A Systematic Review Update of the Clinical Effectiveness and Cost Effectiveness of Glycoprotein IIb/IIIa Antagonists

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Authors:

Mike Robinson
Clinical Senior Lecturer
Nuffield Institute for Health
University of Leeds
(0113) 2333954

Laura Ginnelly
Research Fellow
Centre for Health Economics
University of York
(01904) 433543
Email: lg116@york.ac.uk

Mark Sculpher
Professor of Health Economics
Centre for Health Economics
University of York
(01904) 433441
Email: mjs23@york.ac.uk

Lisa Jones
Reviewer
NHS Centre for Reviews and Dissemination
University of York
(01904) 434578

Rob Riemsma
Reviews Manager
NHS Centre for Reviews and Dissemination
University of York
(01904) 433710
Email: **rpr1@york.ac.uk**

Stephen Palmer
Research Fellow
Centre for Health Economics
University of York
(01904) 434566

Zoe Philips
Research Fellow
Centre for Health Economics
University of York
(01904) 433636

Julie Glanville
Associate Director

NHS Centre for Reviews and Dissemination
University of York
(01904) 433496

Correspondence to:
Rob Riemsma
Reviews Manager
NHS Centre for Reviews and Dissemination
University of York

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CONTRIBUTIONS OF AUTHORS

Julie Glanville: Devised the search strategy and carried out the literature searches. Wrote the search methodology sections of the review.

Laura Ginnelly: Responsible for the cost effectiveness and clinical-effectiveness sections of the report. Involved in selection of studies, data extraction, report writing. Involved in the development of the economic model.

Lisa Jones: Responsible for the clinical-effectiveness sections of the report, involved in selection of studies, data extraction and report writing.

Stephen Palmer: Provided input at all stages, commented on various drafts of report. Contributed to discussion sections. Responsible for the economic model. Involved in data extraction of cost-effectiveness studies.

Zoe Philips: Provided input at all stages, commented on various drafts of report. Contributed to discussion sections. Responsible for the economic model. Involved in data extraction of cost-effectiveness studies.

Rob Riemsma: Provided input at all stages, commented on various drafts of report. Contributed to discussion sections

Mike Robinson: Provided overall supervision of the systematic review. Provided input at all stages, commented on various drafts of report. Contributed to report writing.

Mark Sculpher: Provided input at all stages, commented on various drafts of report. Contributed to discussion sections. Responsible for the economic model.

CONFLICTS OF INTEREST

This report was commissioned by the NHS R&D HTA programme.

Within the Review Team, Mark Sculpher has acted as a consultant to Eli Lilly, but on unrelated products. Colleagues within the Centre for Health Economics (but not members of the Review Team) have acted as consultants to, or received research funding from, one or more of the manufacturers of GP IIb/IIIa antagonists, but not for work on that product. CHE receives funding from Schering-Plough for a Research Fellowship in Health Economics.

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Professor Alistair S Hall. (Consultant Cardiologist. BHF Heart Research Centre at Leeds, Leeds General Infirmary)

Dr Ameet Bakhai (SpR & Research Fellow. Clinical Trials & Evaluation Unit, Royal Brompton and Harefield NHS Trust)

Dr David Gray (Cardiovascular Medicine. University Hospital, Queen's Medical Centre, Nottingham)

Dr Eugene Milne (C.P.H.M. Newcastle and North Tyneside HA)

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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. GP IIb/IIIa antagonists 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**.**

The first GP IIb/IIIa antagonist became commercially available in 1995. The initial indication was as an adjunct to coronary angioplasty in which there was judged to be a high risk of abrupt vessel closure. Promising results in this initial setting have led to a progressive widening of the indications for which the agents have been used.

This systematic review focuses on the use of GP IIb/IIIa antagonists in three indications:

1. As part of the medical management of non-ST elevation acute coronary syndrome in conjunction with aspirin and heparin. See below.
2. As an adjunct to percutaneous coronary intervention (PCI) in various groups of patients. This is a development of the original indication for GP IIb/IIIa antagonists.
3. As a supplement to thrombolytic therapy in patients with acute myocardial infarction. This is the most recently developed indication.

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 NICE in 2000.

Non-ST elevation acute coronary syndrome includes a spectrum of patients who may also be labelled as unstable angina or non-Q wave acute myocardial infarction. 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-thrombolytic therapy, there is a substantial risk of death, non-fatal myocardial infarction 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. GP IIb/IIIa antagonists were used successfully with PCI when this was undertaken for non-ST elevation ACS. The high risk of adverse outcomes, the ineffectiveness of thrombolytics, and the success in association with PCI led to the use of GP IIb/IIIa antagonists for non-ST elevation ACS irrespective of PCI.

Intravenous thrombolytics were a major therapeutic advance for ST elevation acute coronary syndrome in the 1980s, so there has been less pressure to explore other pharmacological approaches. Despite refinements to this approach since that time, only 50-55% of vessels are re-perfused by thrombolytic therapy alone. This is less than the approximately 75% of AMI patients who obtain equivalent flow after primary

PCI[1] and hence raised the issue of whether GP IIb/IIIa antagonists could also improve outcome in ST-elevation ACS when used in conjunction with thrombolytics.

The major risk of harm with GP IIb/IIIa antagonists is increased bleeding, either minor or major, and if intra-cerebral, potentially causing a disabling stroke. All the trials in this review have reported the rates of bleeding. The potential for harm needs to be taken into account when assessing overall benefits.

Summary of findings of previous rapid reviews

Two rapid reviews were undertaken in preparation for the technology appraisal of GP IIb/IIIa antagonists carried out by NICE in summer 2000:

1. A Systematic Review of the Clinical Effectiveness and Cost Effectiveness of Glycoprotein IIb/IIIa Antagonists in the Treatment of Unstable Angina, June 2000, prepared by the NHS Centre for Reviews and Dissemination, University of York.

2. Glycoprotein IIb/IIIa Inhibitors in Association with Percutaneous Transluminal Coronary Angioplasty (PTCA) with or without Stents, prepared by the Alastair Fischer, Ruth Frankish and Rod Taylor for the National Institute for Clinical Excellence, 26th June 2000

The first review considered 7 trials concerned with the intravenous use of tirofiban, eptifibatide, or lamifiban, 4 trials concerned with oral GP IIb/IIIa antagonists, and 7 economic studies, 2 of which were unpublished company submissions. The main findings were:

- Intravenous use of the drugs showed only small benefits (risk differences for composite outcome at 30 days ranging from 1.0-3.8%), but this appeared to be greater in Troponin-positive subgroup analyses (risk difference about 8%). Major bleeding was more common in the treatment arms, by 1.0 to 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 saved at 30 days.

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

- A consistent benefit of the use of GP IIb/IIIa antagonists during PCI (risk difference for composite outcome at 30 days and six months about 5%)
- An increased risk of major bleeding of about 5%, less with low molecular weight heparin
- Major limitations to estimates of cost-effectiveness, with values for the incremental cost per life year gained ranging from £1700 to £10000.

NICE subsequently issued guidance on GP IIb/IIIa antagonists to the NHS in September 2000.

Specification for update

The following were agreed with NICE:

- Oral agents to be excluded
- Update on medical management (indication 1) to be restricted to those drugs licensed in the UK (abciximab, tirofiban, and eptifibatide). In addition lamifiban had been included in the initial review, but is not considered here.
- Update on adjunctive use with PCI (indication 2) and de novo review for adjunctive use with thrombolytics (indication 3) similarly restricted to abciximab, tirofiban, and eptifