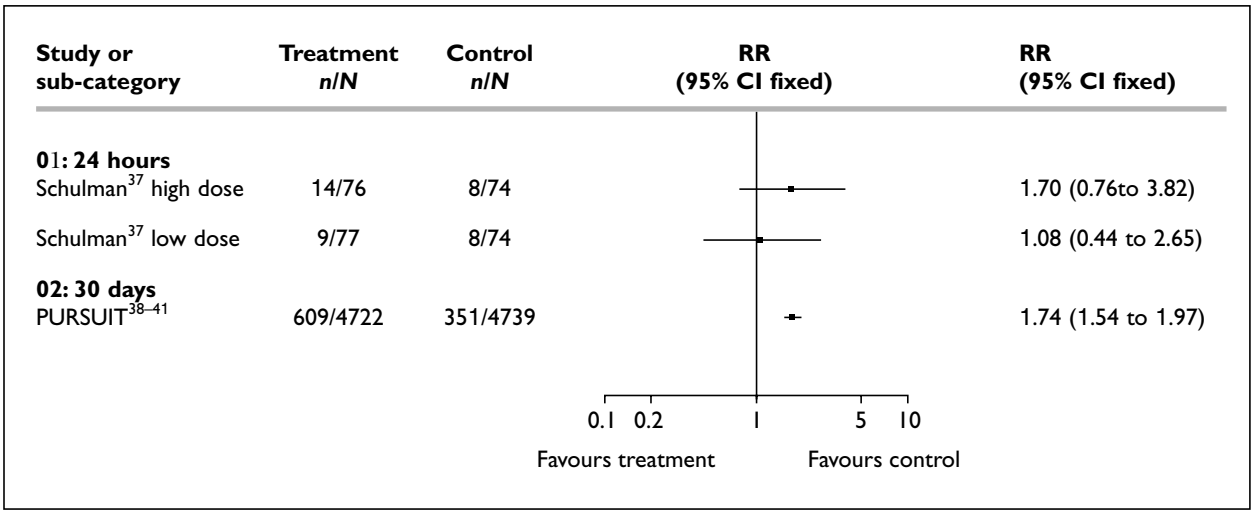

FIGURE 6 *Effect of eptifibatide on minor bleeding for patients receiving glycoproteins as part of medical management*

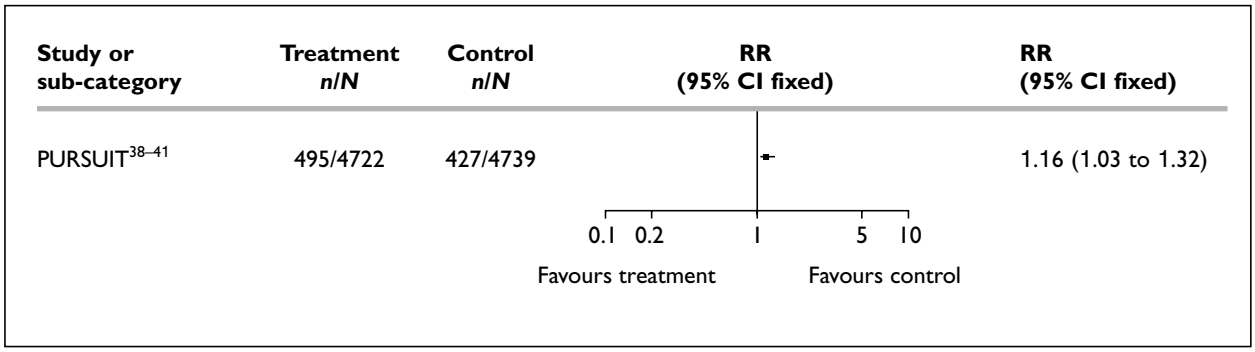

FIGURE 7 *Effect of eptifibatide on major bleeding at 30 days for patients receiving glycoproteins as part of medical management*

TABLE 15 *Definitions of bleeding used in eptifibatide medical management studies*

Study	Major/minor bleeding
PURSUIT: Harrington, 1997[38]	***Primary – according to TIMI trial criteria*** 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 haemoglobin. Minor bleeding = a drop of 12% in haematocrit or 4 g/dl in haemoglobin (with no identifiable bleeding source) ***Secondary – according to GUSTO trial criteria: mild, moderate, severe or life-threatening*** Severe or life-threatening = intracranial haemorrhage or bleeding that caused homodynamic compromise and required intervention. Moderate = bleeding that required blood transfusion without causing haemodynamic compromise
Schulman *et al.*, 1996[37]	Not defined, but petechiae, ecchymoses, haematomas, haemoptysis, haematemesis, haematuria and rectal bleeding were reported and included here as minor bleeding. Blood transfusions within 24 hours of stopping study drug, and haemoglobin levels at 24 hours were reported

Thrombocytopenia

In the PURSUIT study,[38–41] the rate of thrombocytopenia was very similar in both groups: 6.8% and 6.9% in the eptifibatide and placebo groups respectively. However, the rate of profound thrombocytopenia (platelet count < 20,000/mm^3) was 0.2% versus 0.1% in the eptifibatide and placebo groups, respectively. This small absolute difference was statistically significant.

Transfusions

The effect of eptifibatide on transfusion of red blood cells (RBC) at 24 hours can be seen in *Figure 8*. Although the risk of requiring a RBC transfusion was much greater in the eptifibatide group the number of patients experiencing an event is small, as can be seen in *Figure 8* (5.2% vs 1.3%).

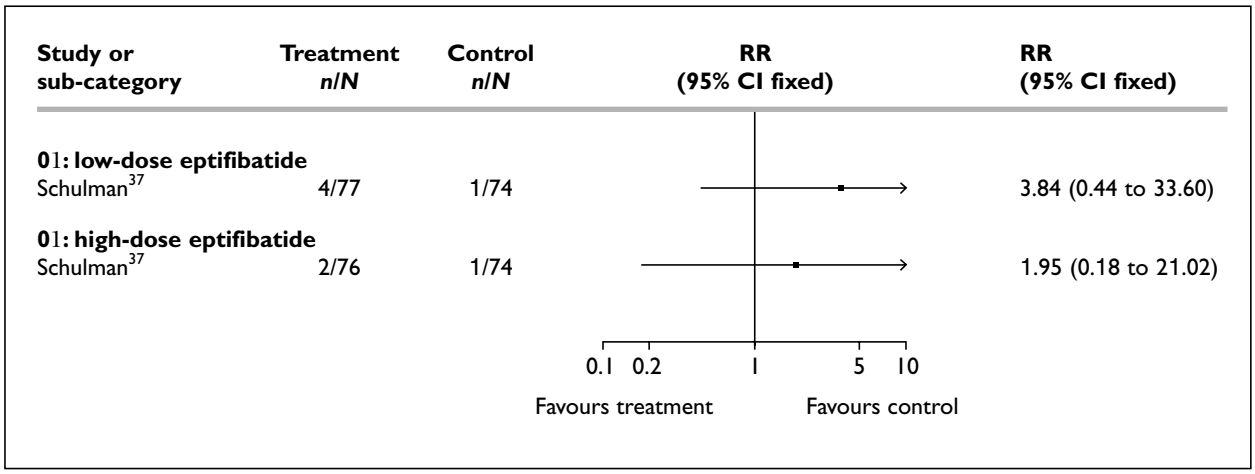

FIGURE 8 *Effect of eptifibatide on RBC transfusions at 24 hours for patients receiving glycoproteins as part of medical management*

Stroke

The effect of eptifibatide on episodes of stroke can be seen in *Figure 9*. Unlike the other adverse events, the risk of stroke was greater in the control group (RR = 0.87). The absolute RR, however, is small (< 0.001 (0.00)).

Composite end-point

The effect of eptifibatide on the composite outcome (as specifically defined in the relevant trial) can be seen in *Figure 10*. Death or non-fatal MI was the composite end-point identified in the PURSUIT study.

A re-analysis of the 96-hour data for death and non-fatal MI in PURSUIT using other definitions of MI was reported by Simoons and colleagues.[39] Small variations in the risk difference (RD) were seen using various definitions of MI.

Tirofiban

The two studies assessing tirofiban were PRISM and PRISM-PLUS. PRISM[42] compared treatment with tirofiban to treatment with heparin. The quality assessment of PRISM was very similar to that of PURSUIT. The random allocation of participants (information on the randomisation process) was not stated. Concealment of randomisation, blinding of persons who implement interventions and loss to follow-up were only partially addressed. In the PRISM study, the primary end-points were MI, recurrent ischaemia, death and the composite end-point at 48 hours (*Table 16*). 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% confidence interval (CI), 0.48 to 0.92) and RI was 0.65

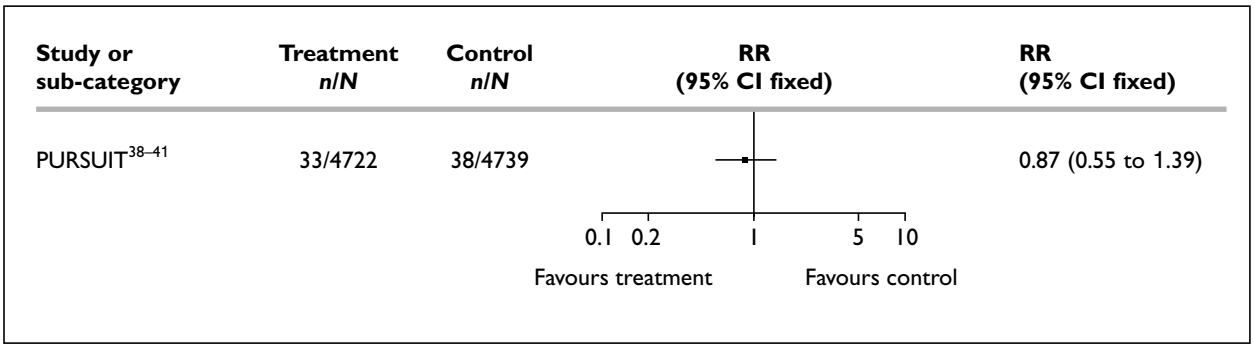

FIGURE 9 *Effect of eptifibatide on incidences of stroke at 30 days for patients receiving glycoproteins as part of medical management*

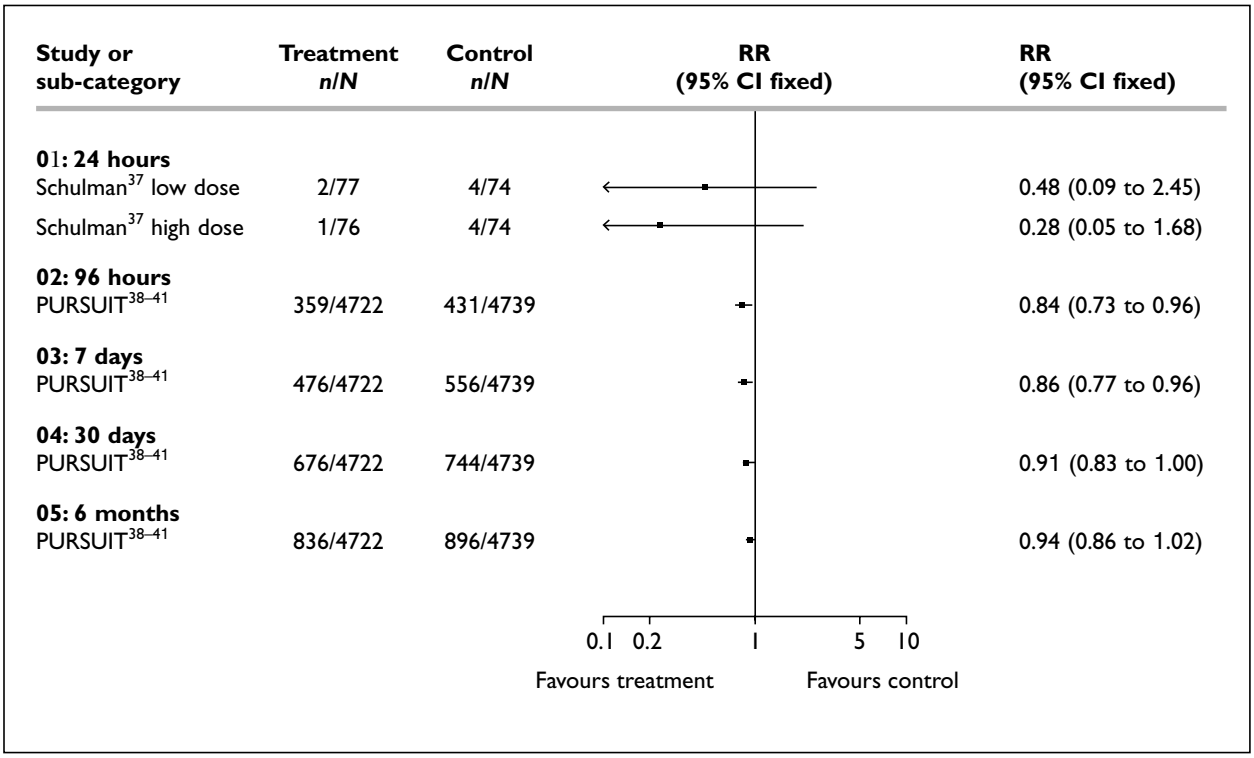

FIGURE 10 *Effect of eptifibatide on the composite outcome for patients receiving glycoproteins as part of medical management*

TABLE 16 *Results from the PRISM study (1998[42])*

Treatment arm	Time-point	MI		Recurrent ischaemia		Death		PTCA		CABG		Composite	
		n	%	*n*	%	*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	348	21	296	18	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	352	22	269	16	276	17.1

(95% CI, 0.46 to 0.91). None of the other outcomes, primary or secondary, were significant at any time-point.

The PRISM-PLUS study[43] examined tirofiban alone, tirofiban plus heparin and heparin alone. The validity assessment of PRISM-PLUS differed to PRISM in that blinding of persons assessing treatment effects was not discussed. Items that were only partially addressed were the randomisation procedure, blinding of persons implementing interventions, and registration of co-interventions. While anti-anginal medication use before and after randomisation were reported, rates of aspirin use were not. The results of PRISM-PLUS are summarised in *Table 17*. 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 was stopped early). These showed a benefit of tirofiban plus heparin at 6 months RD for death or MI of 3.0% (95% CI, –0.4 to 6.4; number needed to treat (NNT) = 33).

Death from any cause

The effect of tirofiban on death can be seen in *Figure 11*. One comparison for each study is presented in the plots of RR. The results for PRISM-PLUS relate to the comparison of tirofiban + heparin versus heparin. Results are conflicting. A beneficial effect of tirofiban on death is seen in PRISM-PLUS at 48 hours and 30 days, and PRISM at 7 days and 30 days. However, a negative effect of tirofiban on death is seen in PRISM at 48 hours and PRISM-PLUS at 7 days and 6 months.

Myocardial infarction

The effect of tirofiban on non-fatal MI can be seen in *Figure 12*. One comparison for each study is presented in the plots of RD; results for multiple comparisons can be seen in McDonagh and colleagues.[3] The results show a statistically

TABLE 17 *Results from the PRISM-PLUS study (Bazzino* et al., *1998[43])*[*]

Treatment arm	Time-point	MI		Recurrent ischaemia		Death		PTCA		CABG		Composite	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Tirofiban	48 hours	2	0.6	–	–	2	0.6	–	–	–	–	26	7.5
(*n* = 345)	7 days	16	4.6	–	–	16	4.6	–	–	–	–	59	17.1
	30 days	21	6.1	–	–	21	6.1	–	–	–	–	81	23.5
	6 months	25	7.2	–	–	25	7.2	–	–	–	–	105	30.4
Tirofiban + heparin	48 hours	6	0.8	37	4.8	1	0.1	–	–	–	–	44	5.7
(*n* = 773)	7 days	30	3.9	72	9.3	15	1.9	–	–	–	–	100	12.9
	30 days	51	6.6	82	10.6	28	3.6	239	30.9	26	3.4	143	18.5
	6 months	64	8.3	82	10.6	53	6.9	–	–	–	–	214	27.7
Heparin	48 hours	19	2.4	47	5.9	2	0.3	–	–	–	–	62	7.8
(*n* = 797)	7 days	56	7.0	101	12.7	15	1.9	–	–	–	–	143	17.9
	30 days	73	9.2	107	13.4	36	4.5	236	29.6	20	2.5	178	22.3
	6 months	84	10.5	107	13.4	56	7.0	–	–	–	–	256	32.1

[*] *The study was stopped prematurely for the tirofiban-only group because of excess mortality at 7 days (4.6% compared with 1.1% in the heparin-only group)*

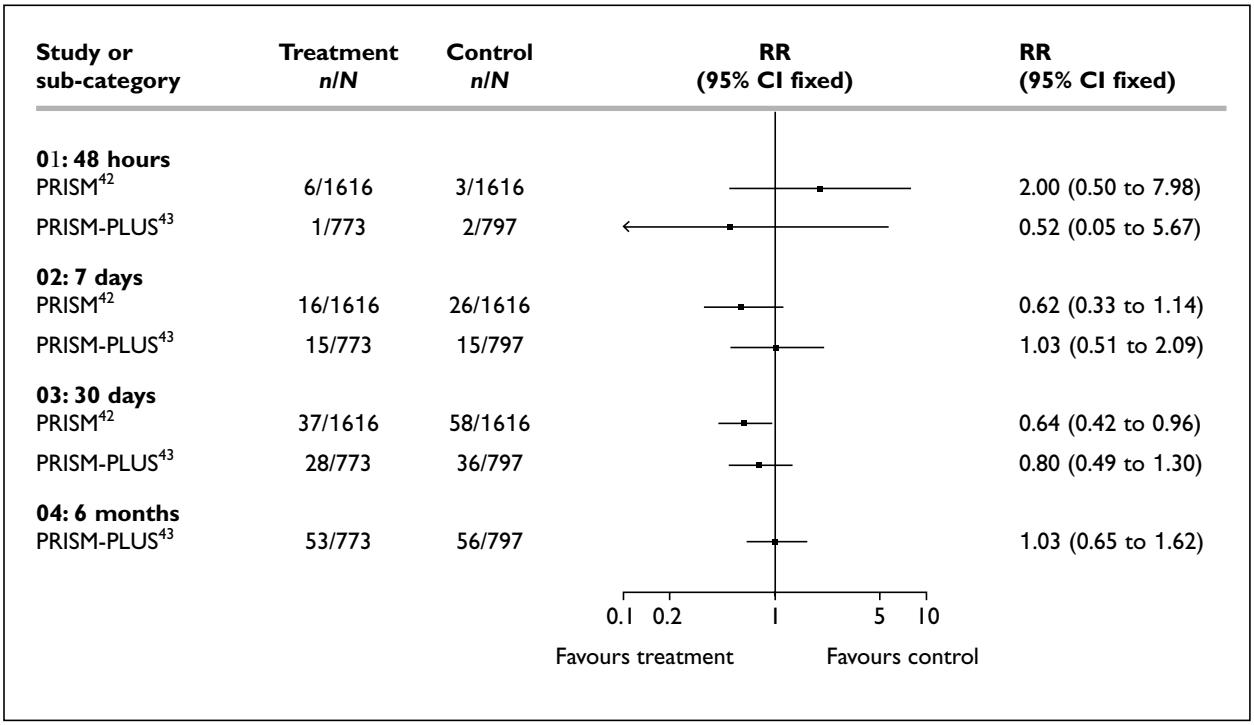

FIGURE 11 *Effect of tirofiban on death for patients receiving glycoproteins as part of medical management*

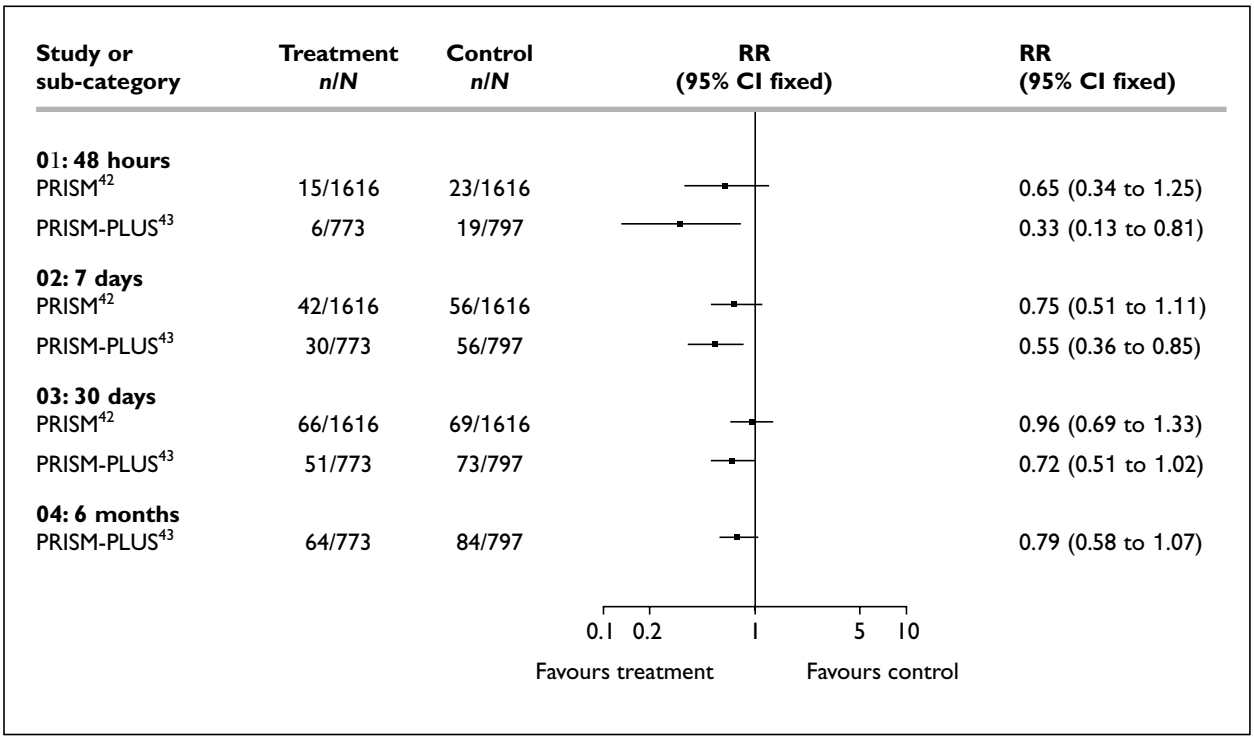

FIGURE 12 *Effect of tirofiban on MI for patients receiving glycoproteins as part of medical management*

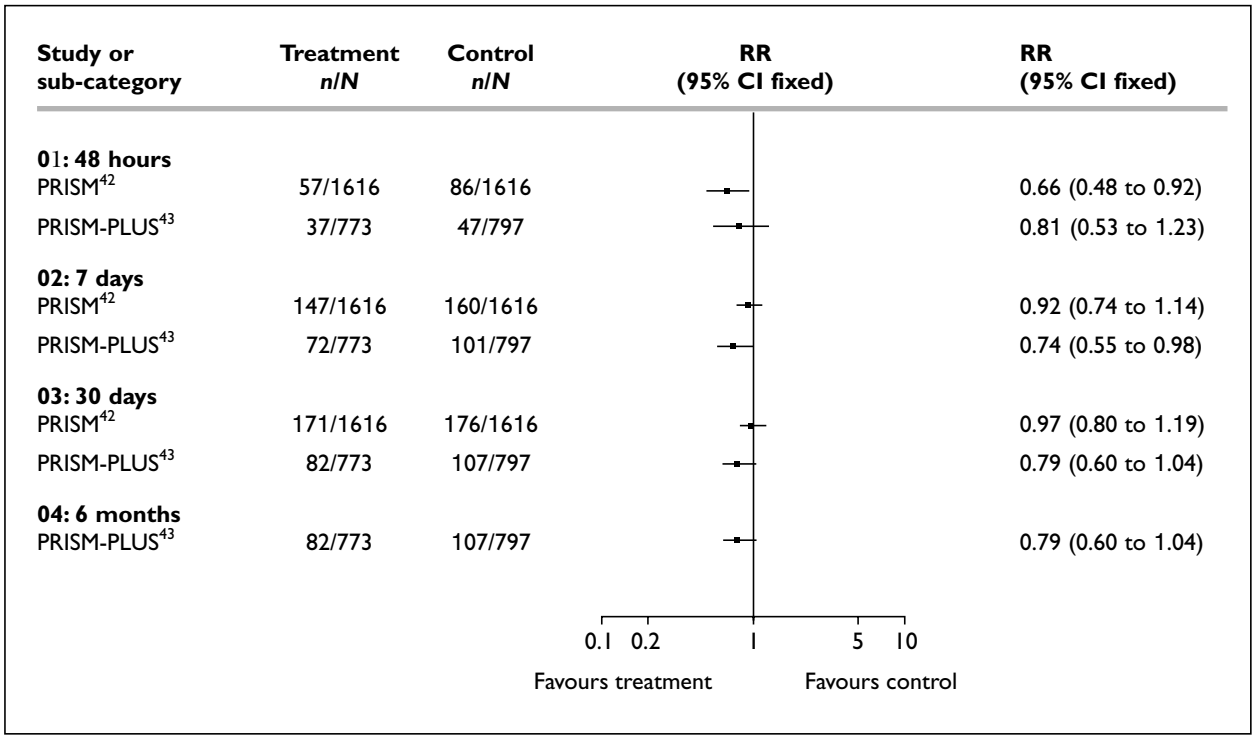

FIGURE 13 *Effect of tirofiban on recurrent ischaemia for patients receiving glycoproteins as part of medical management*

significant positive effect of tirofiban on MI at various follow-up points.

Recurrent ischaemia

The effect of tirofiban on recurrent ischaemia can be seen in *Figure 13*. Rates were not reported for the tirofiban only group in the PRISM-PLUS study.

Revascularisation

The effect of tirofiban on revascularisation rates can be seen in *Figures 14* and *15*. Rates of both angioplasty and bypass were higher in PRISM-PLUS than in PRISM.

Adverse events

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

Bleeding

The effect of tirofiban on episodes of bleeding can be seen in *Figures 16* and *17*. The definitions of bleeding used in the two trials can be seen in *Table 18*. PRISM used the TIMI (Thrombolysis in Myocardial Infarction) trial criteria for bleeding. PRISM-PLUS used an independent definition, but also evaluated bleeding based on the TIMI criteria.

The incidence of minor bleeding episodes at 72 hours is approximately the same in the PRISM study (32/1616 vs 31/1616) for tirofiban and placebo respectively. The PRISM study also showed no differences in major bleeding, with six patients in each arm experiencing an event. The PRISM-PLUS trial, however, showed the risk of major bleed was greater in the tirofiban + heparin group compared with the heparin alone group: RR = 1.33 (95% CI, 0.79 to 2.25).

Thrombocytopenia

Both studies showed an increased rate of thrombocytopenia in the treatment groups (1.1% vs 0.49% in the PRISM trial and 1.9% versus 0.8% in the PRISM-PLUS trial for tirofiban and heparin respectively). As heparin can also cause thrombocytopenia, the increased rate found with the combination (PRISM-PLUS) may be expected.

Transfusions

The effect of tirofiban on transfusions can be seen in *Figure 18*. Both studies showed an increased risk of transfusions in the tirofiban group (RR = 1.35 and 1.45 for the PRISM and PRISM-PLUS studies respectively). The percentage of patients undergoing transfusions, however, was small (PRISM = 1.9% in the tirofiban group and 1.4% in the heparin group; PRISM-PLUS = 4.0% in the tirofiban group and 2.8% in the heparin group).

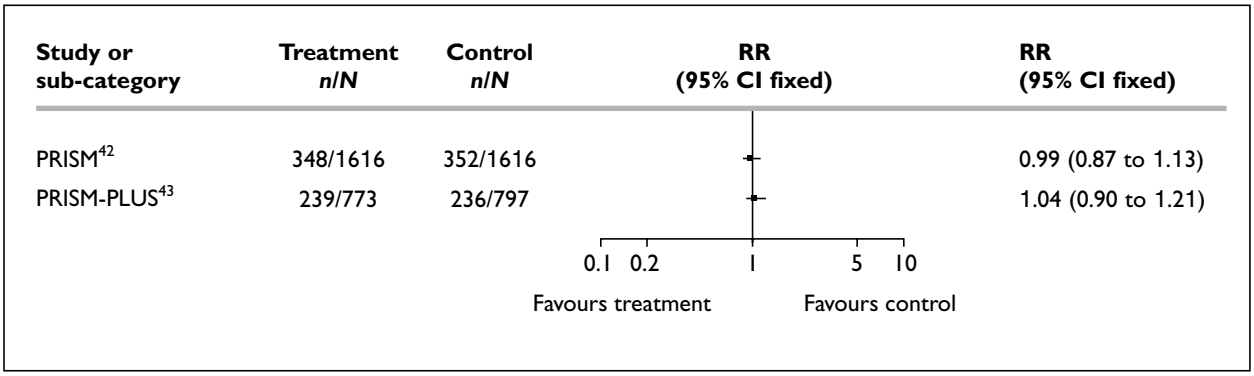

FIGURE 14 *Effect of tirofiban on rates of PTCA at 30 days for patients receiving glycoproteins as part of medical management*

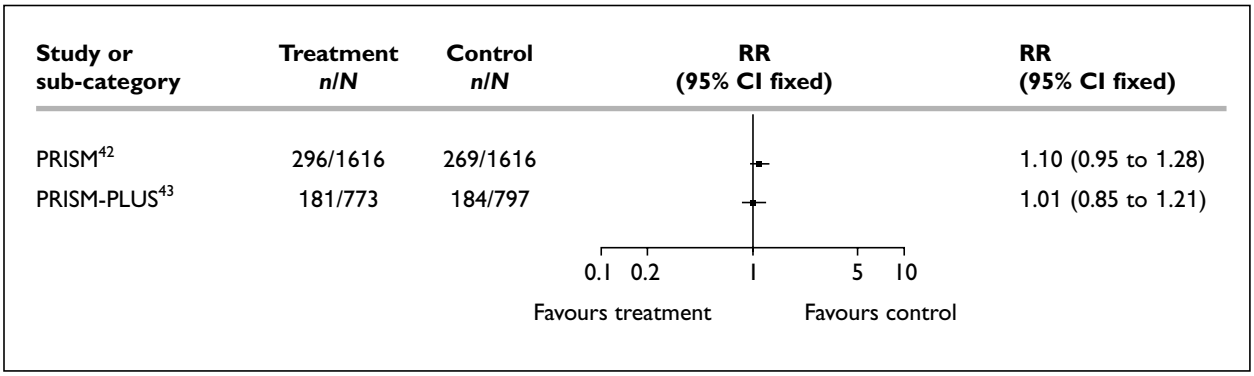

FIGURE 15 *Effect of tirofiban on rates of CABG at 30 days for patients receiving glycoproteins as part of medical management*

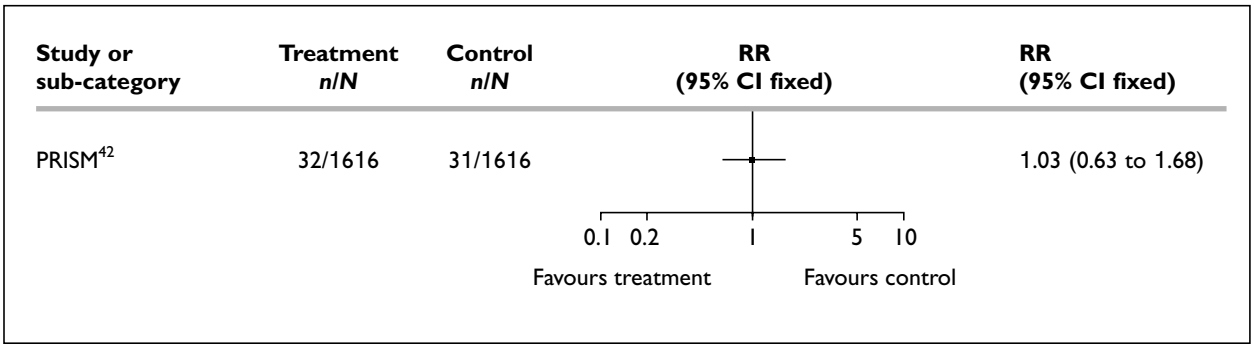

FIGURE 16 *Effect of tirofiban on minor bleeding for patients receiving glycoproteins as part of medical management*

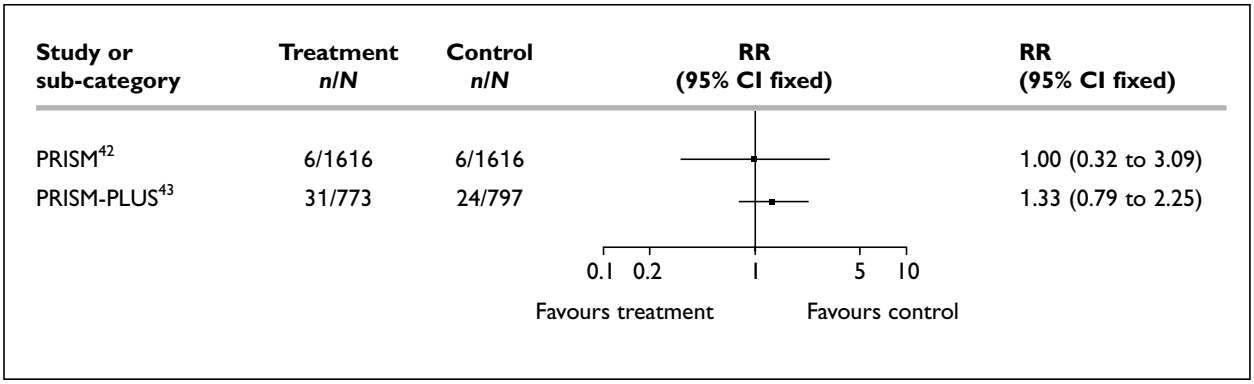

FIGURE 17 *Effect of tirofiban on major bleeding for patients receiving glycoproteins as part of medical management*

TABLE 18 *Definitions of bleeding in tirofiban trials*

Study	Major/minor bleeding
PRISM, 1998[42]	According to the TIMI trial criteria: • major bleeding is a decrease in the haemoglobin level of 50 g/l, intracranial haemorrhage, or cardiac tamponade • minor bleeding was defined as a decrease in the haemoglobin level of more than 30 g/l from an identified site, spontaneous gross haematuria, haematemesis or haemoptysis
PRISM-PLUS: Bazzino *et al.*, 1998[43]	Decrease in blood haemoglobin level of more than 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

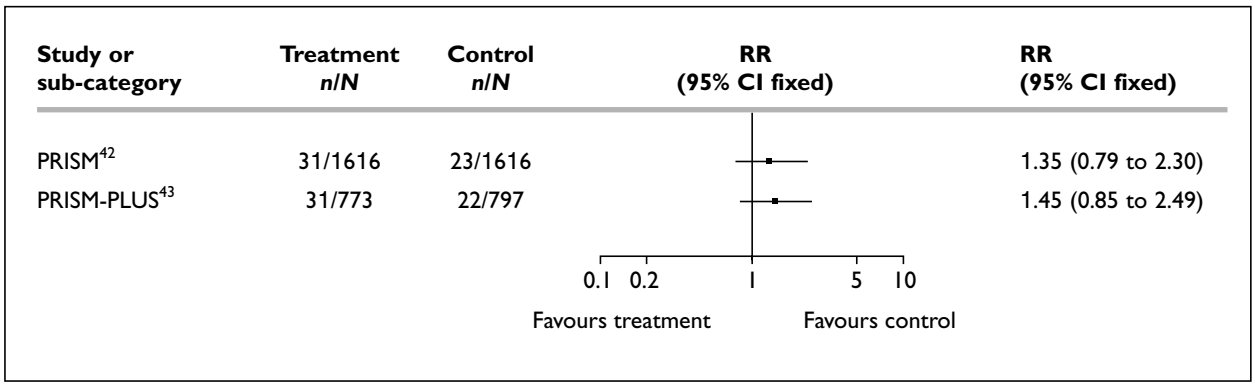

FIGURE 18 *Effect of tirofiban on all transfusions for patients receiving glycoproteins as part of medical management*

Composite end-point
The effect of tirofiban on the composite end-point can be seen in *Figure 19*. The composite end-point used in the PRISM and PRISM-PLUS studies was death from any cause, non-fatal MI and RI. Re-hospitalisation for unstable angina is also included at 7 days, 30 days and 6 months in PRISM-PLUS.

Abciximab

The use of abciximab in the medical management of ACS patients has been studied in just one trial, GUSTO IV-ACS.[36] This looked at abciximab versus placebo in high-risk ACS patients with either ST-segment depression or raised troponins, and in whom no PCI was planned. Two different infusion lengths were compared: 24-hour and 48-hour infusions. The results of GUSTO IV-ACS are summarised in *Table 19*. Small differences were observed between the three groups.

Death from any cause
The effect of abciximab on death using 24-hour and 48-hour infusion times can be seen in *Figure 20*. The NNT to avert one death in the GUSTO IV-ACS trial was 189 (95% CI, 64; no upper bound) at 30 days for 24-hour infusion versus placebo. None of the differences in mortality rates between 24-hour infusion and placebo was statistically significant. The 48-hour infusion was associated with an excess of deaths over placebo at all three time-points, and the difference at 48 hours was statistically significant.

Myocardial infarction
The effect of abciximab on non-fatal MI using 24-hour and 48-hour infusion times can be seen in *Figure 21*. All differences were small and not statistically significant.

Recurrent ischaemia
Rates of recurrent ischaemia were not reported in the GUSTO IV-ACS trial.

Revascularisation
The effect of abciximab on revascularisations can be seen in *Figures 22* and *23*. Procedures were done at similar rates in the three arms of the trial.

Adverse events
The main concerns for adverse effects in the GUSTO IV-ACS trial of abciximab were related to an extension of the pharmacologic effect: bleeding, thrombocytopenia and procedures resulting from these (e.g. blood transfusions).

Bleeding
The effect of abciximab on minor and major bleeding episodes can be seen in *Figures 24* and *25*.

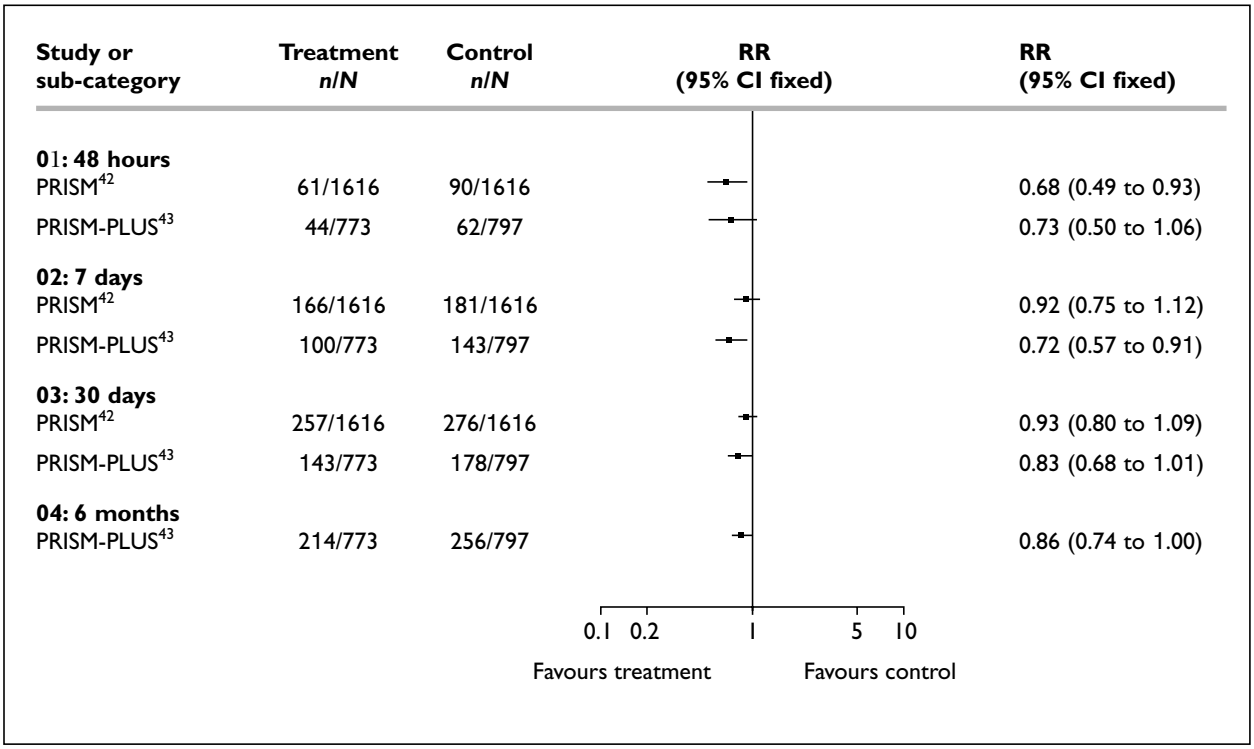

FIGURE 19 *Effect of tirofiban on the composite outcome for patients receiving glycoproteins as part of medical management*

TABLE 19 *Results from the GUSTO IV-ACS study (Simoons, 2001[36])*

Treatment arm	Time-point	MI		Death		PTCA		CABG		Composite	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%
Abciximab 24-hour infusion (*n* = 2590)	48 hours	34	1.3	18	0.7	–	–	–	–	50	1.9
	7 days	69	2.7	39	1.5	–	–	–	–	103	4.0
	30 days	146	5.6	88	3.4	471	18	285	11	212	8.2
Abciximab 48-hour infusion (*n* = 2612)	48 hours	37	1.4	23	0.9	–	–	–	–	58	2.2
	7 days	67	2.6	53	2.0	–	–	–	–	106	4.1
	30 days	153	5.9	111	4.3	522	20	282	11	238	9.1
Placebo (*n* = 2598)	48 hours	34	1.3	8	0.3	–	–	–	–	40	1.5
	7 days	80	3.1	46	1.8	–	–	–	–	116	4.5
	30 days	133	5.1	102	3.9	512	20	292	11	209	8.0

Bleeding was defined as major, minor or insignificant. Major bleeding during hospital stay was defined as either intracranial haemorrhage or bleeding associated with a decrease in haemoglobin concentration of more than 50 g/l. Minor bleeding was defined as one of the following: spontaneous gross haematuria or haematemesis; observed blood loss with a decrease in haemoglobin concentration of more than 30 g/l but less than or equal to 50 g/l; or decrease in haemoglobin concentration of more than 30 g/l but less than or equal to 50 g/l without an identified bleeding site.

The risk of major and minor bleeding is greater in both the 24-hour infusion arm and the 48-hour infusion arm compared with placebo: 2.5% of 24-hour infusion, 3.6% of 48-hour infusion and 1% of placebo patients experienced a minor bleeding episode. Relative to placebo, the excess of minor bleeding in both of the abciximab arms was statistically significant.

The risk of major bleeding was also greatest in the 48-hour infusion group: 0.6%, 0.9% and 0.2% in the 24-hour infusion, 48-hour infusion and placebo groups respectively. Relative to placebo, the excess

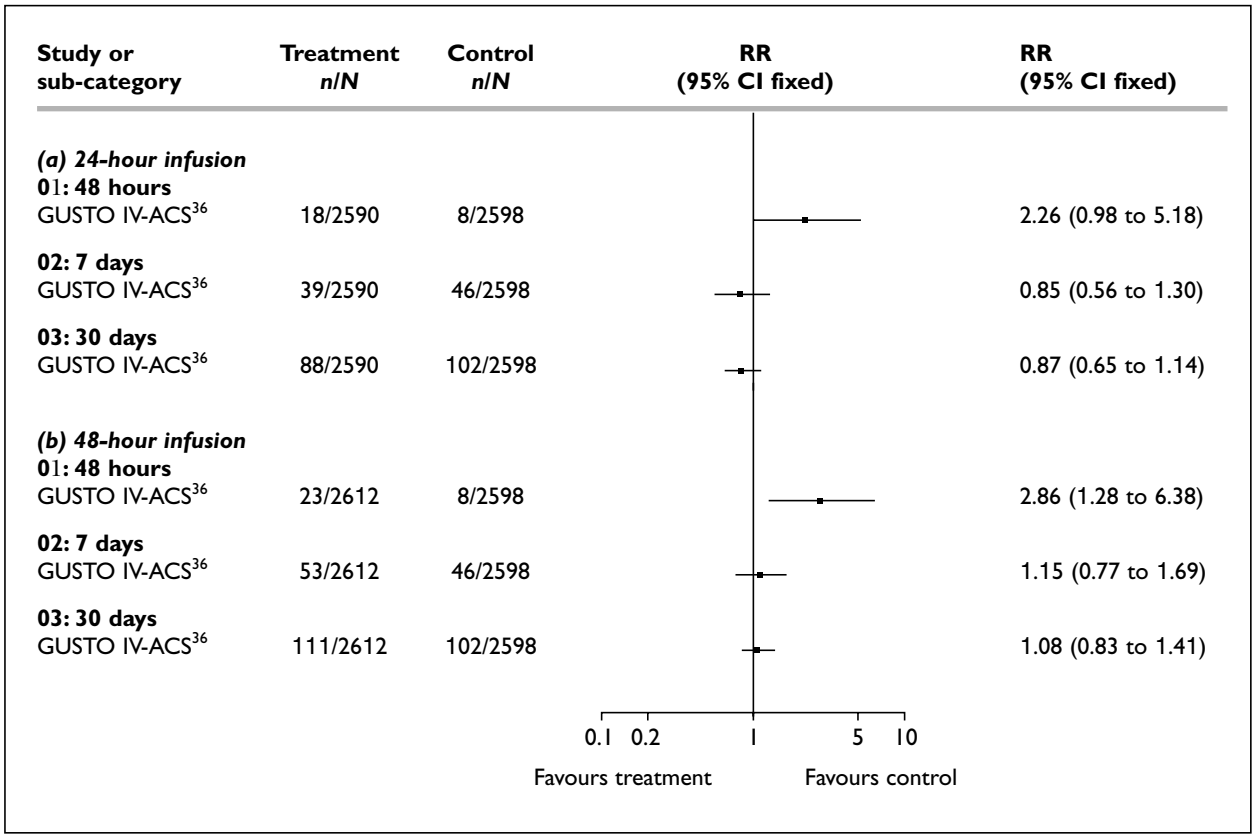

FIGURE 20 *Effect of abciximab on death for patients receiving glycoproteins as part of medical management: (a) 24-hour infusion; (b) 48-hour infusion*

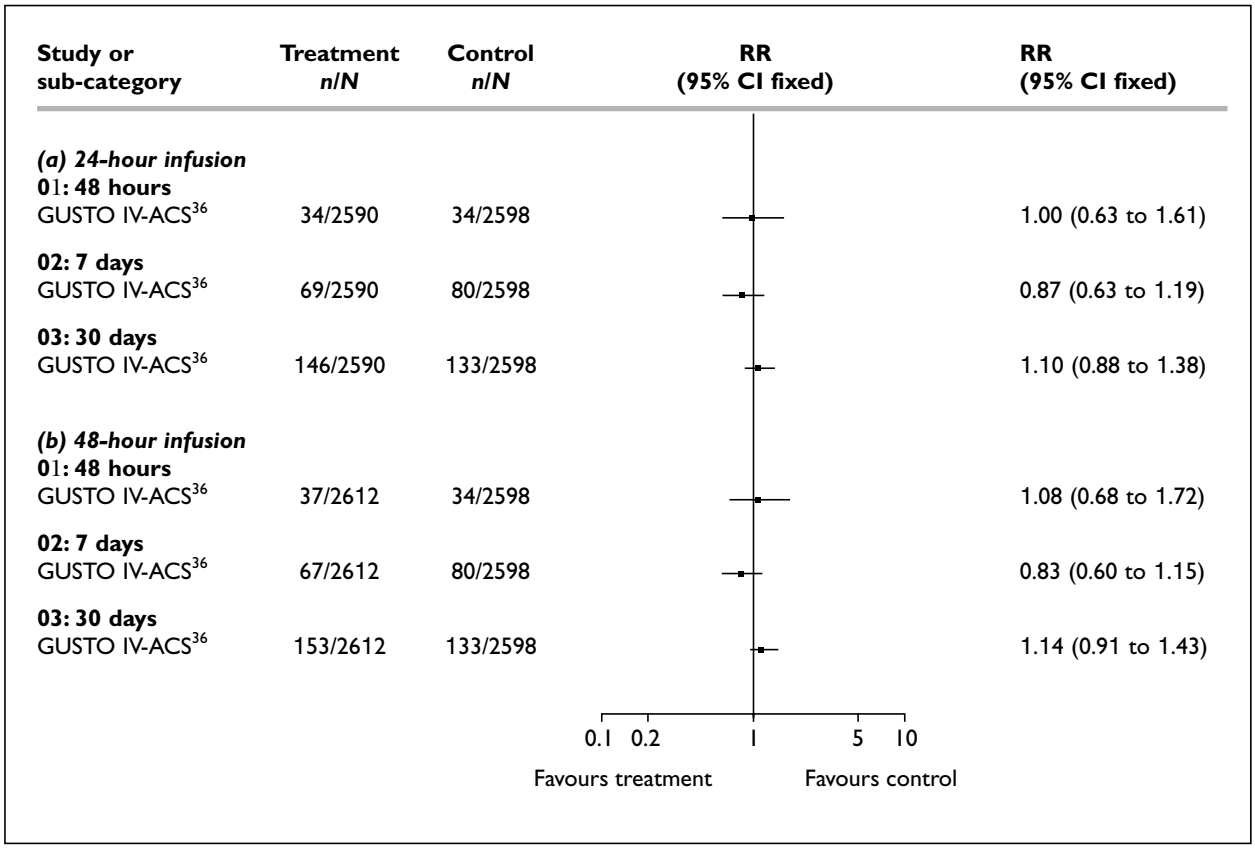

FIGURE 21 *Effect of abciximab on MI for patients receiving glycoproteins as part of medical management: (a) 24-hour infusion; (b) 48-hour infusion*

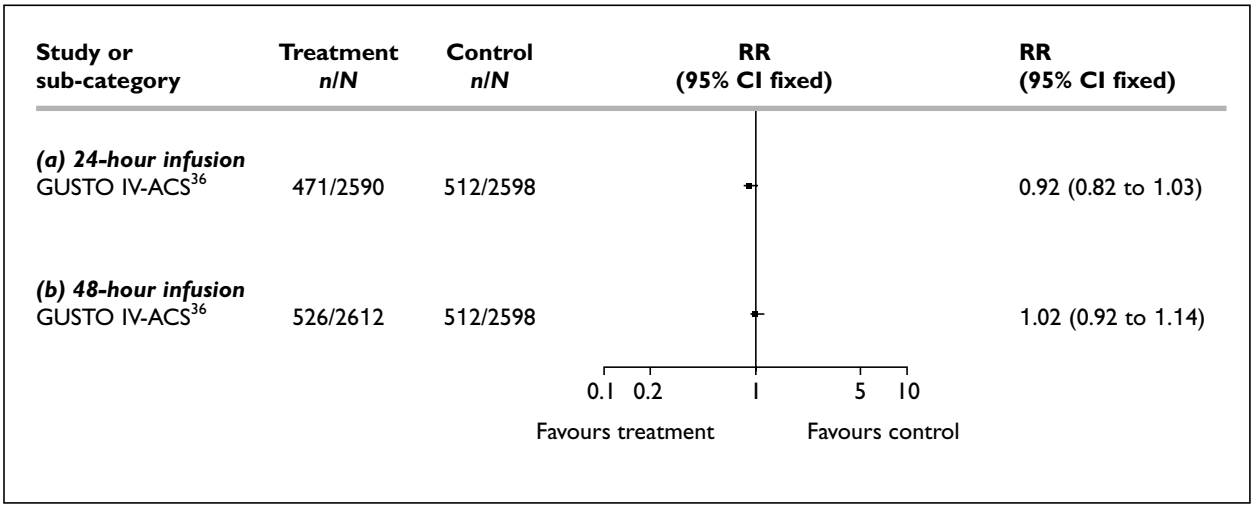

FIGURE 22 *Effect of abciximab on PTCA at 30 days for patients receiving glycoproteins as part of medical management: (a) 24-hour infusion; (b) 48-hour infusion*

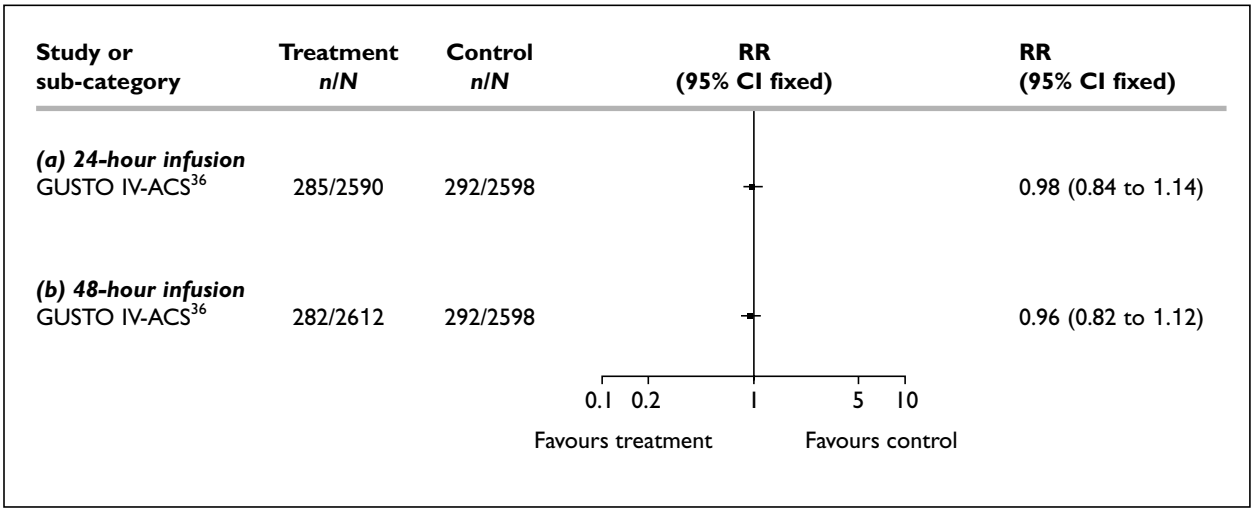

FIGURE 23 *Effect of abciximab on CABG at 30 days for patients receiving glycoproteins as part of medical management: (a) 24-hour infusion; (b) 48-hour infusion*

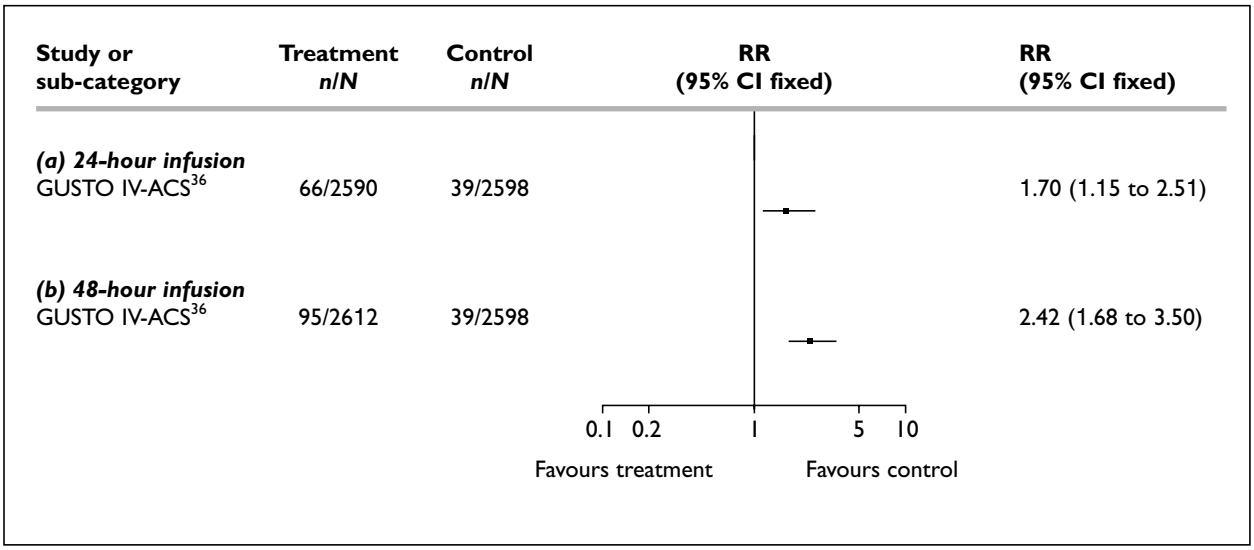

FIGURE 24 *Effect of abciximab on minor bleeding at 30 days for patients receiving glycoproteins as part of medical management: (a) 24-hour infusion; (b) 48-hour infusion*

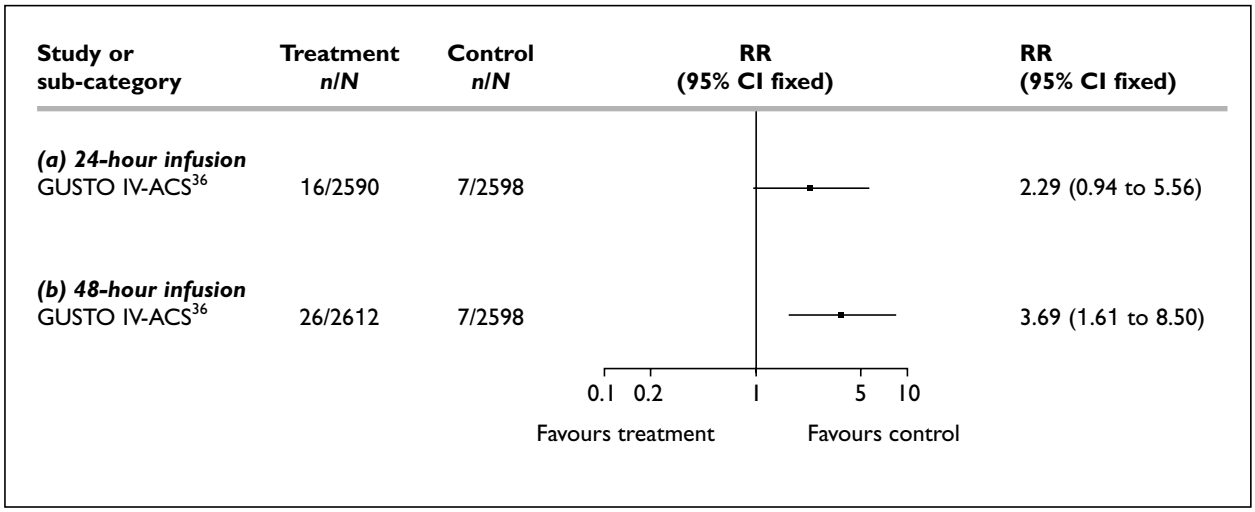

FIGURE 25 *Effect of abciximab on major bleeding at 30 days for patients receiving glycoproteins as part of medical management: (a) 24-hour infusion; (b) 48-hour infusion*

major bleeding in the 48-hour infusion arm was statistically significant.

Thrombocytopenia

Thrombocytopenia (platelet count < 50 000/μl) was seen in 78 (1.5%) of abciximab patients compared to one placebo patient.

Transfusions

The effect of abciximab on RBC transfusions can be seen in *Figure 26*. As with bleeding events, the risk of an event was greatest in the 48-hour infusion group: RR = 1.91 (95% CI, 1.31 to 2.79). The 24-hour infusion group were also more likely to require a RBC transfusion compared with the placebo group, but this excess rate was not statistically significant: RR = 1.43 (95% CI, 0.96 to 2.13).

Composite end-point

The effect of abciximab on the composite end-point can be seen in *Figure 27*. The composite outcome was defined as death or MI. In both the 24-hour and 48-hour infusion groups the composite end-point is more common in treatment than control arms at 48 hours and 30 days follow-up. At 7 days, the 24-hour and 48-hour infusion groups were less likely to experience a death or MI. The RR at 7 days was 0.89 (95% CI, 0.69 to 1.15) for the 24-hour infusion group compared to placebo and 0.91 (95% CI, 0.70 to 1.18) for the 48-hour infusion group compared to placebo. None of the differences in the composite outcome was statistically significant.

Results for high-risk groups

Outcomes for the four high-risk groups (elderly, ST-depression, troponin-positive

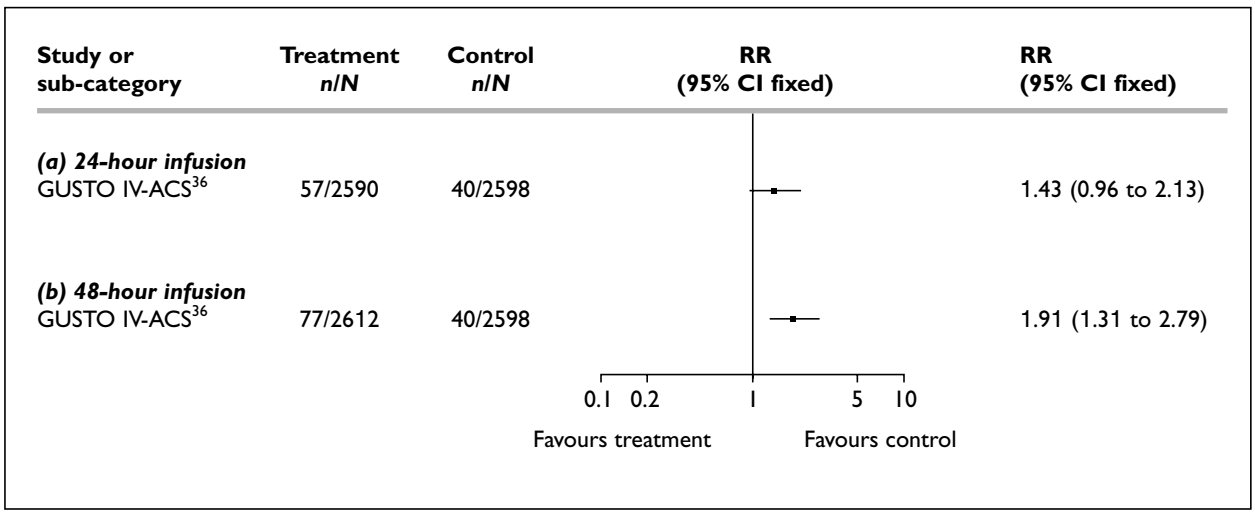

FIGURE 26 *Effect of abciximab on RBC transfusions at 30 days for patients receiving glycoproteins as part of medical management: (a) 24-hour infusion; (b) 48-hour infusion*

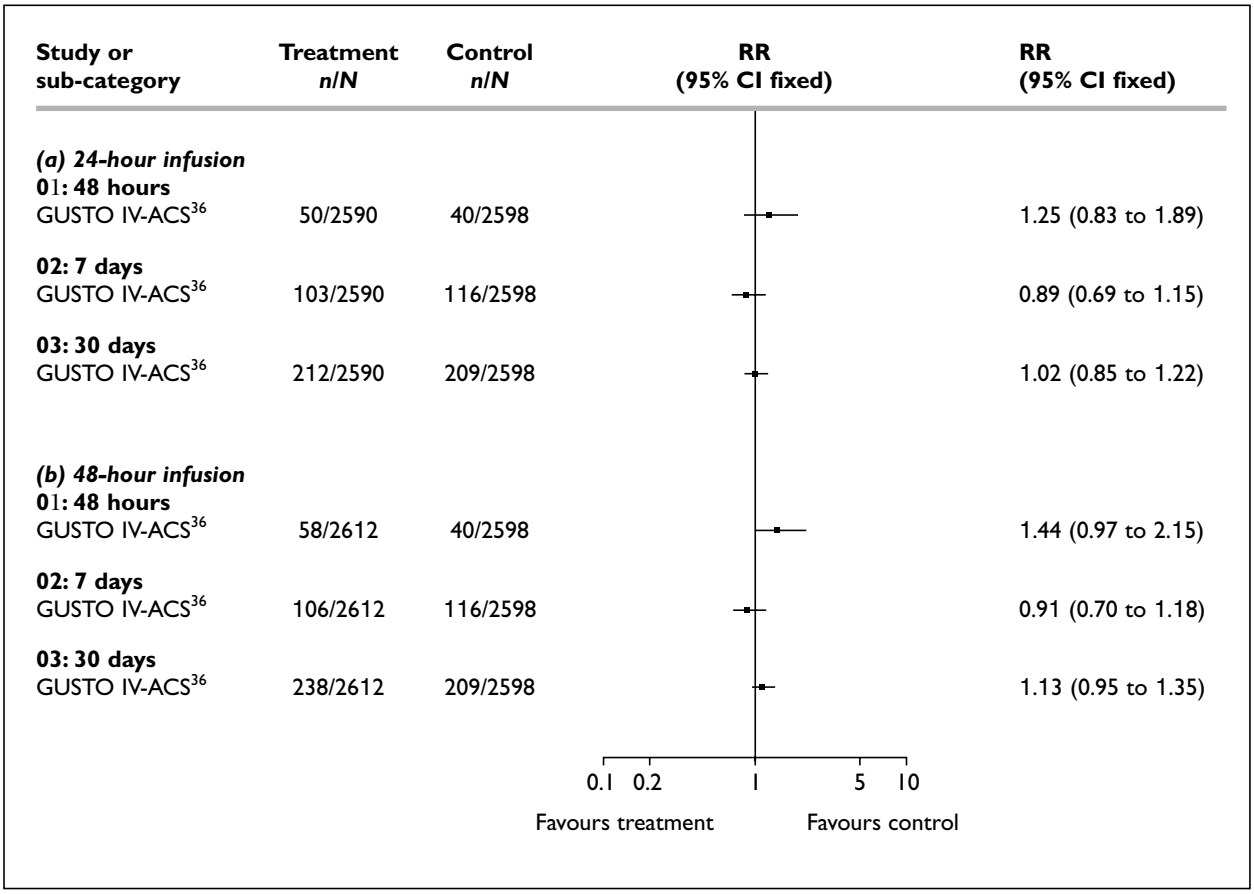

FIGURE 27 *Effect of abciximab on the composite outcome for patients receiving glycoproteins as part of medical management: (a) 24-hour infusion; (b) 48-hour infusion*

and diabetics) specified ('Study designs', page 7), are presented in *Tables 20–23*. Studies did not state in the trial protocols which subgroups would be reported on, so it may be that those chosen have been selected on a *post-hoc* basis.

TABLE 20 *Outcomes for diabetic patients receiving glycoproteins as part of medical management*

Trial	Death	MI	Death/MI	Composite	Bleeding
PURSUIT[38–41*]	–	–	OR approx. 0.95 (eptifibatide better)	–	–
PRISM, 1998[42]	–	–	–	Diabetics = RR 0.4 (approx.)	–
PRISM-PLUS: Bazzino *et al.*, 1998[43]	–	–	–	Tirofiban + heparin = 25/169 (14.8%) Heparin = 42/193 (21.8%)	–
GUSTO IV-ACS: Simoons, 2001[36]	–	–	Abciximab 24-hour infusion = 9.6% Abciximab 48-hour infusion = 11.0% Placebo = 11.4%	–	–
PRISM-PLUS: subgroup analysis by Theroux *et al.*, 2000[45]	–	–	–	Tirofiban + heparin: 48-hour infusion = 7.7%; 7 days =14.8%; 30 days = 20.1%; 6 months = 32.0% Heparin: 48-hour infusion = 8.3%; 7 days = 21.8%; 30 days = 29.0%; 6 months = 39.9%	Tirofiban + heparin: minor 7.1%; major 0.6% Heparin: minor 6.7%; major 0.5%

* *Harrington, 1997[38]; PURSUIT Trial Investigators, 1997[38A]; Simoons, 1999[39]; Mahaffey* et al., *1999[40]; PURSUIT Trial Investigators, 1998[41]*

TABLE 21 *Outcomes for elderly patients receiving glycoproteins as part of medical management*

Trial	Death	MI	Death/MI	Composite
PURSUIT[38–41*]	–	–	OR approx. 0.98 (eptifibatide better) in age ≥ 65	–
PRISM, 1998[42]	–	–	–	> 75 years = RR 0.6 (approx.)
PRISM-PLUS: Bazzino *et al.*, 1998[43]	–	–	–	Tirofiban + heparin = 66/371 (17.8%) Heparin = 93/395 (23.5%)
GUSTO IV-ACS: Simoons, 2001[36]	–	–	Abciximab 24-hour infusion = 10.6% Abciximab 48-hour infusion = 12.4% Placebo = 11.1%	–
PURSUIT: subgroup analysis by Hasdai *et al.*, 2000[46]	Eptifibatide: < 50 = 5 (0.8%) 50–59 = 15 (1.4%) 60–69 = 45 (3%) 70–79 = 71 (5.8%) > 80 = 29 (11.7%)	Eptifibatide: < 50 = 54 (8.2%) 50–59 = 100 (9%) 60–69 = 188 (12.6%) 70–79 = 194 (15.9%) > 80 = 57 (22.9%)	Eptifibatide: < 50 = 57 (8.7%) 50–59 = 107 (9.7%) 60–69 = 212 (14.3%) 70–79 = 223 (20.1%) > 80 = 73 (29.3%)	–
	Placebo: < 50 = 6 (0.9%) 50–59 = 16 (1.5%) 60–69 = 54 (3.5%) 70–79 = 78 (6.6%) > 80 = 23 (9%)	Placebo: < 50 = 63 (9.5%) 50–59 = 138 (12.8%) 60–69 = 203 (13.0%) 70–79 = 194 (16.5%) > 80 = 46 (17.9%)	Placebo: < 50 = 64 (9.6%) 50–59 = 148 (13.8%) 60–69 = 235 (18.6%) 70–79= 237 (20.1%) > 80 = 61 (23.7%)	

* *Harrington, 1997[38]; PURSUIT Trial Investigators, 1997[38A]; Simoons, 1999[39]; Mahaffey* et al., *1999[40]; PURSUIT Trial Investigators, 1998[41]*

TABLE 22 *Outcomes for troponin-positive patients receiving glycoproteins as part of medical management*

Trial	Death	MI	Death/MI	Composite
GUSTO IV-ACS: Simoons, 2001[36]	–	–	Abciximab 24-hour infusion = 10.0% Abciximab 48-hour infusion = 11.6% Placebo = 10.0%	–
PRISM: subgroup analysis by Heeschen *et al.*, 1999[44]	Tirofiban: 48 hours = 0 7 days = 2 (0.7%) 30 days = 5 (1.6%)	Tirofiban: 48 hours = 1 (0.3%) 7 days = 4 (1.3%) 30 days = 8 (2.6%)	–	Tirofiban: 48 hours = 1 (0.3%) 7 days = 6 (2.0%) 30 days = 13 (4.3%)
	Heparin: 48 hours = 2 (0.6%) 7 days = 12 (3.7%) 30 days = 20 (6.2%)	Heparin: 48 hours = 9 (2.8%) 7 days = 18 (5.6%) 30 days = 22 (6.8%)		Heparin: 48 hours = 11 (3.4%) 7 days = 30 (9.3%) 30 days = 42 (13.0%)

Boersma and colleagues[47] looked at the relationship between baseline characteristics, including ST-depression, diabetes and age on 30-day outcomes. Rates and odds ratios (ORs) for the relationship were presented for all the baseline characteristics in combination and not those specified as relevant for this review, and therefore it has not been possible to extract relevant results from this paper.

The analysis of diabetics included in the PRISM-PLUS trial undertaken by Theroux and colleagues[45] showed little difference in

TABLE 23 *Outcomes for patients with ST-depression receiving glycoproteins as part of medical management*

Trial	Death	MI	Death/MI	Composite
PRISM, 1998[42]	–	–	–	RR 0.5 (approx.)
PRISM-PLUS: Bazzino *et al.*, 1998[43]	–	–	–	Tirofiban + heparin = 16.6% Heparin = 21.7%
GUSTO IV-ACS: Simoons, 2001[36]	–	–	Abciximab 24-hour infusion = 8.5% Abciximab 48-hour infusion = 9.9% Placebo = 8.4%	–

absolute relative risk (ARR) of the primary end-point of death, new MI or RI at 7 days between diabetics and overall results: diabetics 7.0% (14.8% in tirofiban and heparin group versus 21.8% in control group; not statistically significant); overall 5.0% (12.9% and 17.9% respectively, $p = 0.004$). However, the excess rate of bleeding in the treatment arm was lower in diabetics than non-diabetics: absolute increase in minor bleeding 0.4% in diabetics; 3.0% in non-diabetics; 0.1% and 0.9% respectively for major bleeding.

The analysis of PURSUIT data by age group by Hasdai and colleagues[46] showed that occurrences of death and MI were more common in the older age groups (70–79 and > 80). This was true for both eptifibatide and placebo groups. The benefit of treatment with eptifibatide also appeared to be greater in the > 80 age group, with death/MI at 29.3% in the eptifibatide group compared to 23.7% in the placebo group.

The GUSTO IV-ACS study[36] showed a negative effect of 48-hour infusion with abciximab in elderly patients: death/MI occurred in 12.4% of abciximab patients and 11.1% of placebo patients.

The subgroup analysis of troponin status by Heeschen and colleagues[44] showed that troponin-positive patients receiving tirofiban were significantly less likely to suffer an event at 30 days than troponin-positive patients receiving placebo (4.3% versus 13.0%). Equivalent figures for all patients in PRISM were 15.9% and 17.1% for tirofiban and heparin arms respectively. GUSTO IV-ACS was the only other trial to report any results in troponin-positive patients. There was no difference in the number of deaths or MIs in the abciximab 24-hour infusion group and placebo group, whereas a negative effect of abciximab was found in the 48-hour infusion compared with placebo groups (11.6% versus 10.0%). These results were similar to those for all patients in the trial.

The PRISM, PRISM-PLUS and GUSTO IV-ACS studies reported the composite outcome for patients with ST-depression recorded at baseline. PRISM did not report actual numbers of events for patients with ST-depression but stated the RR for the composite end-point at 48 hours as 0.5 for patients with ST-depression compared to 0.67 for all patients. PRISM-PLUS reported the 7-day composite end-point occurred in 16.6% of treated patients with ST-depression compared with 21.7% of controls with ST-depression. Equivalent figures for all patients were 12.9% and 17.9%. GUSTO IV-ACS showed similar results in patients with ST-depression as in all patients: a negative effect of the 48-hour infusion of abciximab (abciximab 48-hour infusion = 9.9%, placebo = 8.4%) and little difference between the 24-hour infusion group and placebo.

In summary, subgroup analyses of those at high-risk confirmed their higher event rates. Treatment effects were also similar, except in the case of troponin-positive patients where there were greater absolute treatment effects.

Conclusions about the effectiveness of glycoproteins in the medical management of ACS patients

Five trials of three intravenous GP IIb/IIIa antagonists were found. The three drugs examined were eptifibatide, tirofiban and abciximab. The validity assessment of these studies indicates that, in general, they were of good methodological quality. However, reporting problems were identified, particularly with blinding of patients or persons providing care, lack of details on randomisation methods, measuring and dealing with imbalances in 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.

The most striking overall conclusion is that the effect sizes observed in these trials are small compared with other interventions for ACSs. For aspirin, the 30-day reduction in mortality is 2.4% (95% CI, 1.6 to 3.2) (NNT = 41 (95% CI, 32 to 62).[49] For thrombolysis, equivalent figures are 1.9% (NNT = 56).[49] Equivalent ARRs in mortality in these trials are 0.2% (PURSUIT), 1.3% in PRISM, 0.9% in PRISM-PLUS (tirofiban + heparin versus heparin). In GUSTO IV-ACS, the risk of death at 48 hours was significantly higher in the two abciximab arms compared with the placebo arm (RR 24-hour infusion = 2.26; 95% CI, 0.98 to 5.18; RR 48-hour infusion = 2.86; 95% CI, 1.28 to 6.38). The increased risk of death continued for longer follow-up periods in the 48-hour infusion (RR at 7 days = 1.15; 95% CI, 0.77 to 1.69; RR at 30 days = 1.08; 95% CI, 0.83 to 1.41). The 24-hour infusion arm did, however, show a positive effect of abciximab on death at longer follow-up (RR at 7 days = 0.85; 95% CI, 0.56 to 1.30; RR at 30 days = 0.87; 95% CI, 0.65 to 1.14), but this effect was not statistically significant. The overall reduction in 30-day mortality quoted in a recent meta-analysis of all medical management trials[2] (including two with lamifiban not included in this review) was 0.25% ($p = 0.14$).

The effects on non-fatal MI were also small. ARRs at 30 days were 1% in PURSUIT (NNT = 110), 0% in PRISM and 3% in PRISM-PLUS (NNT = 39). None of these was significant at the 5% level, although this is a function of the size of the trials as well as the drugs' effectiveness.

Subgroup analyses show more encouraging results, in particular in troponin-positive patients. In the PRISM study, the ARR for death at 30 days was 3.6% and for MI 4.2%. The other trials have not published results for separate end-points for subgroups defined by troponin. In the PURSUIT study, with regard to age, the ARR for death was 2.7% in those > 80 years compared to 0.1% in those aged < 50 years. Equivalent figures for MI were 5% and 1.3%, respectively.

However, such analyses should be treated with caution for the following reasons:

- such analyses are rarely pre-specified in published protocols, so those published may be selected *post-hoc*
- randomisation is not stratified by subgroups so there may be imbalances in prognostic factors resulting in spurious differences in end-points.[50]

Differences between the baseline characteristics of individuals enrolled in the PRISM and PRISM-PLUS studies may partially explain the opposing findings with tirofiban alone. In PRISM-PLUS, more than 90% of patients had baseline ST-T ECG changes, whereas only 39% in PRISM were reported to have these changes. These are highly prognostic of a poor outcome, and suggest more severe disease. Chesebro and Badimon propose that a higher dose or the addition of heparin may be required to produce an effect in these patients.[33] The tirofiban plus heparin arm of PRISM-PLUS did report positive results, although small. The difference between the two PRISM trials is again reflected in the rates of PCI, as more individuals required intervention in PRISM-PLUS than in PRISM. PRISM and PRISM-PLUS allowed intervention during the 48 hours drug infusion only if deemed necessary. PURSUIT left PCI decisions up to the treating physician. When PCI was deemed necessary in PRISM, PRISM-PLUS and PURSUIT, the study drug (active or placebo) was continued. Rates with eptifibatide and tirofiban in PRISM and PURSUIT were slightly smaller compared with placebo, while tirofiban plus heparin resulted in slightly more interventions in PRISM-PLUS.

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 GP IIb/IIIa antagonist) during these studies, then the result would be an underestimate of the real effects of the GP IIb/IIIa antagonists. The treatment effect may also be understated if the patients who are already receiving the study drug and require PCI have more severe disease than those receiving PCI in the reference group. There is evidence that men recruited to these trials are more likely to receive PCI and to be troponin-positive.[2] In addition, the variation in rates of PCI in different geographic locations is well recognised, and was reported in PURSUIT. The PURSUIT and PRISM studies report that patients in North America had better response rates than patients from other areas. PRISM-PLUS did not report results, but commented that both US and non-US patients benefited from tirofiban. If the effect seen in these studies were 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 GP IIb/IIIa antagonists among patients not going on to receive PCI may be much smaller than is reported in these trials. Subgroup analysis in patients not receiving early revascularisation shows effect in some trials but not in others: a reduction in 30-day composite outcome from 16.8% to 14.8% in PRISM-PLUS, and from 15.6% to 14.5% in PURSUIT, but an increase in 30-day death/MI from 8.0% to 8.6% in GUSTO IV-ACS.[51] These subgroup analyses are potentially biased because they compare non-randomised groups.

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 and still include the patients of interest. If data were provided on when PCI occurred and what other interventions were received (i.e. other GPAs) it might be possible to establish the effect of the study drugs in unstable angina/ACS without PCI by adjusting for the propensity to receive PCI.

The effects seen with eptifibatide for the composite end-point at 96 hours are slightly less at 6 months, but the CIs overlap. The effects seen with tirofiban plus heparin for the composite end-point appear to be the greatest at 7 days, and were slightly less at 6 months. However, the CIs again overlap. The precision of the estimates of effect is relatively low, with wide CIs for all trials except PURSUIT. Many of the CIs cross the no effect mark.

The results of GUSTO IV-ACS, the one major trial published since the last review for NICE, were unexpectedly negative. With a lower risk group of patients recruited than envisaged and with longer infusions of abciximab, the possibility of sub-therapeutic platelet inhibition may have led to agonistic activities of the GP IIb/IIIa inhibitor rather than inhibition.[52] Abciximab may differ in this way from the small molecule glycoprotein. Alternatively, all three GP IIb/IIIa inhibitors may be of limited effectiveness in patients not undergoing early invasive management. A recent editorial in *Heart*[51] argued that none of the trials had demonstrated benefits in patients not having early intervention. However, an alternative retrospective re-analysis of PURSUIT[38–41] and PRISM-PLUS[53] demonstrates a significant decrease in events and rates in patients before they receive PCI, suggesting there is an effect of GP IIb/IIIa antagonists independent of the procedure. A meta-analysis of individual patient data including two trials excluded from this review[2] showed similar results.

Adverse effects monitored included bleeding and thrombocytopenia. Most of the definitions of major bleeding included intracranial haemorrhage; however, the incidence of overall stroke was also reported in most studies.

Eptifibatide and tirofiban reported rates of stroke that were similar in both treatment and reference groups. The rate with eptifibatide was 0.8% compared to 0.6% with placebo. A subanalysis of cases of stroke revealed that most of the strokes were non-haemorrhagic (83.5% of all strokes), and this was not higher in the eptifibatide-treated patients.[54] Thrombocytopenia rates were very similar for eptifibatide and placebo in PURSUIT (6.8% vs 6.9%). Rates with tirofiban were higher in the treatment groups in both PRISM and PRISM-PLUS (1.1% vs 0.4% and 1.9% vs 0.8%, respectively). The definitions of thrombocytopenia varied and may help explain the difference in rates observed between PURSUIT and the two PRISM studies.[42,43] PURSUIT defined thrombocytopenia as < 100,000/m^3, while PRISM and PRISM-PLUS defined it as < 90,000/m^3.

In reaching an overall conclusion about the appropriate use of these drugs, the benefits need to be weighed against the harms. Although all trials report an increase in major and minor bleeding, thrombocytopenia and blood transfusions, in most cases the absolute effects are small. The NNH (number treated resulting in one adverse event) from major bleeding ranges from 66 in PURSUIT to 250 in GUSTO IV-ACS. There are too few such events to assess whether adverse effects are more common in those subgroups, which receive the largest benefits. Although numbers needed to harm tend to be much larger than the NNTs, their qualitative impact on individual patients is quite different. The individual whose death or infarction has been prevented by GP IIb/IIIa antagonists is difficult to recognise, whereas it is the reverse for that individual whose major bleed or stroke may have been caused in this way. A recent case report published by *The Lancet* illustrates this.[55]

Although there is evidence from all five trials of a reduction in composite outcome at some time-point for ACS patients overall, given the uncertainty of subgroup analysis there remains doubt about the effectiveness in specific subgroups, such as those patients not undergoing early intervention. With regard to the latter, the chairman of the American College of Cardiology/

American Heart Association guidelines group has recently proposed that the recommendation that GP IIb/IIIa antagonists should be used in all high-risk ACS irrespective of intervention should be downgraded.[56] The chairman states: "The totality of evidence with GP IIb/IIIa inhibitors in the treatment of unstable angina, including the results of GUSTO IV-ACS, does not fully support the use of these agents in the treatment of ACS in the absence of PCI (Class II indication), which is a departure from the ACC/American Heart Association guidelines published last year, which recommended a Class I indication for IIb/IIIa inhibition in this setting." However, this statement was not (as far as we are aware) informed by cost-effectiveness modelling such as is described in the accompanying report.[57]

Use of glycoproteins alongside PCI

Efficacy of intravenous GP IIb/IIIa antagonists

The earlier review by Fischer and colleagues[4] reviewed 13 trials looking at the use of glycoproteins alongside PCI. The EXCITE trial[58] was not included in this updated review as it considered the use of xemilofiban, which is not licensed in the UK. In addition to these 12 trials, the update searches identified another five trials (PRICE,[59] ADMIRAL,[60] TACTICS-TIMI,[61] TARGET[62] and ESPRIT[63]). A sixth trial, CADILLAC[64] has been excluded because only brief details were available in abstract form. The results and methodology of the five newly published studies are discussed and extracted alongside the results of the Fischer review.

General details

The 17 trials all took place between 1992 and 2001 (*Table 24*), with two conducted in an international setting, eight took place in the USA, three in the USA and Canada, and one each in Taiwan, Italy, France and Germany. All trials were classified as randomised placebo controlled trials apart from Galassi and colleagues,[77] TARGET[62] and PRICE,[59] which did not include placebo as a comparator and TACTICS-TIMI[61] in which all patients received tirofiban.

Abciximab was evaluated in ten of the trials, with similar doses used between studies. Eptifibatide was assessed by IMPACT-II,[65] ESPRIT[63] and Harrington and colleagues.[80] Tirofiban was assessed in the RESTORE[66,67] and TARGET[62] and TACTICS-TIMI[61] trials. These trials were included in the review despite not formally satisfying the inclusion criteria because they do extend the evidence base and were referred to in some company submissions.

The length of follow-up ranged from 36 hours in CAPTURE[68] (although longer follow-up was also assessed) to 7 years in EPIC[69–71] (7-year data submitted as part of company submission).

Patient characteristics and inclusion criteria

The inclusion criteria used in the trials were heterogeneous: nine trials included a broad cross-section of patients undergoing elective or emergency PCI (IMPACT-II,[65] EPISTENT,[75] ERASER,[76] Galassi and colleagues,[77] Harrington and colleagues,[80] TARGET,[62] ESPRIT,[63] PRICE,[59] EPILOG[72,73]; one trial focused on ACS patients (RESTORE[66]; two trials concentrated solely on unstable angina patients (CAPTURE,[68] TACTICS-TIMI[61]; three on primary PCI after MI (RAPPORT,[74] ADIMIRAL,[60] ISAR-II[79]; and two selected patients at high risk of cardiac complications (EPIC,[69–71] and Chen and colleagues[78]. Inclusion and exclusion criteria used in each trial can be seen in *Table 25*.

The number of participants in each trial varied quite significantly: PURSUIT[38–41] was the largest trial with 9461 participants and the Chen study the smallest trial with 42 participants. The median age of participants was approximately the same between trials, ranging from 59 in ERASER to 70 in Chen. Prognostic information collected in each trial shows that participants differed to some degree with respect to previous interventions and co-morbidities. The percentage of diabetic patients in Chen was significantly higher than other trials at 35.5%, this being more than double the number of diabetic patients in ERASER (14.2%) for example. The number of patients experiencing hypertension was greatest in the trial by Harrington and colleagues. The number of patients who had experienced a prior MI was relatively low in the RAPPORT, CAPTURE and ADMIRAL trials: 19%, 17% and 16%, respectively. The baseline characteristics of participants can be seen in *Table 26*.

Data collected on prior interventions was only reported for half of the trials, and showed that patients did not differ significantly between trials with the exception of Chen, which had a relatively small percentage of patients included who had a prior CABG (3%).

Length of observation before PCI and timing of drug administration before PCI

Only five trials gave the timing of administration of the intervention drug before PCI, but those that

TABLE 24 *Details of included studies of intravenous GP IIb/IIIa antagonists*

Study	Setting	Design/phase	Treatment arms	Number of participants	Follow-up times
EPIC[69–71*]	USA	Multicentre, double-blind, placebo RCT	Abciximab + infusion Abciximab + placebo Placebo + placebo infusion	1695 2708 696	30 days 6 months 3 years 7 years
IMPACT-II, 1997[65]	USA	Double-blind, placebo RCT	Eptifibatide high dose Eptifibatide low dose Placebo	1349 1333 1328	30 days 6 months
CAPTURE, 1997[68]	12 countries	Double-blind, placebo RCT	Abciximab Placebo	630 635	≤ 36 hours before PTCA ≤ 72 hours after randomisation 30 days 6 months
EPILOG[72,73†]	USA & Canada	Double-blind, placebo RCT	Abciximab + high-dose heparin Abciximab + standard dose heparin Placebo	935 918 939	30 days 6 months 4.5 years
RESTORE[66,67‡]	Inter-national	Double-blind, placebo RCT	Tirofiban Placebo	1071 1070	30 days 6 months
RAPPORT: Brener *et al.*, 1998[74]	USA	Double-blind, placebo RCT	Abciximab Placebo	241 242	7 days 30 days 6 months
EPISTENT: Topol *et al.*, 1998[75]	USA & Canada	Double-blind, RCT	Abciximab + stent Abciximab + balloon Placebo + stent	794 796 809	30 days 6 months 1 year (some) 3 years
ERASER: Ellis *et al.*, 1999[76]	USA	Multicentre, double-blind, placebo RCT	Abciximab 12-hour infusion Abciximab 24-hour infusion Placebo	79 75 71	6 months
Galassi *et al.*, 1999[77]	Italy	Randomised trial, not placebo	No abciximab Abciximab	52 54	30 days
Harrington *et al.*, 1995[80]	USA	RCT, some double-blinding	Eptifibatide Placebo	54 19	Until discharge
Chen *et al.*, 2000[78]	Tiawan	Double-blind, placebo RCT	Abciximab Placebo	22 20	30 days
ISAR-II: Neumann *et al.*, 2000[79]	Germany	Single-blind, RCT	Abciximab Heparin	201 200	30 days 1 year
TACTICS-TIMI: Cannon *et al.*, 1998[61]	USA	Double-blind, RCT	Invasive Conservative (all patients received tirofiban)	1114 1106	30 days 6 months
TARGET: Topol *et al.*, 2001[62]	USA	Multicentre, double-blind, double-dummy trial	Tirofiban Abciximab	2398 2411	30 days
ESPRIT: O'Shea *et al.*, 2001[63]	USA & Canada	Multicentre, randomised, placebo-controlled, parallel-group trial	Eptifibatide Placebo	1040 1024	48 hours 30 days 6 months 1 year
PRICE: Lam *et al.*, 2001[59]	USA	Randomised, double-blind study	Abciximab Eptifibatide	163 157	30 days
ADMIRAL: Montalescot *et al.*, 2001[60]	France	Randomised, placebo-controlled trial	Abciximab Placebo	149 151	30 days 6 months

* *1994*[69]*;Topol* et al., *1994*[70]*;Topol* et al., *1997*[71]
† *Lincoff* et al., *1999*[72]*; 1997*[73]
‡ *Hanrath* et al., *1997*[66]*; Gibson* et al., *1998*[67]

TABLE 25 *Inclusion and exclusion criteria from published texts*

Study	Inclusion criteria	Exclusion criteria
EPIC[69–71]*	Patients needing coronary angioplasty or directional atherectomy, with an evolving or recent MI, unstable angina, or high-risk angiographic lesion morphology or clinical characteristics	Tendency to bleed; > 80 years old; stroke within last 2 years or major surgery ≤ 2 weeks prior to study entry
IMPACT-II, 1997[65]	Scheduled for elective, urgent, or emergency coronary intervention with a device approved by the Food and Drug Administration (balloon angioplasty, directional coronary atherectomy, rotational atherectomy, or excimer laser ablation); representative cross-section of patients undergoing percutaneous revascularisation	History of bleeding diathesis; severe hypertension (SBP > 200 mmHg or DBP > 100 mmHg on therapy); major surgery ≤ 6 weeks; history of stroke or other disorders of the CNS; pregnancy; GI- or GU-bleeding ≤ 30 days; other major illness
CAPTURE, 1997[68]	Patients with refractory unstable angina undergoing PTCA; refractory unstable angina defined as chest pain rest with concomitant ECG abnormalities compatible with MI (ST-segment depression, ST-segment elevation or abnormal T-waves), one or more episodes of chest pain, ECG abnormalities or all; latest episode of ischaemia within the last 48 hours before enrolment; patients who had undergone angiography and had significant CAD with a culprit lesion suitable for angioplasty; patients enrolled within 24 hours of angiography	Recent MI, unless CK values had returned to below twice the upper limit of normal; features of persisting ischaemia that would require immediate intervention; a greater than 50% occlusion of the left main coronary artery or a culprit lesion located in a bypass graft; bleeding risk factors; cerebrovascular or accident within the previous 2 years
EPILOG[72,73]†	Patients undergoing elective or urgent PCI, over 21 with a target lesion stenosis of at least 60% diameter of the vessel (excludes patients with MI or unstable angina with ECG changes in last 24 hours)	AMI or unstable angina with associated ECG changes < 24 hours; planned stent implantation or rotational atherectomy; PCI performed ≤ 3 months; left main coronary artery stenosis > 50% not protected by collateral vessels; concurrent warfarin therapy or a baseline prothrombin time > 1.2 times the control value; cerebrovascular event ≤ 2 years or a residual neurologic deficit intracranial neoplasm; aneurysm arteriovenous malformation; history of vasculitis; known haemorrhagic diathesis or active internal bleeding; SBP > 180 mmHg or DBP >100 mmHg; major surgery GI- or GU-bleeding ≤ 6 weeks inability to give written consent
RESTORE[66,67]‡	Patients undergoing coronary interventions (balloon angioplasty or directional colour angiography) within 72 hours of presentation of ACS (unstable angina or acute MI); also included if MI occurred in last 72 hours	Received thrombolytic therapy ≤ 24 hours; contraindication to anticoagulation history of platelet disorder or thrombocytopenia; history of stroke or other intracranial pathology likely to predispose to bleeding; scheduled for elective stent placement or if angioplasty using a rotablator or transluminal extraction catheter device was planned
RAPPORT: Brener *et al.*, 1998[74]	Patients within 12 hours of onset of MI, deemed candidates for PTCA	Severe thrombocytopenia; baseline prothrombin time > 1.2 times control; ongoing internal bleeding or recent major surgery; previous stroke; severe uncontrolled hypertension; PTCA of the infarct artery within 3 months; cardiogenic shock or prolonged resuscitation; vasculitis; prior administration of abciximab or fibrinolytic therapy; inability to give written consent; PCI within ≤ 3 months

continued

***TABLE 25* contd** *Inclusion and exclusion criteria from published texts*

Study	Inclusion criteria	Exclusion criteria
EPISTENT: Topol *et al*., 1998[75]	Patients who were scheduled to undergo elective or urgent PCI; patient is eligible if (1) target lesions had caused stenosis of at least 60% amenable to balloon angioplasty or stenting, (2) target vessel was not an unprotected left-mainstream stenosis, and (3) patient did not have bleeding diathesis, intracranial neoplasm, history of stroke in previous 2 years, uncontrolled hypertension or PCI within last 3 months	Bleeding diathesis, intracranial neoplasm, history of stroke in the previous 2 years; uncontrolled hypertension (SBP > 180 mmHg, DBP > 100 mmHg); recent surgery or PCI within ≤ 3 months; concurrent warfarin therapy of an INR > 1.5 at baseline
ERASER: Ellis *et al*., 1999[76]	Patients required to have a *de novo* target coronary stenosis of ≥ 50% in vessel of diameter 2.75–3.5 mm, and has been referred for intracoronary stent implantation	MI within 72 hours before randomisation; evident intracoronary thrombus; previous coronary intervention within the past 6 months; planned de- bulking before stent placement; expected inability to target lesion by IVUS or standard contraindications
Galassi *et al*., 1999[77]	Patients with demonstrable ischaemia and a target *de novo* complex lesion stenosis ≥ 70% in a native vessel	Acute MI; bleeding diathesis thrombocytopenia, history of stroke in previous 2 years, internal bleeding; hypertension; major trauma/surgery within 6 weeks
Harrington *et al*., 1995[80]	Patients undergoing elective coronary intervention	Bleeding disorders; recent GI-bleeding; major surgery within 6 weeks; major trauma or coronary bypass surgery within 6 months, previous coronary angioplasty during the index hospital admission, history of stroke or other CNS structural abnormality; severe hypertension; known pregnancy; elevated prothrombin time; haematocrit < 30%; platelet count < 100,000/µl or creatinine > 40 mg/dl
Chen *et al*., 2000[78]	Patients undergoing angioplasty at high risk for cardiac complications, not at high risk of bleeding	> 80 years of age; bleeding diatheses; major surgery within 6 preceding weeks; stroke within preceding 2 years; not patients who were to undergo planned stent implantation, directional atherectomy or rotational atherectomy
ISAR-II: Neumann *et al*., 2000[79]	AMI patients undergoing revascularisation by stent placement within 48 hours after onset of pain, and typical anginal pain lasting > 30 minutes; ST-segment elevation of a least 1 mm in two or more contiguous leads; elevation in CK to at least three times the upper limit of normal; coronary artery occlusion with angiographic appearance of fresh thrombus	Inability to give informed consent; contraindications to one of the study drugs
TACTICS-TIMI: Cannon *et al*., 1998[61]	18 years of age with accelerating pattern; prolonged or recurrent anginal pain at rest or minimal effort < 24 hours; at least one of (1) ischaemic ECG changes, (2) elevated cardiac markers and a history of MI, (3) CAD, (4) PCI or CABG; AMI patients excluded	Individuals excluded for any of the following reasons: persistent ST-segment elevation, secondary angina, a history of percutaneous coronary revascularisation or CABG within the preceding 6 months, factors associated with an increased risk of bleeding, LBBB or paced rhythm, severe CHF or cardiogenic shock, serious systemic disease, a serum creatine level > 2.5 mg/dl (221 µmol/l), or current participation in another study; patients were also excluded if they were taking warfarin or had received ticlopidine or clopidogrel for more than 3 days before enrolment
TARGET: Topol *et al*., 2001[62]	Patients undergoing PCI; anatomy appropriate for stenting, elective or ACS (except primary PCI MI); creatinine < 2.5 mg/dl; AMI patients excluded	Patients with cardiogenic shock or an acute MI with electrographic evidence of ST-segment elevation; serum creatine levels ≥ 2.5 mg/dl; ongoing bleeding or a bleeding diathesis, including platelet count < 120,000 mm^2

continued

***TABLE 25* contd** *Inclusion and exclusion criteria from published texts*

Study	Inclusion criteria	Exclusion criteria
ESPRIT: O'Shea *et al.*, 2001[63]	Patients with CAD, scheduled to undergo PCI with stent implantation in a native coronary artery, and who, in the opinion of the treating physician, would not routinely be treated with a GP IIb/IIIa inhibitor during PCI; AMI patients excluded	MI within 24 h before randomisation, continuing chest pain precipitating urgent referral for PCI, PCI within the previous 90 days; previous stent implantation at the target lesion; anticipated staged PCI in the 30 days after randomisation; treatment with a GP IIb/IIIa or athienopyridine in the 30 days before randomisation; stroke or transient ischaemic attack within 30 days before randomisation; any history of haemorrhagic stroke; history of bleeding diathesis or evidence of abnormal bleeding within 30 days before randomisation; major surgery within previous 6 weeks; uncontrolled hypertension with a SBP > 200 mmHg or a DBP > 110 mmHg; documented thrombocytopenia with a platelet count less than 100 x 10/l; or a serum creatine > 350 µmol/l
PRICE: Lam *et al.*, 2001[59]	Patients aged > 21 years, undergoing elective, non-urgent coronary balloon angiography or stent implantation at one of two specified institutions	For any of the following reasons: (1) acute MI < 48 hours; (2) unstable angina with new or presumably new concomitant ST-segment or T-wave, or haemodynamic instability, < 12 hours; (3) degenerated saphenous vein graft lesions; (4) American College of Cardiology/American Heart Association type C lesions; (5) history of haemorrhagic diathesis or major surgery or trauma < 6 weeks before randomisation; (6) known baseline platelet count < 100,000 mm^3; (7) planned rotational atherectomy; (8) baseline serum creatine level > 3 mg/dl; (9) administration of abciximab or eptifibatide within 7 days of randomisation; (10) planned staged interventional procedure during index hospitalisation; (11) participation in other clinical research studies within 30 days of randomisation
ADMIRAL: Montalescot *et al.*, 2001[60]	AMI patients scheduled for primary coronary revascularisation; more than 18 years old; first symptoms of acute MI within 12 hours; ST-segment elevation of more than 1 mm in at least two contiguous leads of the ECG	Bleeding diathesis; administration of thrombolytic agents for the current episode; neoplasm; recent stroke; uncontrolled hypertension; recent surgery; oral anti-coagulant therapy; limited life expectancy; childbearing potential; contra-indications to therapy with aspirin, ticlopidine, or heparin

* *1994*[69]*;Topol* et al., *1994*[70]*;Topol* et al., *1997*[71]
† *Lincoff* et al., *1999*[72]*; 1997*[73]
‡ *Hanrath* et al., *1997*[66]*; Gibson* et al., *1998*[67]

did indicated another source of heterogeneity. The Chen, EPISTENT and EPILOG studies were similar in that bolus was administered around 10–60 minutes before PCI. CAPTURE patients received abciximab much earlier at 18–24 hours and TACTICS-TIMI patients at 4–48 hours before PCI. ESPRIT patients were given eptifibatide immediately before PCI.

Only two studies reported on the length of observation before PCI. RAPPORT observed patients for 12 hours and TACTICS-TIMI for 4–48 hours. Patients in CAPTURE had undergone angiography within the 24 hours before randomisation.

Concomitant medication

Use of concomitant medication before and after randomisation did not differ significantly between studies and can be seen in the extraction tables. Only CAPTURE reported use of anti-anginal medication before randomisation. All patients received an initial bolus of heparin not exceeding 100 U/kg or 10,000 units in total.

Use of anti-anginal medication after enrolment can be seen in *Table 27*. All patients received aspirin in varying amounts. Heparin use during intervention was recommended in Galassi, CAPTURE, RESTORE, TACTICS-TIMI, TARGET, ESPRIT and IMPACT-II. Continued use 12 hours after PTCA was recommended in EPIC and Chen; Harrington, PURSUIT and ERASER did not specify timing but stated that heparin was given to patients. EPISTENT, RAPPORT, ESPRIT, ISAR-II, PRICE, ADMIRAL and EPILOG did not recommend the use of heparin during the procedure.

TABLE 26 *Baseline characteristics of participants in trials of intravenous drugs*

Study	Prognostic indicators	Intervention 1	Intervention 2	Control
EPIC[69–71]*	Median age	62	60	61
	Diabetes (%)	23	23	26
	Hypertension (%)	54	55	55
	Elevated cholesterol (%)	55	59	57
	History of smoking (%)	68	71	65
IMPACT-II, 1997[65]	Median age	62	60	60
	Diabetes (%)	23	23	22
	Hypertension (%)	54	55	54
	Hypercholesterolaemia (%)	53	66	53
	Smokers (%)	65	65	66
CAPTURE, 1997[68]	Median age	61	–	61
	Diabetes (%)	15	–	18
	Hypertension (%)	43	–	41.4
	Current smoker (%)	37	–	40.8
EPILOG[72,73] †	Median age	60	60	60
	Diabetes (%)	23	22	24
	Previous bypass (%)	13	12	13
RESTORE[66,67] ‡	Median age	59	–	59
	Diabetes (%)	20	–	20
	Hypertension (%)	54	–	56
	Elevated cholesterol (%)	50	–	49
	History of smoking (%)	64	–	67
	Previous MI (%)	35	–	34
	Previous angioplasty (%)	21	–	20
	Previous CABG (%)	6	–	8
RAPPORT: Brener *et al.*, 1998[74]	Median age	62	–	65
	Hypertension (%)	46	–	50
	Current smoker (%)	41	–	41
	Diabetes (%)	23	–	22
	Previous MI (%)	17	–	21
	Prior revascularisation (%)	14	–	14
EPISTENT: Topol *et al.*, 1998[75]	Median age	59	59	60
	Hypertension (%)	47	55	55
	Diabetes (%)	20	19	21
	Smoker (%)	37	34	39
ERASER: Ellis *et al.*, 1999[76]	Median age	58	62	58
	Diabetes (%)	12	18	11
	Hypertension (%)	46	52	50
	Smoker (%)	29	36	28
	Prior PCI (%)	12	12	16
Galassi *et al.*, 1999[77]	Median age	63	61	–
	Family history of CAD (%)	40	44	–
	Diabetes (%)	26	27	–
	Hypertension (%)	34	33	–
	Smoking (%)	67	72	–
	Hypercholesterolaemia (%)	26	22	–
Harrington *et al.*, 1995[80]	Median age	61	–	58
	Systematic hypertension (%)	67	–	74
	Diabetes (%)	31	–	21
	Smoking (%)	74	–	68
	Family history of premature CAD (%)	57	–	63
	Prior MI (%)	52	–	26
	Prior bypass surgery (%)	20	–	42

continued

***TABLE 26* contd** *Baseline characteristics of participants in trials of intravenous drugs*

Study	Prognostic indicators	Intervention 1	Intervention 2	Control
Chen *et al.*, 2000[78]	Median age	70	–	70
	Current smoker (%)	36	–	55
	Diabetes (%)	36	–	35
	Hypertension (%)	68	–	65
	Hypercholesterolaemia (%)	18	–	15
	Prior MI (%)	41	–	50
	Previous angioplasty (%)	9	–	15
	Prior CABG (%)	5	–	0
ISAR-II: Neumann *et al.*, 2000[79]	Median age	60	64	–
	Active smoker (%)	42.8	43.5	–
	Diabetes (%)	17.4	2.25	–
	Previous PTCA (%)	7.5	6.0	–
	Previous CABG (%)	4.0	4.5	–
TACTICS-TIMI: Cannon *et al.*, 1998[61]	Median age	62	62	–
	Diabetes (%)	28	27	–
	ST-segment or T-wave changes (%)	48	47	–
	Prior MI (%)	39	39	–
	Elevated troponin T (%)	56	52	–
TARGET: Topol *et al.*, 2001[62]	Median age	62	62	–
	Diabetes (%)	23	23	–
	Hypertension (%)	64	65	–
	Smoker (%)	65	64	–
	CABG (%)	17	17	–
	MI (%)	40	39	–
ESPRIT: O'Shea *et al.*, 2001[63]	Median age	62	–	62
	Diabetes (%)	20	–	21
	Hypertension (%)	59	–	59
	Smoker (%)	24	–	23
	Stable angina (%)	39	–	38
	Unstable angina/non-Q-wave MI (2–180 days)	32	–	33
	Unstable angina/non-Q-wave MI (within 2 days)	13	–	14
	ST-elevated MI (7 days)	4	–	5
	Prior PCI (%)	23	–	24
	Prior MI (%)	32	–	31
	Prior CABG (%)	10	–	10
PRICE: Lam *et al.*, 2001[59]	Mean age	63	63	–
	Hypertension (%)	68	71	–
	Diabetes (%)	25	33	–
	CHF (%)	9	9	–
	Smoker (%)	63	71	–
	Prior CABG (%)	22	20	–
	Prior PCI (%)	37	37	–
ADMIRAL: Montalescot *et al.*, 2001[60]	Mean age	59.6	62.1	–
	Diabetes (%)	15.4	19.9	–
	Current smoker (%)	45.0	39.7	–
	History of hypertension (%)	34.2	41.1	–
	History of MI (%)	14.1	7.3	–
	History of unstable angina (%)	8.7	14.6	–
	History of stable angina (%)	12.1	12.0	–
	History of heart failure (%)	2.0	2.0	–
	CHF (%)	0.7	9.3	–

* *1994*[69]*; Topol* et al., *1994*[70]*; Topol* et al., *1997*[71]
† *Lincoff* et al., *1999*[72]*; 1997*[73]
‡ *Hanrath* et al., *1997*[66]*; Gibson* et al., *1998*[67]

TABLE 27 *Use of concomitant medications*

Study	Treatment arm	Aspirin	Heparin	Nitrates	Calcium channel blocker	Beta-blocker
EPIC[69–71*]	Abciximab + infusion Abciximab + placebo Placebo + placebo infusion	325 mg oral aspirin at least 2 hours before procedure; at discharge patients given 325 mg dose of aspirin	Initial bolus dose of 10,000–12,000 units followed by incremental bolus doses of up to 3000 units at 15-minute intervals	–	–	–
IMPACT-II, 1997[65]	Eptifibatide high dose Eptifibatide low dose Placebo	325 mg oral aspirin before intervention	100 U/kg bolus of heparin, additional heparin given during procedure	–	–	–
CAPTURE, 1997[68]	Abciximab Placebo	Aspirin at minimum daily dose of 50 mg. If not on aspirin previously first dose at least 250 mg	Heparin until at least 1 hour after PTCA	All patients received these percentages and amounts not reported		
EPILOG[72,73 †]	Abciximab + high-dose heparin Abciximab + standard dose heparin Placebo	325 oral aspirin 2 hours before PCI, and daily thereafter	–	–	–	–
RESTORE[66,67‡]	Tirofiban Placebo	325 mg aspirin within 12 hours before PTCA	Preprocedure heparin 150 µg/kg for patients weighing < 70 kg; heparin as required during procedure	–	–	–
RAPPORT: Brener *et al.*, 1998[74]	Abciximab Placebo	Patients received aspirin	100 U/kg heparin bolus prior to angioplasty, followed by additional weight-adjusted doses	Additional anti-anginal medication, left to investigator's discretion		
EPISTENT: Topol *et al.*, 1998[75]	Abciximab + stent Abciximab + balloon Placebo + stent	325 mg oral aspirin at least 2 hours before PCI	–	–	–	–
ERASER: Ellis *et al.*, 1999[76]	Abciximab 12-hour Abciximab 24-hour Placebo	200 mg ≥ oral aspirin ≥ 2 hours before procedure. Aspirin continued for ≥ 6 months	Patients received heparin	Patients received nitrates	–	–
Galassi *et al.*, 1999[77]	No abciximab Abciximab	325 mg oral aspirin before intervention, and then daily	–	–	–	–
Harrington *et al.*, 1995[80]	Eptifibatide Placebo	375 mg oral aspirin before administration of study drug; aspirin 325 mg daily continued until discharge	Patients received heparin	–	–	–
Chen *et al.*, 2000[78]	Abciximab Placebo	325 mg aspirin daily continued until discharge	Heparin administered in an initial bolus of 70 U/kg (max. 7000 units), additional bolus given	–	–	–

continued

***TABLE 27* contd** *Use of concomitant medications*

Study	Treatment arm	Aspirin	Heparin	Nitrates	Calcium channel blocker	Beta-blocker
ISAR-II: Neumann *et al.*, 2000[79]	Abciximab Heparin	500 mg aspirin i.v. before catheterisation	500 units heparin i.v. before catheterisation	–	–	–
TACTICS-TIMI: Cannon *et al.*, 1998[61]	Invasive Conservative (all patients received abciximab)	325 mg aspirin daily	Initial dose 5000 units i.v. unfractionated heparin (bolus)	–	–	–
TARGET: Topol *et al.*, 2001[62]	Tirofiban Abciximab	All patients received 250–500 mg aspirin before the procedure	< 70 U/kg administered at the start of the procedure	–	–	–
ESPRIT: O'Shea *et al.*, 2001[63]	Eptifibatide Placebo	Patients received aspirin	Initial bolus of heparin of 60 U/kg not exceeding 6000 units	–	–	–
PRICE: Lam *et al.*, 2001[59]	Abciximab Eptifibatide	325 mg administered at least 2 hours before PCI and daily thereafter	All patients received weight-adjusted heparin (70 U/kg) before the procedure	–	–	–
ADMIRAL: Montalescot *et al.*, 2001[60]	Abciximab Placebo	Aspirin plus heparin, initial bolus 70 U/kg (max. 7000 units)		–	–	–

* *1994*[69]*;Topol* et al., *1994*[70]*;Topol* et al., *1997*[71]
† *Lincoff* et al., *1999*[72]*; 1997*[73]
‡ *Hanrath* et al., *1997*[66]*; Gibson* et al., *1998*[67]

Outcomes recorded and definition of outcomes

All studies except Harrington defined a composite outcome; however, this did not include the same types of events in each trial. Trials typically used a wide range of events in their composite outcome, including death, MI, and urgent and non-urgent repeat revascularisation. ERASER defined its composite outcome as the percentage in-stent volume obstruction of target lesion measured at 6 months by intravascular ultrasound (IVUS) (*Table 28*).

Trials also varied in how AMI was defined. The extent to which an enzyme rise had to exceed the upper limit of normal to qualify as a procedure-related AMI varied from twice in Harrington to five times in EPISTENT.

Assessment of internal validity

Assessment of the internal validity of the studies included is presented in *Table 29*. Many items were assigned a question mark. This may reflect poor reporting only and does not necessarily indicate bad study design or study conduct.

There are areas that are consistently not addressed in the included trials for this indication. The importance of the selection of prognostically homogeneous sub-populations and pre-stratification on prognostically relevant variables to avoid heterogeneity was discussed for the previous indication in 'Use of Glycoproteins in the medical management of ACS' (page 9). All of the trials included tables of baseline characteristics of patients enrolled but, again, it is difficult to determine if the groups are truly homogeneous. As with the previous indication, pre-stratification of groups at randomisation would have helped when making comparisons with results from different trials, but few if any trials appear to have been designed with this application in mind.

The description of the randomisation procedure was on the whole poorly reported. More than half of the included trials gave unsatisfactory descriptions, or did not describe the procedure at all. It is essential that a suitable randomisation procedure be used in order to guarantee true random allocation to treatment and to minimise potential selection bias.

Only two of the included trials were not double-blind: one was an open-label trial (TACTICS-TIMI) and the other was single-blind (ISAR-II). However, none of the trials reported whether the success of blinding was checked. Also, in the majority of

TABLE 28 *Outcomes recorded and definition of outcomes*

Study	Acute MI	Severe recurrent angina/RI	Composite end-point
EPIC[69–71*]	Patients entering trial within 24 hours of an MI: MB isoenzyme at least three times upper normal limit, or activity of CB or MB isoenzyme increased by at least 100% and remained three times upper limit of normal after a 50% decrease from a previous peak level During the follow-up period: new significant Q-wave of 0.04 of a second or more in duration or with a depth above a quarter of the corresponding R-wave amplitude in two or more contiguous leads, or CK-MB above twice the upper limit of normal	Interventions resulting from recurrent ischaemia recorded	30 days: composite end-points of death from any cause, non-fatal MI, unplanned revascularisation, unplanned repeat PCI, unplanned stenting or insertion of balloon pump for RI 6 months: as 30 days but not including stenting or balloon insertion 3 years: death, MI or coronary revascularisation
IMPACT-II, 1997[65]	If no history of MI or enrolled more than 24 hours after infarction, end-point MI during hospital admission defined as any rise in total CK-MB concentration to three times upper normal limit plus development of new Q-waves. Patients with MI within 24 hours before intervention re-infarction based on one or two criteria (MB isoenzyme, previous peak)	–	Occurrence within 30 days of death, MI, urgent or emergency CABG or repeat coronary intervention, or index placement of a stent
CAPTURE, 1997[68]	During hospital stay: values of CK or its MB isoenzyme more than three times the upper limit of normal in at least two samples, increased by 50% over the previous value, BCG with new Q-waves in 2+ contiguous leads After discharge: concentration of CK or its MB isoenzyme above twice upper normal limit, or new Q-wave in 2+ contiguous ECG leads	–	Death (from any cause), MI, or urgent intervention for treatment of recurrent ischaemia, within 30 days
EPILOG[72,73 †]	In-hospital: new clinically significant Q-waves in 2+ contiguous leads or elevation in CK or its MB isoenzyme to at least three times repeat PCI within 30 days upper normal limit After discharge: occurrence of Q-waves or elevation of CK or its MB isoenzyme to more than twice upper normal limit	–	Composite of death from any cause, MI or re-infarction, severe MI requiring urgent CABG or Secondary end-point same outcomes as at 6 months

continued

the trials it was unknown or not stated whether persons assessing treatment effects were blinded to treatment allocation. Knowledge of patient assignment by the patients themselves, the investigators and those assessing treatment effects may have a substantial influence on the interpretation of results.

The majority of the trials lacked a description of how missing values were dealt with. As discussed in the section 'Use of glycoproteins in the medical management of ACS' (page 9), the description of how many missing values there were, as well as how they were dealt with in the analysis could have a significant impact on the interpretation of the results.

Any pooling of study results is inappropriate or hazardous due to the differences between the trials with regard to drugs studied, dosages used, type of patients enrolled, co-treatment strategies, end-point definitions, composite

***TABLE 28* contd** *Outcomes recorded and definition of outcomes*

Study	Acute MI	Severe recurrent angina/RI	Composite end-point
RESTORE[66,67‡]	Before hospital discharge: Unstable angina patients with normal CK/CK-MB values without history of MI within 72 hours: (1) typical chest pain with new ST-T changes or new pathological Q-waves and an elevated CK-MB level; (2) CK-MB ≥ three times normal upper limit Patients entering study within 72 hours after an acute MI: (1) CK-MB level ≥ three times normal upper limit After hospital discharge: (1) typical chest pain with new ST-T changes or new pathological Q-waves and an elevated CK-MB level or (2) CK-MB level ≥ twice upper limit of normal or (3) CK-MB level ≥ twice upper limit of normal with elevated CK-MB level, unaccompanied by chest pain and/or ECG changes	RI resulting in CABG or repeat angioplasty	Occurrence of any of these: death, MI, CABG surgery owing to angioplasty failure or recurrent ischaemia, repeat angioplasty for recurrent ischaemia or insertion of stent
RAPPORT: Brener *et al.*, 1998[74]	Ischaemic chest pain lasting more than 20 minutes accompanied by significant ST elevation in two contiguous leads or by new complete LBBB pattern. Re-infarction within 24 hours defined as re-elevation of CK-MB by at least 33% or 100% from preceding nadir, reaching at least three times normal value in addition to ischaemic symptoms. Re-infarction after 24 hours defined as new Q-waves or re-elevation of CK-MB to > three times normal (24 hours to discharge) or > twice normal if after hospital discharge	Urgent revascularisation defined as repeat PTCA or CABG performed within 24 hours of recurrent ischaemia	Measured as occurrence of death, re-infarction or urgent TVR
EPISTENT: Topol *et al.*, 1998[75]	New pathological Q-waves or a value of CK or its MB isoenzyme at least five times upper laboratory limit	–	Combination of death from any cause, MI, re-infarction or severe myocardial ischaemia requiring urgent coronary artery surgery or revascularisation within 30 days
ERASER: Ellis *et al.*, 1999[76]	1) New significant Q-wave of ≥ 0.04 seconds or depth of ≥ 25% of the corresponding R-wave amplitude in ≥ two contiguous leads 2) CK-MB ≥ three times the upper limit of normal	–	Per cent in-stent volume obstruction of target lesion measured at 6 months by IVUS
Galassi *et al.*, 1999[77]	Q-wave MI: occurrence of new pathologic Q-waves in conjunction with an elevation of CK levels greater than three times the upper limit of normal Non-Q-wave: elevation of cardiac enzymes greater than three times the normal value without pathologic Q-waves	–	Cardiac events: MI, death, and revascularisation

continued

***TABLE 28* contd** *Outcomes recorded and definition of outcomes*

Study	Acute MI	Severe recurrent angina/RI	Composite end-point
Harrington *et al*., 1995[80]	Appearance of new pathological Q-waves on ECG, CK-MB isoenzyme fraction elevation of three times local laboratory limit, or total CK elevation of twice upper limit of normal	Not stated	Composite outcome not reported
Chen *et al*., 2000[78]	In hospital MI: new clinically significant Q-waves in two or more contiguous leads; elevation in CK or its MB isoenzyme to at least three times the upper limit of normal After discharge MI: occurrence of Q-waves or elevation of CK or its MB isoenzyme to more than twice upper limit of normal	–	Occurrence of any within 30 days: death, non-fatal MI, unplanned surgical revascularisation, unplanned repeat PCI, unplanned stenting or insertion balloon pump
ISAR-II: Neumann *et al*., 2000[79]	Not stated	Not stated	Death, recurrent non-fatal MI and target lesion revascularisation
TACTICS-TIMI: Cannon *et al*., 1998[61]	Not stated in original (see *N Engl J Med* 22 November 2001 for definition submitted later)	–	Death, MI or re-hospitalisation for ACS
TARGET: Topol *et al*., 2001[62]	Levels of the MB isoform of CK that were at least three times the upper limit of the normal range in two separate blood samples or by the finding of abnormal Q-waves in two or more contiguous leads	–	Death, non-fatal MI, urgent target revascularisation within 30 days
ESPRIT: O'Shea *et al*., 2001[63]	Enzymatic MI: two or more values of CK-MB isoenzyme, for the first 24 hours after PCI, were at least three times the upper limit of normal Clinical MI: reported by investigator and adjudicated as an end-point by clinical events committee. Corroboration in the form of a clinical syndrome consistent with MI, and supportive electrocardiographic or cardiac marker data	–	Primary: death, MI, urgent target revascularisation and thrombotic bailout glycoprotein therapy within 48 hours after randomisation Secondary: death, MI and urgent target revascularisation at 30 days
PRICE: Lam *et al*., 2001[59]	Not defined, but measures of CPK and CPK-MB isoenzyme levels were obtained from patients	Not stated	Not stated
ADMIRAL: Montalescot *et al*., 2001[60]	Defined according to clinical symptoms and new electrographic changes with a new elevation of the CK or CK-MB isoenzyme levels	Not stated	Primary outcome: death, re-infarction, or urgent revascularisation of the target vessel at 30 days Secondary outcome: as above at 30 days and 6 months

* *1994*[69]*;Topol* et al., *1994*[70]*;Topol* et al., *1997*[71]
† *Lincoff* et al., *1999*[72]*; 1997*[73]
‡ *Hanrath* et al., *1997*[66]*; Gibson* et al., *1998*[67]

TABLE 29 *Assessment of internal validity*

Study*	EPIC	IMPACT-II	CAPTURE	EPILOG	RESTORE	RAPPORT	EPISTENT	ERASER	Galassi	Harrington	Chen	TARGET	TACTICS-TIMI	ISAR II	ESPRIT	ADMIRAL	PRICE
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 (% patients lost)	+	+	+	+	?	+	?	+	?	?	?	+	+	+	±	–	–
Blinding of patients	+	+	+	+	+	+	+	+	+	+	+	+	–	?	+	+	+
Blinding of persons who implement interventions	+	+	+	+	+	+	+	+	+	+	+	+	–	?	+	+	+
Registration of co-interventions that affect the outcome for each group	–	–	–	–	–	–	–	–	–	–	–	–	?	–	+	–	–
Blinding of persons assessing treatment effects	+	±	±	+	±	+	+	?	?	?	?	?	–	?	?	?	?
Checking to what extent blinding was successful	?	?	?	?	?	?	?	?	?	?	?	–	NA	–	–	–	–
Data description and analysis																	
Measures of central tendency and their CIs (e.g. SE or SD)	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	±
Statistical measures	+	+	+	+	+	+	+	+	+	+	±	+	+	+	+	+	+
Method of dealing with missing values	?	?	?	?	?	?	?	?	?	?	?	?	±	–	?	–	?
Intention-to-treat analysis	+	+	+	+	+	+	+	+	?	?	?	+	?	+	+	+	+
Distributions of baseline characteristics	+	+	+	+	+	+	+	+	+	+	+	+	?	±	+	±	±
Method of accounting for any imbalances in prognostic variables	+	?	+	+	?	?	?	?	–	?	–	+	+	–	?	+	–

+, Item properly addressed; –, item not properly addressed or not stated; ?, unclear; ±, item partially addressed

* *For full reference details refer to* Table 24

end-point composition, timing of end-point assessment and study validity.

Results of trials

The results of the trials are presented below by drug. In the plots of RR, the vertical line (at 1) indicates the 'no-effect' line. PRICE, TACTICS-TIMI and TARGET have not been included in the plots of RR as they are 'head-to-head' comparisons of two GP IIb/IIIa antagonists that are included for information only.

Abciximab

The use of abciximab alongside PCI was assessed in 11 trials (CAPTURE, Chen, EPIC, EPILOG, EPISTENT, ERASER, Galassi, RAPPORT, ADMIRAL, ISAR-II and PRICE; TARGET is reported in the tirofiban section). The results of these trials are presented in *Tables 30–40*.

Table 30 shows the results of the CAPTURE trial. The main limitation of this study was that it did not pre-stratify on variables that are of potential importance prognostically. The largest effect shown in the trial was in MI rates at 30 days and 6 months. By 6 months follow-up, there was little difference in the composite outcomes in the study.

The results of the Chen study are shown in *Table 31*. The main limitations of the study (*Table 29*) were lack of stratification, absence of details about randomisation and lack of blinding; there was limited detail on a number of methodological aspects of the study. The results of the study should be interpreted with

TABLE 30 *Results from the CAPTURE study (1997[68])*

Treatment arm	Time-point	MI		Death		PTCA		CABG		Composite	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%
Abciximab (*n* = 630)	30 days	26	4.1	6	1.0	–	–	–	–	71	11.3
	6 months	41	6.6	17	2.8	131	21	33	5.2	193	30.6
Placebo (*n* = 635)	30 days	52	8.2	8	1.3	–	–	–	–	101	15.9
	6 months	59	9.3	14	2.2	127	20	44	6.9	193	30.4

TABLE 31 *Results from the Chen* et al. *study (2000[78])*

Treatment arm	Time-point	MI		Death		Urgent PTCA		Urgent CABG		Composite	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%
Abciximab (*n* = 22)	30 days	0	0	0	0	0	0	0	0	2	9
Placebo (*n* = 20)	30 days	3	15	0	0	0	0	1	5	3	15

TABLE 32 *Results from the EPIC[69–71*] study*

Treatment arm	Time-point	MI		Death		PTCA		CABG		Composite	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%
Abciximab + infusion	30 days	37	5.2	12	1.7	–	–	–	–	59	8.5
(*n* = 695)	6 months	48	6.9	22	3.1	–	–	–	–	188	27.0
	1 year	–	–	30	4.2	–	–	–	–	216	30.8
	2 years	–	–	37	5.2	–	–	–	–	253	36.3
	3 years	–	–	47	6.8	–	–	–	–	283	41.1
	7 years	–	–	–	17.3	–	–	–	–	–	–
Abciximab + placebo	30 days	43	6.2	9	1.3	–	–	–	–	79	11.2
(*n* = 708)	6 months	57	8.0	18	2.6	102	14	66	9	231	32.6
	1 year	–	–	29	4.2	–	–	–	–	251	35.4
	2 years	–	–	40	5.6	–	–	–	–	290	41.0
	3 years	–	–	54	7.6	–	–	–	–	321	45.3
	7 years	–	–	–	–	–	–	–	–	–	–
Placebo + infusion	30 days	60	8.6	12	1.7	–	–	–	–	89	12.8
(*n* = 696)	6 months	73	10.5	24	3.4	145	20	76	10	244	35.1
	1 year	–	–	31	4.5	–	–	–	–	266	38.6
	2 years	–	–	46	6.6	–	–	–	–	290	41.7
	3 years	–	–	59	–	–	–	–	–	319	45.8
	7 years	–	–	–	20.1	–	–	–	–	–	–

* *1994[69];Topol* et al., *1994[70];Topol* et al., *1997[71]*

caution given its small numbers, but the difference in MI rates is the most notable.

Table 32 shows the results of the EPIC trial, which showed a high level of quality on most dimensions (*Table 29*). This study provided the longest follow-up of any available, although over much of that period only death rates and composite outcomes were reported. Although the differences in death rate between the abciximab groups and placebo groups were modest, there are larger effects in terms of the composite end-point, particularly between the abciximab plus infusion group and the placebo plus infusion group.

TABLE 33 *Results from the EPILOG[72,73*] study*

Treatment arm	Time-point	MI		Death		Urgent PTCA		Urgent CABG		Composite	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%
Standard dose abciximab (*n* = 918)	30 days	35	3.8	4	0.4	14	1.5	8	0.8	49	5.4
	6 months	48	5.3	13	1.4	–	–	–	–	76	8.3
	4.5 years	–	–	–	8.0	–	–	–	–	–	–
Low-dose abciximab (*n* = 935)	30 days	34	3.7	3	0.3	11	1.1	4	0.4	48	5.2
	6 months	47	5.0	10	1.1	–	–	–	–	78	8.4
	4.5 years	–	–	–	–	–	–	–	–	–	–
Placebo (*n* = 939)	30 days	81	8.7	7	0.8	35	3.7	16	1.7	109	11.7
	6 months	93	9.9	16	1.7	–	–	–	–	138	14.7
	4.5 years	–	–	–	9.6	–	–	–	–	–	–

[*] *Lincoff* et al., *1999*[72]*; 1997*[73]

TABLE 34 *Results from the EPISTENT study (Topol* et al., *1998*[75]*)*

Treatment arm	Time-point	MI		Death		PTCA		CABG		Composite	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%
Abciximab + stent (*n* = 794)	30 days	–	4.5	–	0.3	–	0.6	–	0.8	42	5.3
	6 months	–	5.2	–	0.5	–	1	–	0.8	–	6.4
	1 year	47	5.9	8	1.0	–	–	–	–	160	20.1
	3 years	–	–	–	3.3	–	–	–	–	–	–
Abciximab + balloon (*n* = 796)	30 days	–	5.6	–	0.6	–	1.2	–	1.1	55	6.9
	6 months	–	6.6	–	1.2	–	1.5	–	1.4	–	12.1
	1 year	–	–	–	–	–	–	–	–	–	–
	3 years	–	–	–	–	–	–	–	–	–	–
Placebo (*n* = 809)	30 days	–	5.3	–	0.8	–	1.3	–	0.6	87	10.8
	6 months	–	10.3	–	1.8	–	1.5	–	0.6	–	9.2
	1 year	91	11.3	19	2.4	–	–	–	–	194	24.0
	3 years	–	–	–	4.6	–	–	–	–	–	–

The results of the EPILOG trial are shown in *Table 33*. With the exception of lack of stratification and registration of co-interventions that may bear on outcomes, it was of reasonable quality (*Table 29*). In terms of outcomes, both doses of abciximab show improved composite outcomes compared with placebo. This is driven principally by lower MI and urgent PTCA rates in the abciximab groups.

Table 34 shows the results of the EPISTENT trial. The methodological limitations of this study were similar to those in other trials (*Table 29*), but details of the randomisation procedure were also not stated. The composite outcome is again more favourable in the abciximab arms, with differences in MI rates being the main factor behind this.

The results of the ERASER trial are shown in *Table 35*. Limitations in the quality of this study were similar to others (*Table 29*), and the randomisation procedure was again not detailed. Differences in the composite outcome measure again favoured the abciximab arms, with MI rates driving these differences.

The results of the Galassi study are shown in *Table 36*. This small trial (*n* = 106) had similar methodological limitations to other studies: lack of stratification, detail of randomisation procedure and registration of co-interventions. The results were also consistent with other abciximab trials, with favourable composite outcomes in the experimental arm, largely explained by a lower MI rate.

Table 37 summarises the results of the RAPPORT trial, which shows similar quality limitations to the other trials, including a failure to describe the randomisation procedure. Limited details of the

TABLE 35 *Results from the ERASER study (Ellis* et al., *1999[76])*

Treatment arm	Time-point	MI		Death		PTCA		CABG		Composite	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%
Abciximab 12-hour infusion (*n* = 79)	30 days	4	5.1	0	0	0	0	0	0	4	5.1
	6 months	6	7.6	0	0	1	1.3	0	0	16	20.3
Abciximab 24-hour infusion (*n* = 75)	30 days	7	9.3	0	0	0	0	0	0	7	9.3
	6 months	7	9.3	0	0	10	13.3	0	0	16	21.3
Placebo (*n* = 71)	30 days	8	11.3	0	0	1	1.4	0	0	8	11.3
	6 months	9	12.7	2	2.8	11	15.5	0	0	16	22.5

TABLE 36 *Results from the Galassi* et al. *study (1999[77])*

Treatment arm	Time-point	MI		Death		Urgent PTCA		Urgent CABG		Composite	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%
Abciximab (*n* = 54)	30 days	2	3.7	0	0	0	0	0	0	2	3.7
Heparin (*n* = 52)	30 days	5	9.5	1	1.9	0	0	0	0	8	15.3

TABLE 37 *Results from the RAPPORT study (Brener* et al., *1998[74])*

Treatment arm	Time-point	MI		Death		Composite	
		n	%	*n*	%	*n*	%
Abciximab (*n* = 241)	30 days	Death/repeat		6	2.5	32	13.3
	6 months	MI reported		10	4.1	68	28.2
Placebo (*n* = 242)	30 days	Death/repeat		5	2.1	39	16.1
	6 months	MI reported		11	4.5	68	28.1

TABLE 38 *Results from ADMIRAL study (Montalescot* et al., *2001[60])*

Treatment arm	Time-point	MI		Death		Any revascularisation		Composite	
		n	%	*n*	%	*n*	%	*n*	%
Abciximab (*n* = 149)	30 days	–	–	5	3.4	11	7.4	9	6.0
	6 months	–	–	5	3.4	26	17.4	11	7.4
Placebo (*n* = 151)	30 days	–	–	10	6.6	19	12.6	22	14.6
	6 months	–	–	11	7.3	36	23.8	24	15.9

individual results of the trial were presented, but the composite outcomes were similar in the two groups.

The results of the ADMIRAL study are shown in *Table 38*. In terms of methodology, similar limitations were evident as in the other trials reviewed here. Composite outcomes were more favourable with abciximab, both at 30 days and 6 months. From the separate outcome results presented, these differences are mainly driven by a lower repeat revascularisation rate in the abciximab group.

The results of the PRICE study are shown in *Table 39*. This was a head-to-head study comparing

TABLE 39 *Results from the PRICE study (Lam* et al., *2001[59])*

Treatment arm	Time-point	MI		Death		Urgent PCI		Urgent CABG		Composite	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%
Abciximab (*n* = 163)	In-hospital	6	3.7	1	0.6	0	0	1	0.6	8	4.9
	30 days	7	4.3	1	0.6	–	–	–	–	9	5.6
Eptifibatide (*n* = 157)	In-hospital	7	4.4	0	0	1	0.6	0	–	8	5.1
	30 days	8	5.1	1	0.6	–	–	–	–	10	6.3

TABLE 40 *Results from the ISAR-II study (Neumann* et al., *2000[79])*

Treatment arm	Time-point	MI		Death		PTCA		CABG		Composite	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%
Abciximab (*n* = 201)	30 days	1	0.5	4	2.0	5	2.5	1	0.5	10	5.0
Heparin (*n* = 200)	30 days	3	1.5	9	4.5	9	4.5	1	0.5	21	10.5

abciximab and eptifibatide, which is presented just for information. This study showed similar results in terms of the composite end-point. The results of the ISAR-II study are shown in *Table 40*. Showing similar weaknesses as other studies (*Table 29*), the composite event rate was lower in the abciximab arm than the heparin arm, but this is based on a small number of events.

Death from any cause

The effect of abciximab on death in the various trials can be seen in the forest plot in *Figure 28*. None of the trials show a significant effect on mortality at either 30 days or 6 months.

Myocardial infarction

The effect of abciximab on non-fatal MI can be seen in *Figure 29*. These RRs should be interpreted alongside the baseline risks shown in *Tables 30–40*. Most trials show a statistically significant lower rate of MI, and there is a consistency in the RR of about a 50% reduction.

Recurrent ischaemia

The majority of trials do not report on recurrent ischaemia specifically, but instead report revascularisation procedures (CABG or PTCA) that result from the condition. Two trials restricted to AMI patients (RAPPORT and ADMIRAL) report on re-infarction.

In both AMI studies, re-infarction was less common in the abciximab group. In RAPPORT, at 7 days re-infarction was 1.7% and 3.3%, at 30 days 3.3% and 4.1% and at 6 months 6.6% and 7.4%, in the abciximab and placebo groups respectively.

In the ADMIRAL study, rates were 1.3% and 2.6% at 30 days and 2.0% and 4.0% at 6 months in the abciximab and placebo groups respectively.

Revascularisations

The effect of abciximab on all revascularisation procedures can be seen in *Figure 30*. In addition, ADMIRAL reported in detail on the type of revascularisation procedure performed. The number of patients having urgent target-vessel revascularisations (TVRs), elective TVR, urgent/elective TVR or elective revascularisation at 30 days and 6 months were reported in that trial. The biggest difference between the groups in ADMIRAL was found in the rates of urgent or elective TVR, with 7/149 (4.7%) and 17/151 (11.3%) patients having procedures at 30 days, and 17/149 (11.4%) and 36/151 (24%) patients having procedures at 6 months in the abciximab and placebo groups respectively.

Figure 30 shows that the trials overall showed a reduction in revascularisation at 30 days, although this was statistically significant only in the EPIC.

Adverse events

The main concerns for adverse effects in the trials of abciximab were related to an extension of the pharmacologic effect: bleeding, thrombocytopenia, strokes and procedures resulting from these (e.g. blood transfusions).

Bleeding

The effect of abciximab on episodes of minor and major bleeding can be seen in *Figures 31* and *32*. All trials except the smallest (Chen) show an

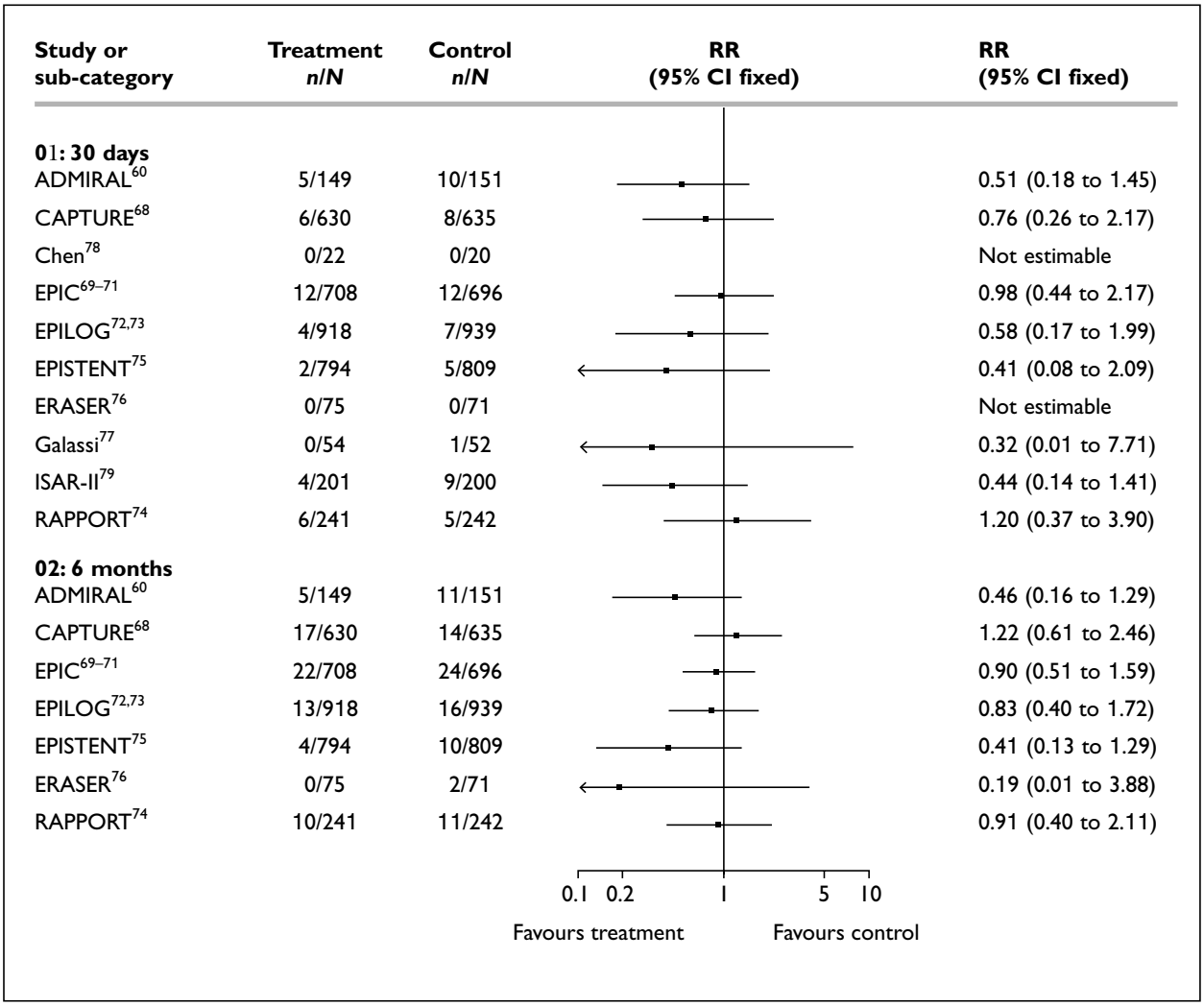

FIGURE 28 *Effect of abciximab on death for patients receiving glycoproteins alongside PCI*

increase in both major and minor bleeds. The biggest increase in minor and major bleeding risk was seen in the ADMIRAL trial: RR = 3.65 (95% CI, 1.39 to 9.57 for minor bleeding and RR = 3.04 (95% CI, 0.12 to 74.04) for major bleeding episodes.

Thrombocytopenia

Only the ADMIRAL trial reported on the rates of thrombocytopenia specifically; these events were recorded at 30 days follow-up. Thrombocytopenia (< 100,000 platelets/mm^3) occurred in 4.7% of abciximab and 1.3% of placebo patients. ADMIRAL also reported the occurrence of severe thrombocytopenia, which was defined as a platelet count of < 50,000 platelets/mm^3. The abciximab and placebo group both reported 1.3% of patients suffering from such an event.

Transfusions

The effect of abciximab on transfusion (RBC and platelet) can be seen in *Figures 33* and *34*. The minority of trials reported these outcomes (Chen, EPIC, ISAR-II, CAPTURE, EPISTENT). There was a significant increase in RBC transfusions in EPIC: RR = 2.19 (95% CI, 1.59 to 3.01. The Chen study showed that abciximab patients were almost twice as likely to have a RBC transfusion than placebo patients; however, this trial only included 42 patients in total. Patients receiving abciximab in the ISAR-II trial had a lower risk of RBC transfusion than placebo patients: RR = 0.77; 95% CI, 0.29 to 2.04 (this was not statistically significant).

No platelet transfusions occurred in the Chen study. Patients receiving abciximab in the EPIC study were significantly more likely to require a platelet transfusion than placebo patients: RR = 2.13; 95% CI, 1.23 to 3.69.

CAPTURE and EPISTENT reported on total transfusions and both found a significant increase in the risk of transfusions in the abciximab group:

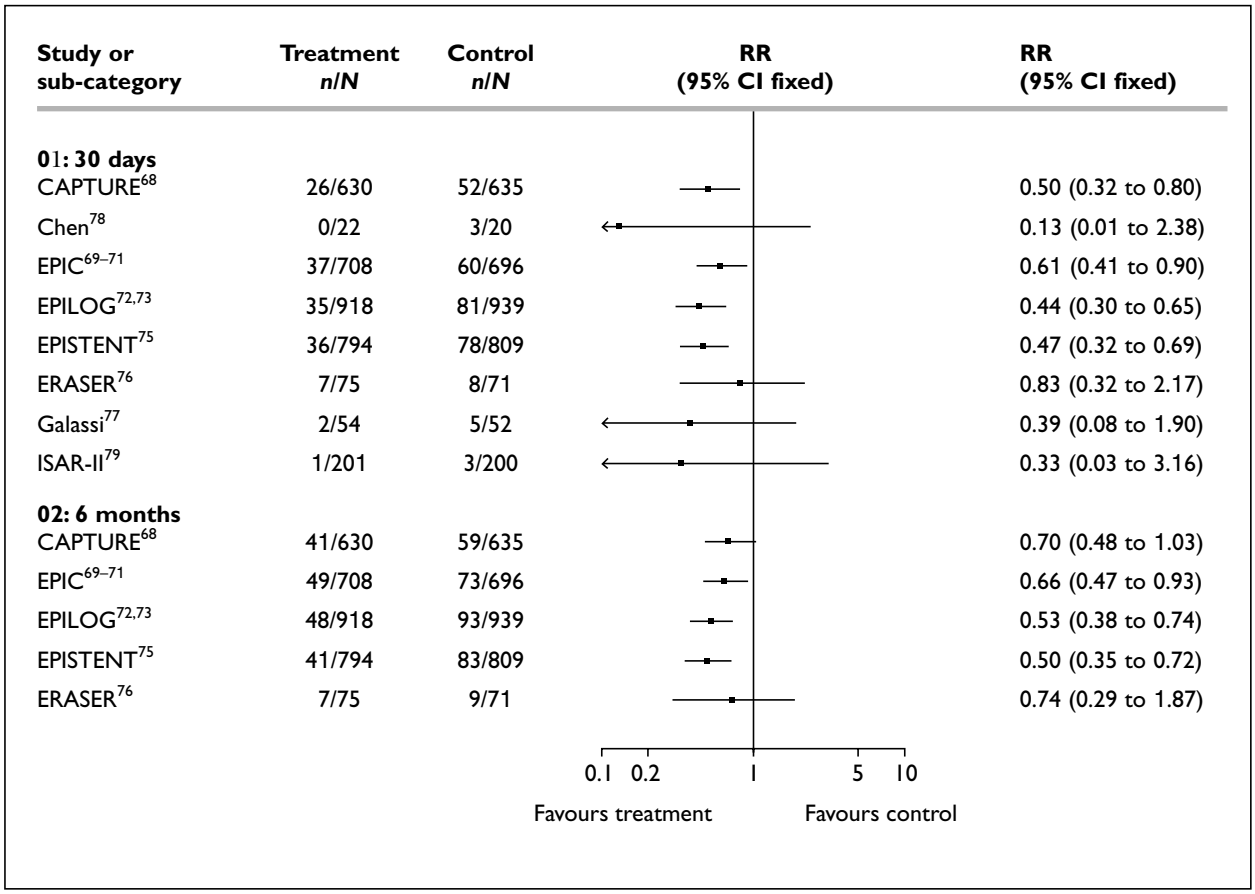

FIGURE 29 *Effect of abciximab on MI for patients receiving glycoproteins alongside PCI*

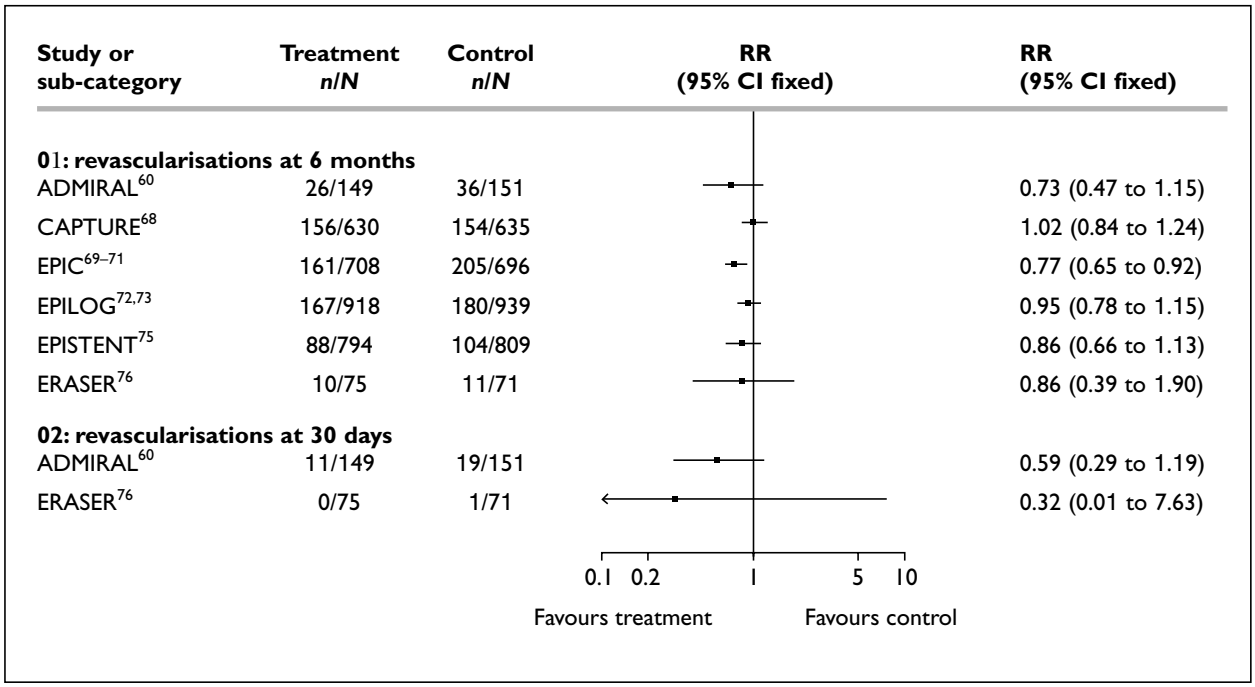

FIGURE 30 *Effect of abciximab on revascularisations for patients receiving glycoproteins alongside PCI*

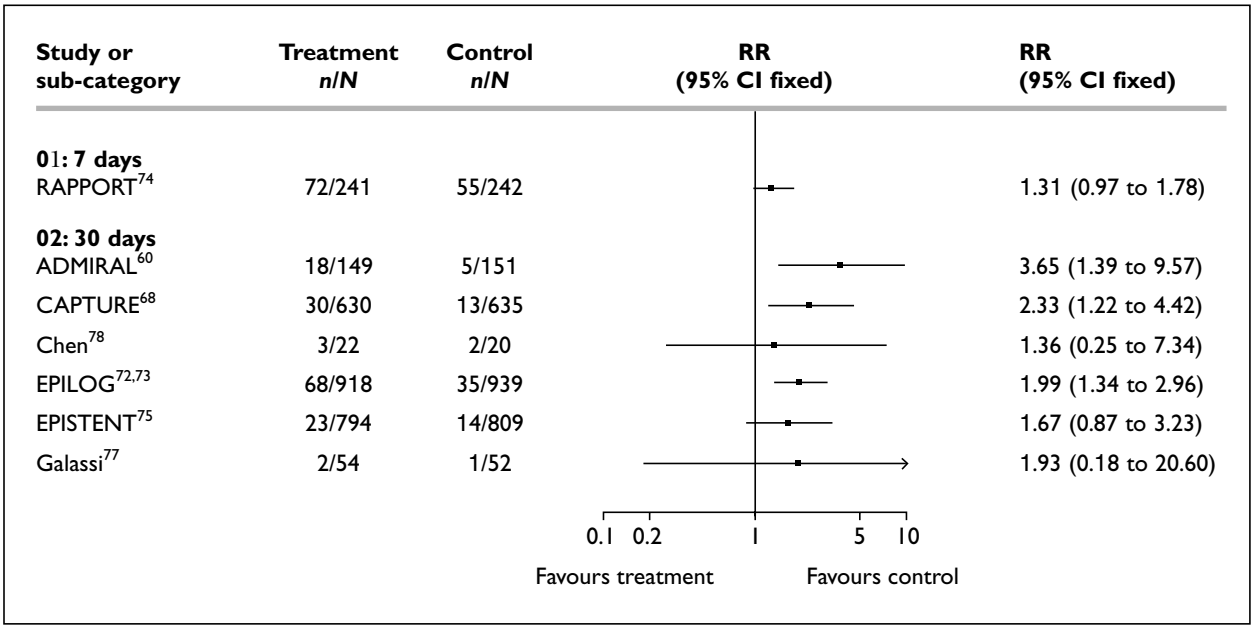

FIGURE 31 *Effect of abciximab on the incidence of minor bleeding for patients receiving glycoproteins alongside PCI*

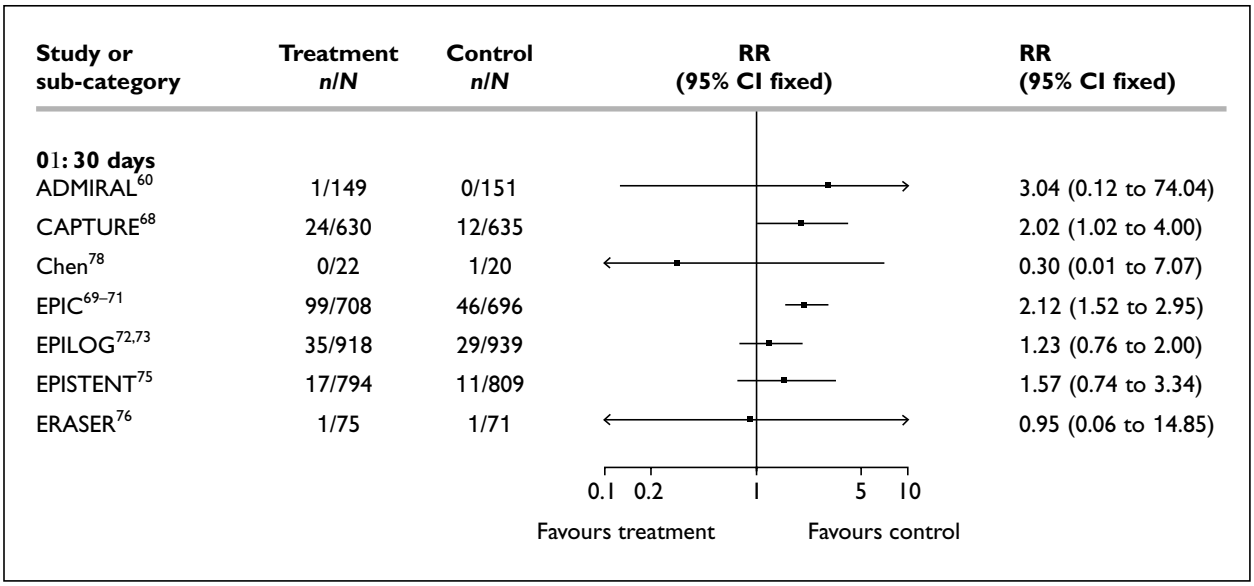

FIGURE 32 *Effect of abciximab on the incidence of major bleeding for patients receiving glycoproteins alongside PCI*

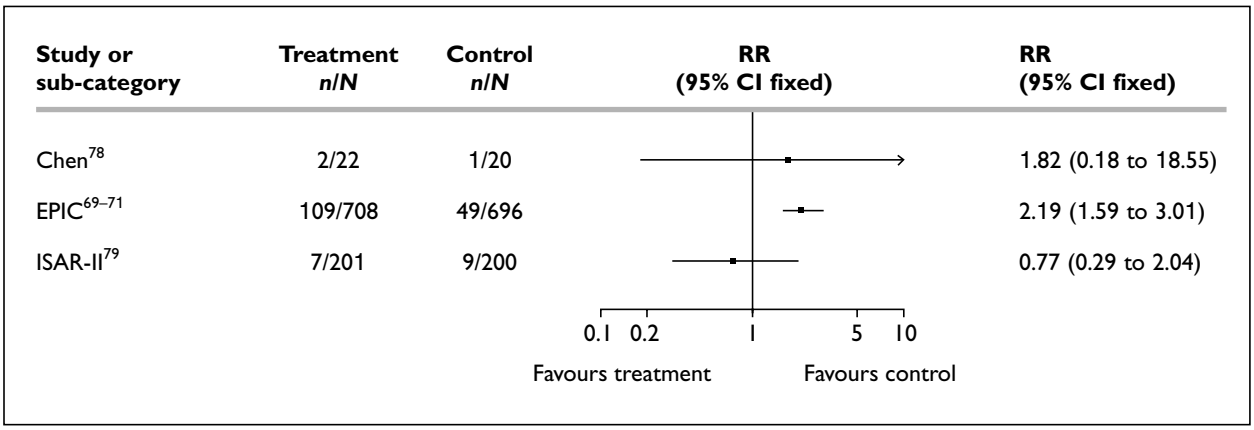

FIGURE 33 *Effect of abciximab on RBC transfusions at 30 days for patients receiving glycoproteins alongside PCI*

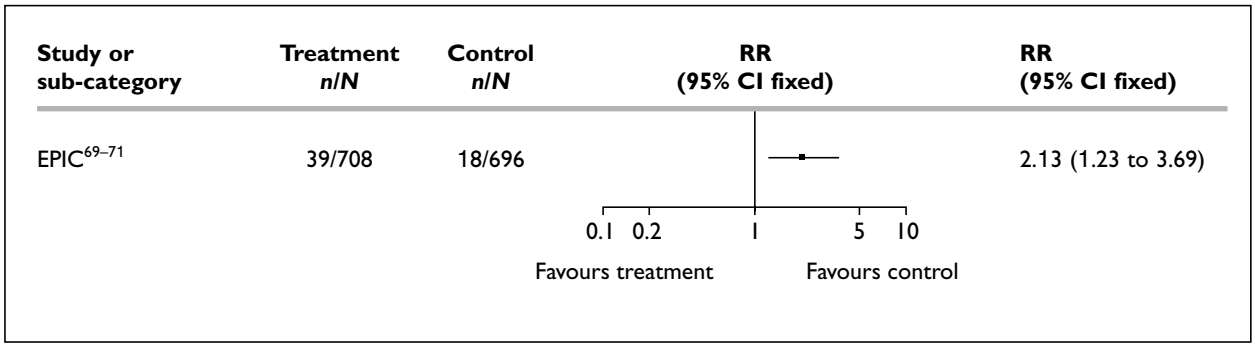

FIGURE 34 *Effect of abciximab on platelet transfusions at 30 days for patients receiving glycoproteins alongside PCI*

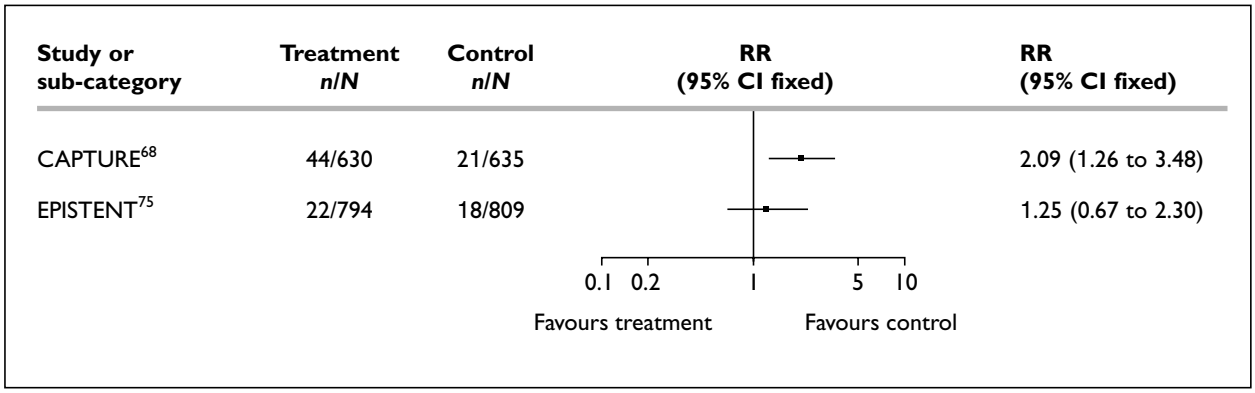

FIGURE 35 *Effect of abciximab on total transfusions at 30 days for patients receiving glycoproteins alongside PCI*

RR = 2.11; 95% CI, 1.27 to 3.51 in the CAPTURE trial; RR = 1.25; 95% CI, 0.67 to 2.30 in the EPISTENT trial. Other studies also reported the number of transfusions in total that were carried out during the study period. This can be seen in *Figure 35*. These again show a greater rate in the treatment arms.

Stroke

Only CAPTURE collected data on all strokes. Only one stroke occurred during the trial and this was in the abciximab group. EPISTENT and EPILOG recorded the number of haemorrhagic and non-haemorrhagic strokes at 30 days. There was a trend towards more strokes in the abciximab group: non-haemorrhagic strokes occurred in 3/794 (0.4%) abciximab patients versus 1/809 (0.1%) control patients in EPISTENT; in the EPILOG study this was 1/918 (0.1%) versus 0/939 in those two groups respectively. Haemorrhagic strokes occurred in 0/794 abciximab patients versus 0/809 control patients in EPISTENT; in the EPILOG study this was 1/918 (0.1%) versus 0/939 in those two groups respectively. The overall incidence of stoke in all three trials was very low.

Composite end-point

The effect of abciximab on the composite outcome is shown in *Figure 36*. Rates were presented for various time-points. All (barring Galassi) favoured abciximab. For the short-term follow-up (7 or 30 days), for all of these studies except Galassi, ERASER, Chen and RAPPORT these differences were statistically significant. However, over a longer-term period of follow-up, although the point estimates of the differences generally continue to favour abciximab, fewer are statistically significant. EPIC has the longest follow-up and continues to show statistically significant benefits in abciximab patients at 3 years follow-up. There should be a degree of caution in interpreting these results given that there is variability on how these composite end-points are defined (*Table 28*).

Eptifibatide

Three studies (ESPRIT, Harrington and IMPACT-II) looked at the use of eptifibatide alongside PCI. The results of these studies are shown in *Tables 41–43*.

The results of the ESPRIT study are shown in *Table 41*. The quality of this study showed some of the limitations exhibited in the abciximab trials, in particular the lack of pre-stratification (*Table 29*). In addition, ESPRIT suffers from the lack of a prognostically homogeneous study population. In terms of the results, there is a

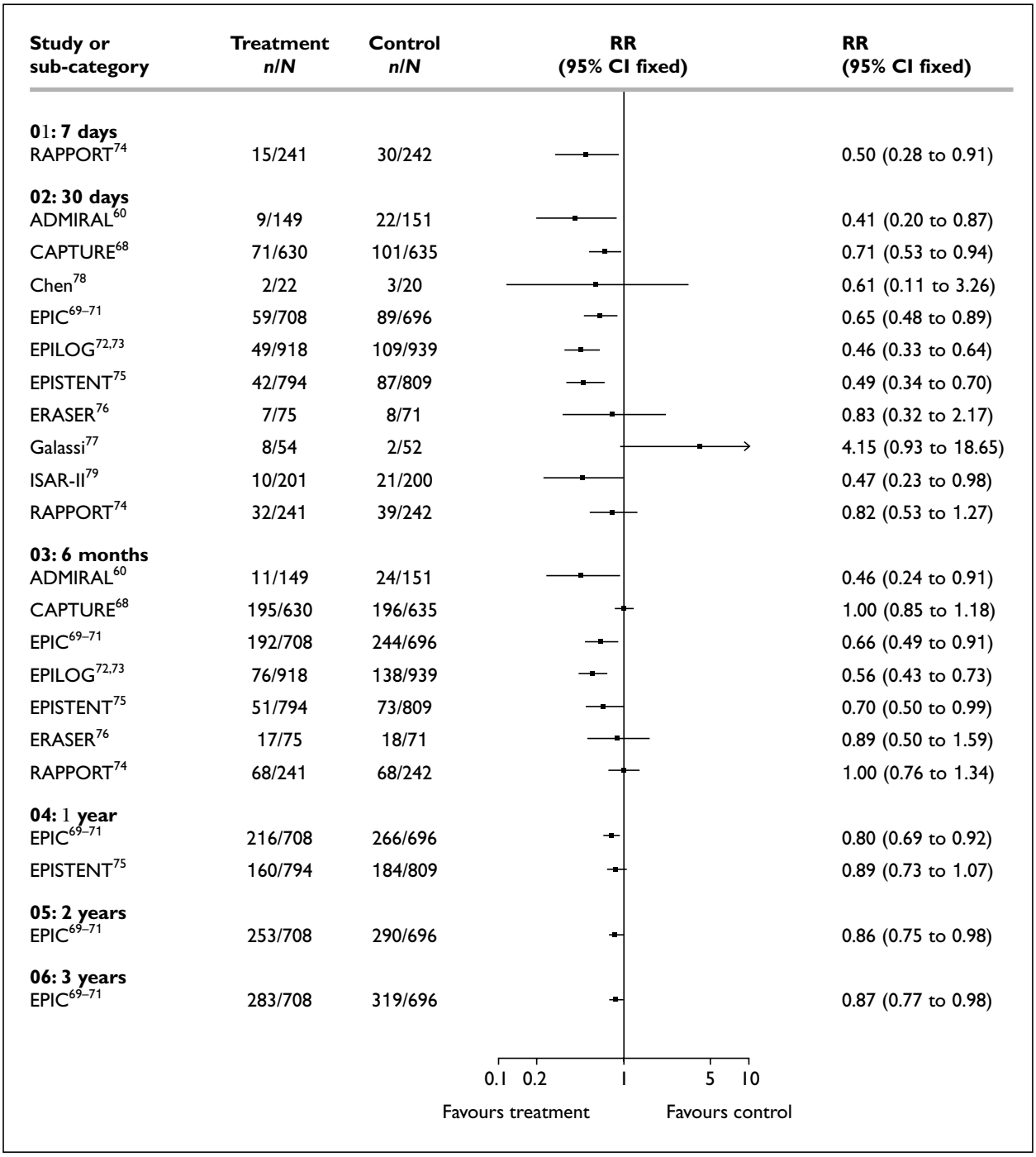

FIGURE 36 *Effect of abciximab on the composite outcome for patients receiving glycoproteins alongside PCI*

favourable effect of eptifibatide on the composite outcome at all time-points (48 hours to 12 months). This appears to have been driven by the MI rate.

The results of the Harrington study are shown in *Table 42*, which showed a number of methodological limitations including lack of details about randomisation (*Table 29*). This trial provided 30-day outcomes only, but its small size ($n = 63$) limits the usefulness of the results.

The results of IMPACT-II are shown in *Table 43*. This study has similar methodological weaknesses to other trials, including lack of details about the randomisation process. In terms of results, both doses of eptifibatide show improved composite outcomes at 30 days (the only point of follow-up). This appears to be driven mainly through a lower MI rate.

Death from any cause

The effect of eptifibatide on death can be seen in *Figure 37*. All trials showed a trend in favour of

TABLE 41 *Results from the ESPRIT study (O'Shea* et al., *2001[63])*

Treatment arm	Time-point	MI		Death		Composite	
		n	%	*n*	%	*n*	%
Eptifibatide (*n* = 1040)	48 hours	56	5.4	1	0.1	69	6.6
	30 days	64	6.2	4	0.4	71	6.8
	6 months	73	7.0	8	0.8	146	14.0
	12 months	74	7.2	14	1.4	178	17.1
Placebo (*n* = 1024)	48 hours	92	9.0	2	0.2	108	10.5
	30 days	99	9.7	6	0.6	107	10.4
	6 months	106	10.4	14	1.4	187	18.3
	12 months	109	10.7	20	2.0	222	21.7

TABLE 42 *Results from the Harrington* et al. *study (1995[80])*

Treatment arm	Time-point	MI		Death		PTCA		CABG		Composite	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%
Eptifibatide (*n* = 54)	30 days	1	2	0	0	1	1.8	0	0	–	–
Placebo (*n* = 19)	30 days	2	11	0	0	2	10.5	1	5.3	–	–

TABLE 43 *Results from IMPACT-II study (1997[65])*

Treatment arm	Time-point	MI		Death		Urgent PTCA		Urgent CABG		Composite	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%
High-dose eptifibatide (*n* = 1333)	30 days	61	4.6	11	0.8	38	2.8	27	2.0	132	9.9
Low-dose eptifibatide (*n* = 1349)	30 days	63	4.7	7	0.5	35	2.5	22	1.6	124	9.2
Placebo (*n* =1328)	30 days	74	5.6	15	1.1	37	2.9	37	2.8	151	11.4

eptifibatide. However, only ESPRIT showed a statistically significant effect at 30 days, and this was no longer statistically significant at 6 months.

Myocardial infarction

The effect of eptifibatide on non-fatal MI can be seen in *Figure 38*. There is a consistent effect across all three trials. The short-term analysis (until 30 days) shows statistically significant lower rates in the larger trials (ESPRIT and IMPACT-II). At 6 months, ESPRIT is the only study to report, and the RR is fairly similar to the short-term results and remains statistically significant.

Recurrent ischaemia

Only the Harrington study reported on the effect of eptifibatide on recurrent ischaemia. Three patients (6%) in the eptifibatide groups suffered from recurrent ischaemia compared with two (11%) patients in the placebo group.

Revascularisation

The effect of eptifibatide on repeat revascularisations was reported in ESPRIT alone at 6 months. The effect can be seen in *Figures 39* and *40*. There was a reduction in PTCA of about 15% (*Figure 39*), but CABG rates were very similar (*Figure 40*). These differences were not significant.

Adverse events

As for abciximab, the main concerns for adverse effects in the trials of eptifibatide, for use alongside PCI, were related to an extension of the pharmacologic effect: bleeding, strokes and procedures resulting from these (e.g. blood transfusions).

Bleeding

The effect of eptifibatide on minor and major bleeding episodes can be seen in *Figures 41* and *42*. IMPACT-II did not report on the incidence of

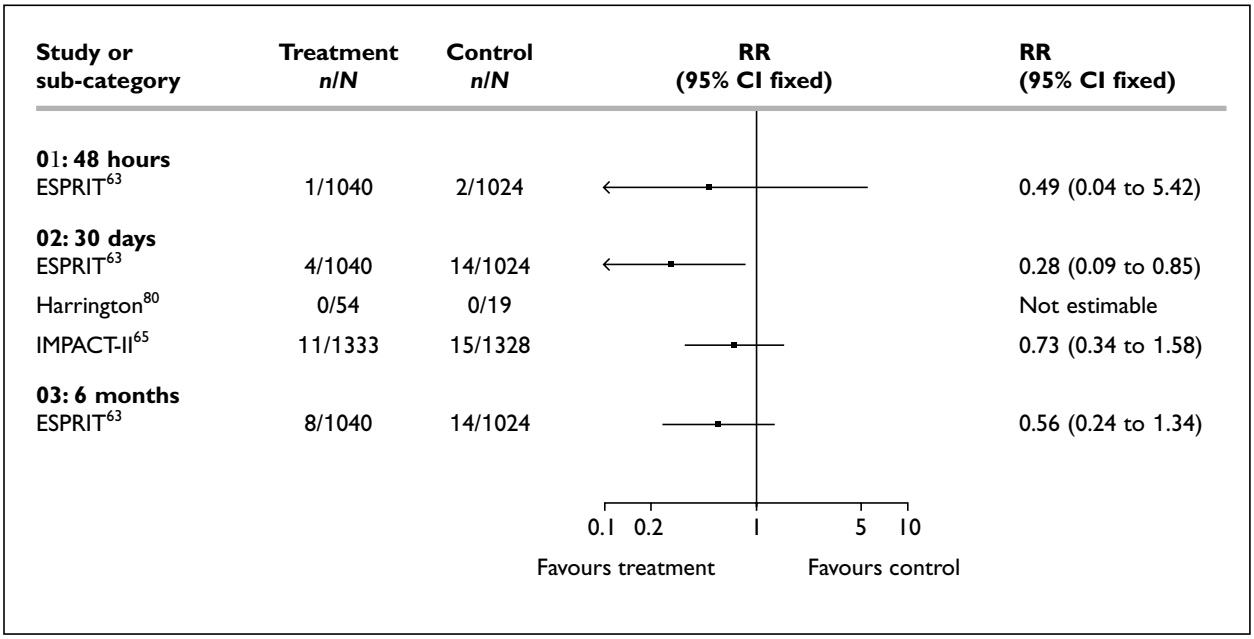

FIGURE 37 *Effect of eptifibatide on death for patients receiving glycoproteins alongside PCI*

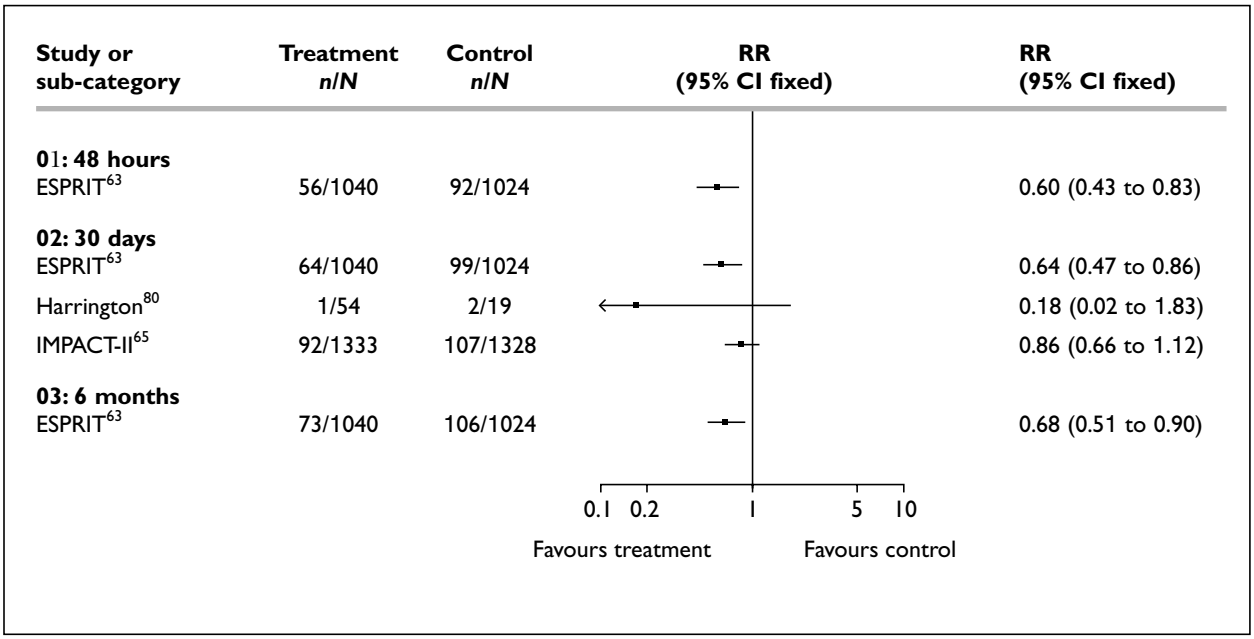

FIGURE 38 *Effect of eptifibatide on MI for patients receiving glycoproteins alongside PCI*

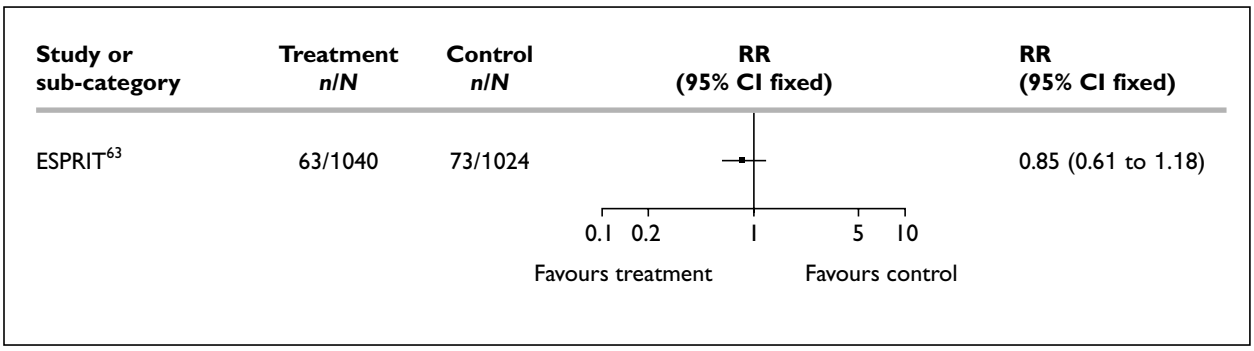

FIGURE 39 *Effect of eptifibatide on PTCA at 6 months for patients receiving glycoproteins alongside PCI*

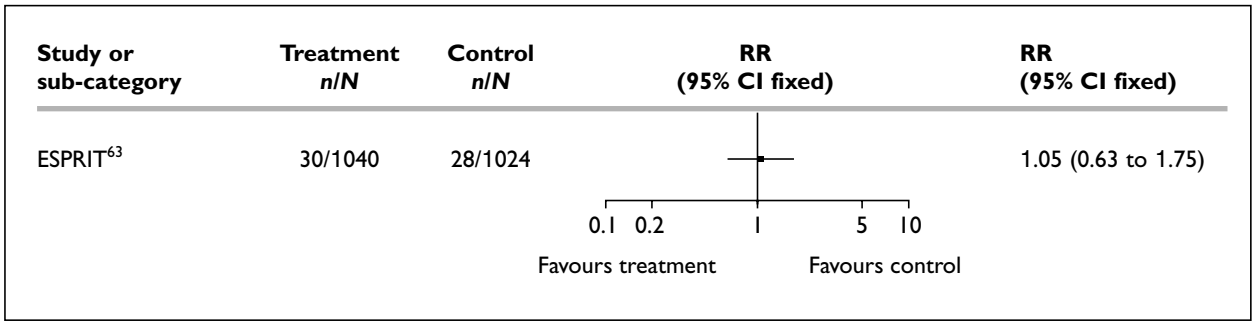

FIGURE 40 *Effect of eptifibatide on CABG at 6 months for patients receiving glycoproteins alongside PCI*

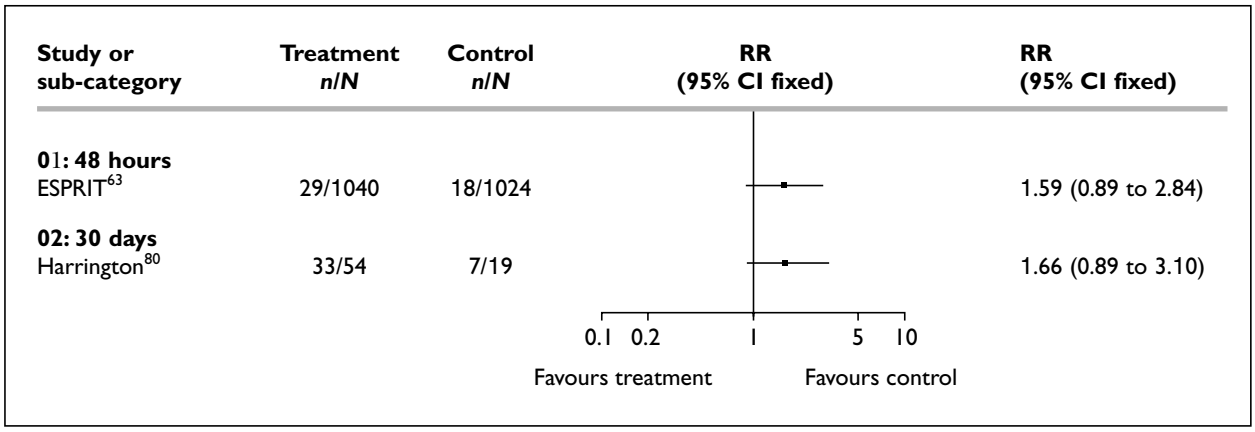

FIGURE 41 *Effect of eptifibatide on the incidence of minor bleeding for patients receiving glycoproteins alongside PCI*

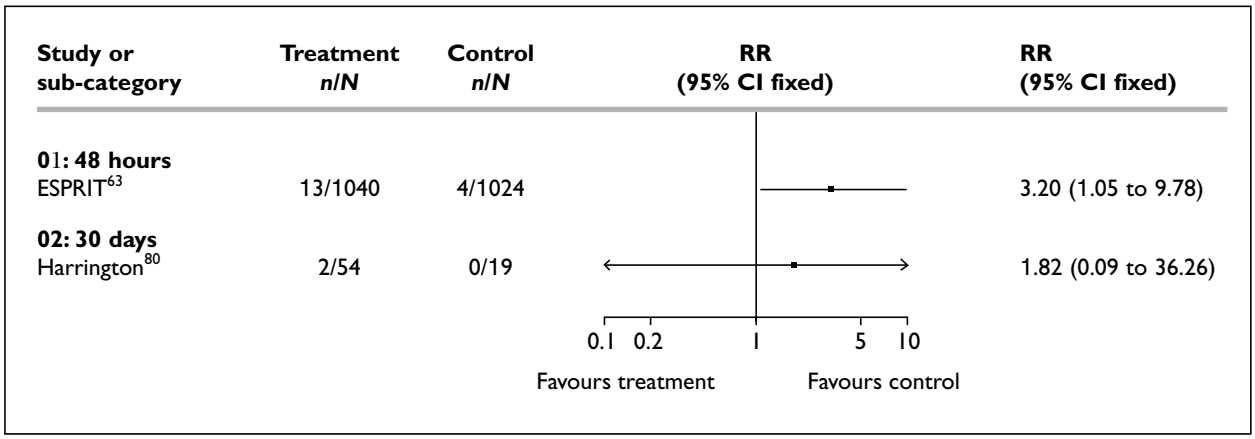

FIGURE 42 *Effect of eptifibatide on the incidence of major bleeding for patients receiving glycoproteins alongside PCI*

bleeding. As with other GP IIb/IIIa antagonists, treatment is associated with increased bleeding risk. The biggest increase in risk is seen in the rate of major bleeding episodes in ESPIRIT: RR = 3.20; 95% CI, 1.05 to 9.78.

Transfusions

The effect of eptifibatide on transfusions can be seen in *Figures 43* and *44*. The Harrington study did not report on transfusions and ESPRIT only reported on RBC transfusions. In line with increased bleeding, an increased requirement for transfusion is reported in the eptifibatide groups, but this is not statistically significant.

Stroke

The two studies that reported data on strokes (Harrington and IMPACT-II) defined strokes as either haemorrhagic or non-haemorrhagic. Harrington reported no strokes in patients randomised. In IMPACT-II, the number of strokes occurring was low: 6/1349 (0.4%) and 7/1328 (0.5%) non-haemorrhagic strokes in the abciximab and placebo groups, respectively,

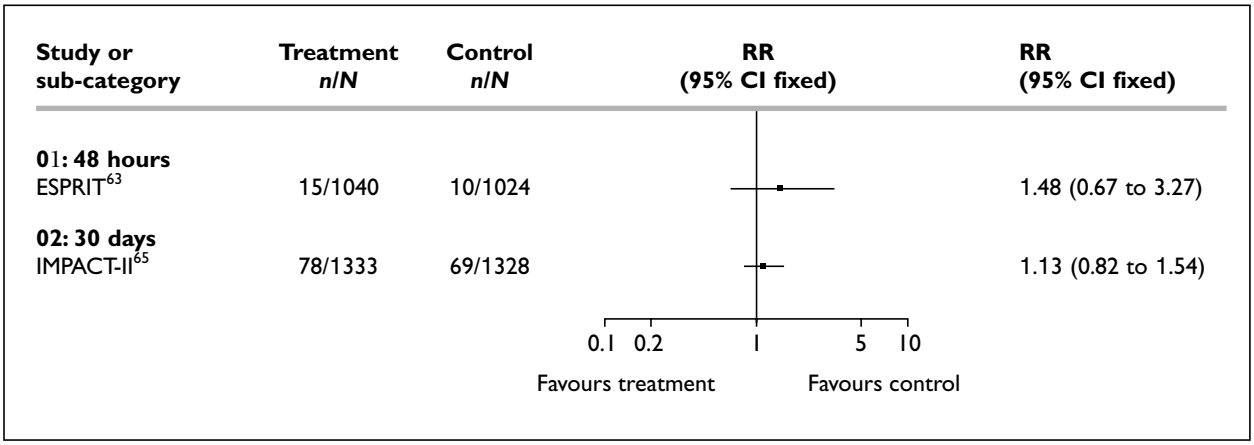

FIGURE 43 *Effect of eptifibatide on RBC transfusions for patients receiving glycoproteins alongside PCI*

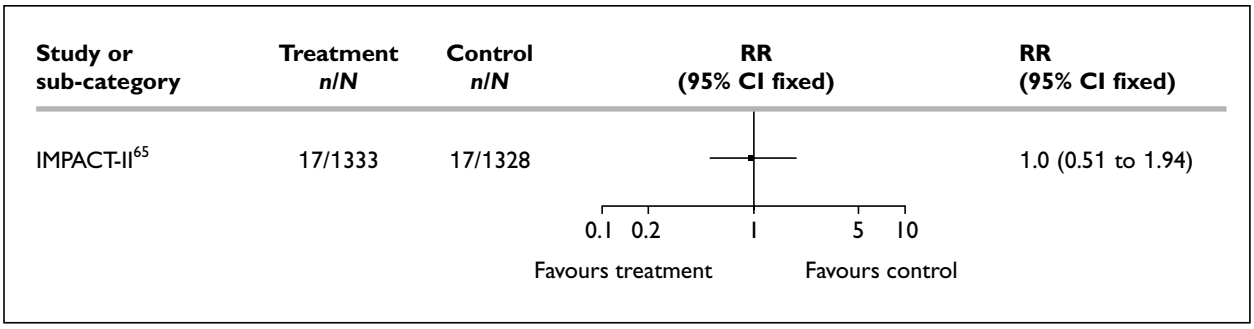

FIGURE 44 *Effect of eptifibatide on platelet transfusions at 30 days for patients receiving glycoproteins alongside PCI*

and 1/1349 (0.007%) and 1/1328 (0.007%) haemorrhagic strokes in the abciximab and placebo groups, respectively.

Composite end-point

The effect of eptifibatide on the composite outcome is shown in *Figure 45*. At 30 days, ESPRIT and IMPACT-II show favourable results for eptifibatide, which are statistically significant for ESPRIT. One-year data were also presented for ESPIRIT, which showed similar results to the 6-month data, in which patients receiving eptifibatide were less likely to suffer an event: RR = 0.79; 95% CI, 0.66 to 0.94.

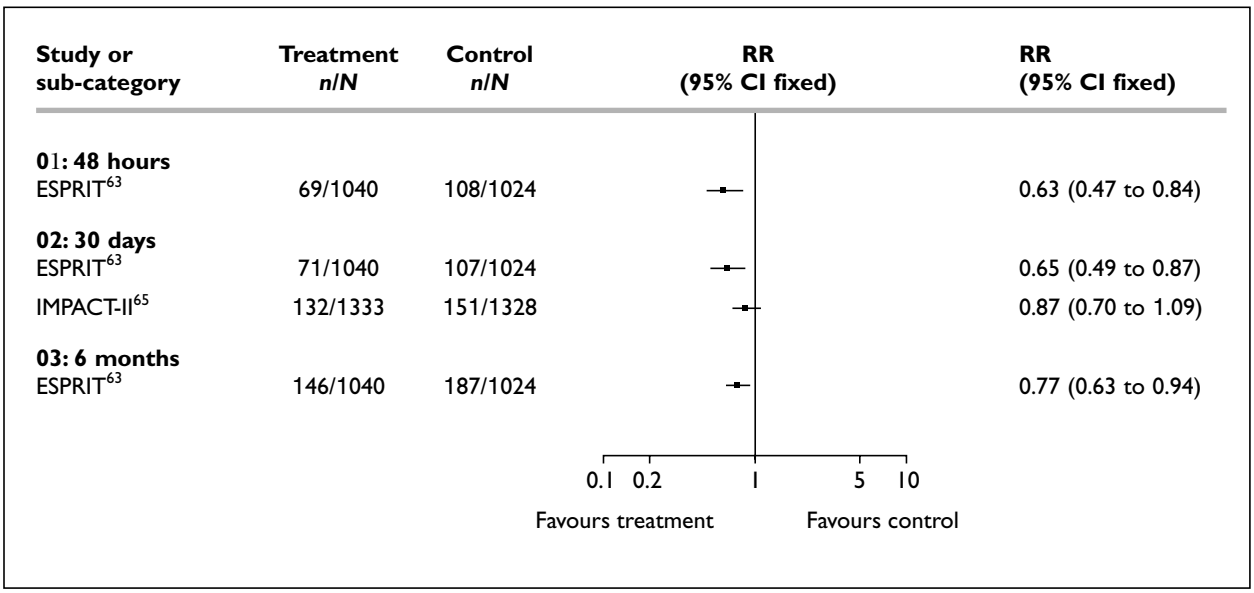

FIGURE 45 *Effect of eptifibatide on the composite outcome for patients receiving glycoproteins alongside PCI*

Tirofiban

The effectiveness of tirofiban for use alongside PCI was studied in three trials (RESTORE, TARGET and TACTICS-TIMI). In the latter trial, all patients received tirofiban and were randomised to receive either conservative or invasive management strategies; therefore results from TACTICS-TIMI are not included in the plots of RR provided below. The TARGET trial compared tirofiban with abciximab; hence, although the results are presented, this trial is also not included in the plots of RR. The results of all three trials are extracted and discussed in *Tables 44–46.*

The results of the RESTORE study are shown in *Table 44.* The study shows similar methodological limitations to the abciximab and eptifibatide trials, including a failure to disclose the randomisation process (*Table 29*). The outcomes of MI, repeat revascularisation and composite effects are favourable to tirofiban, but the effects are not large. There is a small excess death rate in the tirofiban arm at both 30 days and 6 months.

TABLE 44 *Results from the RESTORE study (Hanrath* et al., *1997[66]; Gibson 1998[67])*

Treatment arm	Time-point	MI		Death		PTCA		CABG		Composite	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%
Tirofiban (*n* = 1071)	7 days	22	2.1	13	1.2	29	2.7	13	1.2	67	6.3
	30 days	45	4.2	9	0.8	45	4.2	20	1.9	110	10.3
	6 months	67	6.3	19	1.8	168	15.7	59	5.5	258	24.1
Placebo (*n* = 1070)	7 days	54	5.0	18	1.7	47	4.3	17	1.5	133	12.4
	30 days	61	5.7	8	0.7	58	5.4	23	2.1	130	12.2
	6 months	81	7.6	15	1.4	183	17	73	6.8	290	27.1

TABLE 45 *Results from the TARGET study (Topol* et al., *2001[62])*

Treatment arm	Time-point	MI		Death		Composite	
		n	%	*n*	%	*n*	%
Tirofiban (*n* = 2398)	30 days	165	6.9	12	0.5	182	7.6
Abciximab (*n* = 2414)	30 days	130	5.4	10	0.4	145	6.0

TABLE 46 *Results from the TACTICS-TIMI study (Cannon* et al., *1998[61])*

Treatment arm	Comparators	Time-point	Death *n* (%)	MI *n* (%)	PTCA *n* (%)	CABG *n* (%)	Composite outcome *n* (%)
Total	Invasive	30 days	25 (2.2)	34 (3.1)	–	–	82 (7.4)
		6 months	37 (3.3)	53 (4.8)	472 (42)	243 (22)	177 (15.9)
	Conservative	30 days	18 (1.6)	64 (5.8)	–	–	116 (10.5)
		6 months	39 (3.5)	76 (6.9)	323 (29)	178 (16)	215 (19.4)
ST-segment elevation	Invasive	30 days	–	–	–	–	16.4
	Conservative	6 months	–	–	–	–	26.3
Troponin-positive	Invasive	30 days	–	–	–	–	40 (7.9)
		6 months	–	–	–	–	75 (14.8)
	Conservative	30 days	–	–	–	–	78 (16.2)
		6 months	–	–	–	–	116 (24.2)
Troponin-negative	Invasive	30 days	–	–	–	–	25 (6)
		6 months	–	–	–	–	69 (16.7)
	Conservative	30 days	–	–	–	–	24 (5.6)
		6 months	–	–	–	–	63 (14.8)

The results of TARGET are shown in *Table 45*. It shows a small improvement of outcomes in patients randomised to abciximab.

The results from TACTICS-TIMI are shown in *Table 46*. This shows mixed results from an invasive strategy, with a favourable overall composite effect at 30 days and 6 months, MI at 30 days and 6 months, death at 6 months and PTCA at 6 months. However, CABG rates at 6 months and at 30 days are lower in the conservative group, although the effect is small.

Death from any cause
The effect of tirofiban on deaths reported by the RESTORE trial can be seen in *Figure 46*. Death was more common in the treatment arm, although this difference was not statistically significant.

Myocardial infarction
The effect of tirofiban on the incidence of non-fatal MI in RESTORE can be seen in *Figure 47*. A non-significant reduction associated with tirofiban was reported.

Recurrent ischaemia
None of the three trials reported on the rates of recurrent ischaemia.

Revascularisation
The effect of tirofiban on rates of repeat revascularisation (repeat PTCA and CABG) in

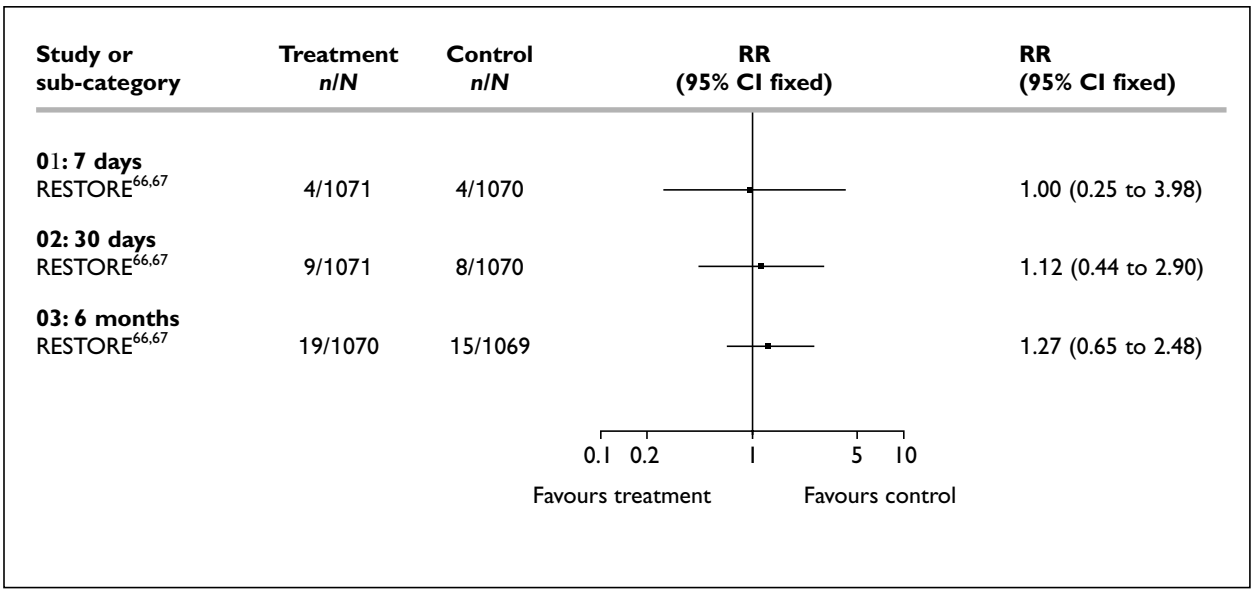

FIGURE 46 *Effect of tirofiban on death for patients receiving glycoproteins alongside PCI*

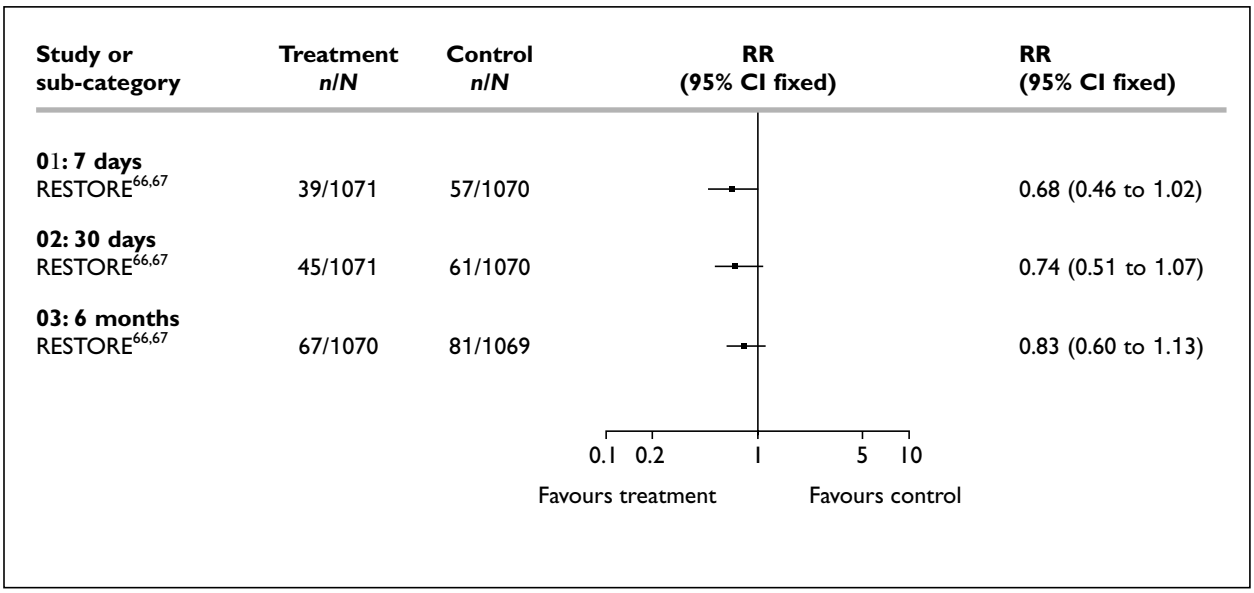

FIGURE 47 *Effect of tirofiban on MI for patients receiving glycoproteins alongside PCI*

RESTORE can be seen in *Figures 48* and *49*. There is a non-significant reduction in both CABG and PTCA.

Adverse events

The main concerns for adverse effects in the RESTORE trial of abciximab was related to bleeding episodes and procedures resulting from these (e.g. blood transfusions).

Bleeding

The effect of tirofiban on the incidence of major bleeding in RESTORE can be seen in *Figure 50*. The RESTORE trial did not report on incidence of minor bleeding. As expected there was an increase associated with tirofiban treatment, but this was not statistically significant: RR = 1.42; 95% CI, 0.96 to 2.11.

Transfusions

The effect of tirofiban on transfusions (all) in RESTORE can be seen in *Figure 51*. There is an increase in the risk of transfusions associated with tirofiban treatment, in line with increased bleeding risk, although this was not statistically significant: RR = 1.58; 95% CI, 0.96 to 2.62.

Composite end-point

The effect of tirofiban on the composite outcome in RESTORE can be seen in *Figure 52*. RESTORE showed a clear benefit at 48 hours but this progressively lessened at 7 and 30 days. Overall there was no benefit of treatment at 30 days.

Conclusions regarding the effectiveness of glycoproteins alongside PCI

A total of 17 trials of the use of GPAs in conjunction with PCI have been reviewed, covering

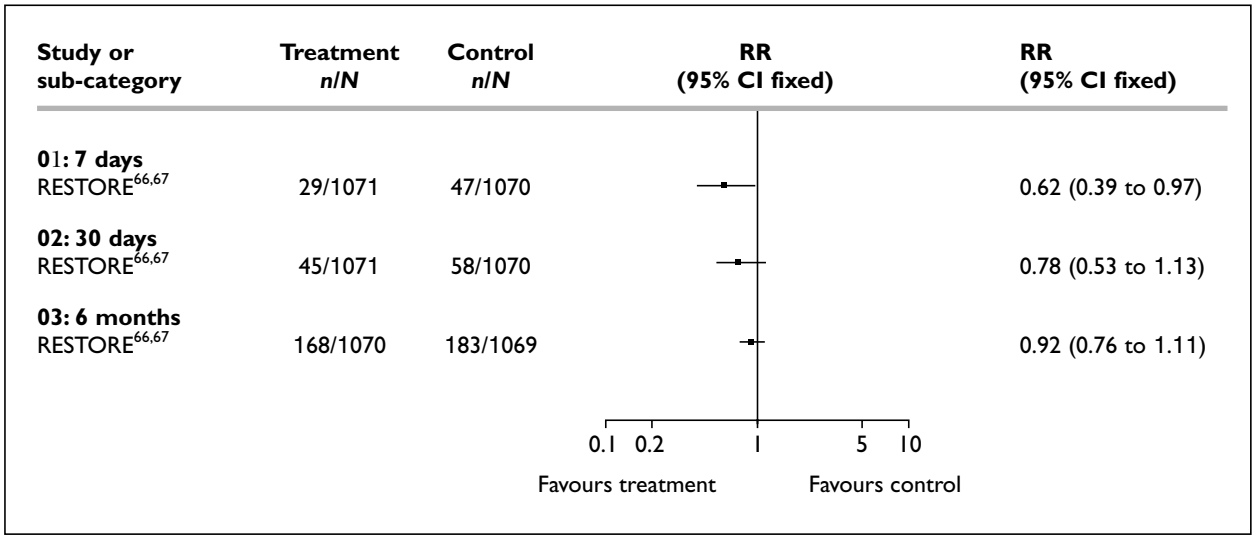

FIGURE 48 *Effect of tirofiban on PTCA rates for patients receiving glycoproteins alongside PCI*

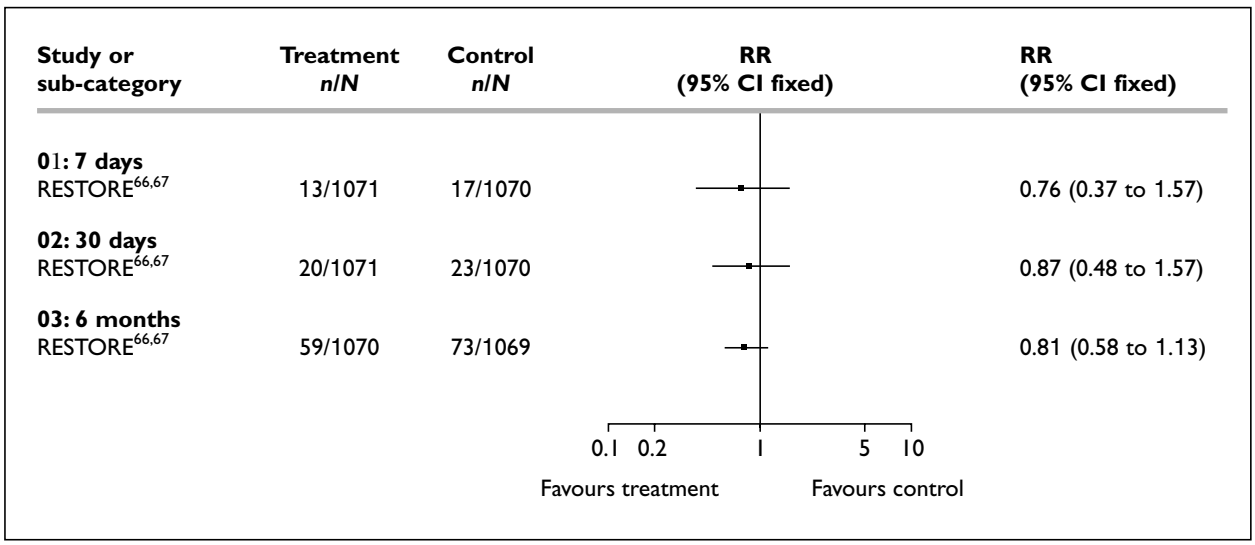

FIGURE 49 *Effect of tirofiban on CABG rates for patients receiving glycoproteins alongside PCI*

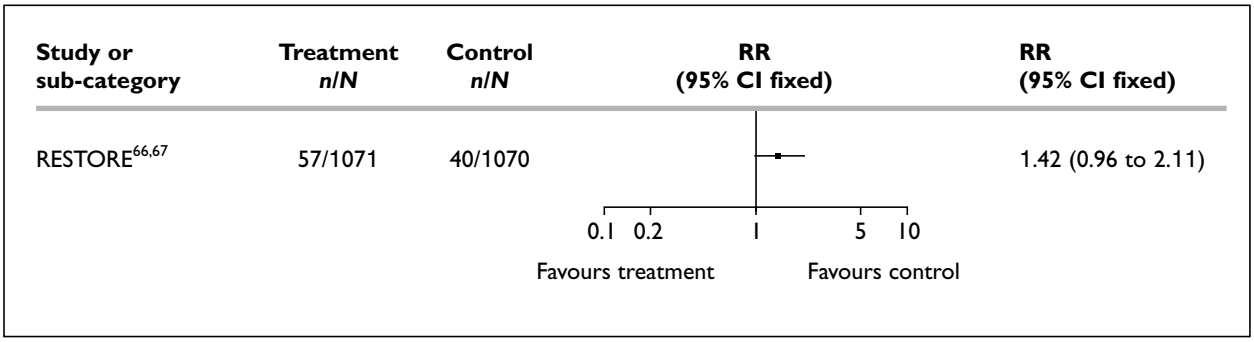

FIGURE 50 *Effect of tirofiban on the incidence of major bleeding at 30 days for patients receiving glycoproteins alongside PCI*

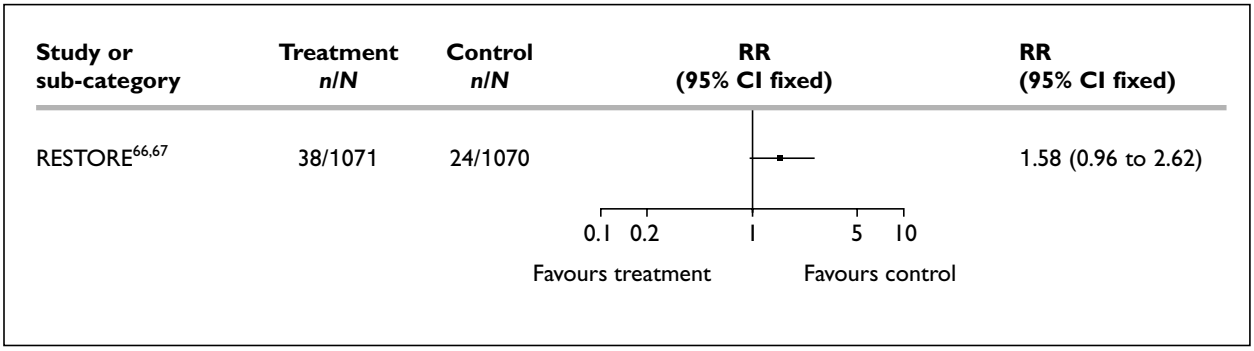

FIGURE 51 *Effect of tirofiban on transfusions at 30 days for patients receiving glycoproteins alongside PCI*

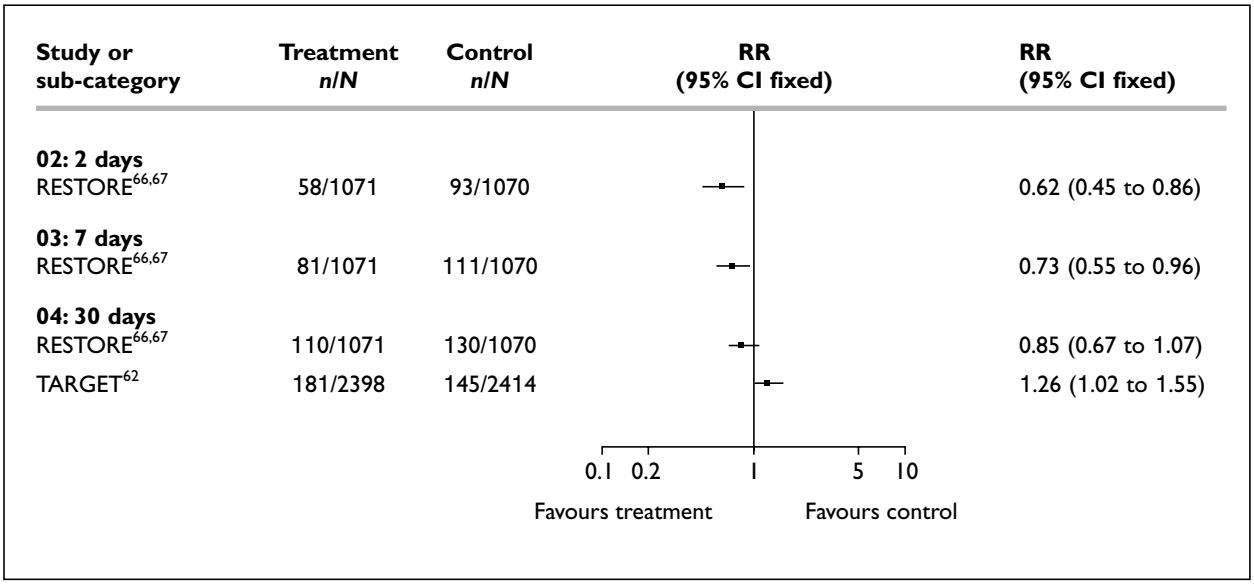

FIGURE 52 *Effect of tirofiban on the composite outcome for patients receiving glycoproteins alongside PCI*

around 25,000 patients in total. Most of the patients were randomised to abciximab. Whilst this scale of research might be expected to produce definite conclusions, the evidence base has a number of limitations.

- Heterogeneity of the trials. This applies to their size, setting and participants. Some trials included all types of patients undergoing PCI; some were restricted to ST-elevation AMI alone; others deliberately excluded this patient type. The results are not surprisingly heterogeneous also.
- Uncertainty in the clinical significance of an important type of measured end-point, namely peri-procedural infarction, which is detected by a rise in cardiac enzymes alone. The inclusion of such end-points increases the number of observed events and hence the statistical power of a trial, but the long-term significance of these

events in terms of patient survival, quality of life and healthcare costs is unknown/ambiguous.
- Changes in the maturity of the concurrent technology: PCI. When the oldest trial, EPIC, was being conducted, very few patients were stented. In the most recent, such as ESPRIT, stenting is routine.
- Differences between the outcomes in the trials and those in routine UK populations.

Despite these caveats, abciximab has shown a clear benefit, particularly for non-fatal MI across a wide range of patients and settings. It has become established as a routine adjunct to PCI, thanks to the results of older trials such as EPIC and EPILOG. Although outcome data across trials have not been pooled here given the extreme heterogeneity, an indicative meta-analysis of 30-day composite outcomes shows a clearly significant effect (ARR = 0.05; 95% CI, 0.03 to 0.07; NNT = 18; 95% CI 13 to 29). The newer trials discovered by the update have not changed this conclusion; however, the newer trials do show some reduction in the magnitude of benefit.

Recent trials that have tested the small molecule agents against abciximab, TARGET and PRICE, have failed to show any clear benefits for the latter over abciximab, either in terms of benefit or of reduced harms (bleeding). There is no evidence in terms of effectiveness to change from abciximab, although the differential cost-effectiveness of the alternative agents may differ.

It is unclear from the trials whether there are subgroups that receive a particular benefit from abciximab, or conversely whether there are subgroups in which there is little effect. A subgroup analysis of the EPIC trial for patients with unstable angina suggested an 8.0% ARR (NNT = 12) for a composite end-point of death, MI, and urgent or repeat revascularisation.[81] As with the trials of GPAs without PCI, such analyses should be interpreted with caution for the reasons stated in the section 'Use of glycoproteins in the medical management of ACS '(page 9).

It is possible with improvements in PCI technique (e.g. new stents) that there is a subgroup of patients (e.g. those with simple lesions undergoing uncomplicated elective procedures) in whom there is no benefit from treatment because the degree of platelet activation is too small. Selective use of abciximab in this manner was common in the UK before the publication of NICE guidance but there is no evidence to support it. Further research would need to be undertaken to confirm it was safe and effective.

Use of thrombolytics alongside glycoproteins

The two existing earlier reviews (McDonagh and colleagues[3] and Fischer and colleagues[4]) did not consider the use of glycoproteins alongside thrombolytics in patients with AMI. The update searches therefore sought to identify relevant studies dating back to the original search period.

Efficacy of intravenous glycoproteins alongside thrombolytics

The searches identified five trials (ASSENT-3,[82] TIMI 14,[83] IMPACT-AMI,[84] GUSTO V[85] and Ronner and colleagues[86]) and these have been extracted and discussed in a manner similar to the other indications. One further study (SPEED) was identified but excluded because it was a pilot for GUSTO V.

General details

Three of the five trials were conducted in the USA (ASSENT-3, IMPACT-AMI and GUSTO V); TIMI 14 was conducted in the USA, Canada, UK, Belgium, Netherlands, France and Germany; and Ronner was conducted in The Netherlands (*Table 47*). Three of the studies (TIMI 14, IMPACT-AMI and Ronner) were smaller and preliminary in nature. The other two (ASSENT-3 and GUSTO V) were large multicentre studies, powered to demonstrate an effect on mortality. ASSENT-3 was designed to test the effectiveness of a low molecular weight heparin adjunct to thrombolysis as well as a GP IIb/IIIa antagonist adjunct.

Length of follow-up ranged from 24 hours in IMPACT-AMI to 1 year in GUSTO V. It is unlikely that 24 hours would allow all clinically relevant events to be observed, but IMPACT-AMI was not expected to affect mortality. Also, it had the smallest number of patients in the trial at 48, in comparison with GUSTO V which randomised 16,588 patients to receive treatment.

Trials looked at the use of the glycoproteins abciximab and eptifibatide in conjunction with the thrombolytics tenecteplase, streptokinase, alteplase and reteplase. The number of trials is too small to look at the effect of individual thrombolytics in conjunction with glycoproteins and therefore no distinction is made between the thrombolytics used.

Patient characteristics and inclusion criteria

In terms of inclusion and exclusion criteria (*Table 48*) and baseline characteristics (*Table 49*), the various patients in the trials did not differ markedly.

TABLE 47 *Designs of included studies of intravenous GP IIb/IIIa antagonists*

Study	Setting	Design/phase	Treatment arms	Number of participants	Follow-up time-points
ASSENT-3[82]: van de Werf *et al.*, 2001	USA	Randomised open-label trial	Enoxparin + TNK Abciximab + TNK + heparin Heparin + TNK	2040 2017 2038	30 days
TIMI 14[83]: Antman *et al.*, 2000	International	Multicentre randomised trial	Abciximab + reteplase (5 + 5 units) Abciximab + reteplase (10 + 5 units) Reteplase + heparin	105 92 102	30 days
IMPACT-AMI[84]: Ohman *et al.*, 1997	USA	Placebo-controlled dose ranging trial (only dose confirmation phase randomised Phase II)	Phase II: Eptifibatide + alteplase Placebo + alteplase	 35 13	24 hours
GUSTO V[85]: Topol, 2001	USA	Randomised multicentre study	Reteplase Abciximab + half-dose reteplase	8260 8328	30 days 1 year
Ronner *et al.*, 2000[86]	The Netherlands	Phase III dose escalation, randomised, double-blind study	Eptifibatide 0.75 µg/kg bolus + streptokinase Eptifibatide 1.33 µg/kg bolus + streptokinase Eptifibatide 2.00 µg/kg bolus + streptokinase Placebo + streptokinase	44 45 30 62	30 days

Concomitant medication

Only the two large studies (GUSTO V and ASSENT-3) reported on the use of other cardiac medication before randomisation. The number and percentages of patients receiving aspirin less than 12 hours before or upon randomisation was the same in all three groups in the ASSENT-3 trial, at 97%. Details of other medications were not given. GUSTO V reported on the number of patients receiving beta-blockers and ACE inhibitors before or at randomisation. The use of concomitant medication after enrolment in the study can be seen in *Table 50*.

Outcomes recorded and definition of outcomes

The definitions of outcomes reported in the trials can be seen in *Table 51*. Overall, the reporting of definitions of outcomes was extremely poor in the thrombolytics trials in comparison with trials for the other indications.

Assessment of internal validity

The assessment of the internal validity of the studies included is presented in *Table 52*. Many items were assigned a question mark. This may reflect poor reporting only and does not necessarily indicate bad study design or study conduct.

As with the two previous indications, validity assessment identified key areas, which were consistently not addressed by the included studies. As previously reported, pre-stratification on prognostically relevant variables prior to randomisation would have helped to minimise potential heterogeneity between groups. Only two of the five trials were double-blind, but to what extent blinding was successful was not reported in either study. Furthermore, in the two larger studies (GUSTO V and ASSENT-3) end-points (except neurological end-points in GUSTO V) were determined by the investigators themselves. The importance of blinding was discussed in the section 'Use of glycoproteins alongside PCI' (page 37).

None of the trials reported how missing values where dealt with which, as previously discussed in the section 'Use of glycoproteins in the medical management of ACS' (page 9), can impact on the interpretation of study results. Two studies did not report whether data were analysed according to the intention-to-treat principle. Analysing patients in the groups they were originally allocated to helps to minimise selection bias.

The registration of co-interventions varied greatly between the included trials. It is important that

TABLE 48 *Inclusion and exclusion criteria from published texts*

Study	Inclusion criteria	Exclusion criteria
ASSENT-3[82]: van de Werf *et al.*, 2001	Age 18 years or older, onset of symptoms less than 6 hours before randomisation, ST-segment elevation of at least 0.1 mV in two or more limb leads or at least 0.2 mV in two or more contiguous precordial leads, or LBBB	Exclusion criteria on admission: SBP > 189 mmHg, DBP > 110 mmHg, or both on repeated measurements; use of abciximab or other glycoprotein inhibitors within the preceding 7 days; major surgery; biopsy of a parenchymal organ or substantial trauma within 2 months; any head injury or other trauma occurring after onset of current MI; any known history of stroke; transient ischaemic attack or dementia; any known structural damage to the CNS; current treatment with oral anticoagulants; treatment with unfractionated heparin of more than 5000 units or a therapeutic subcutaneous dose of low molecular weight heparin within 6 hours; known thrombocytopenia; known renal insufficiency; sustained cardiopulmonary resuscitation in previous 2 weeks; pregnancy; lactation or parturition in previous 30 days; active participation in another drug or device study in previous 30 days; previous enrolment in this study; any other disorder that would place patient at increased risk; and inability to follow protocol and comply with follow-up
TIMI 14[83]: Antman *et al.*, 2000	Aged 18–75 years; qualifying episode of ischaemic discomfort of at least 30 minutes duration within previous 12 hours; at least 0.1 mV segment elevation in two contiguous leads	ECG pattern that obscured identification of the infarct-related artery; increased bleeding risk due to neurological or haematological conditions; hypertension; prior/concomitant therapy; plus general administrative criteria
IMPACT-AMI[84]: Ohman *et al.*, 1997	Aged 18–65 years; within 6 hours of acute MI onset, defined as > 30 minutes of angina and ST-segment depression in leads V1 to V6 with posterior current of injury; ST-segment elevation ≥ 0.1 mV in at least two inferior leads (II, III or a VF), precordial leads (V1 to V6), or leads I and aVL; primary ST-segment change in the inferior or anterior leads with LBBB	Childbearing potential; weight > 125 kg; bleeding diathesis; severe hypertension; prior stroke or CNS structural abnormality; current warfarin therapy or a prothrombin time > 1.2 times the local control time; haematocrit < 30%; GI-bleeding or genitourinary bleeding within 6 weeks; platelet count < 100,000/mm^3; haemorrhagic retinopathy; serum creatine > 4.0 mg/dl; recent non-compressible vascular punctures; co-morbid conditions likely to alter prognosis; prolong cardiopulmonary resuscitation within 2 weeks; severe trauma within 6 months; known or suspected vasculitis; participation in another study of an experimental drug within 7 days before enrolment
GUSTO V[85]: Topol, 2001	Continuous symptoms of chest discomfort for at least 30 minutes and fewer than 6 hours from onset to the time of randomisation, along with electrocardiographic criteria of ST-elevation MI or new left-bundle branch block	Age < 18 years; planned catheter-based reperfusion; active bleeding or a non-compressible vascular puncture site; SBP > 180 mmHg and DBP > 110 mmHg, warfarin therapy; stroke within the past 2 years; weight >120 kg; platelet count < 100,000 cells/µl
Ronner *et al.*, 2000[86]	Evolving MI and onset of chest pain within 6 hours, ST-elevation of 0.1 mV in two or more standard leads or 0.2 mV in two or more precordial leads; patients > 75 years had to weigh > 50 kg	Previous CVD; previous CABG; current anticoagulant therapy; recent GI- or urinary tract bleeding; severe trauma or major surgery; known thrombocytopenia; known liver and kidney function abnormalities; suspected streptokinase intolerance; < 18 years old

the use of concomitant medications is reported as they may influence the overall prognosis of patients within the trial.

The included trials varied with regard to comparators, types of patient enrolled, co-treatment strategies and definition of end-point. For example, TIMI 14 enrolled patients with qualifying symptoms within the previous 12 hours compared to within 6 hours for ASSENT-3 and GUSTO V. Such differences between the trials probably makes any pooling of study results inappropriate.

Results of trials

Results of published trials are presented below, according to the glycoprotein used with a

TABLE 49 *Baseline characteristics of participants in trials of intravenous drugs*

Study	Prognostic indicators	Intervention 1	Intervention 2	Intervention 3	Control
ASSENT-3[82]: van de Werf *et al.*, 2001	Mean age	61	61	–	61
	Hypertension (%)	41	41	–	41
	Diabetes (%)	19	18	–	18
	Previous MI (%)	14	13	–	14
	Prior CABG (%)	3.6	3.3	–	2.6
	Prior PCI (%)	6.2	6.0	–	6.4
	Current smoker (%)	44	47	–	47
TIMI 14[83]: Antman *et al.*, 2000	Mean age	59	60	–	60
	Diabetes (%)	13	12	–	15
	Smoker (%)	50	30	–	29
	Prior MI (≤ 30 days) (%)	0	53	–	40
	Prior MI (> 30 days) (%)	8	1	–	0
IMPACT-AMI[84]: Ohman *et al.*, 1997	Mean age	55	61	–	–
	Hypertension (%)	40	42	–	–
	Diabetes (%)	17	15	–	–
	Prior angina (%)	23	69	–	–
	Prior infarction (%)	23	8	–	–
	Prior angioplasty (%)	11	15	–	–
	Prior CABG (%)	11	0	–	–
GUSTO V[85]: Topol, 2001	Mean age	61.1	61.6	–	–
	Diabetes (%)	16	6	–	–
	Smoker (%)	46	45	–	–
	Previous MI (%)	15	16	–	–
	Previous CHF (%)	3	3	–	–
	Prior CABG (%)	3	3	–	–
	Prior PTCA (%)	7	7	–	–
Ronner *et al.*, 2000[86]	Mean age	63	60	62	58
	Hypertension (%)	27	20	20	23
	Diabetes (%)	7	18	3	16
	Smoking (%)	73	71	63	66
	Previous infarct	5	16	7	5
	PTCA (%)	5	7	10	2

thrombolytic agent. Three trials (ASSENT-3, GUSTO V and TIMI 14) looked at abciximab in conjunction with a thrombolytic and two trials (IMPACT-AMI and Ronner) looked at eptifibatide in conjunction with a thrombolytic agent.

Abciximab

Three trials (ASSENT-3, GUSTO IV-ACS and TIMI 14) looked at abciximab in conjunction with a thrombolytic agent. The results from these trials can be seen below in *Tables 53–55*.

Because all of the three trials used different comparators and multiple comparisons it was impossible to combine the results in any meaningful way and therefore forest plots of pooled RRs have not been included. Instead, results of individual trials are presented below.

Death from any cause

The effect of glycoprotein + thrombolytic combination therapy, reported in each trial, on the incidence of death can be seen in *Figures 53–55*. None of the trials showed a significant treatment effect. The abciximab 5 + 5 U arm as 10 + 5 U in TIMI 14 had no events. In ASSENT-3, death was more common in the abciximab than the enoxaparin arm.

Recurrent MI

All three trials reported on the number of repeat AMIs. The forest plots can be seen in *Figures 56–58*.

Recurrent ischaemia

GUSTO V and ASSENT-3 reported the effect of abciximab combination therapy on recurrent ischaemia. The rates at up to 7 days and in-hospital are presented in *Table 56*. ASSENT-3 also reported on re-infarction rates and these can also be seen in *Table 56*. Small benefits in favour of abciximab were demonstrated in each case.

TABLE 50 *Use of concomitant medications*

Study	Treatment arm	Aspirin	Heparin	Nitrates	Calcium channel blockers	Beta-blocker
ASSENT-3[82]: van de Werf *et al.*, 2001 (*n* = 6095)	Arm 1 Arm 2 Arm 3	96% 95% 95%	–	73% 71% 73%	11% 10% 11%	84% 84% 83%
TIMI 14[83]: Antman *et al.*, 2000 (*n* = 299)	Arm 1 Arm 2 Arm 3	150–325 mg orally or 250–500 mg intravenously	–	–	–	–
IMPACT-AMI[84]: Ohman *et al.*, 1997 (*n* = 48)	Arm 1 Arm 2	325 mg, before study drug initiation and thereafter	Bolus of 40 U/kg, followed by an infusion of 15 U/kg per hour	–	–	–
GUSTO V[85]: Topol, 2001 (*n* = 16,588)	Arm 1 Arm 2	150–325 mg orally or 250–500 mg intravenously at time of randomisation and then 75–325 orally daily for remainder of study	Arm 1 received 5000-unit bolus followed by 1000 U/h infusion for those < 80 kg, or 800 U/h infusion for those > 80 kg Arm 2 received a 60 U/kg bolus followed by infusion of 7 U/kg per hour	–	–	–
Ronner *et al.*, 2000[86]	All	–	–	–	–	–

TABLE 51 *Outcomes recorded and definition of outcomes*

Study	Acute MI	Severe, recurrent angina/RI	Composite end-point
ASSENT-3[82]: van de Werf *et al.*, 2001	Not defined	Not defined	Primary end-point: mortality, in-hospital re-infarction, or RI Primary end-point + safety end-point: as above plus in-hospital intracranial haemorrhage or in-hospital major bleed
TIMI 14[83]: Antman *et al.*, 2000	Standardised definitions – not reported	As before	Not assessed
IMPACT-AMI[84]: Ohman *et al.*, 1997	Not defined	Not defined	Death, re-infarction, stroke, percutaneous or surgical coronary revascularisation, or new in-hospital heart failure or pulmonary oedema
GUSTO V[85]: Topol, 2001	Not defined	Not defined	Listed as end-point but not defined (included death)
Ronner *et al.*, 2000[86]	Listed as end-point but not defined	Not defined	Listed as end-point but not defined (included death)

TABLE 52 *Assessment of internal validity*

Study	ASSENT-3[82]: van de Werf *et al.*, 2001	TIMI 14[83]: Antman *et al.*, 2000	IMPACT-AMI[84]: Ohman *et al.*, 1997	GUSTO V[85]: Topol, 2001	Ronner *et al.*, 2000[86]
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 (% patients lost)	+	–	–	+	+
Blinding of patients	–	?	+	–	+
Blinding of persons who implement interventions	–	?	+	–	+
Registration of co-interventions that affect the outcome for each group	+	–	–	+	–
Blinding of persons assessing treatment effects	–	?	+	–	?
Check to what extent blinding was successful	NA	–	–	NA	–
Data description and analysis					
Measures of central tendency and their CIs (e.g. SE or SD)	+	±	±	+	–
Statistical measures	+	±	+	+	–
Method of dealing with missing values	?	?	?	?	–
Intention-to-treat analysis	+	–	+	+	?
Distributions of baseline characteristics	+	+	+	+	+
Method of accounting for any imbalances in prognostic variables	–	–	–	–	–

+, Item properly addressed; ±, item partially addressed; –, item not properly addressed or not stated; ?, unclear

TABLE 53 *Results from the ASSENT-3 study (Van de Werf* et al., *2001[82])*

Treatment arm	Time-point	Recurrent MI		Death		Revascularisation		Composite	
		n	%	*n*	%	*n*	%	*n*	%
Enoxaparin (*n* = 2037)	30 days	50	2.7	109	5.4	661	32.5	233	11.4
Abciximab (*n* = 2017)	30 days	44	2.2	133	6.6	645	32.1	223	11.1
Heparin (*n* = 2038)	30 days	86	4.2	122	6.0	791	38.8	314	15.4

TABLE 54 *Results from the GUSTO V study (Topol, 2001[85])*

Treatment arm	Time-point	Recurrent MI		Death		PTCA		CABG		Composite	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%
Reteplase	6 hours	–	–	–	–	710	8.6	83	1.0	–	–
(*n* = 8260)	24 hours	–	–	188	2.8	–	–	–	–	–	–
	7 days	289	3.5	368	4.5	–	–	–	–	1701	20.6
	30 days	–	–	488	5.9	2304	27.9	306	3.7	–	–
Abciximab + reteplase	6 hours	–	–	–	–	466	5.6	83	1.0	–	–
(*n* = 8328)	24 hours	–	–	182	2.2	–	–	–	–	1349	16.2
	7 days	192	2.3	359	4.3	–	–	–	–	–	–
	30 days	–	–	468	5.6	2115	25.4	250	3.0	–	–

TABLE 55 *Results from the TIMI 14 study (Antman* et al., *2000[83])*

Treatment arm	Time-point	Recurrent MI		Death		PTCA		CABG		Composite	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%
Abciximab + reteplase (5 + 5 units) (*n* = 105)	30 days	4	4	3	3	63	60	12	12	–	–
Abciximab + reteplase (10 + 5 units) (*n* = 92)	30 days	1	1	–	–	72	78	3	3	–	–
Placebo (*n* = 102)	30 days	2	2	2	2	49	48	8	8	–	–

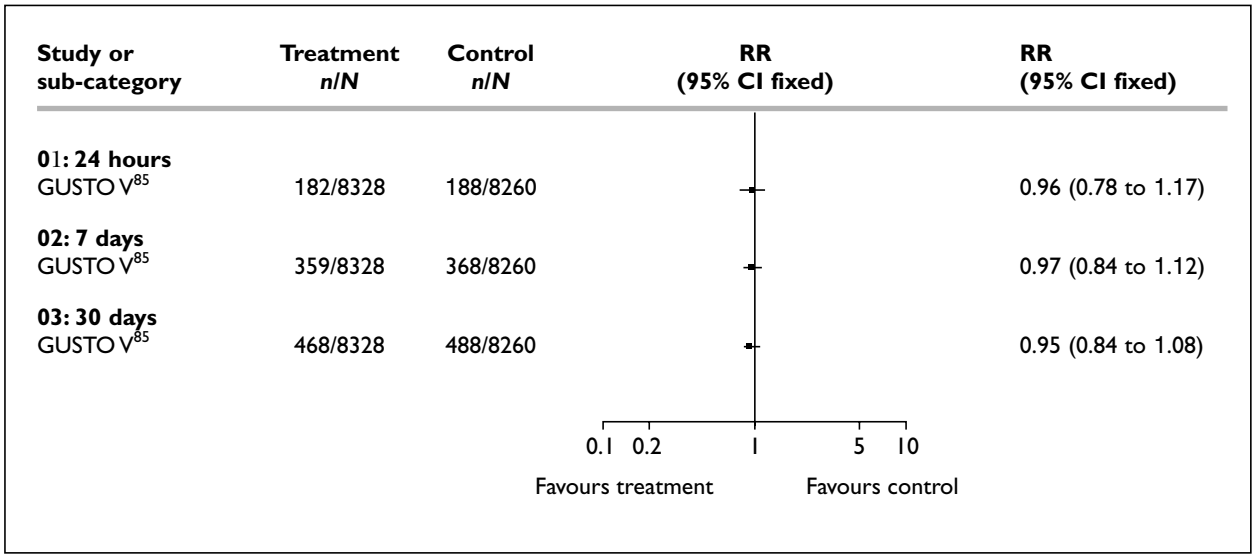

FIGURE 53 *Effect of abciximab + half-dose reteplase on death for patients receiving glycoproteins as an adjunct to thrombolytic therapy*

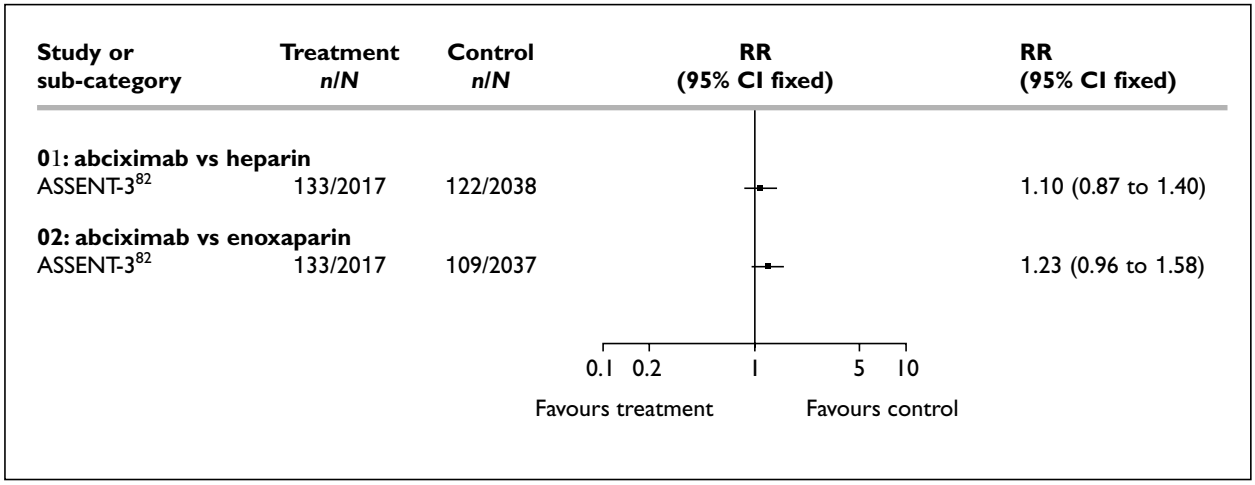

FIGURE 54 *Effect of abciximab + tenecteplase on death at 30 days for patients receiving glycoproteins as an adjunct to thrombolytic therapy*

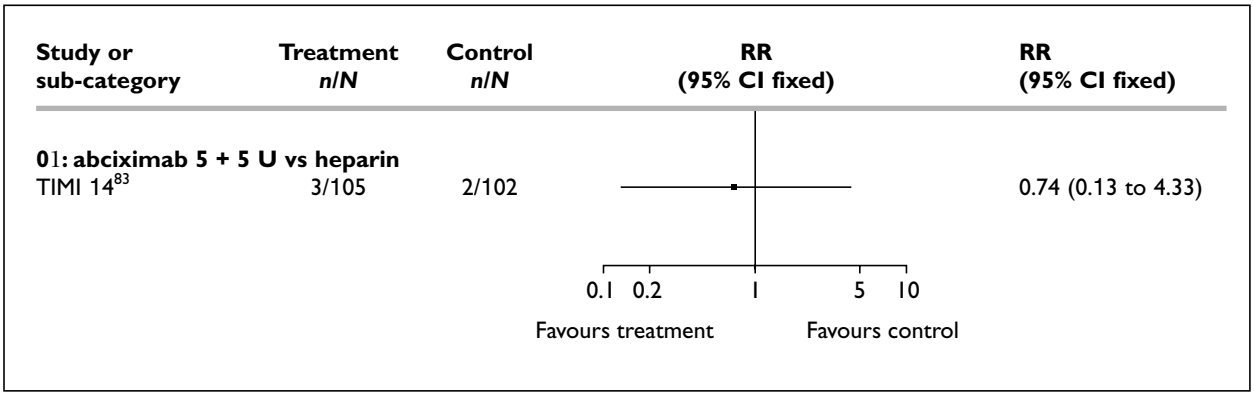

FIGURE 55 *Effect of abciximab + reteplase on death at 30 days for patients receiving glycoproteins as an adjunct to thrombolytic therapy*

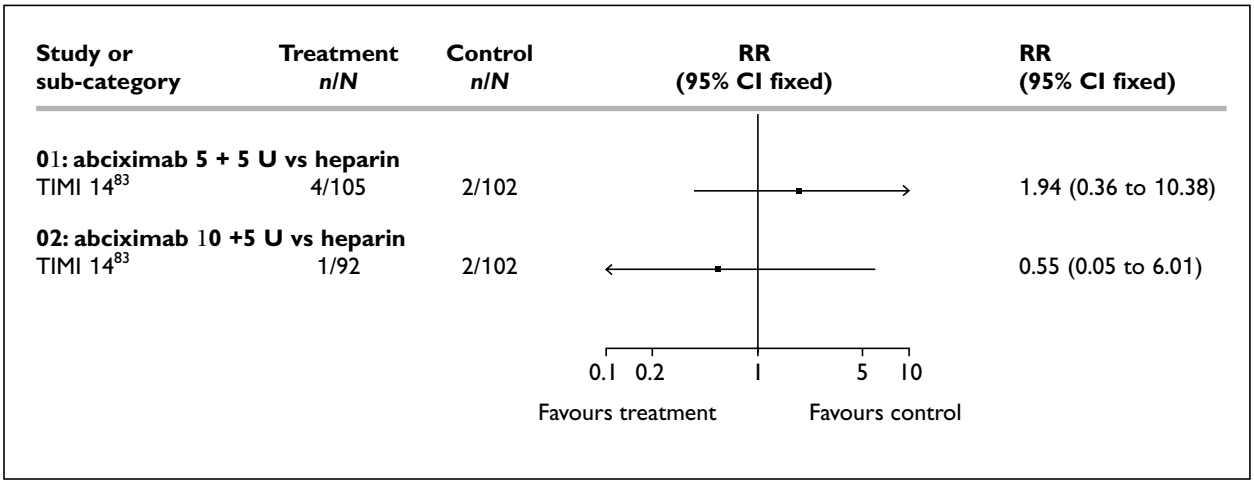

FIGURE 56 *Effect of abciximab + reteplase on repeat MI at 30 days for patients receiving glycoproteins as an adjunct to thrombolytic therapy*

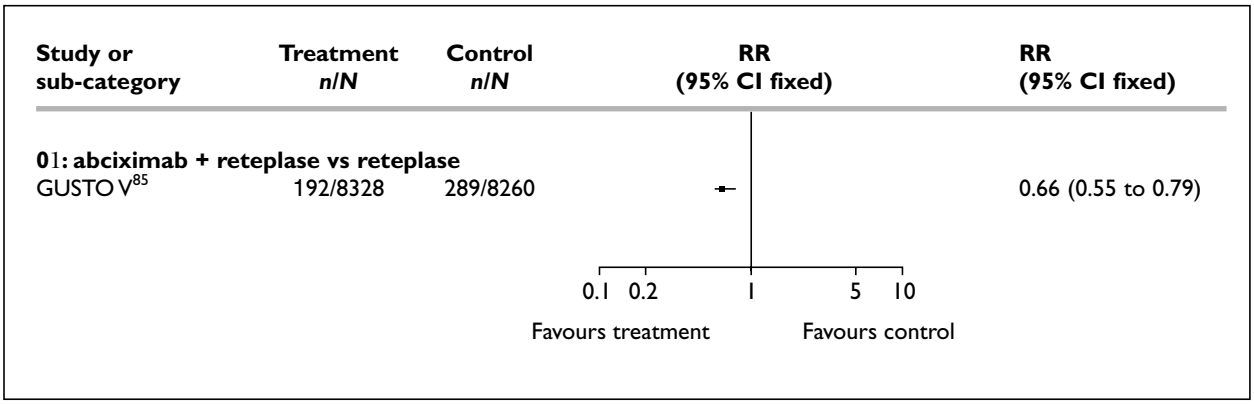

FIGURE 57 *Effect of abciximab + half-dose reteplase on repeat MI at 7 days for patients receiving glycoproteins as an adjunct to thrombolytic therapy*

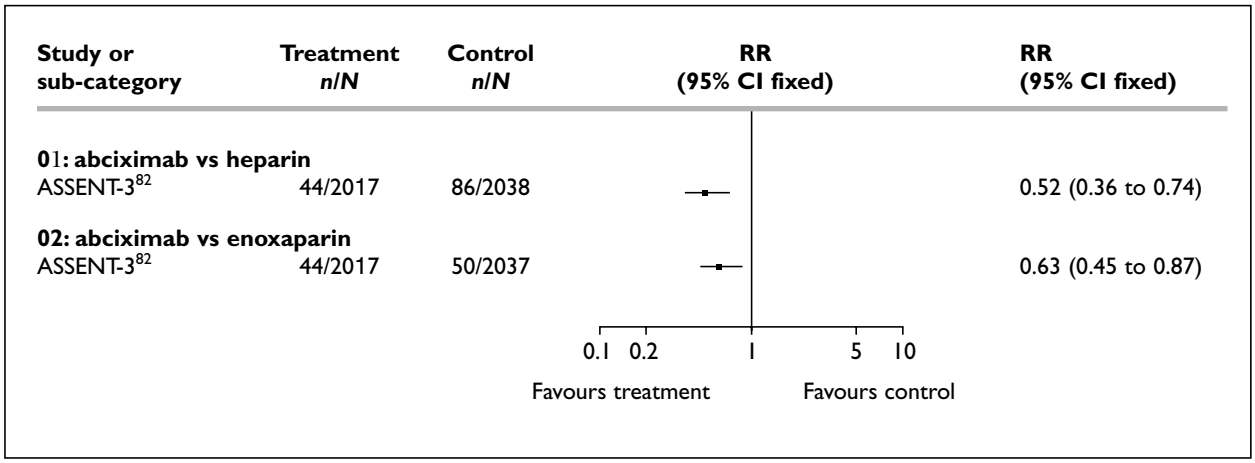

FIGURE 58 *Effect of abciximab + tenecteplase on repeat MI at 30 days for patients receiving glycoproteins as an adjunct to thrombolytic therapy*

TABLE 56 *Effect of abciximab + thrombolytics on recurrent ischaemia*

Study	Time-point	Recurrent ischaemia	Re-infarction
GUSTO V[85]: Topol, 2001	7 days	Reteplase = 12.8% Abciximab + reteplase half-dose = 11.3%	–
ASSENT-3[82]: van de Werf *et al.*, 2001	In-hospital	Enoxaparin + TNK = 4.6% Abciximab + TNK = 3.2% Heparin + TNK = 6.5%	Enoxaparin + TNK = 2.7% Abciximab + TNK = 2.2% Heparin + TNK = 4.2%

TIMI 14 reported the number of patients experiencing severe ischaemia requiring urgent revascularisation. The two abciximab groups were less likely to experience an event than the placebo group, with 26%, 18% and 22% of patients having such an event in the placebo, 5 + 5 U abciximab and 10 + 5 U abciximab groups respectively.

Revascularisation

The effect of combination therapy with abciximab on the rates of revascularisations can be seen in *Figures 59–63*. In most cases a reduction is observed in the treatment arms. These results show a statistically significant reduction on the rates of PTCA at 6 hours, and 7 and 30 days; and for PTCA and CABG at 7 and 30 days.

Adverse events

The main concerns for adverse effects in the trials of abciximab + thrombolytics were related to bleeding, thrombocytopenia, stroke and procedures resulting from these (e.g. transfusions).

Bleeding

The effect of combination therapy on the incidences of minor, moderate, major and severe

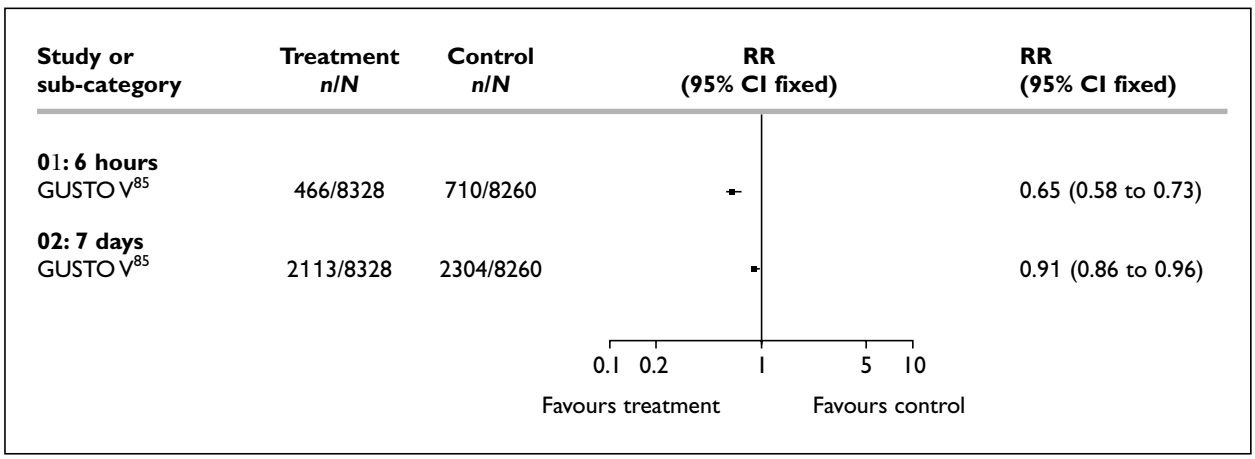

FIGURE 59 *Effect of abciximab + half-dose reteplase on PTCA for patients receiving glycoproteins as an adjunct to thrombolytic therapy*

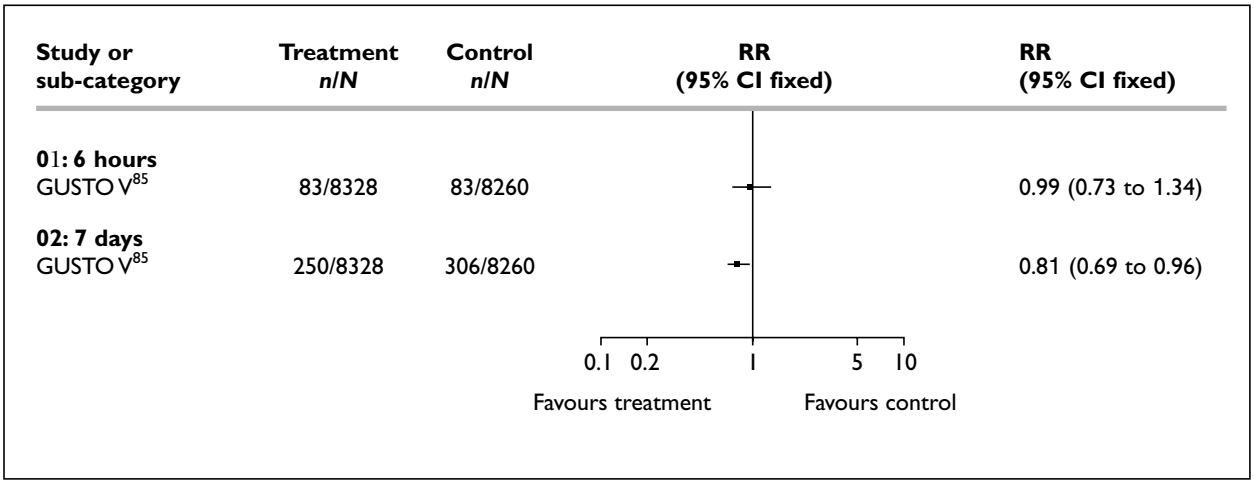

FIGURE 60 *Effect of abciximab + half-dose reteplase on CABG for patients receiving glycoproteins as an adjunct to thrombolytic therapy*

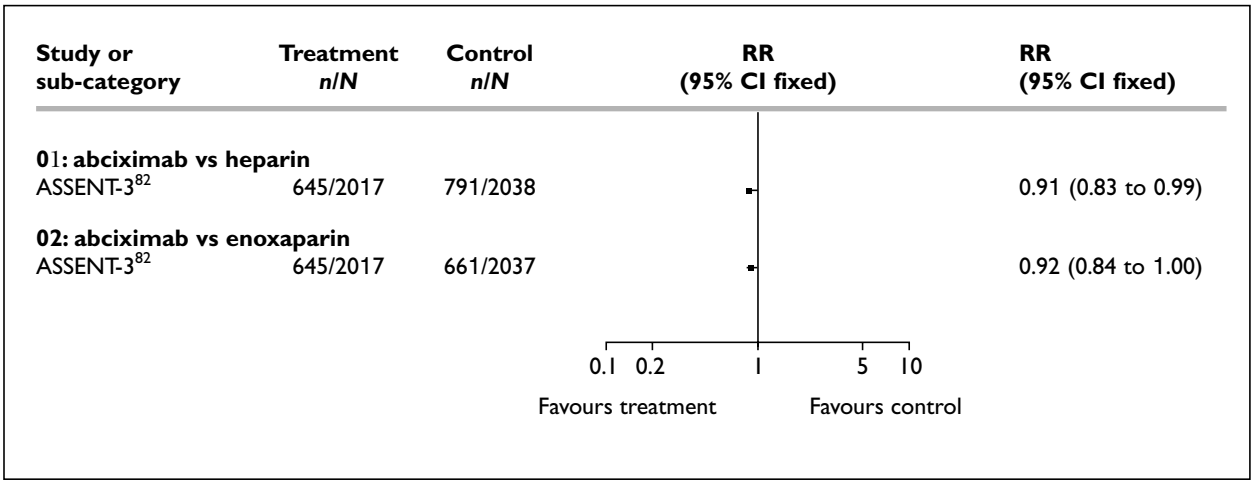

FIGURE 61 *Effect of abciximab + tenecteplase on all revascularisations at 30 days for patients receiving glycoproteins as an adjunct to thrombolytic therapy*

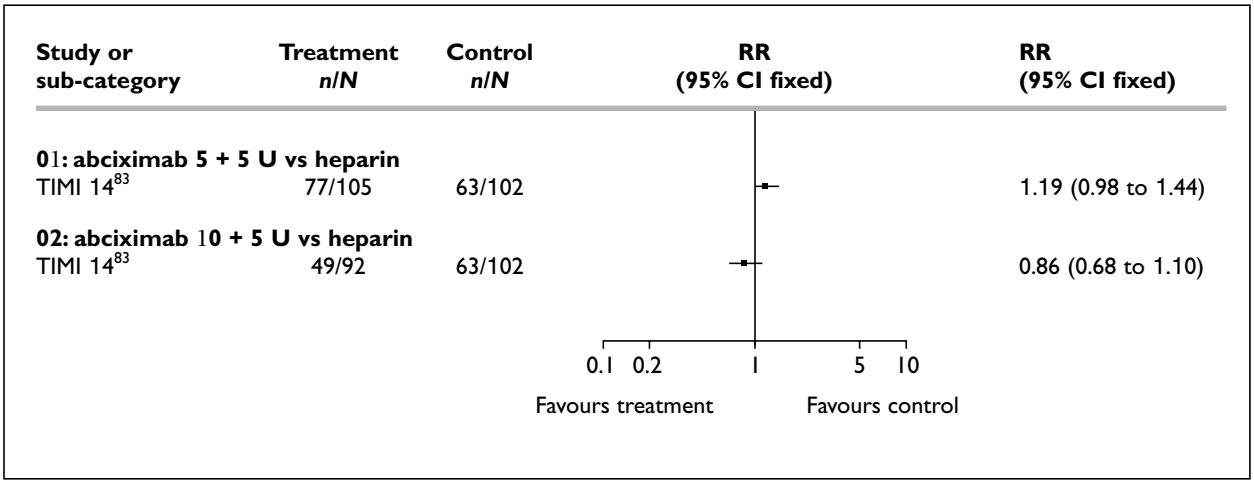

FIGURE 62 *Effect of abciximab + reteplase on PTCA at 30 days for patients receiving glycoproteins as an adjunct to thrombolytic therapy*

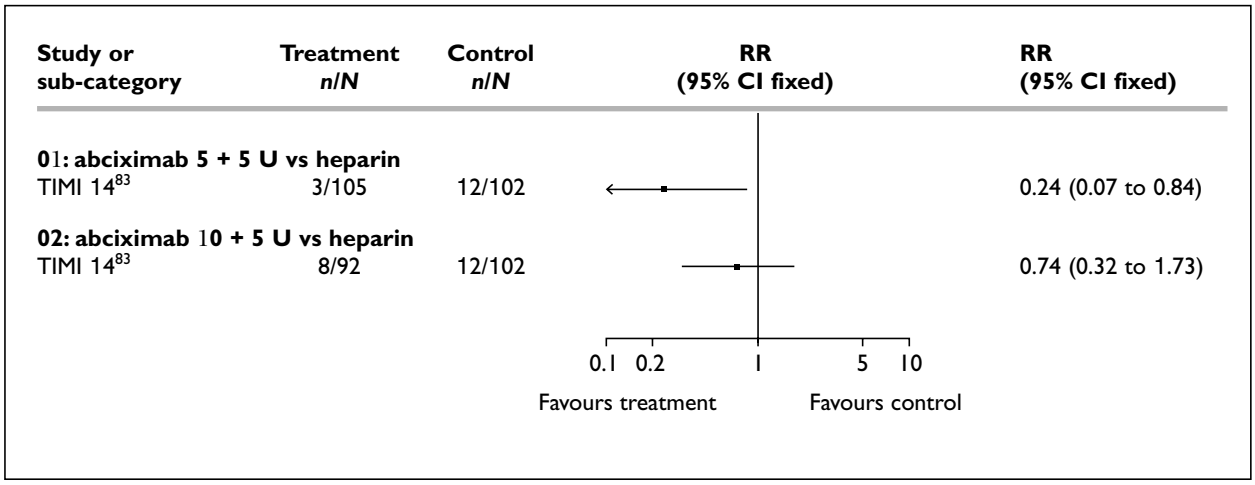

FIGURE 63 *Effect of abciximab + reteplase on CABG at 30 days for patients receiving glycoproteins as an adjunct to thrombolytic therapy*

bleeding can be seen below in *Figures 64–67*; TIMI 14 did not report on bleeding events. The definitions of bleeding used in the two trials can be seen in *Table 57*. In the ASSENT-3 study, the abciximab arm showed no increase in intracranial haemorrhage but major bleeding was 1.3% more common than in the enoxaparin arm, and minor bleeding 12.0% more frequent. Excess major bleeding was particularly noticeable in patients > 75 years old and in diabetic patients, the rates in the abciximab and enoxaparin arms being 13.3% versus 4.1%, and 7.0% versus 2.2% respectively. All analyses showed a statistically significant increase associated with combination treatment.

Stroke

The effect of combination therapy on incidences of stroke can be seen in *Figures 68* and *69*. TIMI 14 did not report on stroke. There are no significant differences in the risk of stroke in the intervention arms compared with control arms of the trials.

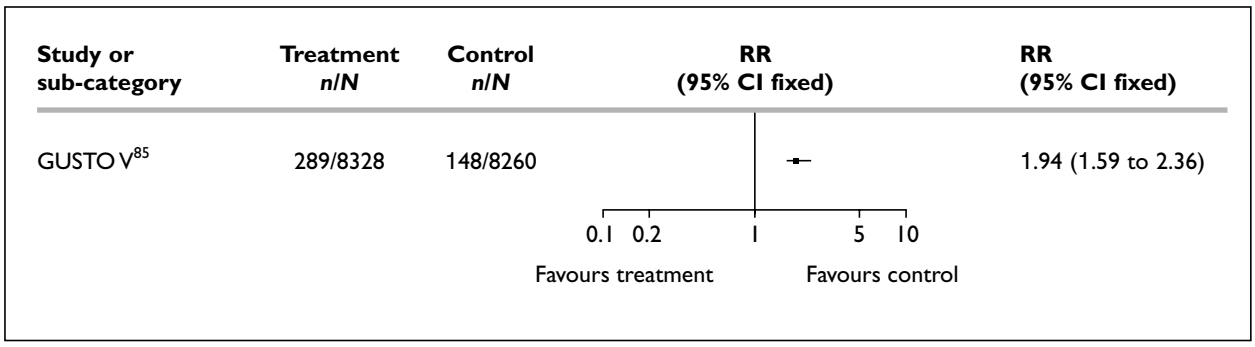

FIGURE 64 *Effect of abciximab + half-dose reteplase on moderate bleeding for patients receiving glycoproteins as an adjunct to thrombolytic therapy*

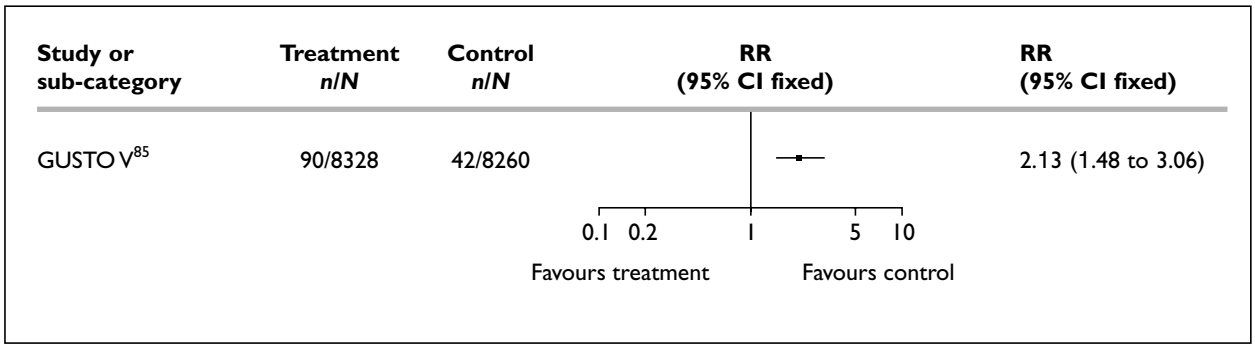

FIGURE 65 *Effect of abciximab + reteplase on severe bleeding for patients receiving glycoproteins as an adjunct to thrombolytic therapy*

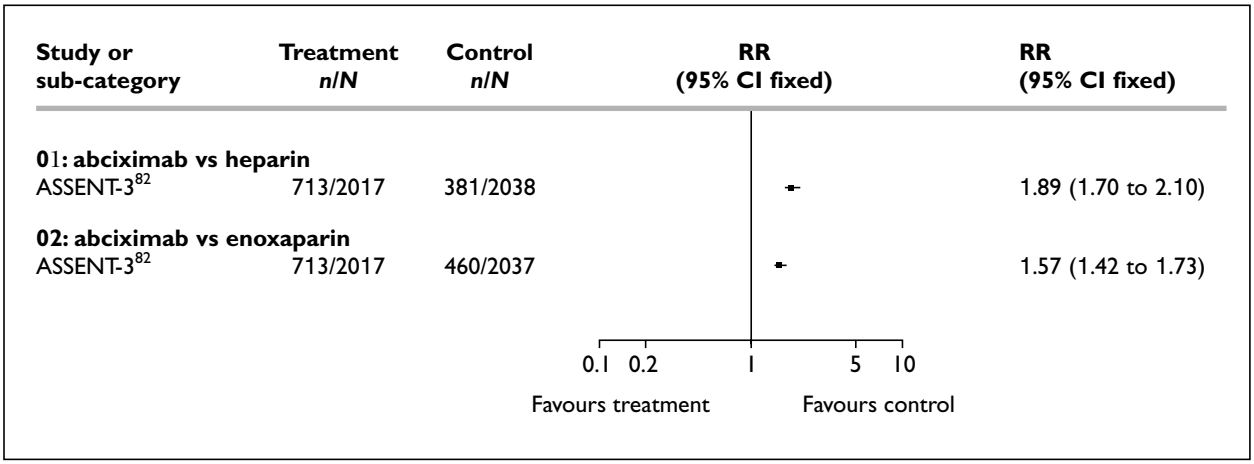

FIGURE 66 *Effect of abciximab + tenecteplase on minor bleeding for patients receiving glycoproteins as an adjunct to thrombolytic therapy*

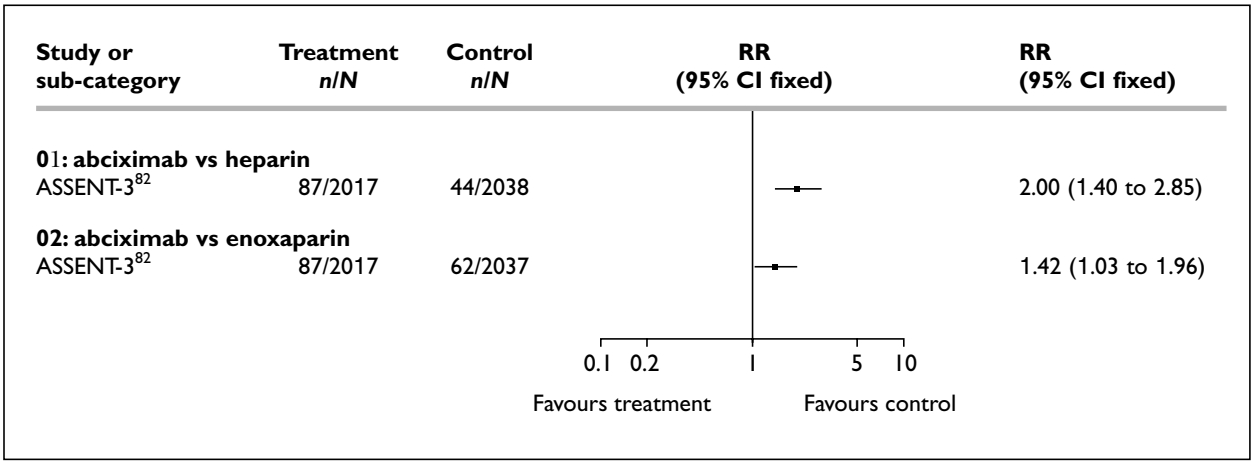

FIGURE 67 *Effect of abciximab + tenecteplase on major bleeding for patients receiving glycoproteins as an adjunct to thrombolytic therapy*

TABLE 57 *Definitions of bleeding used in trials of combination therapy with abciximab*

Study	Minor/moderate/major bleeding
GUSTO V[85]: Topol, 2001	Classified as severe when associated with haemodynamic compromise, moderate when requiring transfusion without haemodynamic compromise, and mild without transfusion or haemodynamic compromise
ASSENT-3[82]: van de Werf *et al.*, 2001	Non-cerebral bleeding complications were defined as major (requiring transfusion, intervention because of haemodynamic compromise, or both) or minor

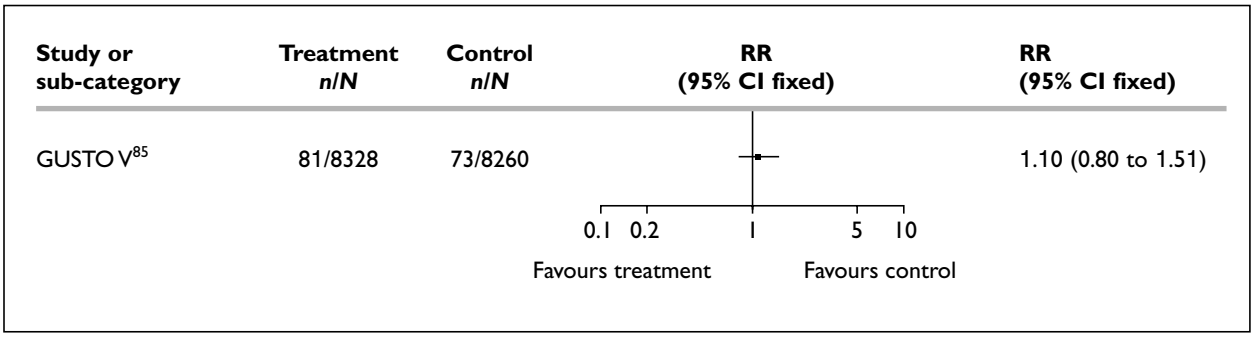

FIGURE 68 *Effect of abciximab + half-dose reteplase on incidences of stroke for patients receiving glycoproteins as an adjunct to thrombolytic therapy*

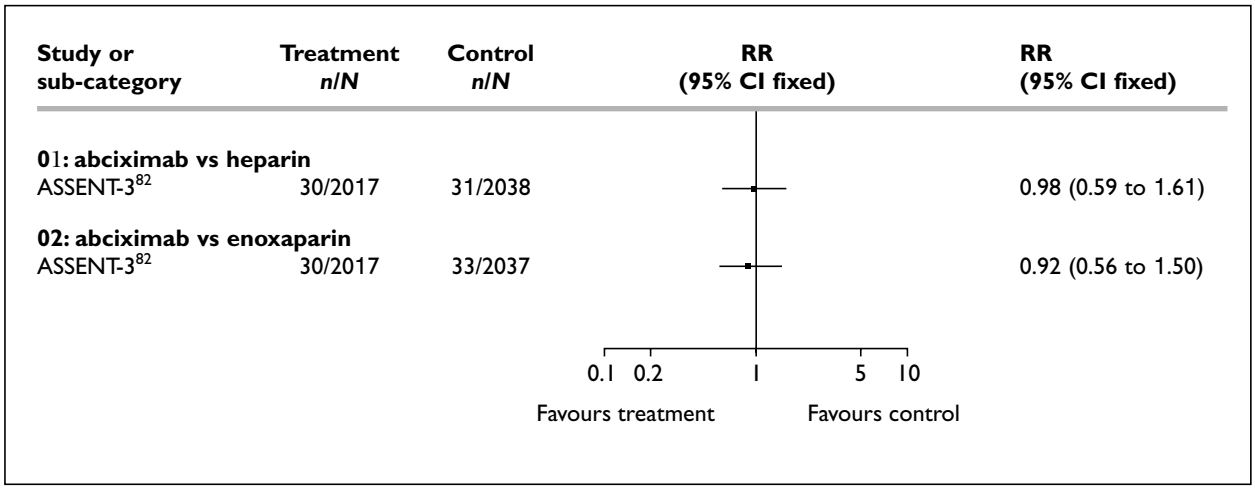

FIGURE 69 *Effect of abciximab + tenecteplase on incidences of stroke for patients receiving glycoproteins as an adjunct to thrombolytic therapy*

Thrombocytopenia

TIMI 14 did not report on the incidence of thrombocytopenia, but GUSTO V and ASSENT-3 did report these events. However, the platelet count used to describe an episode of thrombocytopenia differed between the two trials. The effect of abciximab combination therapy on thrombocytopenia can be seen in *Table 58*. Increased thrombocytopenia with abciximab is observed throughout.

Transfusions

The effect of abciximab + reteplase on the number of patients requiring transfusions can be seen in *Figure 70*. Only the GUSTO IV-ACS trial reported on the number of patients requiring transfusions. As with bleeding, a significant increase in the risk of transfusions is associated with the intervention: RR = 1.43; 95% CI, 1.25 to 1.64.

Composite end-point

The effect of combination therapy on the composite outcomes can be seen in *Figures 71* and *72*. GUSTO V showed a statistically significant benefit of abciximab + reteplase on the composite outcome. Less favourable results were observed comparing abciximab with enoxaparin: the efficacy end-point was 0.3% less frequent (NNT = 300) and the safety plus efficacy end-point (incorporating bleeding as well as death and re-infarction) was 0.4% more common. The TIMI 14 trial did not report a composite.

Eptifibatide

The two small trials (IMPACT-AMI and Ronner) looked at the use of the glycoprotein eptifibatide in combination with thrombolytics. The Ronner study looked at the thrombolytic alteplase in combination with different doses of eptifibatide and IMPACT-AMI looked at streptokinase in

TABLE 58 *Effect of abciximab combination therapy on thrombocytopenia*

Study	Definition of thrombocytopenia				
	< 20 cells/μl	20–50 cells/μl	< 50 cells/μl	50–100 cells/μl	< 100 cells/μl
GUSTO V[85]: Topol, 2001	–	–	Reteplase = 0.7% Abciximab + reteplase = 2.9%	–	Reteplase = 0.1% Abciximab + reteplase = 1.2%
ASSENT-3[82]: van de Werf *et al.*, 2001	Enoxaparin combination = 0.1% Abciximab combination = 0.5% Heparin combination = 0.2%	Enoxaparin combination = 0.2% Abciximab combination = 0.6% Heparin combination = 0.2%	–	Enoxaparin combination = 0.9% Abciximab combination = 2.0% Heparin combination = 1.0%	–

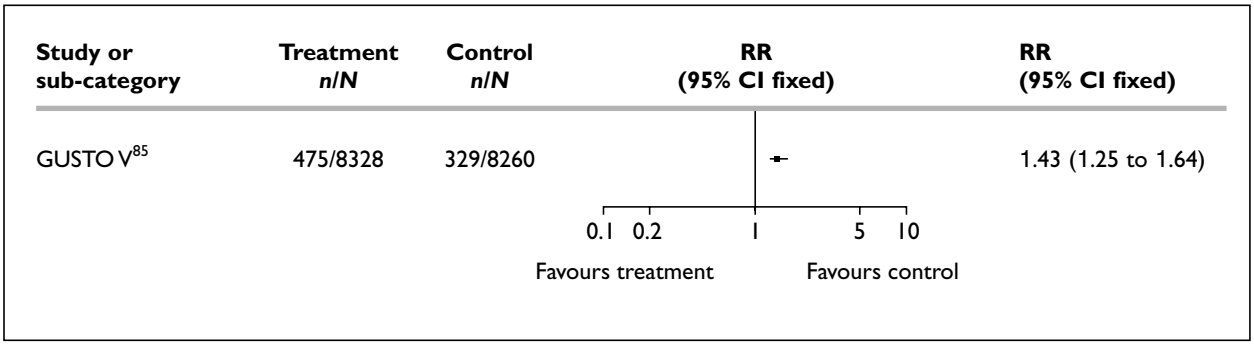

FIGURE 70 *Effect of abciximab + half-dose reteplase on transfusions for patients receiving glycoproteins as an adjunct to thrombolytic therapy*

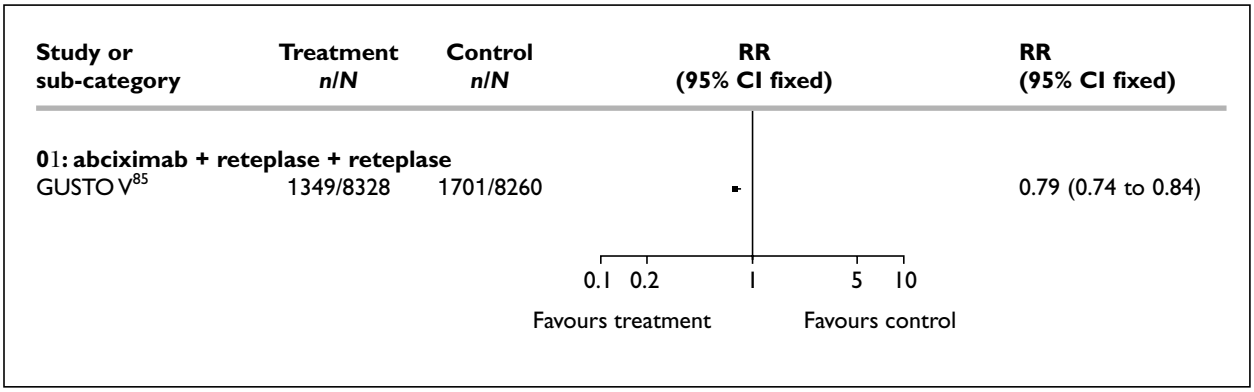

FIGURE 71 *Effect of abciximab + half-dose reteplase at 7 days on the composite outcome for patients receiving glycoproteins as an adjunct to thrombolytic therapy*

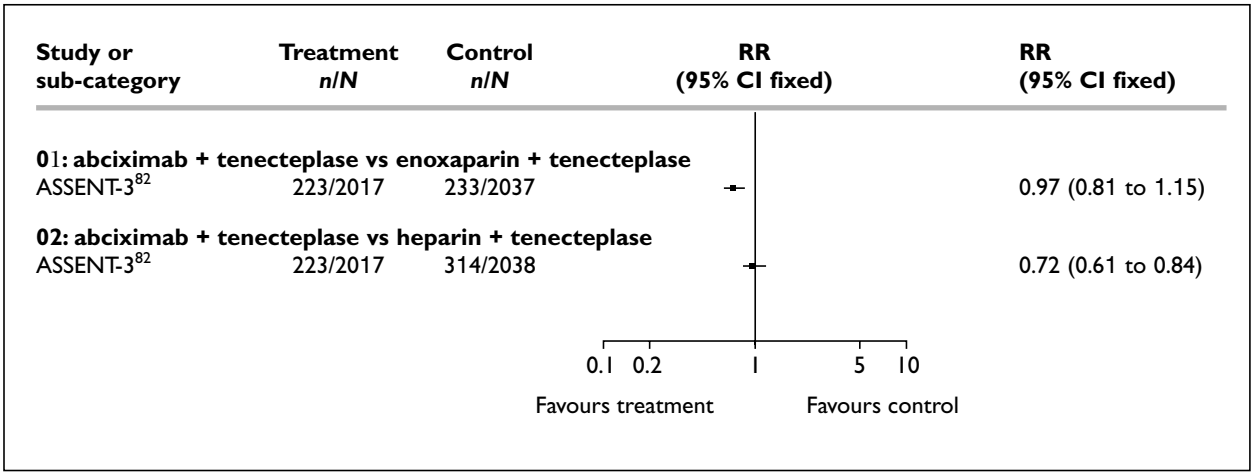

FIGURE 72 *Effect of abciximab + tenecteplase on the composite outcome at 30 days for patients receiving glycoproteins as an adjunct to thrombolytic therapy*

combination with one dose of eptifibatide. Fewer than 200 patients were included in each of the two trials and hence the results lack statistical power and should be interpreted with caution (*Tables 59* and *60*).

Death from any cause

The effect of eptifibatide + alteplase (IMPACT-AMI) or eptifibatide + streptokinase (Ronner) on the number of deaths recorded can be seen in *Figures 73* and *74*. A benefit of eptifibatide + streptokinase was seen in the low-dose versus placebo and medium-dose versus placebo; however this was not statistically significant. A negative effect on deaths was seen on the high-dose versus placebo and eptifibatide + alteplase versus placebo comparisons.

TABLE 59 *Results from the IMPACT-AMI study (Ohman* et al., *1997[84])*

Treatment arm	Time-point	Recurrent MI		Death		PTCA		CABG		Composite	
		n	%	*n*	% (range)	*n*	%	*n*	%	*n*	% (range)
Eptifibatide (*n* = 35)	24 hours	0	0	4	11 (1–22)	6	17	10	29	18	51 (35–68)
Placebo (*n* = 13)	24 hours	0	0	0	0	2	15	3	23	5	39 (12–65)

TABLE 60 *Results from the Ronner* et al. *study (2000[86])*

Treatment arm	Time-point	Recurrent MI		Death		PTCA		Composite	
		n	%	*n*	%	*n*	%	*n*	%
Eptifibatide low-dose infusion (*n* = 44)	30 days	Listed as end-point, but not reported		1	2.2	8	18	–	–
Eptifibatide medium-dose infusion (*n* = 45)	30 days	Listed as end-point, but not reported		2	4.4	2	4.4	–	–
Eptifibatide high-dose infusion (*n* = 30)	30 days	Listed as end-point, but not reported		2	6.6	4	13.3	–	–
Placebo (*n* = 62)	30 days	Listed as end-point, but not reported		4	6.4	0	0	–	–

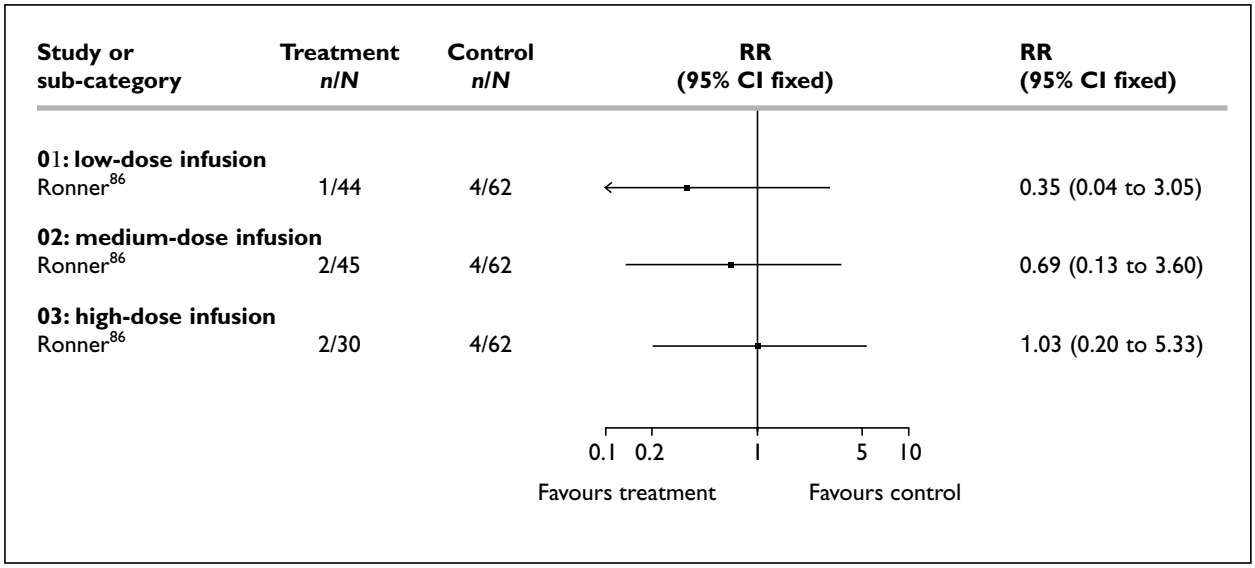

FIGURE 73 *Effect of eptifibatide + streptokinase on death at 30 days for patients receiving glycoproteins as an adjunct to thrombolytic therapy*

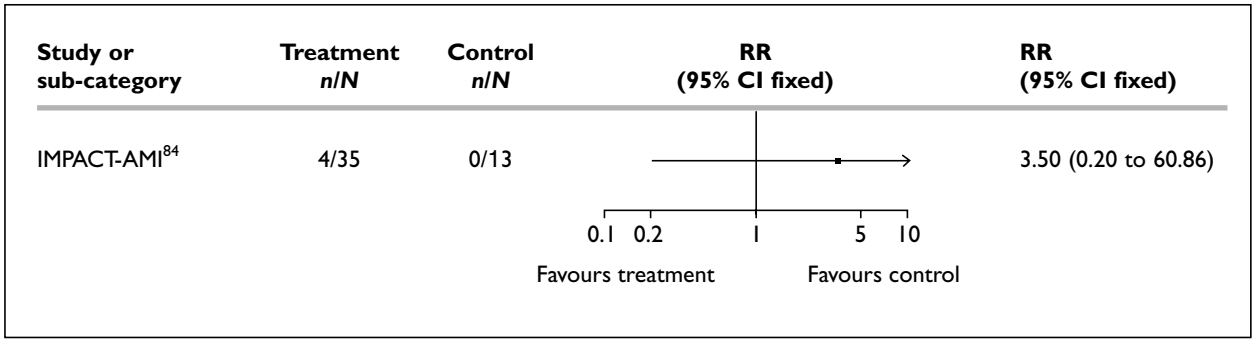

FIGURE 74 *Effect of eptifibatide + alteplase on death for patients receiving glycoproteins as an adjunct to thrombolytic therapy*

Recurrent MI
The Ronner study did not report on recurrent MIs, and no events occurred in the IMPACT-AMI trial.

Recurrent ischaemia
Only the Ronner study reported on recurrent ischaemia, and found that the low-dose combination group (eptifibatide + streptokinase) were the combination group most likely to suffer from recurrent ischaemia; the number of events was, however, the same as the placebo group. The number of events occurring were 7/58, 7/63, 6/60 and 3/62 in the placebo, low-dose eptifibatide, medium-dose eptifibatide and high-dose eptifibatide groups respectively.

Revascularisation
The effect of eptifibatide + streptokinase on the number of PTCAs performed can be seen in *Figure 75*. The effect of eptifibatide + alteplase on the number of PTCAs and CABGs can be seen *Figures 76* and *77*.

Adverse events
The main concerns for adverse effects in the trials of eptifibatide + thrombolytics were related to bleeding, thrombocytopenia, stroke and procedures resulting from these (e.g. transfusions).

Bleeding
The effect of eptifibatide + streptokinase on episodes of minor and major bleeding at 30 days can be seen in *Figures 78* and *79*. As in the large trials of abciximab, a substantial increase in both major and minor bleeding is associated with eptifibatide + thrombolytic treatment.

IMPACT-AMI also reported on the number of bleeding episodes occurring. Bleeding was classified as mild, moderate or severe. Although more common in the eptifibatide + thrombolytic arm, no statistically significant differences between groups were found.

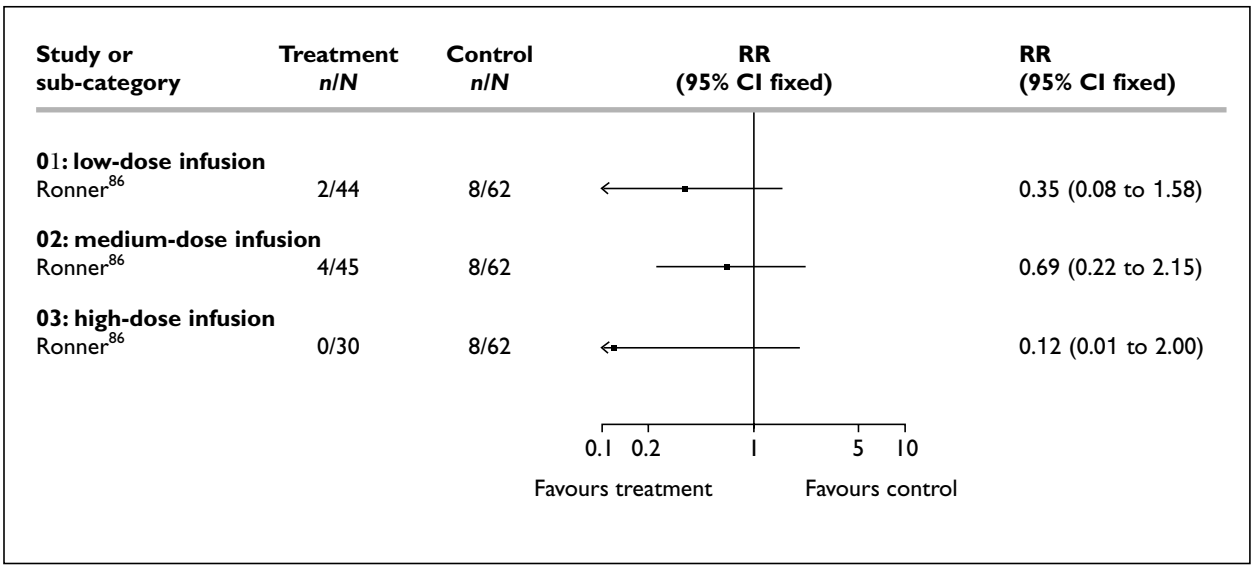

FIGURE 75 *Effect of eptifibatide + streptokinase on PTCA at 30 days for patients receiving glycoproteins as an adjunct to thrombolytic therapy*

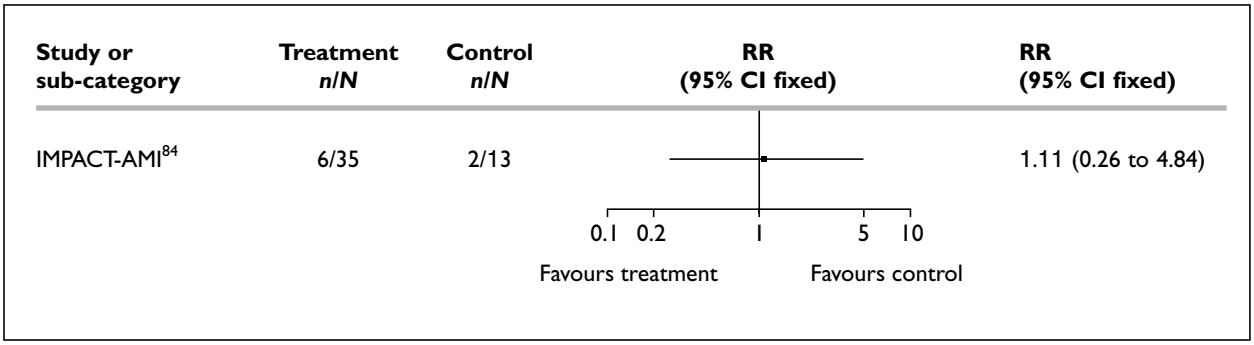

FIGURE 76 *Effect of eptifibatide + alteplase on PTCA at 24 hours for patients receiving glycoproteins as an adjunct to thrombolytic therapy*

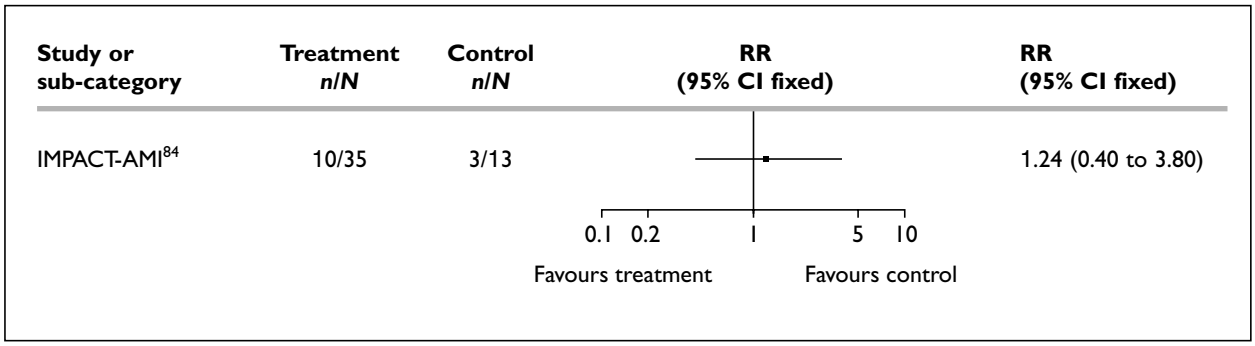

FIGURE 77 *Effect of eptifibatide + alteplase on CABG at 24 hours for patients receiving glycoproteins as an adjunct to thrombolytic therapy*

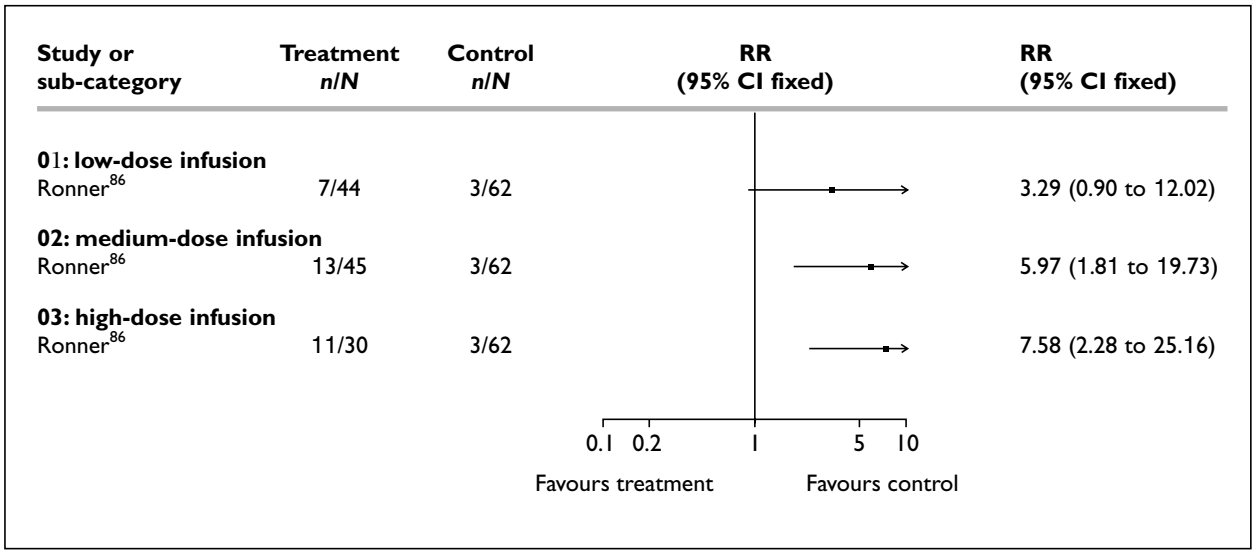

FIGURE 78 *Effect of eptifibatide + streptokinase on minor bleeding at 30 days for patients receiving glycoproteins as an adjunct to thrombolytic therapy*

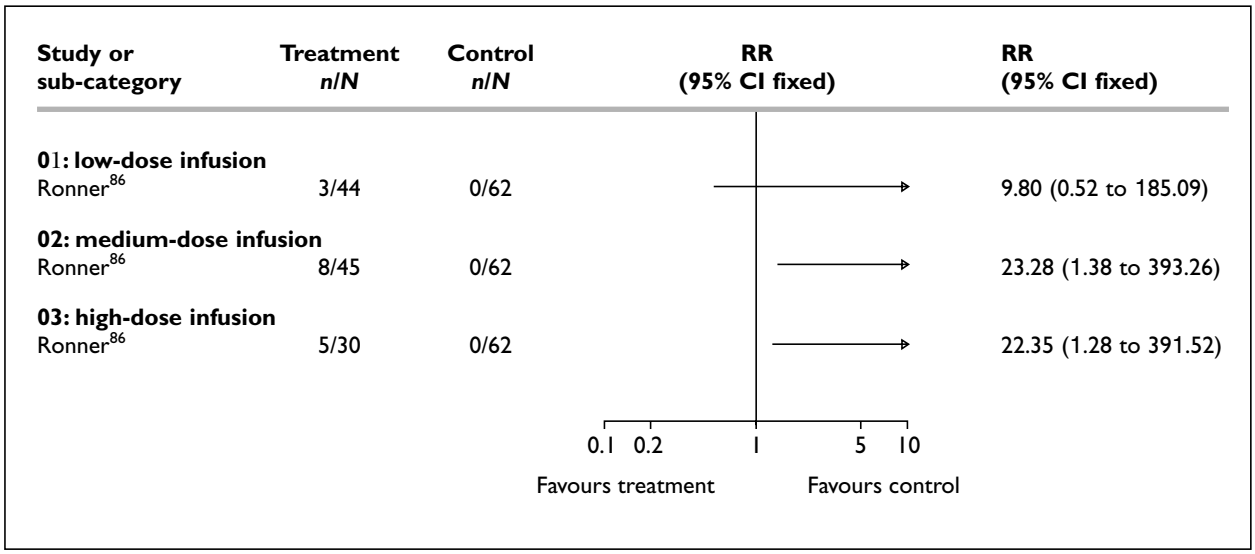

FIGURE 79 *Effect of eptifibatide + streptokinase on major bleeding at 30 days for patients receiving glycoproteins as an adjunct to thrombolytic therapy*

Stroke

The effect of eptifibatide + streptokinase on incidences of stroke can be seen in *Figure 80*. No stroke events occurred in the low-dose infusion or placebo arms of the trial and only one patient in both the medium-dose and high-dose infusion arms suffered a stroke. The differences in risk between medium-dose infusion, high-dose infusion and placebo arms were not statistically significant.

IMPACT-AMI also reported on the incidence of stroke, and categorised these as embolic or intracranial haemorrhagic. Only one intracranial stroke occurred in the eptifibatide + alteplase group.

Thrombocytopenia

Only the IMPACT-AMI trial reported on incidences of thrombocytopenia, and recorded it as a platelet count of < 100 000 cells/(l. A total of 12/35 participants in the eptifibatide + alteplase suffered from thrombocytopenia compared with 0/13 in the placebo + alteplase group.

Transfusions

The effect of eptifibatide + streptokinase on transfusions can be seen in *Figure 81*. Only the Ronner study reported on transfusions. A significant increase in risk of transfusion is associated with all three intervention arms compared with control. The biggest difference was seen in the high-dose infusion group: RR = 16.07; 95% CI,

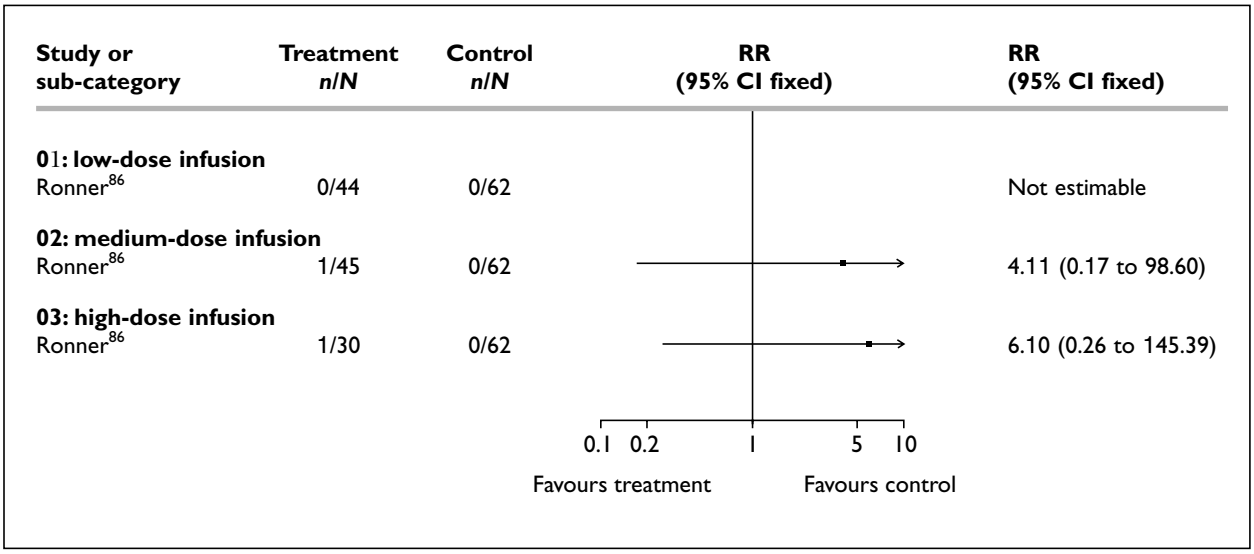

FIGURE 80 *Effect of eptifibatide + streptokinase on incidences of stroke at 30 days for patients receiving glycoproteins as an adjunct to thrombolytic therapy*

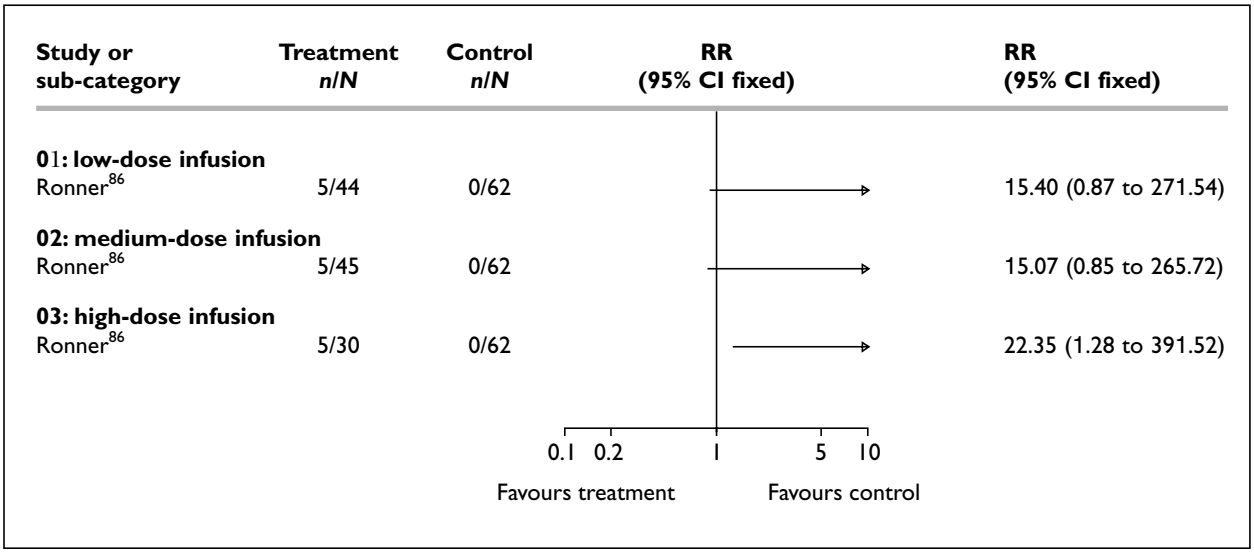

FIGURE 81 *Effect of eptifibatide + streptokinase on transfusions at 30 days for patients receiving glycoproteins as an adjunct to thrombolytic therapy*

0.87 to 271.54 for the low-dose compared with placebo; RR = 16.07; 95% CI, 0.85 to 265.72 for the medium-dose compared with placebo; and RR = 29.35; 95% CI, 1.28 to 391.52 for the high-dose infusion group.

Composite end-point

The effect of eptifibatide + alteplase on the composite outcome, as defined, can be seen in *Figure 82*. The Ronner study did not define a composite. The composite outcome in IMPACT-AMI at 24-hours was observed more frequently in the treatment than in the control arm.

Conclusions regarding effectiveness of thrombolytics alongside glycoproteins for the treatment of AMI

Five trials have been described concerning the use of GPAs in conjunction with thrombolytics for ST-elevated AMI covering about 23,000 patients. The number of patients randomised to tirofiban or eptifibatide is, however, only a very small proportion of these: approximately 2%. Additional trials of these agents are in progress.

Similar to the other two indications already considered, the effect sizes observed are small, and not always in the desired direction (ASSENT-3 showed a RR of 1.10 for the heparin comparison and 1.23 for the enoxaparin comparison for death).

However, a statistically significant reduction in the need for revascularisation was shown in GUSTO V (ARR = 0.02 for PTCA and 0.01 for CABG; NNT = 40 (95% CI, 26 to 86) for PTCA and 142 (95% CI, 80 to 646) for CABG. A smaller and non-significant effect on revascularisation was also seen in the only other large trial (ASSENT-3). Whether such effects can be extrapolated to UK practice with its much lower overall rates of revascularisation is arguable. The authors of the GUSTO V trial have pointed out that the ARR risk reduction in 30-day mortality, which they observed in high-risk patients such as those with anterior infarcts of 1%, may be of clinical importance, in that it is similar to that observed in the GUSTO I[25] trial which was regarded as significant.

Both trials showed an increase in bleeding, major and minor, associated with the drug, in particular in elderly and diabetic patients.

In, summary evidence published to date does not convincingly demonstrate that benefits outweigh harms. There may be a subgroup of AMI patients, such as younger patients in whom PCI is being considered, for whom a combination of thrombolytic and GP IIb/IIIa antagonists is appropriate, but this will need to be shown in further trials before routine use of GP IIb/IIIa antagonists for this indication can be considered.

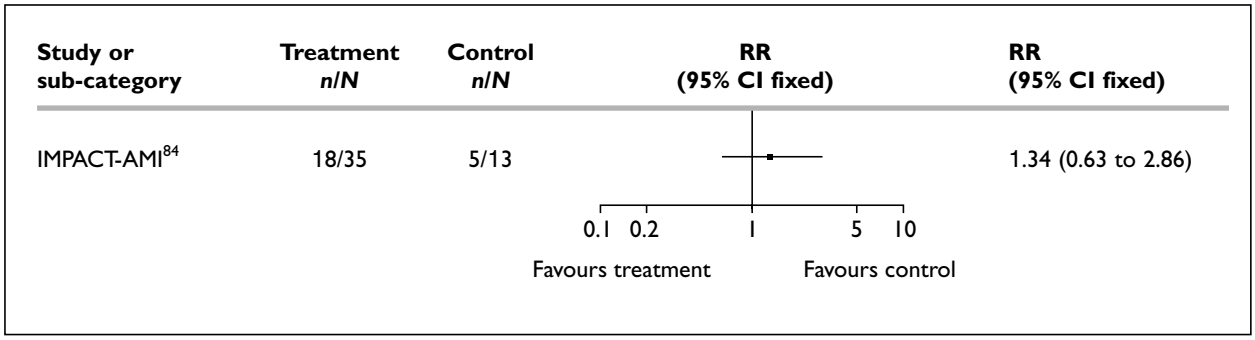

FIGURE 82 *Effect of eptifibatide + alteplase on the composite outcome at 24 hours for patients receiving glycoproteins as an adjunct to thrombolytic therapy*

Chapter 3

Economic analysis

Full economic evaluations for the use of glycoproteins alongside PCI and in the medical management of ACS patients are discussed in this chapter. No economic evaluations of the use of glycoproteins alongside thrombolytics have been identified in the update searches, and it was not an indication considered in the original reviews.

Methods for economic analysis

Search methods

The two earlier reviews of glycoproteins[3,4] commissioned by NICE contained much of the relevant literature. Hence the economics studies identified in those documents were taken as the core of the literature, and an update search undertaken to take the literature up to the date relevant for the project. Search strategies are shown in appendices 1 and 2. These are the same search strategies used by NHS Centre for Reviews and Dissemination (University of York) for their earlier review of GP IIb/IIIa antagonists.[3,4] Hence, the inclusion criteria for the present searches was designed not to repeat but to up-date the searches.

Inclusion criteria

As detailed in the section 'Study designs' (page 7), the inclusion criterion for economic studies was full economic evaluations where both cost and effects have been considered (including cost-effectiveness, cost-minimisation, cost–utility, cost–benefit or cost–consequences analyses).

Data extraction and quality assessment

The data extraction tables set out in the earlier review[3] were used to extract the majority of data from the studies. However, it was felt that, for the purposes of this project, additional information regarding subgroup analysis and methods of extrapolation was needed, so these fields were added onto the extraction tables.

All trials included in the review were assessed using a list of items indicating components of internal validity in a standardised fashion (appendix 6). The checklist for economic studies is based on that used in the earlier reviews; however, some fields have been changed for ease of interpretation.

Search results

The update review identified six papers in addition to the 16 studies identified in the two previous reports.[3,4]

Cost-effectiveness of GP IIb/IIIa antagonists in the medical management of ACS patients

Studies identified

The earlier review identified (see NICE report for search strategy[3]) five published studies (Hillegass and colleagues 1999,[87] Mark and colleagues 2000,[88] McElwee and Johnson 1997,[89] Bell 1999[90] and Szucs and colleagues 1999[91]) plus an additional two economic analyses that were part of industry submissions from Schering-Plough and MSD[92,93] submitted to NICE. Although the industry submissions were not from the published literature they were both conducted in a UK context, and hence it was felt important to include them. The update searches did not identify any additional economic evaluations for this indication. The data extracted from the included economics papers can be seen in appendix 7. The quality of economic evaluations was evaluated using a validity assessment tool. Results of the quality assessment can be seen below in *Table 61*.

A number of the effectiveness trials described in earlier sections of this report were used as a data source for these analyses, and the McElwee[89] analysis looked at the cost-effectiveness of GP IIb/IIIa antagonists both as medical management and alongside PCI in ACS patients.

Of the five published studies, four were conducted in the USA, and Szucs was conducted using Swiss data. Costs were all reported as US dollars, apart from Szucs,[91] which reported in Swiss francs and also converted cost results to Euros.

From the perspective of UK decision-making, the papers by Hillegass,[87] McElwee[89] and Szucs[91] are of limited relevance. This is because they focused on the cost-effectiveness of GP IIb/IIIa antagonists in healthcare systems outside the UK. Given that UK practice with respect to the management of ACS differs from other developed

TABLE 61 *Quality of cost-effectiveness studies for glycoproteins in the medical management of ACS patients*

Study	Mark *et al.*, 2000[88]	McElwee & Johnson, 1997[89]	Bell, 1999[90]	Hillegass *et al.*, 1999[87]	Szucs *et al.*, 1999[91]
Well-defined question posed?	+	+	+	±	+
Comprehensive descriptions of alternatives given?	+	–	+	+	+
Effectiveness established?	+	±	+	±	+
Important/relevant costs and consequences for each alternative identified?	+	±	–	–	–
Methods used to measure costs made explicit?	+	–	+	+	+
Methods used to measure costs and outcomes appropriate?	+	?	–	–	±
Costs and outcomes adjusted for differential timing?	+	±	NA	NA	NA
Incremental analysis of costs and consequences performed?	+	+	+	–	+
Sensitivity analysis performed?	+	±	±	–	+
Study results and discussion include all the issues of concern to users?	+	–	+	–	+

+, Item properly addressed; ±, item partially addressed; –, item not properly addressed or not stated; ?, unclear

countries, particularly regarding the rate of PCI, studies primarily focused on other systems will generate unreliable estimates of cost-effectiveness. Furthermore, the papers by Hillegass and Szucs use condition-specific measures of effect rather than the generic measures of health gains such as life-years and quality-adjusted life-years (QALYs) gained favoured by NICE.[94]

The paper by Mark[88] is focused on the US system but is worth further consideration for two reasons: it was the only prospective economic analysis undertaken alongside a randomised trial and also it was used as a basis of the Schering-Plough UK analysis.

The remainder of this section, therefore, focuses on three economic evaluations that are directly or indirectly relevant to UK decision-making: the studies by Mark and the two company submissions.

Mark and colleagues[88]

Only PURSUIT was planned with a prospective economic analysis. The Mark[88] analysis focused on US patients in that trial. The length of follow-up for the economic analysis was governed by the length of follow-up in the trial: a maximum of 6 months. Mark modelled lifetime costs and outcomes using this short-term follow-up data, data from a relevant database at DUKE University in the USA and a Cox proportional hazards regression model. The model calculated that the use of eptifibatide would cost US$16,491 per life-year gained (LYG) or US$19,693 per QALY gained. This is based on the RD in all-cause death or non-fatal MI at 30 days found in the North American subgroup: 3.5%. If the overall 1.5% RD found in PURSUIT was used, the cost per LYG was US$33,619. It should be noted that the RD for the Western European patients was smaller: 1.0%. Further sensitivity analyses resulted in US$23,449 per QALY gained using a more conservative QALY outcome. The estimated ICERs were quite sensitive to the discount rate. From a base-case ICER of US$16,491 at an annual discount rate of 3%, at 5% the ICER increased to US$20,768 per LYG and at 7% this was further increased to US$25,460. The ICER without applying any discount rate was US$10,954 per LYG.

Although the methods used in the Mark study are strong, the relevance to the UK is limited. Its value in this report is as a source of comparison with the Schering-Plough submission.[92]

Schering-Plough submission[92]

The Schering-Plough[92] study is closely related to the Mark[88] study in that it uses the PURSUIT trial as its main data source. The study used resource use data from both UK (n = 429) and all Western European (n = 3697) patients in PURSUIT, and reported both separately. For the UK analysis, all costs were collected from UK sources. The submission used the results from Western European patients in PURSUIT to estimate the incremental

effectiveness of eptifibatide. This was represented by a 0.37% RD for all-cause survival and a 1.01% RD for MI-free survival at 6 months favouring eptifibatide. Using the modelling approach and life expectancy data detailed in the Mark paper, LYG were calculated. Depending on the discount rate, the life expectancy difference between patients treated with eptifibatide and those on standard treatment (which was not standardised in PURSUIT) was between 8 and 11 days. Using cost data from UK patients, the analysis shows that treatment with eptifibatide is 'dominant', that is the costs for eptifibatide are lower and the effects more favourable. When all Western European PURSUIT patients were used to calculate cost, the cost-effectiveness ratio varied from £8179 to £11,079 per LYG depending on the discount rate used for survival.

The analysis represents an attempt to make the PURSUIT trial relevant to the UK. The analysis it provided (when only resource use in UK patients is considered) may be considered unreliable because this represents a small number of trial patients (only 5% of patients in the trial) and this group may be unrepresentative of UK practice. The analysis of Western European patients may be considered more reliable, although only 12% come from the UK. An important methodological consideration is that, although the lifetime survival duration is modelled, no extrapolation of costs over patients' lifetimes is attempted. Given the differential rate of short-term mortality and non-fatal MI, there will be differences in 'downstream' costs, which are being ignored, and it is not clear which intervention will be favoured.

MSD submission

The cost-effectiveness analysis in the MSD submission focuses on the use of tirofiban as used in the PRISM-PLUS[43] trial. This trial is used as the source of effectiveness data, and the composite measure of effect (all-cause mortality, new MI, RI or readmission for unstable angina or non-Q-wave MI) at 7 and 180 days is the focus. A primary analysis relates the additional costs of tirofiban over standard drugs (heparin) to differences in the composite measure of effect. This generates an incremental cost per event avoided of £8760 using the 7-day effects and £9995 using the 180-day effects.

A secondary analysis includes estimates of the cost offsets associated with the use of tirofiban. UK costs associated with death, MI and RI are estimated based on data from PRAIS-UK[95] and a costing database developed by CHKS Ltd. These are used to value the reduced event rates observed in PRISM-PLUS. On this basis, the authors report that 22% of the cost of tirofiban is offset by savings due to reduced event rates. When these are related to the differential effectiveness seen in the trial, the cost per event avoided is reduced to £6820 based on 7-day effects.

The MSD submission has two important limitations. The first is that it uses a condition-specific measure of effectiveness, which does not assist decision-making in a UK context. The second is that, although UK data are used to cost events seen in the PRISM-PLUS[43] trial, the absolute reduction in event rates associated with tirofiban is not adjusted for UK-specific baseline event rates. It is not clear in which direction this will bias the cost-effectiveness results.

Cost-effectiveness of glycoproteins alongside PCI

Studies identified

From the literature searches for the original review (see appendices 1 and 2 for search strategy) 17 published studies were identified: Dunn and Foster 1999,[96] Mark and colleagues 1996,[97] van Hout and Simoons 1995,[98] van Hout and colleagues 1998,[99] Anderson and colleagues 1999,[100] Sacristan and colleagues 1996,[101] Zed and colleagues 1998,[102] Aristides and colleagues 1998,[103] Goklaney and colleagues 1998,[104] Lorenzoni and colleagues 1999,[105] Hillegass and colleagues 1999,[87] McGregor and Brophy 1999,[106] Bell 1999,[90] Mark and colleagues 2000,[88] Topol and colleagues 1999,[107] Weintraub and colleagues 1999[108] and Hermiller and Kereiakes 1999.[109] The update searches identified an additional six studies: Reed and colleagues 2000,[110] Weintraub and colleagues 2000,[111] Henderson and Brown,[112] Kereiakes 1998,[113] Zwart-van Rijkom and van Hout 2001[114] and and the PRICE trial 2001.[59] In addition, an economic analysis submitted to the 2000 review[3] is included here as it is not now commercial in confidence data.[115] The data extracted from the included economics papers can be seen in appendix 8.

The quality of economic evaluations was evaluated using a validity assessment tool. Results of the quality scoring can be seen in *Table 62*.

Overall results

A number of cost-effectiveness studies were undertaken to assess the cost-effectiveness of abciximab compared with standard therapy in the EPIC trial.[69–71] With the exception of the early Mark and colleagues' cost analysis,[97] most studies have concluded that, although abciximab may

TABLE 62 *Quality of cost-effectiveness studies for glycoproteins alongside PCI*

Study	Dunn & Foster, 1999[96]	Mark *et al.*, 1996[97]	Van Hout & Simoons 1995[98]	Van Hout *et al.*, 1998[99]	Anderson *et al.*, 1999[100]	Sacristan *et al.*, 1996[101]	Zed *et al.*, 1998[102]	Aristides *et al.*, 1998[103]	Goklaney *et al.*, 1998[104]	Lorenzoni *et al.*, 1999[105]	Hillegass *et al.*, 1999[87]	McGregor & Brophy, 1999[106]	Bell, 1999[90]	Mark *et al.*, 2000[88]	Topol *et al.*, 1999[107]	Weintraub *et al.*, 1999[108]	Henderson & Brown, 1999[112]	Reed *et al.*, 2000[110]	Weintraub *et al.*, 2000[111]	Hermiller & Kereiakes, 1999[109]	Kereiakes, 1998[113]	PRICE, 2001[59]	Zwart-van Rijkom & van Hout, 2001[114]
Well-defined question posed?	+	+	+	+	–	+	+	+	?	+	–	+	?	+	+	+	+	+	+	–	+	+	+
Comprehensive descriptions of alternatives given?	+	NA	+	+	–	+	+	+	–	?	?	+	?	?	+	+	?	±	+	–	–	+	+
Effectiveness established?	+	+	+	+	NA	+	+	+	?	?	+/?	+	?	–	+	–	–	+	-	+	+	+	+
Important/relevant costs and consequences for each alternative identified?	+	+	+	+	NA	+	+	+	?	?	-/?	+	–	+	+	+	+	+	?	?	–	–	±
Methods used to measure costs made explicit?	–	–	–	+	+	–	–	–	±	?	+	+	+	+	+	+	+	+	?	–	–	+	+
Methods used to measure costs and outcomes appropriate?	?	+	+	+	NA	+	+	+	?	?	–	+	–	+	+/?	–	+	–	?	?	?	?	?
Costs and outcomes adjusted for differential timing?	+	NA	NA	NA	NA	NA	NA	?	NA	?	NA	NA	NA	+	+	NA	NA	NA	+	+	NA	NA	NA
Incremental analysis of costs and consequences performed?	+	NA	+	+	NA	+	+	+	NA	?	±	+	+	+	+	?	–	+	?	+	+	–	+
Sensitivity analysis performed?	–	–	±	+	NA	±	+	±	±	?	–	+	±	+	–	–	–	+	+	–	+	–	+
Study results and discussion include all the issues of concern to users?	+	+	+	+	?	+	+	+	?	?	–	+	–	?	+	?	?	+	?	?	?	?	?

+, Item properly addressed; ±, item partially addressed; –, item not properly addressed or not stated; ?, unclear; +/?, item appears to have been partially addressed; –/?, unable to determine if item assessed

result in some cost offsets, there would be an increase in overall costs as a result of the use of the drug. These studies used short-term data from EPIC and the condition-specific measure of effect of freedom from ischaemic events. Studies were undertaken using local costs for health systems in Australia,[103] Spain,[101] The Netherlands[98] and Canada.[116] The general conclusion of these studies was that abciximab was cost-effective in this indication, although cost-effectiveness has been shown to be superior in high-risk patients such as those with AMI or unstable angina.[98–101]

Some studies have also sought to extrapolate the short-term results of EPIC over a longer time period using simple extrapolation methods.[99,103] However, only Aristides[103] estimated a cost per LYG across all EPIC patients ($5547), which was considered good value for money.

Given the increased use of coronary stents, the economic evaluations undertaken using data from the EPISTENT[75] trial are important to consider. Using 6-month outcome data from the trial, Zwart-van Rijkom[114] and van Hout[99] estimated the cost per additional MI-free survivor of adding abciximab to stents at 12,876 Euros; the incremental cost per major adverse event avoided was 14,198 Euros. Topol[107] used EPISTENT data to estimate long-term cost-effectiveness using similar extrapolation methods to Mark[88] referred to in the previous section on ACS patients (‘Cost-effectiveness of GP IIb/IIIa antagonists in the medical management of ACS patients’, page 87). They estimated the cost per LYG to be US$6213.

Several studies have sought to synthesise the results of a number of trials looking at GP IIb/IIIa antagonists alongside PCI.[87,90,106] Bell[90] estimated the cost per event (death or MI) avoided for all

three GP IIb/IIIa antagonists. For abciximab, she estimated a cost-effectiveness ratio of US$39,201 using effectiveness data from EPIC,[69–71] and US$25,201 using EPILOG[72,73] effectiveness data.

Regarding the small molecule GP IIb/IIIa antagonists, Weintraub[108] used data collected in the RESTORE[66,67] trial to assess the cost-effectiveness of tirofiban versus standard care in high-risk PCI. Using US costs, the study found no difference in the costs of the two forms of management, suggesting economic dominance given the reduction in 30-day event rates in the trial. In contrast, Bell's synthesis estimated cost per event avoided from RESTORE data to be US$74,047. From IMPACT-II[65] data, Bell estimated the cost per event avoided of eptifibatide to be $10,695.

Cost-effectiveness for UK decision-making

Although most studies generally conclude that the GP IIb/IIIa antagonists are cost-effective alongside PCI, there is considerable variation in their methods, data sources and patient groups. Most studies have serious limitations as inputs into decision-making in the UK. All studies use trial data, which have mainly been collected outside the UK and, given their focus, have not adjusted their data to UK practice. As for the use of GP IIb/IIIa antagonists as medical management in ACS, the variation in practice in the UK compared with other countries requires caution in interpreting the results of economic studies using international trials. In particular, PCI rates in the UK have been lower than elsewhere, and the types of patients undergoing these procedures are likely to be different. Furthermore, the use of EPIC as the source of data for many of the economic studies further limits their relevance to current UK practice given the increasing use of stents.

Only one study has sought to estimate cost-effectiveness in a UK setting. This was the Eli Lilly submission[115] to the initial NICE review undertaken in 2000 focusing on the cost-effectiveness of abciximab alongside PCI. These data are extracted in appendix 9 and quality assessed in *Table 47*. The analysis used absolute reductions in the rate of clinical events observed in EPIC, EPILOG and EPISTENT at 30 days and 1 year and valued these using UK unit costs. To estimate the impact of therapy on LYG it was assumed that those patients in the trial surviving the first year would live for a further 15 years. No differential costs were assumed as part of this longer-term extrapolation. QALYs were estimated assuming a quality-adjustment factor of 0.8 for all living patients. These assumptions generated estimates of cost per LYG from abciximab of £3554 for EPISTENT, £6247 for EPILOG and £12,421 for EPIC. The authors argue that analyses based on EPISTENT and EPILOG are the most relevant to UK practice given the (anticipated) use of abciximab in general PCI patient rather than only high-risk patients, and the increasing use of coronary stents. Sensitivity analyses reveal that the maximum cost per life-year for EPILOG is £13,191 and £11,196 for EPISTENT (assuming a lower reduction in mortality for both trials). Cost per QALY gained estimates a range between £6941 and £9053 for EPILOG and £3949 and £5151 for EPISTENT. The authors consider two specific subgroups – ACS and AMI – and conclude that abciximab is likely to be at least as cost-effective in these groups as in all trial patients.

The Eli Lilly submission has a number of weaknesses. First, the basis of the attempt to make the results relevant to the UK is to use UK unit costs to value changes in events seen in the trial. However, as described above, the management of CHD differs in the UK from many other developed countries. In particular, the lower PCI rates are likely to mean that the case mix (and hence the baseline risk of events) is different in the UK from the trials. As have most of the country-specific analyses undertaken outside the UK detailed in appendix 8, the submission has assumed that the absolute reduction in clinical events in the trials would be achieved in the UK, but this is highly uncertain. The estimated incremental cost-effectiveness ratios should, therefore, be interpreted with some caution.

The second limitation of the submission is that the extrapolation methods may be overly simplistic. The assumption that all patients surviving the 1-year period after PCI will live for a further 15 years ignores variability in prognosis, particularly the fact that patients who experience a non-fatal MI in the first year will probably have a worse prognosis than those who do not. Also, the assumption that costs do not differ between the treatment options over the extrapolation period (years 2–15) ignores the fact that those patients who live for the full 15-year period will doubtless incur additional costs related to their CHD. The first assumption is likely to be conservative with respect to abciximab because fewer patients on that therapy experience a non-fatal MI in the first year. In contrast, the second assumption will probably work on favour of abciximab because more patients on that drug live during the

15-year extrapolation period. The overall 'net' effect is not clear, but would probably not change the ICERs markedly.

Conclusions regarding economic evidence

For purposes of decision-making in the UK, the economic evaluations in the literature and company submissions have a number of limitations. The first is the widespread use of condition-specific measures of effectiveness such as cardiac events avoided. The use of these measures reflect the popularity of composite measures of effectiveness in the clinical trials, but provide a more limited insight into cost-effectiveness across disease areas and specialities than life-years and, preferably, QALYs gained. The second limitation is the fact that all the trials of the GP IIb/IIIa antagonists were undertaken largely or wholly outside the UK. Given different practice patterns (e.g. low rates of PCI) in this country, the baseline risks, and possibly the RRs associated with GP IIb/IIIa antagonists, may be different to those in the UK. Some subgroup analysis was feasible for UK or Western European countries in the ACS studies, but not for the PCI studies.

Notwithstanding these limitations, it is possible to reach some broad conclusions about published and submitted studies. In the case of the use of GP IIb/IIIa antagonists in ACS, the cost-effectiveness of eptifibatide has been assessed in several studies based on the PURSUIT trial. The most directly applicable to the UK is the study submitted by Schering-Plough, which suggests that the drug is dominant (the costs for eptifibatide are lower and the effects more favourable) when cost data are based on only UK patients. However, given that this represents only 5% of patients in the trial, the estimates provided using cost and effectiveness data on all Western European PURSUIT patients are probably more reliable. These suggest costs per LYG ranging between £8179 and £11,079. The cost-effectiveness of tirofiban for the UK is estimated based on PRISM-PLUS, but no estimate of cost per LYG or QALY gained are provided.

A UK model has been developed as part of this review which pools relevant clinical and economic evidence. The results of this analysis will be reported separately.

Company submissions

For the update, review evidence relating to the use of glycoproteins was submitted from each of the three manufacturers MSD, Schering-Plough and Eli Lilly, for the initial reviews undertaken in 2000. For this update review, companies were asked to submit any relevant new evidence. A summary table, indicating the sources of evidence cited in the submissions in presented in appendix 9.

Chapter 4
Discussion

Clinical effectiveness

This review has considered three separate indications for the use of GP IIb/IIIa antagonists:

- as part of the initial medical management of non-ST-elevation ACS
- adjunctive to PCI (urgent or elective)
- in combination with intravenous thrombolytics for ST-elevation AMI.

Specific discussion of the clinical effectiveness for each indication is included elsewhere: section entitled 'Conclusions about the effectiveness of glycoproteins in the medical management of ACS patients' (page 34) for medical management; section entitled 'Conclusions regarding effectiveness of glycoproteins alongside PCI' (page 65) for use with PCI; and section entitled 'Conclusions regarding effectiveness of thrombolytics alongside glycoproteins for the treatment of AMI' (page 85) for use with thrombolytics. Here we consider overarching issues and summarise how our conclusions have developed from those of the previous rapid reviews conducted for NICE.

Quality of the trials included

While there are some validity issues that were unsatisfactorily addressed in the published reports of these studies, in general they were 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 heparin), and possible heterogeneity of the enrolled individuals with regard to baseline risk. 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.

The use of composite end-points may be a concern where the RR between treatment and reference groups in the components (i.e. MI, death) of the composite end-point are very small, but when added together the effect becomes clinically important. With the intravenous GP 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 RR, 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.

Generalisability of trial results

Most of the trials described in this report were conducted in the USA or were multicentre international studies. Although there are always uncertainties about the extrapolation of results from trials to routine practice, because these trials have been conducted outside the UK, this is likely to increase this uncertainty for the following two reasons.

- Early invasive management strategies are much less commonly applied in the UK than elsewhere. It has been suggested that the effectiveness of GPAs may be related to the frequency of PCI, and this is supported by the results from the one international trial (PURSUIT[38–41]) where a geographical subgroup analysis of this type has been published and by the results from GUSTO IV-ACS[36] in ACS.
- Age – the mean age of individuals enrolled in these trials (range 59–67 years) is notably lower than is generally seen in UK general medical practice.

Another important limitation of all the trials reviewed in this report is that they do not include clopidogrel as part of the concomitant medication. Now that there is clear evidence of its effectiveness from the CURE[117] trial, this is likely to become part of standard care for all ACS patients, and may also be used as an adjunct to PCI. Initial analysis of patients undergoing PCI within the CURE study showed a statistically significant 1.9% reduction in the composite outcome of death, MI and urgent repeat revascularisation at 30 days.[118] Use of GP IIb/IIIa antagonists was discouraged and this may have meant that high-risk patients were excluded from the trial. Randomised trials of combination therapy will be required. These may show that clopidogrel has an entirely independent effect from that of the GPAs but this is unlikely given that both act to inhibit platelet aggregation. It is likely to be several years before trials of sufficient size are completed, so the present evidence must continue

to be used in decision-making with this additional uncertainty in mind.

Variations in effectiveness by subgroup

An important issue with any new technology is whether there are specific subgroups within the overall indication in whom clinical effectiveness is noticeably greater or less than average. This is particularly relevant for a technology like GP IIb/IIIa antagonists where overall effect sizes are relatively modest (see section entitled 'Conclusions about the effectiveness of glycoproteins in the medical management of ACS patients' (page 34) for further details). If greater effectiveness in a given subgroup can be demonstrated, a second consideration is whether or not this is acquired at the expense of increased adverse effects, specifically bleeding and stroke in this case.

Each of the three indications for GP IIb/IIIa antagonists featured in this review includes patients with a wide range of baseline risk. Recognised adverse prognostic factors in ACS as described in the section entitled 'Coronary heart disease' (page 1) include the frequency and severity of previous angina, age, troponin status and resting ECG abnormalities. C-reactive protein has also been shown to be an independent predictive factor.[119] In the case of PCI, recent unstable angina or AMI, diabetes, and complex coronary morphology are associated with more complications.[69] For AMI, hypotension congestive heart failure (CHF) and continuing ischaemia suggest a poor prognosis.[120] Together these suggest a large number of subgroups where there might be important differences in clinical effectiveness.

The evidence from which conclusions about differential effectiveness between subgroups can be drawn is limited. As has been already pointed out in the discussion for specific indications, most subgroup analyses of trial results are retrospective. Furthermore, the numbers of patients in subgroups are necessarily smaller than in the main analysis so confidence limits around effect sizes are larger. One approach to overcome this difficulty which has been effectively used in other areas of medicine is meta-analysis with individual patient level data,[121] and such an analysis for trials of GP IIb/IIIa antagonist as part of the initial medical management of ACS has recently been accepted for publication.[2] This meta-analysis (which included two trials of lamifiban excluded from this review) concluded that the benefits of GP IIb/IIIa antagonists were consistent across various high-risk subgroups, and it confirmed reports from individual trials that there was no effect in troponin-negative patients.

Given the present context of trial results, the most important unanswered questions about subgroups are:

- What is the effectiveness, if any, of GP IIb/IIIa antagonists in high-risk ACS in the absence of early PCI? As described in the section entitled 'Conclusions about the effectiveness of glycoproteins in the medical management of ACS patients' (page 34), the recent GUSTO IV-ACS trial showed no effect in this situation. Retrospective analyses of other trials that are potentially biased and have produced conflicting results, and the meta-analysis referred to above, suggested a small overall effect. GP IIb/IIIa antagonists appear ineffective in low-risk groups, such as those who are troponin-negative.[44]
- Is there a low-risk subgroup of patients undergoing PCI, in whom GP IIb/IIIa antagonists offer no benefit? This possibility arises because of continual improvements in stent design and insertion technique, reducing to minimal amounts platelet activation and micro-embolisation. We have not discovered any published subgroup analyses that address this question. Although NICE recommended that GP IIb/IIIa antagonists were used for both acute and elective PCI, current practice in the UK suggests there is uncertainty in this respect. Current rates of use in elective PCI in the UK are thought to be no more than 50% (J McLenechan, personal communication).

As explained above, these questions cannot be answered by the evidence presently available. Unless further suitable trials take place (which seems unlikely), it will be necessary to rely on expert opinion in the short term, possibly supplemented by analysis of large case series in the longer term.

Update on clinical effectiveness

Detailed information on how our conclusions update those of the previous rapid reviews is to be found in the relevant section on each indication. In summary, the main differences follow.

- As part of the medical (non-interventional) management of ACS, there is doubt about the effectiveness of GP IIb/IIIa antagonists even in high-risk patients such as those who are troponin-positive. This is based on the results of the GUSTO IV-ACS trial, which was specifically designed to address this issue. In contrast, potentially biased analyses of all patients receiving only medical management in previous trials do show small effects, and a larger and statistically

significant equivalent effect was observed in the troponin-positive subgroup of PRISM: RR = 0.30; 95% CI, 0.10 to 0.81 in medically managed patients compared to RR = 0.37; 95% CI, 0.15 to 0.93 in those undergoing revascularisation. The troponin substudy from another trial, excluded from this review because the drug concerned (lamifiban) is unlicensed in the UK, suggested a similar preservation of effect in medically managed patients.[122] The recent meta-analysis does not report the effect in the absence of early revascularisation in troponin-positive patients across the trials as a whole. The previous rapid review had concluded that there were small to very small benefits overall, which might be larger in troponin-positive cases. The nub of the uncertainty is how evidence from one randomised study designed for the purpose should be balanced against less reliable analysis from several earlier trials.

- There is no evidence for the clinical superiority of small molecule GP IIb/IIIa antagonists over the more widely used agent, abciximab, as an adjunct to PCI. Two head-to-head trials for this indication have been published since the previous rapid review.
- Poor evidence that the benefits of GP IIb/IIIa antagonists in addition to thrombolytics for AMI outweigh the harms of increased bleeding. The previous rapid reviews had not considered this indication, as the evidence base was only developmental at that time.

Cost-effectiveness

For two of the three indications considered in this report – the use of GP IIb/IIIa antagonists for the medical management of ACS and alongside PCI – there are quite a large number of published economic studies, as well as those submitted by the drug manufacturers. However, most of these studies exhibit at least one fundamental weakness, which limits their value for resource allocation decision-making in the UK. The first limitation is the use of condition-specific measures of effectiveness such as cardiac events avoided. It is easy to understand the reason why these measures of effect predominate in the economic studies, as most of the trials on which the cost-effectiveness studies are based are designed to detect differences in composite outcomes such as all-cause mortality and non-fatal MI. However, without generic measures of health gain such as QALYs and life-years, it is not possible to compare the value for money of interventions across the boundaries of disease and speciality.

The second weakness of the economic studies reviewed here is that the vast majority relate to healthcare systems outside the UK. The trials on which the economic studies are based contain few UK patients and do not reflect UK clinical practice, and this will surely affect absolute treatment effects, resource use, cost and cost-effectiveness.

The third weakness is the reluctance to estimate cost-effectiveness over a longer time horizon than that dictated by the maximum follow-up in the trials, which was rarely longer than a year and, in many cases, 6 months or less. These truncated time horizons limit the usefulness of the cost-effectiveness estimates because the use of GP IIb/IIIa antagonists to prevent premature death or non-fatal MI will have long-term implications in terms of generating differences in quality-adjusted survival and CHD-related costs.

These weaknesses have been highlighted in the economic sections of the review. However, there is a further limitation, which reduces the value of the economic studies for decision-making. Most of the trials simply compare the cost-effectiveness of GP IIb/IIIa antagonists with standard therapy in the relevant indication. However, in routine clinical practice, there is a range of different ways in which these agents are likely to be used. This applies, in particular, to the use of the agents in appropriate ACS patients, where possible strategies include the use of GP IIb/IIIa antagonists as a form of medical management in patients regardless of whether they undergo PCI; the use of the agents only in patients undergoing PCI but once a decision has been taken to undertake the procedure rather than in just the peri-procedural period; and use only in patients undergoing PCI and only at the time that procedure is undertaken. No trial has directly compared these sorts of strategies, but their relative cost-effectiveness is the key uncertainty for decision-makers. For this reason, a parallel study to this review has undertaken a modelling exercise which has sought to assess the cost-effectiveness of the three strategies described above, also in comparison with standard care without GP IIb/IIIa antagonists. As well as seeking to compare clinically relevant strategies directly, the model takes a long-term time horizon, measures effects in terms of QALYs and seeks to make the results as directly applicable to UK practice as possible. This model will be reported separately.

Despite the shortcomings of existing economic evidence it is important to present the best estimates of cost per LYG/QALY gained in the

literature. In the case of the use of GP IIb/IIIa antagonists in ACS, the estimates of cost per LYG which seem most relevant to UK practice comes in the Schering-Plough submission for eptifibatide on the basis of Western European patients in the PURSUIT trial.

These estimates range from £8179 to £11,079 per LYG depending on the discount rate used for future survival. In the case of the use of GP IIb/IIIa antagonists alongside PCI, the estimates most relevant to UK decision-making are again contained in the company submission, this time from Eli Lilly for abciximab. It should be noted that their estimates are only UK-specific in terms of costs, with estimates of effectiveness taken directly from the EPIC, EPISTENT and EPILOG trials. The submission estimates cost per life-year to range between £3554 and £13,191, depending on the trial from which effectiveness data are taken and assumptions made.

The absence of any economic studies looking at the cost-effectiveness of GP IIb/IIIa antagonists alongside thrombolysis in AMI patients represents a limitation of this review. However, the absence of a strong clinical case for the glycoproteins in this indication suggests a similarly weak cost-effectiveness argument. Similarly, the absence of studies comparing GP IIb/IIIa antagonists with clopidogrel, or their use alongside clopidogrel, is another limitation.

Recommendations for future research

In order to gain further insights into the effectiveness and cost-effectiveness of GP IIb/IIIa antagonists, the following recommendations for further research are suggested:

- an assessment of the benefits, if any, of GP IIb/IIIa antagonists in non-ST-elevation ACS, in particular subgroups such as women and those not scheduled for PCI
- an assessment of the benefits, if any, of GP IIb/IIIa antagonists in troponin-negative patients, in particular subgroups such as women and those not scheduled for PCI
- an assessment of the benefits of GP IIb/IIIa antagonists as adjunctive to PCI in urgent and elective patients already receiving clopidogrel, or starting clopidogrel at the time of randomisation, and the optimal timing in conjunction with urgent PCI
- an assessment of the cost-effectiveness of GP IIb/IIIa antagonists used with thrombolytics in selected patients with AMI, preferably in a revised formulation which reduces unwanted bleeding.

Further insight into research priorities will be gained on the basis of the decision modelling exercise, which has been undertaken and reported separately.[57]

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Contributions of the authors

Laura Ginnelly (Research Fellow) was responsible for the cost-effectiveness and clinical effectiveness sections of the report. She was involved in the selection of studies, data extraction and report writing as well as in the development of the economic model.

Julie Glanville (Associate Director) devised the search strategy and carried out the literature searches. She also wrote the search methodology sections of the review.

Lisa Jones (Reviewer) was responsible for the clinical effectiveness sections of the report, and was involved in the selection of studies, data extraction and report writing.

Stephen Palmer (Research Fellow) provided input at all stages, commented on various drafts of the report and contributed to the discussion sections. He was responsible for the economic model and was involved in data extraction of the cost-effectiveness studies.

Zoe Philips (Research Fellow) provided input at all stages, commented on various drafts of the report and contributed to the discussion sections. She was responsible for the economic model and was involved in data extraction of the cost-effectiveness studies.

Rob Riemsma (Reviews Manager) provided input at all stages, commented on various drafts of the report and contributed to the discussion sections.

Mike Robinson (Clinical Senior Lecturer) provided overall supervision of the systematic review and input at all stages. He commented on various drafts of the report and contributed to report writing.

Mark Sculpher (Professor of Health Economics) provided input at all stages and commented on various drafts of the report. He contributed to the discussion sections and was responsible for the economic model.

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Appendix 1

Search strategies

Databases

The following databases were searched for trials of the named glycoproteins:

- The Cochrane Library (CD-ROM, 2001/03)
- Conference Papers Index (Dialog®, 1973–2001/09)
- DARE (http://www.york.ac.uk/inst/crd) (searched on 5 September 2001)
- DEC Reports (http://www.doh.gov.uk/research/swro/rd/publicat/dec/index.htm) (searched on 5 September 2001)
- EMBASE (WinSPIRS, 1980–2001/08)
- HTA Database (http://www.york.ac.uk/inst/crd) (searched on 5 September 2001)
- MEDLINE (WinSPIRS, 1966–2001/06)
- National Guideline Clearinghouse<tm> (http://www.guideline.gov/index.asp) (searched on 7 September 2001)
- National Research Register (CD-ROM Issue, 2001/03)
- NCCHTA website (http://www.hta.nhsweb.nhs.uk/) (searched on 7 September 2001)
- NHS EED (http://www.york.ac.uk/inst/crd) (searched on 5 September 2001)
- PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi) (searched on 7 September 2001)
- ScHARR–Lock's Guide to the Evidence (http://www.shef.ac.uk/uni/academic/R-Z/scharr/ir/scebm.html) (searched on 7 September 2001)
- SIGN (http://www.show.scot.nhs.uk/sign/index.html) (searched on 7 September 2001)
- TRIP Database (http://www.tripdatabase.com/) (searched on 5 September 2001).

Search results were de-duplicated against previous results obtained for the HTA review and the Leeds update project.

Search strategies

1. The Cochrane Library

1. Angina-Pectoris*:ME
2. Myocardial-Infarction*:ME
3. Atherectomy*:ME
4. Catheter-Ablation:ME
5. Angioplasty-Balloon*:ME
6. Myocardial-Revascularization*:ME
7. Stents:ME
8. #1 or #2 or #3 or #4 or #5 or #6 or #7
9. "myocardi* infarct*"
10. "heart attack*"
11. "coronary syndrome*"
12. crescendo
13. "unstable angina"
14. "percutaneous coronary intervention*"
15. "percutaneous transluminal coronary angioplasty"
16. ptca
17. "balloon angioplasty"
18. Platelet-Glycoprotein-GPIIb-IIIa-Complex:ME
19. abciximab or reopro
20. eptifibatide or integrilin or integrelin
21. tirofiban or aggrastat
22. glycoprotein*
23. gpiib* or gp2b* or glycoproteiniib* or glycoprotein2b*
24. #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
25. #18 or #19 or #20 or #21 or #22 or #23
26. #24 and #25

2. Conference Papers Index (Dialog®)

1. S angina()pectoris
2. S myocardial()infarct?
3. S atherectomy
4. S catheter()ablation
5. S balloon()angioplasty
6. S myocardial()revascularization
7. S coronary()stent?
8. S heart()attack?
9. S coronary()syndrome?
10. S crescendo
11. S unstable()angina
12. S percutaneous()coronary()intervention?
13. S percutaneous()transluminal()coronary()angioplasty
14. S ptca
15. S s1:s14
16. S glycoprotein()GPIIb?
17. S abciximab or reopro
18. S eptifibatide or integrilin or integrelin
19. S tirofiban or aggrastat
20. S (gp? or glycoprotein?)(w)(iib? or 2b?)

21. S gpiib? or gp2b? or glycoproteiniib? or glycoprotein2b?
22. S s16:s22
23. S s15 and s22

3. DARE/NHS EED/HTA Database

The CRD databases were searched on the CRD website. All databases were searched simultaneously using the following strategy (and truncation is automatic):

1. glycoprotein or gpii or abciximab or reopro or eptifibatide or intrifiban or integrilin or integrilen or tirofiban or integrin or aggrastat

4. DEC Reports

The index was scanned by eye. No DEC reports have been added since March 2000.

5. EMBASE (SilverPlatter)

1. explode "Angina-Pectoris" / all subheadings
2. explode "Heart-Infarction" / all subheadings
3. "Artery-Catheterization" / all subheadings
4. "Percutaneous-Transluminal-Angioplasty" / all subheadings
5. "Transluminal-Coronary-Angioplasty" / all subheadings
6. "Heart-Muscle-Revascularization" / all subheadings
7. "Coronary-Stent" / all subheadings
8. "Heart-Muscle-Ischemia" / all subheadings
9. myocardi* infarct* in ti,ab
10. heart attack* in ti,ab
11. coronary syndrome* in ti,ab
12. crescendo in ti,ab
13. unstable angina in ti,ab
14. percutaneous coronary intervention* in ti,ab
15. percutaneous transluminal coronary angioplasty in ti,ab
16. ptca in ti,ab
17. balloon angioplasty in ti,ab
18. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #11 or #12 or #13 or #14 or #15 or #16 or #17
19. "Glycoprotein-IIb" / all subheadings or "glycoprotein-IIIa" / all subheadings
20. "abciximab" / all subheadings
21. "eptifibatide" / all subheadings
22. "tirofiban" / all subheadings
23. (abciximab or reopro) in ti,ab
24. (eptifibatide or integrilin or integrelin) in ti,ab
25. (tirofiban or aggrastat) in ti,ab
26. ((gp* or glycoprotein*) near (iib* or 2b*)) in ti,ab
27. (gpiib* or gp2b* or glycoproteiniib* or glycoprotein2b*) in ti,ab
28. #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27
29. #18 and #28
30. explode "Clinical-Trial"/all subheadings
31. "crossover-procedure" / all subheadings
32. "Randomization" / all subheadings
33. "Double-Blind-procedure" / all subheadings
34. "Single-Blind-procedure" / all subheadings
35. explode "Clinical-Trials" / all subheadings
36. "Evaluation" / all subheadings
37. explode "Comparative-study" / all subheadings
38. "Placebo" / all subheadings
39. "Follow-Up" / all subheadings
40. "Controlled-Study" / all subheadings
41. "Prospective-Study" / all subheadings
42. ((intervention or clinical) near (trial* or study or studies)) in ti,ab
43. ((singl* or doubl* or treble* or tripl*) near (blind* or mask*)) in ti,ab
44. (random* or placebo or rct) in ti,ab
45. ((controlled or uncontrolled) near (trial* or study or studies)) in ti,ab
46. ((multicentre* or multicenter*) near (trial* or study or studies)) in ti,ab
47. ((cross over or crossover or evaluation or prospective) near (trial* or study or studies)) in ti,ab
48. ((follow up or followup) near (trial* or study or studies)) in ti,ab
49. #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48
50. "cost–benefit-analysis" / all subheadings
51. "Cost-effectiveness-analysis" / all subheadings
52. "Cost-minimization-analysis" / all subheadings
53. "Cost–utility-analysis" / all subheadings
54. "Economic-Evaluation" / all subheadings
55. (cost effect*) in ti,ab
56. (cost benefit*) in ti,ab
57. (economic evaluation*) in ti,ab
58. (technology assessment*) in ti,ab
59. pharmacoeconomic* in ti,ab
60. cost util* in ti,ab
61. #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60
62. #29 and (#49 or #61)

6. MEDLINE (SilverPlatter)

1. explode "Angina-Pectoris" / all subheadings
2. explode "Myocardial-Infarction" / all subheadings
3. explode "Atherectomy" / all subheadings
4. "Catheter-Ablation" / all subheadings
5. explode "Angioplasty-Balloon" / all subheadings

6. explode "Myocardial-Revascularization" / all subheadings
7. "Stents" / all subheadings
8. #1 or #2 or #3 or #4 or #5 or #6 or #7
9. myocardi*
10. infarct*
11. myocardi* infarct* in ti,ab
12. heart attack* in ti,ab
13. coronary syndrome* in ti,ab
14. crescendo in ti,ab
15. unstable angina in ti,ab
16. percutaneous coronary intervention* in ti,ab
17. percutaneous transluminal coronary angioplasty in ti,ab
18. ptca in ti,ab
19. balloon angioplasty in ti,ab
20. #8 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
21. "Platelet-Glycoprotein-GPIIb-IIIa-Complex" / all subheadings
22. (abciximab or reopro) in ti,ab
23. (eptifibatide or integrilin or integrelin) in ti,ab
24. (tirofiban or aggrastat) in ti,ab
25. ((gp* or glycoprotein*) near (iib* or 2b*)) in ti,ab
26. (gpiib* or gp2b* or glycoproteiniib* or glycoprotein2b*) in ti,ab
27. #21 or #22 or #23 or #24 or #25 or #26
28. #20 and #27
29. exact{CLINICAL-TRIAL} in PT
30. "Randomized-Controlled-Trials" / all subheadings
31. "Random-Allocation" in MIME,MJME
32. "Double-Blind-Method" in MIME,MJME
33. "Single-Blind-Method" in MIME,MJME
34. explode "Clinical-Trials" / all subheadings
35. "Placebos" / all subheadings
36. "Research-Design" / all subheadings
37. explode "Evaluation-Studies" / all subheadings
38. "Follow-Up-Studies" in MIME,MJME
39. "Prospective-Studies" in MIME,MJME
40. #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39
41. (clin* near trial*) in ti,ab
42. ((singl* or doubl* or treble* or tripl*) near (blind* or mask*)) in ti,ab
43. random* in ti,ab
44. placebo* in ti,ab
45. exact{COMPARATIVE-STUDY} in TG
46. (control* or prospectiv* or volunteer*) in ti,ab
47. #40 or #41 or #42 or #43 or #44 or #45 or #46
48. explode "Economics" / all subheadings
49. explode "Costs-and-Cost-Analysis" / all subheadings
50. explode "Economics-Hospital" / all subheadings
51. explode "Economics-Medical" / all subheadings
52. "Economics-Nursing" / all subheadings
53. "Economics-Pharmaceutical" / all subheadings
54. #48 or #49 or #50 or #51 or #52 or #53
55. (cost effect*) in ti,ab
56. (cost benefit*) in ti,ab
57. (economic evaluation*) in ti,ab
58. (technology assessment*) in ti,ab
59. pharmacoeconomic* in ti,ab
60. cost util* in ti,ab
61. #54 or #55 or #56 or #57 or #58 or #59 or #60
62. #28 and (#47 or #61)
63. exact{ANIMAL} in TG
64. exact{HUMAN} in TG
65. #63 not (#63 and #64)
66. #62 not #65

7. National Guideline Clearinghouse™

The website was searched using the keywords individually:

1. glycoprotein
2. glycoproteins
3. gpiib
4. gpiiia
5. abciximab
6. reopro
7. eptifibatide
8. intrifiban
9. integrilin
10. integrilen
11. tirofiban
12. integrin
13. aggrastat

8. National Research Register

1. Angina-Pectoris*:ME
2. Myocardial-Infarction*:ME
3. Atherectomy*:ME
4. Catheter-Ablation:ME
5. Angioplasty-Balloon*:ME
6. Myocardial-Revascularization*:ME
7. Stents:ME
8. #1 or #2 or #3 or #4 or #5 or #6 or #7
9. "myocardi* infarct*"
10. "heart attack*"
11. "coronary syndrome*"
12. crescendo
13. "unstable angina"
14. "percutaneous coronary intervention*"
15. "percutaneous transluminal coronary angioplasty"
16. ptca
17. "balloon angioplasty"

18. Platelet-Glycoprotein-GPIIb-IIIa-Complex:ME
19. abciximab or reopro
20. eptifibatide or integrilin or integrelin
21. tirofiban or aggrastat
22. glycoprotein*
23. gpiib* or gp2b* or glycoproteiniib* or glycoprotein2b*
24. #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
25. #18 or #19 or #20 or #21 or #22 or #23
26. #24 and #25

9. NCCHTA website

The publications section of the website was searched using the separate keywords:

1. glycoprotein
2. gpiib
3. gpiiia
4. abciximab
5. reopro
6. eptifibatide
7. intrifiban
8. integrilin
9. integrilen
10. tirofiban
11. integrin
12. aggrastat

10. PubMed

PubMed was searched on the Internet with search results restricted to those added in the last 180 days.

PubMed truncates terms automatically and maps search terms to both (exploded) MeSH and to text word alternatives.

1. search gpiib or gpiiia or glycoproteiniib or glycoproteiniiia Limits: 180 days
2. search tirofiban or aggrastat or iib or iiia Limits: 180 days
3. search eptifibatide or integrilin or integrelin Limits: 180 days
4. search abciximab or reopro Limits: 180 days
5. search platelet glycoprotein gpiib gpiiia complex Limits: 180 days
6. search #1 or #2 or #3 or #4 or #5
7. search balloon angioplasty Limits: 180 days
8. search ptca Limits: 180 days
9. search percutaneous transluminal coronary angioplasty Limits: 180 days
10. search percutaneous transluminal angioplasty Limits: 180 days
11. search percutaneous coronary intervention Limits: 180 days
12. search unstable angina Limits: 180 days
13. search crescendo Limits: 180 days
14. search crescendocoronary syndrome Limits: 180 days
15. search coronary syndrome Limits: 180 days
16. search heart attack Limits: 180 days
17. search stents Limits: 180 days
18. search myocardial revascularization Limits: 180 days
19. search angioplasty balloon Limits: 180 days
20. search catheter ablation Limits: 180 days
21. search atherectomy Limits: 180 days
22. search myocardial infarction Limits: 180 days
23. search angina pectoris Field: All Fields, Limits: 180 days
24. search angina pectoris
25. #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
26. #6 and #25

11. ScHARR–Lock's Guide to the Evidence

This resource does not seem to have been updated recently.

The following headings were searched:

1. angina
2. myocardial Infarction
3. atherectomy
4. catheter ablation
5. angioplasty balloon
6. myocardial revascularization
7. stents

12. SIGN

The list of published guidelines was scanned.

13. TRIP Database

Searches were carried out one at a time: the 'not' operator was used to exclude items already found in the first search (glycoprotein). TRIP truncates search terms automatically.

1. glycoprotein
2. GpII not glycoprotein
3. abciximab not glycoprotein
4. reopro not glycoprotein
5. eptifibatide not glycoprotein
6. integrilin not glycoprotein
7. integrelin not glycoprotein
8. tirofiban not glycoprotein
9. aggrastat not glycoprotein
10. integrin not glycoprotein

Appendix 2

Original search strategy for previous glycoprotein review

1. CD-ROM resources

The Cochrane Library

Search strategy for licensed glycoprotein antagonists (searched on 19 February 2000)

The first search undertaken was limited to the three glycoprotein antagonists currently licensed in the UK (abciximab, eptifibatide and tirofiban). Using 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 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 (searched on 5 April 2000)

After it was decided that the review should include unlicensed glycoprotein antagonists a second search strategy was conducted. This search strategy was designed to exclude all papers already retrieved and yielded two additional hits. The numerical drug identities were 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)

National Research Register CD-ROM (issue 1, 2000) (searched on 19 January 2000)

Search strategy for licensed glycoprotein antagonists (searched on 19 February 2000)

The first search was limited to the three glycoprotein antagonists currently licensed in the UK (abciximab, eptifibatide and tirofiban). Using 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 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 (searched 5 April 2000)

After it was decided that the review should include unlicensed glycoprotein antagonists a second search strategy was conducted. This search strategy was designed to exclude all papers already retrieved and 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)

2. EMBASE: SilverPlatter

Search strategy for licensed glycoprotein antagonists (searched on 19 February 2000)

The first set of searches was limited to the three glycoprotein antagonists currently licensed in the UK (abciximab, eptifibatide and tirofiban). The first search was limited to cost-effectiveness studies relating to unstable angina and the second search to clinical trial studies relating to unstable angina.

The search strategy used to find cost-effectiveness studies was as follows:

No.	Records	Request
1.	1,660	"fibrinogen-receptor" / all subheadings
2.	1,014	"fibrinogen-receptor-antagonist" / all subheadings
3.	1,082	"abciximab" / all subheadings
4.	276	"eptifibatide" / all subheadings
5.	429	"tirofiban" / all subheadings
6.	7	fibrinogen-receptor* in ti ab
7.	332	abciximab* in ti ab
8.	89	eptifibatide* in ti ab
9.	99	tirofiban* in ti ab
10.	99	reopro* in ti ab
11.	0	intrifiban* in ti ab
12.	27	integrelin* in ti ab
13.	13	aggrastat* in ti ab
14.	274	integrin* near (IIb* near iiia*)
15.	2,296	((glycoprotein* or gp*) near (iib* near iiia*)) or GPII*
16.	20,428	explode "angina-pectoris" / all subheadings
17.	18,875	angina in ti ab
18.	52,760	explode "heart-infarction" / all subheadings
19.	45,660	myocard* infarct*
20.	943	heart attack*
21.	1,154	coronary syndrome*
22.	155	crescendo
23.	34,164	explode "economic-evaluation" / all subheadings
24.	27,117	cost effect*
25.	12,041	cost benefit*
26.	1,528	economic evaluation*
27.	1,555	technology assessment*
28.	7,119	pharmacoeconomic*
29.	600	cost util*
30.	4,134	#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.	82,173	#16 or #17 or #18 or #19 or #20 or #21 or #22
32.	48,160	#23 or #24 or #25 or #26 or #27 or #28 or #29
33.	107	#30 and #31 and #32
34.	28,572	explode "animal" / all subheadings
35.	3,438,241	explode "human" / all subheadings
36.	23,537	#34 not (#34 and #35)
37.	107	#33 not #36

The search strategy used to find clinical trial studies was as follows:

No.	Records	Request
1.	1,660	"fibrinogen-receptor" / all subheadings
2.	1,014	"fibrinogen-receptor-antagonist" / all subheadings
3.	1,082	"abciximab" / all subheadings
4.	276	"eptifibatide" / all subheadings
5.	429	"tirofiban" / all subheadings
6.	7	fibrinogen-receptor* in ti ab
7.	332	abciximab* in ti ab
8.	89	eptifibatide* in ti ab
9.	99	tirofiban* in ti ab
10.	99	reopro* in ti ab
11.	0	intrifiban* in ti ab
12.	27	integrelin* in ti ab
13.	13	aggrastat* in ti ab
14.	274	integrin* near (IIb* near iiia*)
15.	2,296	((glycoprotein* or gp*) near (iib* near iiia*)) or GPIIB*
16.	20,428	explode "angina-pectoris" / all subheadings
17.	18,875	angina in ti ab
18.	52,760	explode "heart-infarction" / all subheadings
19.	45,660	myocard* infarct*
20.	943	heart attack*
21.	1,154	coronary syndrome*
22.	155	crescendo
23.	174,982	explode "Clinical-Trials" / all subheadings
24.	51,540	(clin* near trial*) in ti ab
25.	54,877	((singl* or doubl* or trebl* or tripl*) near (blind* or mask*)) in ti ab
26.	564	Placebos
27.	58,244	placebo* in ti ab
28.	42,369	random in ti ab
29.	42,725	"randomized-controlled-trial" / all subheadings
30.	4,134	#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.	82,173	#16 or #17 or #18 or #19 or #20 or #21 or #22
32.	295,390	#23 or #24 or #25 or #26 or #27 or #28 or #29
33.	574	#30 and #31 and #32
34.	28,572	explode "animal" / all subheadings

35.	3,438,241	explode "human" / all subheadings
36.	23,537	#34 not (#34 and #35)
37.	574	#33 not #36

Search strategy for unlicensed glycoprotein antagonists (searched on 5 April 2000)

After it was decided that the review should include unlicensed glycoprotein antagonists, a second set of searches was conducted. This search strategy was designed to exclude all papers already retrieved and yielded no additional hits.

The search strategy used to find cost-effectiveness studies was as follows:

No.	Records	Request
1.	1,660	"fibrinogen-receptor" / all subheadings
2.	1,014	"fibrinogen-receptor-antagonist" / all subheadings
3.	1,082	"abciximab" / all subheadings
4.	276	"eptifibatide" / all subheadings
5.	429	"tirofiban" / all subheadings
6.	7	fibrinogen-receptor* in ti ab
7.	332	abciximab* in ti ab
8.	89	eptifibatide* in ti ab
9.	99	tirofiban* in ti ab
10.	99	reopro* in ti ab
11.	0	intrifiban* in ti ab
12.	27	integrelin* in ti ab
13.	13	aggrastat* in ti ab
14.	274	integrin* near (IIb* near iiia*)
15.	2,296	((glycoprotein* or gp*) near (iib* near iiia*)) or GPII*
16.	20,428	explode "angina-pectoris" / all subheadings
17.	18,875	angina in ti ab
18.	52,760	explode "heart-infarction" / all subheadings
19.	45,660	myocard* infarct*
20.	943	heart attack*
21.	1,154	coronary syndrome*
22.	155	crescendo
23.	34,164	explode "economic-evaluation" / all subheadings
24.	27,117	cost effect*
25.	12,041	cost benefit*
26.	1,528	economic evaluation*
27.	1,555	technology assessment*
28.	7,119	pharmacoeconomic*
29.	600	cost util*
30.	4,134	#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.	82,173	#16 or #17 or #18 or #19 or #20 or #21 or #22
32.	48,160	#23 or #24 or #25 or #26 or #27 or #28 or #29
33.	107	#30 and #31 and #32
34.	28,572	explode "animal" / all subheadings
35.	3,438,241	explode "human" / all subheadings
36.	23,537	#34 not (#34 and #35)
37.	107	#33 not #36
38.	241	lamifiban or ro 44-9883
39.	67	sibrafiban or xubix or ro 44-3888 or ro 48-3657
40.	43	fradafiban or bibu
41.	26	lefradafiban
42.	132	xemilofiban or sc-54701a or sc-54684a
43.	48	orbofiban or sc-57099b
44.	343	#38 or #39 or #40 or #41 or #42 or #43
45.	21	#31 and #32 and #44
46.	21	#45 not #36
47.	0	#46 not #37

The search strategy used to find clinical trial studies was as follows:

No.	Records	Request
1.	1,660	"fibrinogen-receptor" / all subheadings
2.	1,014	"fibrinogen-receptor-antagonist" / all subheadings
3.	1,082	"abciximab" / all subheadings
4.	276	"eptifibatide" / all subheadings
5.	429	"tirofiban" / all subheadings
6.	7	fibrinogen-receptor* in ti ab
7.	332	abciximab* in ti ab
8.	89	eptifibatide* in ti ab
9.	99	tirofiban* in ti ab
10.	99	reopro* in ti ab
11.	0	intrifiban* in ti ab
12.	27	integrelin* in ti ab
13.	13	aggrastat* in ti ab
14.	274	integrin* near (IIb* near iiia*)
15.	2,296	((glycoprotein* or gp*) near (iib* near iiia*)) or GPIIB*
16.	20,428	explode "angina-pectoris" / all subheadings
17.	18,875	angina in ti ab
18.	52,760	explode "heart-infarction" / all subheadings
19.	45,660	myocard* infarct*
20.	943	heart attack*
21.	1,154	coronary syndrome*
22.	155	crescendo
23.	174,982	explode "Clinical-Trials" / all subheadings
24.	51,540	(clin* near trial*) in ti ab

25.	54,877	((singl* or doubl* or trebl* or tripl*) near (blind* or mask*)) in ti ab
26.	564	Placebos
27.	58,244	placebo* in ti ab
28.	42,369	random in ti ab
29.	42,725	"randomized-controlled-trial" / all subheadings
30.	4,134	#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.	82,173	#16 or #17 or #18 or #19 or #20 or #21 or #22
32.	295,390	#23 or #24 or #25 or #26 or #27 or #28 or #29
33.	574	#30 and #31 and #32
34.	28,572	explode "animal" / all subheadings
35.	3,438,241	explode "human" / all subheadings
36.	23,537	#34 not (#34 and #35)
37.	574	#33 not #36
38.	241	lamifiban or ro 44-9883
39.	67	sibrafiban or xubix or ro 44-3888 or ro 48-3657
40.	43	fradafiban or bibu
41.	26	lefradafiban
42.	132	xemilofiban or sc-54701a or sc-54684a
43.	48	orbofiban or sc-57099b
44.	343	#38 or #39 or #40 or #41 or #42 or #43
45.	146	#31 and #32 and #44
46.	146	#45 not #36
47.	3	#46 not #37

3. MEDLINE: SilverPlatter

Search strategy for licensed glycoprotein antagonists (searched on 19 February 2000)

The first set of searches was limited to the three glycoprotein antagonists currently licensed in the UK (abciximab, eptifibatide and tirofiban). The first search was limited to cost-effectiveness studies relating to unstable angina and the second search to clinical trial studies relating to unstable angina.

The search strategy used to find cost-effectiveness studies was as follows:

No.	Records	Request
1.	1,252	"Platelet-Glycoprotein-GPIIb-IIIa-Complex" / all subheadings
2.	374	abciximab*
3.	67	reopro*
4.	8	aggrastat*
5.	47	eptifibatide*
6.	0	intrifiban*
7.	97	integrelin*
8.	98	tirofiban*
9.	2,144	((gp* or glycoprotein*) near (iib* near iiia*)) or GPIIB*
10.	246	integrin* near (iib* near iiia*)
11.	3,015	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
12.	24,547	explode "Angina-Pectoris" / all subheadings
13.	33,440	angina
14.	77,507	explode "Myocardial-Infarction" / all subheadings
15.	90,173	myocard* infarct*
16.	1,132	heart attack*
17.	1,047	coronary syndrome*
18.	202	crescendo
19.	114,387	#12 or #13 or #14 or #15 or #16 or #17 or #18
20.	482	#11 and #19
21.	16,712	cost effect*
22.	19,914	cost benefit*
23.	923	economic evaluation*
24.	2,613	technology assessment*
25.	475	pharmacoeconomic*
26.	366	cost util*
27.	156,887	explode "Economics" / all subheadings
28.	168,135	#21 or #22 or #23 or #24 or #25 or #26 or #27
*29.	29	#20 and #28

The search strategy used to find clinical trial studies was as follows:

No.	Records	Request
1.	1,252	"Platelet-Glycoprotein-GPIIb-IIIa-Complex" / all subheadings
2.	374	abciximab*
3.	67	reopro*
4.	8	aggrastat*
5.	47	eptifibatide*
6.	0	intrifiban*
7.	97	integrelin*
8.	98	tirofiban*
9.	2,144	((gp* or glycoprotein*) near (iib* near iiia*)) or GPIIB*
10.	246	integrin* near (iib* near iiia*)
11.	3,015	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
12.	24,547	explode "Angina-Pectoris" / all subheadings
13.	33,440	angina
14.	77,507	explode "Myocardial-Infarction" / all subheadings
15.	90,173	myocard* infarct*
16.	1,132	heart attack*
17.	1,047	coronary syndrome*

18.	202	crescendo
19.	114,387	#12 or #13 or #14 or #15 or #16 or #17 or #18
20.	482	#11 and #19
21.	80,314	explode "Clinical-Trials" / all subheadings
22.	53,706	(clin* near trial*) in ti ab
23.	56,340	((singl* or doubl* or treble* or tripl*) near (blind* or mask*)) in ti ab
24.	19,407	"Placebos" / all subheadings
25.	180,594	random* in ti ab
26.	58,647	placebo* in ti ab
27.	310,381	#21 or #22 or #23 or #24 or #25 or #26
*28.	230	#20 and #27

Search strategy for unlicensed glycoprotein antagonists (searched on 5 April 2000)

After it was decided that the review should include unlicensed glycoprotein antagonists a second set of searches was conducted. This search strategy was designed to exclude all papers already retrieved and yielded no additional hits.

The search strategy used to find cost-effectiveness studies was as follows:

No.	Records	Request
1.	1,347	"Platelet-Glycoprotein-GPIIb-IIIa-Complex" / all subheadings
2.	417	abciximab*
3.	75	reopro*
4.	8	aggrastat*
5.	55	eptifibatide*
6.	0	intrifiban*
7.	101	integrelin*
8.	108	tirofiban*
9.	2,215	((gp* or glycoprotein*) near (iib* near iiia*)) or GPIIB*
10.	250	integrin* near (iib* near iiia*)
11.	3,155	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
12.	24,766	explode "Angina-Pectoris" / all subheadings
13.	33,794	angina
14.	78,253	explode "Myocardial-Infarction" / all subheadings
15.	91,184	myocard* infarct*
16.	1,142	heart attack*
17.	1,136	coronary syndrome*
18.	204	crescendo
19.	115,672	#12 or #13 or #14 or #15 or #16 or #17 or #18
20.	533	#11 and #19
21.	17,212	cost effect*
22.	20,415	cost benefit*
23.	966	economic evaluation*
24.	2,681	technology assessment*
25.	499	pharmacoeconomic*
26.	382	cost util*
27.	159,145	explode "Economics" / all subheadings
28.	170,713	#21 or #22 or #23 or #24 or #25 or #26 or #27
29.	34	#20 and #28
30.	106,636	UD > 200001
31.	5	#29 and #30
32.	50	lamifiban or ro 44-9883
33.	17	sibrafiban or ro 44-3888 or ro 48-3657 or xubix
34.	7	fradafiban or bibu
35.	5	lefradafiban
36.	8	xemilofiabn or sc-54701A or sc-54684A
37.	2	orbofiban or sc-57099B
38.	79	#32 or #33 or #34 or #35 or #36 or #37
39.	2	#19 and #28 and #38
40.	0	#39 not #29

The search strategy used to find clinical trial studies 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. UD > 200001
30. #29 and #28
31. lamifiban or ro 44-9883
32. sibrafiban or xubix or ro 44-3888 or ro 48 3657
33. fradafiban or bibu
34. lefradafiban
35. xemilofiban or sc-54701A or sc-54684A
36. orbofiban or sc-57099b
37. #31 or #32 or #33 or #34 or #35 or #36
38. #19 and #27 and #37
39. #38 not #28

Appendix 3

Assessment of internal validity tool

Study					
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 who implement interventions					
Registration of co-interventions that affect the 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 confidence intervals (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					

Appendix 4

Included and excluded studies

Included

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.

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Appendix 5

Outcomes for high-risk groups: medical management indication

Heeschen *et al.*, 1999[44]: PRISM subgroup analysis by troponin-I status

Study details

Comparators	No. of individuals enrolled (total and high risk)	No. of individuals lost to follow-up	Median age (SD)	Prognosis indicators *n* (%) for continuous variables (e.g. blood pressure, heart rate)						
				History of MI	History of PCI	History of CABG	History of CHF	Hyper-tension	Hypercolest-erolaemia	Diabetes
Troponin-I positive	629	Not stated	62.5 (11.1)	274 (43.5%)	58 (9.2%)	96 (15.2%)	78 (12.4%)	320 (50.9%)	281 (44.7%)	123 (19.6%)
Troponin-I negative	1593	–	66.2 (11.0)	750 (47.1%)	271 (17%)	312 (19.6%)	167 (10.5%)	900 (56.5%)	781 (49.0%)	335 (21%)

Other medication (specify separately for high-risk patients)

Comparators	Selected anti-anginal medication before randomisation (%)		Selected anti-anginal medication after randomisation (%)	
	Aspirin	Heparin	Aspirin	Heparin
Troponin-I positive	592 (94.1%)	155 (24.6%)	608 (96.7%)	Not stated
Troponin-I negative	1509 (94.7%)	336 (21.1%)	1537 (96.5%)	Not stated

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

Comparators	Time-point	Acute MI*		Severe recurrent angina/RI*		Death*		Measurement of quality of life*	Composite outcome (death, MI)*		Other
		T-I positive	T-I negative	T-I positive	T-I negative	T-I positive	T-I negative		T-I positive	T-I negative	
Arm 1: tirofiban (*n* = 1097)	48 hours	1 (0.3)	4 (0.5)	10 (3.3)	17 (2.1)	0	3 (0.4)	–	1 (0.3)	7 (0.9)	–
	7 days	4 (1.3)	17 (2.1)	26 (8.5)	59 (7.4)	2 (0.7)	7 (0.9)	–	6 (2.0)	24 (3.0)	–
	30 days	8 (2.6)	27 (3.6)	31 (10.2)	72 (9.1)	5 (1.6)	18 (2.3)	–	13 (4.3)	45 (5.7)	–
Control: heparin (*n* = 1125)	48 hours	9 (2.8)	5 (0.6)	30 (9.3)	24 (3.05)	2 (0.6)	0	–	11 (3.4)	5 (0.6)	–
	7 days	18 (5.6)	14 (1.8)	47 (14.5)	53 (6.6)	12 (3.7)	3 (0.4)	–	30 (9.3)	18 (2.2)	–
	30 days	22 (6.8)	21 (2.6)	48 (14.8)	60 (7.5)	20 (6.2)	18 (2.3)	–	42 (13.0)	39 (4.9)	–

* *Data given as* n *(%)*

T-I, troponin-I

Theroux *et al.*, 2000[45]: subgroup analysis on diabetic patients from PRISM-PLUS

Study details

Study design	Definition of high-risk group (if any)	Inclusion criteria/ exclusion criteria	Interventions (specified by protocol)	Follow-up duration
Subgroup analysis on diabetic patients from the PRISM-PLUS trial	–	See PRISM-PLUS[43] Patients assigned to diabetic or non-diabetic subgroup on the basis of the presence or absence of a history of DM at enrolment	Tirofiban bolus + infusion (0.10 µg) + heparin Tirofiban placebo + heparin (three arms of therapy considered in main trial)	48 hours 7 days 30 days 180 days

Characteristics of participants

Comparators	No. of individuals enrolled (total and high risk)		No. of individuals lost to follow-up		Mean age ± SD		Prognosis indicators given as % for continuous variables (e.g. blood pressure, heart rate)											
							Previous MI		Previous PCI		Previous CABG		Smoking		Unstable angina		Non-ST elevation MI	
	DM	No DM	DM	No DM	DM	No DM	DM	No DM	DM	No DM	DM	No DM	DM	No DM	DM	No DM	DM	No DM
Arm 1: tirofiban + heparin	169	604	Not stated. Only patients from 2 of the treatment arms included in substudy		65 ± 10.2	63 ± 12.1	50	43	10	8.8	20	14	29	34	54	56	42	44
Arm 2: heparin	193	604			66 ± 9.8	62 ± 11.9	44	37	12	8.4	15	13	21	34	59	52	41	48

Other medication

Comparators	Selected anti-anginal medication* before enrolment (%)				Selected anti-anginal medication* after enrolment†
	Nitrates	Beta-blocker	Channel calcium blocker	Insulin	
Arm 1: tirofiban + heparin	DM = 88 No DM = 88	DM = 61 No DM = 53	DM = 53 No DM = 40	DM = 27 No DM = 0.5	See PRISM-PLUS[43] Not stated for subgroup
Arm 2: heparin	DM = 89 No DM = 87	DM = 57 No DM = 52	DM = 50 No DM = 35	DM = 27 No DM = 0	

* *Selected anti-anginal drugs to be considered: anti-platelet agents (aspirin, ticlodipine, clopidogrel); anticoagulants (unfractionated heparin, low molecular weight heparin, enoxaparin, dalteparin*)
† *Data given as* n *(%)*

Outcomes: results (for diabetic patients only)

Time-point	MI/death (%)	Severe recurrent angina/RI (%)	Death (%)	Measurement of quality of life (%)	Composite outcome (%)
48 hours	0	–	–	–	7.7
7 days	1.2	–	–	–	14.8
30 days	4.7	–	–	–	20.1
6 months	11.2	–	–	–	32.0
48 hours	3.1	–	–	–	8.3
7 days	9.3	–	–	–	21.8
30 days	15.5	–	–	–	29.0
6 months	19.2	–	–	–	39.9

Adverse effects (specify separately for high-risk patients)

Comparators	TIMI major bleeding (%)		TIMI minor bleeding (%)		All TIMI bleeding (%)		Other adverse effects requiring treatment
			DM	No DM	DM	No DM	
Arm 1: tirofiban + heparin	0.6	1.7	7.1	11.4	9.5	13.4	Not reported
Arm 2: heparin	0.5	0.8	6.7	8.4	8.3	10.1	

Hasdai *et al.*, 2000[46]: subgroup analysis on PURSUIT

Study details

Study design (any subgroup analyses?)	Definition of high-risk group (if any)	Inclusion criteria/ exclusion criteria	Interventions (specified by protocol)	Follow-up duration
Study looking at impact of age on clinical outcomes of patients in the PURSUIT trial	–	See PURSUIT[38–41]	Eptifibatide versus placebo	30 days

Characteristics of participants

Comparators	No. of individuals enrolled (total and high risk)	No. of individuals lost to follow-up	Prognosis indicators*						
			Current smoker	Previous MI	History of CAD	History of CHF	History of hyper-tension	History of diabetes	Prior CABG
Age < 50	1324	Not stated	769 (58%)	324 (25%)	661 (50%)	52 (4%)	553 (42%)	172 (13%)	87 (7%)
Age 50–59	2184	Not stated	893 (41%)	620 (28%)	876 (40%)	152 (7%)	1115 (51%)	409 (19%)	236 (11%)
Age 60–69	3049	Not stated	717 (24%)	1065 (35%)	1022 (34%)	342 (11%)	1790 (59%)	767 (25%)	411 (13%)
Age 70–79	2398	Not stated	266 (11%)	857 (36%)	676 (28%)	395 (16%)	1466 (61%)	692 (29%)	347 (14%)
Age ≥ 80	506	Not stated	32 (6%)	198 (39%)	88 (17%)	106 (21%)	314 (62%)	123 (24%)	53 (10%)

* *Data given as* n *(%)*

Other medication

Selected anti-anginal medication* before enrolment (%)	Selected anti-anginal medication* after enrolment†
See PURSUIT[38–41]	See PURSUIT[38–41]

* *Selected anti-anginal drugs to be considered: anti-platelet agents (aspirin, ticlodipine, clopidogrel); anticoagulants (unfractionated heparin, low molecular weight heparin, enoxaparin, dalteparin)*
† *Data given as* n *(%)*

Outcomes: definitions and measures

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

* *Data given as* n *(%)*

Boersma *et al.*, 2000[47]: subgroups analysis on PURSUIT

Study details

Study design (any subgroup analyses?)	Definition of high-risk group (if any)	Inclusion criteria	Interventions (specified by protocol)	Follow-up duration
Analysed the relation between baseline characteristics and the 30-day incidence of death or MI in 9461 patients with ACS enrolled in the PURSUIT trial, using univariable and multivariable logistic regression	4308 patients with elevated CK-MB (classified as having MI) and remaining 5129 patients were classified as having UAP	Patients were eligible if they presented within 24 hours of an episode of ischaemic chest pain (> 10 minutes) and had either transient ST-segment elevation (> 0.5 mm), transient or persistent ST-segment depression (> 0.5 mm), T-wave inversion (> 1.0 mm), or elevation of CK-MB fraction above the upper limit of normal Exclusion: persistent (> 30 minutes) ST-segment elevation For full inclusion criteria see PURSUIT[38–41]	See PURSUIT[38–41]	30 days

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

Comparators	
Arm 1: eptifibatide Arm 2: placebo	See PURSUIT[38–41] for demographic details

Other medication (specify separately for high-risk patients)

Comparators	Selected anti-anginal medication* before enrolment†	Selected anti-anginal medication* after enrolment†
Arm 1: eptifibatide	See PURSUIT[38–41] for data	
Arm 2: placebo		

* *Selected anti-anginal drugs to be considered: anti-platelet agents (aspirin, ticlodipine, clopidogrel); anticoagulants (unfractionated heparin, low molecular weight heparin, enoxaparin, dalteparin)*
† *Data given as* n *(%)*

Outcomes: definitions and measures

Acute MI	Death	Composite outcome
Within 18 hours of enrolment: ischaemic chest pain and new ST-segment elevation After 18 hours: new Q-waves or new or repeated CK-MB elevations above the upper limit of normal. For patients undergoing PCI or CABG; CK-MB elevation above 3 or 5 times the upper limit of normal	See PURSUIT[38–41] for definition	Death and MI at 30 days

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

Comparators	Death		Composite outcome	
	Rate (%)	OR (95% CI)	Rate (%)	OR (95% CI)
Arm 1: eptifibatide	3.5	UAP: 1.25 (0.89 to 1.76) MI: 0.74 (0.56 to 0.99)	14.2	0.89 (0.79 to 0.99)
Arm 2: placebo	3.7	1	15.7	1

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

Comparators	Death OR (95% CI)	Composite outcome OR (95% CI)
Arm 1: eptifibatide	UAP: 1.28 (0.91 to 1.81) MI: 0.79 (0.58 to 1.07)	0.90 (0.80 to 1.01)
Arm 2: placebo	1	1

Appendix 6

Validity assessment tool for economic evaluations

Study						
Well-defined question posed?						
Comprehensive descriptions of alternatives given?						
Effectiveness established?						
Important/relevant costs and consequences for each alternative identified?						
Methods used to measure costs made explicit?						
Methods used to measure costs and outcomes appropriate?						
Costs and outcomes adjusted for differential timing?						
Incremental analysis of costs and consequences performed?						
Sensitivity analysis performed?						
Study results and discussion include all the issues of concern to users?						
+, Item properly addressed; –, item not properly addressed; ±, item partially addressed; ?, unknown						

Appendix 7

Economic evaluations of glycoproteins in the medical management of ACS patients

Hillegass *et al.*, 1999[87]

What question(s) does the study address?	Country/ currency	Comparator(s)	Study population	Subgroup analysis	Length of follow-up
Review of the available information regarding the economic implications of the use of IIb/IIIa agents during PCI and ACS	USA, year not stated US dollars	Eptifibatide and tirofiban versus placebo	Patients with ACS, initially going to be medically managed Patients who were undergoing PCI for whom GPAs were used as an adjunctive agent	None reported	30 days
Methods/type of study	**Source of effectiveness data**	**Source of cost data**	**Methods of extrapolation**	**Analysis of uncertainty**	**Main conclusions**
Cost-effectiveness analysis based on literature review	Data from PRISM, PRISM-PLUS and PURSUIT for ACS patients For PCI patients, data from EPIC, EPILOG, IMPACT-II, RESTORE, CAPTURE	Drug costs from Merck and Cor pharmaceuticals and Premier Purchasing Partners	None used	No analysis of uncertainty performed	Expenditures per death or MI prevented in patients with ACS range from $32,000 to $82,000. Only high-risk groups are likely to have cost-effectiveness ratios that most Western health-care systems can afford Inpatients undergoing PCI expenditures per death or MI prevented range from $15,477 to $37,100. As a group, GPAs appear to be more cost-effective for patients undergoing PCI

Mark *et al.*, 2000[88]

What question(s) does the study address?	Country/ currency	Comparator(s)	Study population	Subgroup analysis	Length of follow-up
The cost-effectiveness of eptifibatide plus standard care versus standard care alone, in non-ST-elevation ACS	USA, 1996 US dollars	Eptifibatide, placebo	Cohort of 3522 US patients enrolled in PURSUIT trial. Mean age 62 years, 65% male. Unstable angina or non-Q-wave MI	None reported	6-month data used to extrapolate over lifetime
Methods/type of study	**Source of effectiveness data**	**Source of cost data**	**Methods of extrapolation**	**Analysis of uncertainty**	**Main conclusions**
2-part economic sub-study of patients enrolled in PURSUIT. Medical costs up to 6 months after hospitalisations. Lifetime cost-effective analyses. Some non-medical costs, outpatient care and productivity costs omitted	US population of PURSUIT study	Medical resource use and costs measured starting at hospitalisation and extending through the 6-month follow-up period. Resource use was determined from clinical case reports. Charges to costs calculated for hospital costs	Composite end-point extrapolated into life expectancy for each treatment cohort. Four models used to extrapolate life expectancy for PURSUIT population: (1) Cox proportional hazards regression model to model initial 6 months; (2) Cox proportional hazards regression model constructed using factors available from Dukes database and PURSUIT database; (3) model number of DUKE patients had a MI in first 30 days; (4) logistic regression to model probability of 30-day end-point MI adjusted for age, sex and treatment	Sensitivity analysis conducted on main starting parameters on base case model. Costs varied according to 95% CI around cumulative 6-month cost differences	Incremental cost-effectiveness ratio for eptifibatide versus placebo $16,491 per year of life saved. Based on PURSUIT, the addition of eptifibatide to standard care for non-ST-elevation ACS patients ise co-nomically attractive by conventional standards

McElwee & Johnson, 1997[89]

What question(s) does the study address?	Country/ currency	Comparator(s)	Study population	Subgroup analysis	Length of follow-up
Estimates the cost-effectiveness ratio for various scenarios using IIb/IIIa's receptor inhibitors in patients with unstable angina and non-Q-wave MI Looked at the role of GPAs in reducing complications associated with abrupt closure after PCI and the use of GPAs for ACS patients	USA, 1996 US dollars	Abciximab's effects used to generalise to all IIb/IIIa versus placebo	Unstable angina patients with non-Q-wave MI	Patients with unstable angina compared with those who undergo PTCA. Rates of death/ MI available. Treatment effects applied as a range (20%, 30%, 40%)	Lifetime survival estimated using average survival for patients with AMI observed in GUSTO trial* (15.4 years)
Methods/type of study	**Source of effectiveness data**	**Source of cost data**	**Methods of extrapolation**	**Analysis of uncertainty**	**Main conclusions**
Decision analytic model used to estimate the value (cost-effectiveness) of IIb/IIIa therapy under various conditions Survival discounted at 6% Perspective of the treating hospital	IMPACT-II, EPIC and CAPTURE data used for the model. GUSTO used to estimate lifetime survival	Costs assigned to revascularisation procedures and AMI (non-fatal) estimated from regression analysis of IMPACT-II and other sources (unknown)	None used	Treatment effects of 20%, 30% and 40% used. Revascularisation rates 25–65% used. Death and MI rates after stenting varied (decreased by 50%). Did not change conclusions	Results suggest IIb/IIIa as primary therapy will be exceptionally good value: ≤ $20,000 per LYG at treatment effects of 30% and 40% and in the range considered acceptable: ≤ $50,000 per LYG at treatment effect of 20% Primary therapy is wise in unstable angina patients compared with treating only patients who undergo PCI

* *Mark DB, Hlatky MA, Califf RM, Naylor CD, Lee KL, Armstrong PW,* et al. *Cost effectiveness of thrombolytic therapy with tissue plasminogen activator as compared with streptokinase for acute myocardial infarction*. N Engl J Med *1995;**332**:1418–24*.

Bell, 1999[90]

What question(s) does the study address?	Country/ currency	Comparator(s)	Study population	Subgroup analysis	Length of follow-up
Comparison of the acquisition costs and outcomes of 3 IIb/IIIa inhibitors	USA, 1998 US dollars	Abciximab, tirofiban, eptifibatide	As in PURSUIT and PRISM-PLUS for all patients who underwent early PCI. For medically managed patients only North American cohort	None reported	30 days
Methods/type of study	**Source of effectiveness data**	**Source of cost data**	**Methods of extrapolation**	**Analysis of uncertainty**	**Main conclusions**
Providers perspective. NNT and drug acquisition costs expended to prevent one MI or death calculated Literature review: studies chosen because of their perceived importance in changing medical practice	PURSUIT and PRISM-PLUS studies. Outcomes for patients who were medically managed in PURSUIT and PRISM-PLUS were determined using only patients enrolled in the North American cohort of PURSUIT	Cost of therapy based on wholesale acquisition cost (written communication)	Not used	Sensitivity analysis conducted by varying ARR and wholesale costs. 95% CI used for maximum and minimum values	Expenditures per death or MI prevented in patients with ACS range from $40,000 to $46,000 For PCI patient's expenditures per death or MI prevented ranged from $10,695 to $74,046. In unstable angina patients, eptifibatide and tirofiban may be cost-effective if administered to populations at high risk for adverse outcomes of ACS or PCI

Szucs *et al.*, 1999[91]

What question(s) does the study address?	Country/ currency	Comparator(s)	Study population	Subgroup analysis	Length of follow-up
The study aimed to conduct an incremental cost analysis of tirofiban plus heparin and aspirin versus standard treatment with heparin plus aspirin for patients enrolled in the PRISM-PLUS trial. Main hypothesis tested was whether the costs of additional tirofiban treatment would be partially or completely offset by a reduction in additional inpatient resource use due to complications and MI	Switzerland, 1998 Swiss franc European currency at a rate of 1 Euro to 1.64 Swiss francs	Tirofiban plus heparin plus aspirin versus heparin plus aspirin	100 patients with acute UAP and/or non-Q-wave MI from PRISM-PLUS trial	None reported	7 days
Methods/type of study	**Source of effectiveness data**	**Source of cost data**	**Methods of extrapolation**	**Analysis of uncertainty**	**Main conclusions**
Cost–consequence analysis. Perspective of the admitting hospital. Hypothetical cohort of 100 patients with acute UAP and/or non-Q-wave MI	Clinical efficacy data from PRISM-PLUS. Unstable angina defined as prolonged, repetitive angina at rest with 12 hours prior to randomisation and ECG evidence of ischaemia or elevated cardiac enzymes	Costs of managing ischaemic complications based on typical practice patterns in Swiss hospitals. Revascularisation from secondary sources	None used	Univariate sensitivity analyses performed: unit cost resource ± 50%, threshold analysis for drug costs, 95% CI for RD reported in PRISM-PLUS	Tirofiban is cost-saving in ACS and improves the economics of managing these patients during initial hospitalisation. Tirofiban saved 549 Swiss francs per patient

Schering-Plough Ltd, 2000[92]

What question(s) does the study address?	Country/ currency	Comparator(s)	Study population	Subgroup analysis	Length of follow-up
The cost-effectiveness of eptifibatide for patients with CAD undergoing planned, elective PCI with stenting	Focus on Western European patients in multi-national trial Costs reported in UK pounds sterling	Eptifibatide, placebo	2000 patients with CAD	None reported	Resource use data up to 6-months follow-up
Methods/type of study	**Source of effectiveness data**	**Source of cost data**	**Methods of extrapolation**	**Analysis of uncertainty**	**Main conclusions**
Double-blind, placebo-controlled	PURSUIT trial: Western European patients' increase in life expectancy data	PURSUIT trial. Costs reported for UK and all Western European patients Hospital rates from 3 cardio-vascular centres (UK), hospital administration costs from accounting system, procedures based on actual con-sumables and equipment, PTCA and CABG costs from Mckenna *et al.* (1997)*, magnetic resonance imaging costs from charge data, stroke follow-up costs from Personal Social Services Research Unit and Healthcare Resource Group, and drug costs from the *British National Formulary*	6-month survival and 30-day non-fatal MIs modelled to estimate life expectancy 4 models developed by Mark *et al.* (2000)[88] integrated to obtain survival estimates Life expectancy estimated using follow-up data from DUKE database	Sensitivity analysis conducted on unit costs, discount rate and resource use	Cost per LYG for eptifibatide versus placebo in UK patients; at all 3 discount rates eptifibatide dominates (using all Western European data): no discounting = £8179; 1.5% = £9749; 3% = £11,079 per LYG

* *McKenna M, Wheeldon N, Buxton MJ. Costing cardiac revascularisation for economic evaluation: micro-costing versus routine data?* Br J Med Econ *1997;**11**:65–79*

Merck Sharp & Dohme Ltd, 2000[93]

What question(s) does the study address?	Country/ currency	Comparator(s)	Study population	Subgroup analysis	Length of follow-up
Cost-efficacy analysis of tirofiban compared with placebo in patients with unstable angina or non-Q-wave MI	Effect data taken from US trial UK pounds sterling	Tirofiban + heparin versus heparin	PRISM-PLUS patients. Unstable angina and non-Q-wave MI	None reported	180 days for primary cost-effective analysis; 7 days for secondary cost-effective analysis
Methods/type of study	**Source of effectiveness data**	**Source of cost data**	**Methods of extrapolation**	**Analysis of uncertainty**	**Main conclusions**
Primary and secondary cost-effectiveness analysis conducted	PRISM-PLUS	Drug use data from PRISM-PLUS Treatment patterns for cohort of 1046 UK patients in PRAIS-UK Case mix data used to assign costs	None used	95% CI provided for effects, costs and ICERs	ICER of tirofiban over placebo for 7-day timeframe = £8760 ICER for 180-day timeframe = £9955

Appendix 8

Economic evaluations of glycoproteins used alongside PCI

Hillegass *et al.*, 1999[87]

What question(s) does the study address?	Country/ currency	Comparator(s)	Study population	Subgroup analysis	Length of follow-up
Review of available economic data on IIb/IIIa therapy given to patients undergoing PCI	USA US dollars	Abciximab, tirofiban, eptifibatide	As in individual trials	None reported	As in respective trials
Methods/type of study	**Source of effectiveness data**	**Source of cost data**	**Methods of extrapolation**	**Analysis of uncertainty**	**Main conclusions**
Retrospective review of available economic evidence	EPIC, CAPTURE, EPILOG, RAPPORT, EPISTENT, RESTORE, IMPACT-II	From respective studies	–	–	Western countries can probably only afford to treat high-risk (e.g. elevated troponin, unstable angina) patients Costs of death/MI averted reported for individual trials

Mark *et al.*, 2000[88]*

What question(s) does the study address?	Country/ currency	Comparator(s)	Study population	Subgroup analysis	Length of follow-up
Economic analysis of PURSUIT results, assessing the cost-effectiveness of eptifibatide in patients with non-ST elevation ACS	US dollars	Eptifibatide versus placebo	US cohort of 3522; 33% received PTCA during study; mean age 62; 65% male	None reported	6-month trial data. Cost-effectiveness analysis conducted over a lifetime
Methods/type of study	**Source of effectiveness data**	**Source of cost data**	**Methods of extrapolation**	**Analysis of uncertainty**	**Main conclusions**
Prospective economic sub-study. Societal perspective, some societal costs omitted	PURSUIT	Hospital billing data from 2464 (70%) of cohort. Converted to costs using department-specific correction factors Average whole-sale price of eptifibatide Medicare fee schedule for physician costs. For those patients without billing records linear-regression imputation models developed	Using PURSUIT primary end-point results, projected life-expectancy using data from DUKE database. Estimates were derived using 4 models integrated to predict lifetime survival Analysis assumed no major differences in costs after 6-month period	Three major assumptions (reduction in primary end-point, definition of primary end-point, need to account for end-point MI size) subjected to sensitivity analysis. Discount rates, incremental costs and health state values also varied	ICER for eptifibatide versus placebo was $16,491 per year of life saved. ICER not calculated for 6-month trial data; authors felt study not powered to detect difference in life expectancy

* *Mark* et al. *(2000) featured in both McDonagh* et al. *(2000[3]) and Fischer* et al. *(2000[4]) reviews; table refers to data extracted from Fischer* et al.

Bell, 1999[90]

What question(s) does the study address?	Country/ currency	Comparator(s)	Study population	Subgroup analysis	Length of follow-up
Comparison of acquisition costs and outcomes of GPAs in patients undergoing PCI	US dollars	Abciximab, eptifibatide, tirofiban	As in trials	None reported	As in trials
Methods/type of study	**Source of effectiveness data**	**Source of cost data**	**Methods of extrapolation**	**Analysis of uncertainty**	**Main conclusions**
Retrospective review NNT and drug acquisition costs to prevent one MI or death	EPIC, EPILOG, IMPACT-II, PURSUIT, RESTORE, PRISM-PLUS	Wholesale drug acquisition costs	–	Effectiveness CI used as ranges. No other sensitivity analysis undertaken	RESTORE, with high-risk PCI patients reported the highest cost per event prevented at $74,046

Dunn & Foster, 1999[96]

What question(s) does the study address?	Country/ currency	Comparator(s)	Study population	Subgroup analysis	Length of follow-up
Cost-effectiveness of abciximab in patients undergoing PCI. High risk, including unstable angina	US dollars, Australian dollars, Spanish pesetas, Dutch guilders	Abciximab	Patients undergoing PCI who received abciximab	Subgroup analyses in high-risk patients	As individual trials
Methods/type of study	**Source of effectiveness data**	**Source of cost data**	**Methods of extrapolation**	**Analysis of uncertainty**	**Main conclusions**
Retrospective review of economic evidence, hospital perspective	Various trials (EPIC, EPILOG, EPISTENT, CAPTURE)	As in original studies	Mentions Aristides *et al.* (1998[103]) which projected a 10-year survival for those surviving the initial period	As individual trials; descriptions not clear	Abciximab was cost-saving in patients with unstable angina and other less high-risk groups

Mark *et al.*, 1996[97]

What question(s) does the study address?	Country/ currency	Comparator(s)	Study population	Subgroup analysis	Length of follow-up
Cost-effectiveness of abciximab after high-risk angioplasty	USA US dollars	As in EPIC trial	97% of patients enrolled in EPIC (some with unstable rest angina)	Differences in resource consumption reported for unstable angina	6 months
Methods/type of study	**Source of effectiveness data**	**Source of cost data**	**Methods of extrapolation**	**Analysis of uncertainty**	**Main conclusions**
Regression analysis used to examine economic impact of reduced ischaemic events and increased bleeding rates. Cost minimisation analysis	EPIC trial	Hospital charges converted costs; charge to cost ratios taken from Medicare cost report of hospital	–	SDs reported for parameters	Treatment is cost-saving by $268 for urgent PTCA at 6 months, when cost of bleeding complications considered ($531), cost-saving disappears. Non-urgent PTCA has a net cost of £25, with bleeding included

Van Hout & Simoons, 1995[98]

What question(s) does the study address?	Country/ currency	Comparator(s)	Study population	Subgroup analysis	Length of follow-up
The cost-effectiveness of abciximab in high-risk patients undergoing PCI	The Netherlands Dutch guilder, 1995	Abciximab bolus and 12-hour infusion; abciximab bolus and placebo infusion; placebo bolus and placebo infusion	2099 patients enrolled in EPIC	Results for unstable angina or MI patients reported, also for different weight subgroups	EPIC looked at outcomes after 30 days, and then after 6-month follow-up
Methods/type of study	**Source of effectiveness data**	**Source of cost data**	**Methods of extrapolation**	**Analysis of uncertainty**	**Main conclusions**
Retrospective economic analysis, applying cost data from The Netherlands to effectiveness results shown in EPIC. Primary outcomes: non-fatal MI, emergency CABG, emergency PCI, stent placement, death, balloon pump insertion. Risk of bleeding also considered	EPIC study conducted in the USA	Taken from Dutch patients in HELVETICA or CAPTURE	Not undertaken	Sensitivity analysis performed: increase cost estimates by 20%, differences in effects decreased by 20%	Recommend abciximab as cost-effective for high-risk patients but not yet for others. Costs of bleeding are a crucial factor

Van Hout *et al.*, 1998[99]

What question(s) does the study address?	Country/ currency	Comparator(s)	Study population	Subgroup analysis	Length of follow-up
Economic evaluation of abciximab in high-risk patients undergoing PCI. Analysis in unstable angina subgroup	Costs presented in Dutch guilders	1. Abciximab bolus + 12-hour infusion 2. Abciximab bolus + placebo infusion 3. Placebo bolus + placebo infusion	EPIC patients scheduled to undergo coronary angiography or atherectomy in high-risk situations involving severe unstable angina, evolving AMI or high-risk coronary morphologic characteristics	Unstable angina subgroup analysis. Results reported separately – probability that cost per additional survivor is less than Fl 150,464	1 year
Methods/type of study	**Source of effectiveness data**	**Source of cost data**	**Methods of extrapolation**	**Analysis of uncertainty**	**Main conclusions**
Cost-effectiveness analysis Primary end-point: death, non-fatal MI, emergency PTCA, emergency CABG, stent placement, balloon pump insertion. Bleeding rates also considered	EPIC trial	Taken from Dutch patients in HELVETICA or CAPTURE	Extrapolation of survival data to life expectancy estimates as in Mark *et al.*, 1995*	Probabilistic sensitivity analysis Uncertainties in cost-effective estimates presented as probability ellipses. 95% CI presented	Unstable angina patients: probability that abciximab treatment combines additional effectiveness with cost-savings is 61%; probability that abciximab is less effective and more costly than standard treatment is 0.72%

* *Mark DB, Hlatky MA, Califf RM, Naylor CD, Lee KL, Armstrong PW*, et al. *Cost effectiveness of thrombolytic therapy with tissue plasminogen activator as compared with streptokinase for acute myocardial infarction*. N Engl J Med *1995;**332**:1418–24*

Anderson *et al.*, 1999[100]

What question(s) does the study address?	Country/ currency	Comparator(s)	Study population	Subgroup analysis	Length of follow-up
Review of two study designs, for trials with abciximab	USA US dollars	Placebo bolus followed by 12-hour placebo infusion; abciximab bolus followed by 12-hour placebo infusion; abciximab bolus followed by 12-hour abciximab infusion	Patients in EPIC trial	Subset of patients with unstable angina. Separate costs/ outcomes reported	See EPIC[69–71]
Methods/type of study	**Source of effectiveness data**	**Source of cost data**	**Methods of extrapolation**	**Analysis of uncertainty**	**Main conclusions**
Cost-effectiveness analysis	EPIC	Hospital bills from baseline hospitalisation and subsequent treatment in study. Cost to charge ratios calculated from Medicare cost reports	Not undertaken	SDs reported	Abciximab appears to be particularly cost-effective in unstable angina patients undergoing PTCA

Sacristan *et al.*, 1996[101]

What question(s) does the study address?	Country/ currency	Comparator(s)	Study population	Subgroup analysis	Length of follow-up
The cost-effectiveness of abciximab compared to standard therapy in high-risk patients undergoing PCI	Spanish cost data Spanish pesetas	Abciximab. Standard care: heparin + aspirin	Patients enrolled in EPIC trial. High-risk patients scheduled for PCI or directional atherectomy	Subgroup of patients with MI and unstable angina. Effectiveness data and cost-effectiveness results reported separately. Unstable angina ICER = $5446	6 months
Methods/type of study	**Source of effectiveness data**	**Source of cost data**	**Methods of extrapolation**	**Analysis of uncertainty**	**Main conclusions**
Decision analytic model used to look at costs and outcomes of strategies. Spanish health service perspective used. Additional cost calculated for each patient who did not have ischaemic complications or need to repeat PCI, CABG or both	EPIC	Published Spanish data	–	Sensitivity analysis performed on cost of ischaemic complications and revascularisation	Incremental cost-effectiveness of abciximab compared with standard therapy was $5804 for each patient without ischaemic complications or repeat revascularisation procedures at 6 months post PTCA

Zed *et al.*, 1998[102]

What question(s) does the study address?	Country/ currency	Comparator(s)	Study population	Subgroup analysis	Length of follow-up
Assesses the cost-effectiveness of abciximab therapy versus traditional therapy in high-risk patients receiving PTCA	Canada Canadian dollars	Abciximab IV bolus 10 minutes prior to PTCA followed by abciximab infusion 12 hours after versus no abciximab at time of PTCA	Patients in EPIC and CAPTURE	None reported	6 months follow-up
Methods/type of study	**Source of effectiveness data**	**Source of cost data**	**Methods of extrapolation**	**Analysis of uncertainty**	**Main conclusions**
Decision analytic model used to assess costs and outcomes. Composite end-point of death, MI and repeat revascularisation via PTCA or CABG. Bleeding complications also considered. Institutional perspective	Probability estimates from EPIC and CAPTURE. Weighted average of composite event rates. Bleeding rates from CAPTURE. Other probabilities from the Vancouver Hospital and Health Services Center	Patient costing department – actual resource consumption. Cost of major bleeding from published source	–	Univariate sensitivity analysis conducted: abciximab costs, event rates and major bleeding complications	Average cost per patient for each strategy was $3261 in abciximab versus $2073 in no abciximab arm. With an ICER of $29,700 per event-free patient

Aristides *et al.*, 1998[103]

What question(s) does the study address?	Country/ currency	Comparator(s)	Study population	Subgroup analysis	Length of follow-up
Cost-effectiveness of abciximab in preventing restenosis after PTCA	Australian dollars	Abciximab, placebo	Patients who were at high risk for ischaemic complications after PTCA	None reported	EPIC lasted 6 months. Long-term model extended to over 10 years
Methods/type of study	**Source of effectiveness data**	**Source of cost data**	**Methods of extrapolation**	**Analysis of uncertainty**	**Main conclusions**
Outcomes used: repeat revascularisation, main composite end-point and combined risk/ benefit measure	EPIC	Unit costs from Australian national casemix costs	Survival, event-free survival estimated over 10-year period. Markov process used linking the effectiveness data from EPIC with outcomes data from an earlier study	For trial-based analysis, incremental ratios recalculated using event rates based on 95% CIs. Eliminating survival benefit for single vessel disease patients and halving the number of event-free years gained analysed in sensitivity analysis	Cost per additional LYG = $5547 and cost per additional year event-free = $4285

Goklaney *et al.*, 1998[104]

What question(s) does the study address?	Country/ currency	Comparator(s)	Study population	Subgroup analysis	Length of follow-up
Review of the economic evidence of abciximab during PCI	US dollars	Abciximab, standard therapy	As in EPIC, CAPTURE and EPILOG trials	None reported	As in EPIC, CAPTURE and EPILOG trials
Methods/type of study	**Source of effectiveness data**	**Source of cost data**	**Methods of extrapolation**	**Analysis of uncertainty**	**Main conclusions**
Cost analysis and cost-effectiveness; retrospective review	EPIC, CAPTURE, EPILOG	Not stated	Not undertaken	95% CI on EPIC cost difference	Evidence shows cost-savings in high-risk groups

Lorenzoni *et al.*, 1999[105]

What question(s) does the study address?	Country/ currency	Comparator(s)	Study population	Subgroup analysis	Length of follow-up
–	Italian lira	–	As in EPIC, CAPTURE and EPILOG trials	None reported	As in EPIC, CAPTURE and EPILOG trials
Methods/type of study	**Source of effectiveness data**	**Source of cost data**	**Methods of extrapolation**	**Analysis of uncertainty**	**Main conclusions**
Cost-effectiveness analysis	EPIC, CAPTURE, EPILOG	Unit costs from diagnostic-related groups	–	Not reported	ICER 34.3 million lira per event prevented; cost of a LYG = 32.3 million lira

McGregor & Brophy, 1999[106]

What question(s) does the study address?	Country/ currency	Comparator(s)	Study population	Subgroup analysis	Length of follow-up
To estimate the clinical benefits and costs of abciximab at the time of angioplasty	Canadian dollars	Abciximab	RAPPORT: patients with evolving MI; EPIC: unstable angina + AMI; EPILOG: MI or unstable angina; CAPTURE: refractory unstable angina. Combined study had more patients with unstable angina and evolving MI than stable angina	None reported	As in EPIC, EPILOG, RAPPORT and CAPTURE trials
Methods/type of study	**Source of effectiveness data**	**Source of cost data**	**Methods of extrapolation**	**Analysis of uncertainty**	**Main conclusions**
Primary outcomes were death, MI and revascularisation procedures, also given as composite Events avoided by abciximab calculated	EPIC, CAPTURE, EPILOG, RAPPORT	Personal communication: S. Grover. Costs for a Vancover hospital from Zed *et al.*, 1998[102]	Not undertaken	One-way sensitivity analysis on MI and revascularisation rate gives the range Can$15,500–56,600. Monte Carlo on same inputs gives the range Can$12,000–91,000	Costs of preventing one MI at time of PCI with abciximab in high-risk populations = $44,073. When MI and revascularisation taken together cost = $26,933

Topol *et al.*, 1999[107]

What question(s) does the study address?	Country/ currency	Comparator(s)	Study population	Subgroup analysis	Length of follow-up
Outcomes for potent antiplatelet therapy at the time of stenting	US dollars	Abciximab + stenting; stenting + placebo; PCI + abciximab	EPISTENT: patients about to undergo planned or emergency PCI	Outcomes in diabetic patients assessed. Modelling used to assess differences in outcomes in patients with complications	1-year follow-up
Methods/type of study	**Source of effectiveness data**	**Source of cost data**	**Methods of extrapolation**	**Analysis of uncertainty**	**Main conclusions**
Lifetime cost-effectiveness model based on USA cost data and overall survival data from the trial. Societal perspective used. Cost per additional LYG calculated year	EPISTENT	Hospital bills	Survival data from EPISTENT used to extend results to lifetime. DUKE database patients matched with EPISTENT-type patients. Regression modelling used to extrapolate (described in Mark *et al.*, 1995*, 2000[88])	Sensitivity analysis not reported	Compared with stent + placebo, stent + abciximab had a cost-effectiveness ratio of $6213 per added life-year. Compared with PCI + abciximab, stent + abciximab had a cost-effectiveness ratio of $5291 per added life-

* *Mark DB, Hlatky MA, Califf RM, Naylor CD, Lee KL, Armstrong PW*, et al. *Cost effectiveness of thrombolytic therapy with tissue plasminogen*

Weintraub *et al.*, 1999[108]

What question(s) does the study address?	Country/ currency	Comparator(s)	Study population	Subgroup analysis	Length of follow-up
To assess the impact of tirofiban use on costs during initial hospitalisation and at 30 days among patients undergoing high-risk coronary angioplasty	USA US dollars	Tirofiban versus placebo	RESTORE patients	None reported	30 days
Methods/type of study	**Source of effectiveness data**	**Source of cost data**	**Methods of extrapolation**	**Analysis of uncertainty**	**Main conclusions**
Cost comparison of patients with or without eptifibatide angioplasty for 6 countries. Societal perspective	RESTORE trial	Country-specific costs	–	None described	Clinical benefit can be achieved at no additional cost in high-risk patients during initial hospitalisation and at 30 days

Hermiller & Kereiakes, 1999[109]

What question(s) does the study address?	Country/ currency	Comparator(s)	Study population	Subgroup analysis	Length of follow-up
Review to determine how cost-effective GP IIb/IIIa receptor blockade is in comparison with other frequently used accepted therapeutic modalities	US dollars	EPIC, EPILOG and CAPTURE	Patients from EPIC, EPILOG and CAPTURE trials	Subgroup analysis of EPIC unstable angina population described	EPIC, EPILOG and CAPTURE
Methods/type of study	**Source of effectiveness data**	**Source of cost data**	**Methods of extrapolation**	**Analysis of uncertainty**	**Main conclusions**
Review of the literature	EPIC trial	As in trials	–	–	Overall the available data suggest that the clinical benefit of abciximab is worth the net increment in the cost of therapy

Reed *et al.*, 2000[110]

What question(s) does the study address?	Country/ currency	Comparator(s)	Study population	Subgroup analysis	Length of follow-up
Estimates the cost per ischaemic event avoided at 6 months in high-risk patients undergoing revascularisation treated with abciximab during routine care	US dollars	Abciximab versus no abciximab	Patients at high risk for ischaemic events, including patients who underwent a PCI	Numbers of unstable/stable angina, post MI angina and AMI given for each cohort. Results not reported separately for different groups	6 months
Methods/type of study	**Source of effectiveness data**	**Source of cost data**	**Methods of extrapolation**	**Analysis of uncertainty**	**Main conclusions**
Retrospective matched cohort study (according to gender, hyperlipidaemia, DM and stenting). Third-party payer perspective. Variability in results presented as ellipses	Non-random matched cohort study	Hospital billing data. Cost to charge ratio used	–	Confidence ellipses using Fiellers theorem used to assess variability in results	Abciximab patients had an ICER of $21,789 (95% CI = –infinity to –$115,461 and $391 to +infinity)

Weintraub *et al.*, 2000[111]

What question(s) does the study address?	Country/ currency	Comparator(s)	Study population	Subgroup analysis	Length of follow-up
Cost-effectiveness of GP IIb/IIIa therapy targeted to patients according to their level of risk	US dollars	GP IIb/IIIa versus no GP IIb/IIIa	4962 patients at Emory University Hospitals, Atlanta. All underwent coronary intervention procedures. Study included patients having procedures for unstable angina	Results presented according to different risk groups (probability of an event)	Lifetime
Methods/type of study	**Source of effectiveness data**	**Source of cost data**	**Methods of extrapolation**	**Analysis of uncertainty**	**Main conclusions**
Prospective economic analysis, using decision modelling. QALY calculated	Patients at Emory University Hospitals	Hospital billing data used. Charges converted to costs using departmental cost-to-charge ratio. Professional charges and Current Procedural Terminology codes for episodes of care converted using Resource-based Relative Value Scale	Long-term survival determined using Kaplan–Meier method. Data from 21,535 patients undergoing PCI	Sensitivity analysis performed on costs of therapy, efficacy of therapy and cut-off probability of complications for initiating therapy on the cost-effectiveness ratio	For high-risk populations there may be cost-savings, but for low-risk populations GP IIb/IIIa's may not be cost-effective

Kereiakes, 1998[113]

What question(s) does the study address?	Country/ currency	Comparator(s)	Study population	Subgroup analysis	Length of follow-up
Analysed the impact of abciximab use during PCI, in terms of costs and clinical outcomes	US dollars	Abciximab during PCI versus no abciximab	Patients undergoing PCI	–	6 months
Methods/type of study	**Source of effectiveness data**	**Source of cost data**	**Methods of extrapolation**	**Analysis of uncertainty**	**Main conclusions**
Cost-effectiveness analysis conducted alongside observational study. Methods applied to adjust for non-randomised nature of study	1338 (demographics presented for 1305) patients undergoing 1472 PCI procedures at Christ Hospital in Cincinnati, Ohio. Data collected prospectively	Resource use collected from patients in study prospectively. Hospital charges applied to resource use (x 0.75)	–	Bootstrapping undertaken on estimates of ICER to produce 95% CIs	Cost per LYG for adjunctive abciximab during PCI ranged from a low of $617/year of life gained for diabetic patients (adjusted to account for non-randomisation) to $5193 (stented patients, unadjusted) Abciximab provides a cost-effective survival advantage in high-volume interventional practice

Zwart-van Rijkom & van Hout, 2001[114]

What question(s) does the study address?	Country/ currency	Comparator(s)	Study population	Subgroup analysis	Length of follow-up
Cost-efficacy of adding a stent to a procedure where the use of abciximab is planned, and adding abciximab to a procedure where use of a stent is planned	Trial conducted in USA Dutch cost data. Costs expressed in 1998 Euros	As in EPISTENT	ACS patients undergoing PTCA. Also looks at a subgroup of diabetic patients	Diabetic patients	30 days
Methods/type of study	**Source of effectiveness data**	**Source of cost data**	**Methods of extrapolation**	**Analysis of uncertainty**	**Main conclusions**
Cost-efficacy analysis looking at: 1. adding a stent to a procedure where the use of abciximab is planned 2. adding abciximab to a procedure where the use of a stent is planned	6-month efficacy data from the EPISTENT trial. Event-free survival estimated from trial data	Estimates of unit costs based on economic evaluation study: BENESTENT II trial	–	Confidence ellipses and 95% CIs for incremental ratios presented Results for diabetic patients appeared to be more uncertain	***ICER adding abciximab*** All patients (MI-free survival) = 12,876; all patients (MACE-free survival) = 14,198; diabetic patients (MI-free survival) = 3695; diabetic patients (MACE-free survival) = 2167 ***ICER adding stents*** All patients (MI-free survival) = 39,463; all patients (MACE-free survival) = 12,228; diabetic patients (MI-free survival) = 33,219; diabetic patients (MACE-free survival) = 8040

PRICE (Lam *et al.*, 2001)[59]

What question(s) does the study address?	Country/ currency	Comparator(s)	Study population	Subgroup analysis	Length of follow-up
–	US dollars	Abciximab versus eptifibatide	Patients undergoing elective, non-urgent balloon angiography or stent implantation	–	–
Methods/type of study	**Source of effectiveness data**	**Source of cost data**	**Methods of extrapolation**	**Analysis of uncertainty**	**Main conclusions**
Cost-effectiveness analysis conducted prospectively alongside a randomised double-blind trial	PRICE	Patient-specific resource use. Costs collected from participating hospitals in PRICE trial	–	Bootstrapping to give 95% CIs around costs	Eptifibatide achieved durable platelet inhibition throughout drug infusion and was associated with lower in-hospital and 30-day costs compared with abciximab in patients undergoing elective PCI

Eli Lilly & Co Ltd, 2000[115]

What question(s) does the study address?	Country/ currency	Comparator(s)	Study population	Subgroup analysis	Length of follow-up
Cost-effectiveness of ReoPro® (abciximab) in a UK setting	UK	Abciximab + aspirin + heparin versus aspirin + heparin	As in 3 trials	Unstable angina subgroup I EPIC	Lifetime
Methods/type of study	**Source of effectiveness data**	**Source of cost data**	**Methods of extrapolation**	**Analysis of uncertainty**	**Main conclusions**
UK specific cost-effectiveness analysis. Cost per LYG calculated	EPIC, EPILOG, EPISTENT Utility data based on consensus in literature, range explored in sensitivity analysis	Majority of costs from McKenna *et al.*[*] Inflated using the consumer price index	No additional costs considered after 1 year. Mortality benefit predicted from short-term reductions in MI. Life expectancy taken from DUKE database	One-way sensitivity analysis conducted on a series of cost and outcome assumptions	Cost per LYG using EPIC = £12,421, EPILOG = £6247, EPISTENT = £3554 Cost per QALY (basecase): EPILOG = £7808, EPISTENT = £4443. Cost-effectiveness may be enhanced in USA subgroup

[*] *McKenna M, Wheeldon N, Buxton MJ. Costing cardiac revascularisation for economic evaluation: micro-costing versus routine data?* Br J Med Econ *1997;**11**:65–79*

Appendix 9

Company submissions

Manufacturers and drug	Relevant trial evidence included in review	Relevant economics evidence included in the review	Additional evidence
Merck Sharp & Dohme Ltd	TACTICS-TIMI, TARGET, RESTORE, PRISM, PRISM-PLUS, GUSTO IV-ACS	–	ACUTE II (not published)
Schering-Plough Ltd	ESPRIT (including 12-month data)	–	–
Eli Lilly & Co Ltd	EPISTENT, GUSTO IV-ACS, TARGET, ASSENT-3, ESPRIT, TACTICS-TIMI, GUSTO V, TARGET, ESPRIT, EPIC, RAPPORT, ISAR-II, ADMIRAL, CAPTURE	Kereiakes, 1998[113] Zwart-van Rijkom & van Hout, 2001[114] Lincoff *et al.*, 1999[72] PRICE: Lam *et al.*, 2001[59]	–

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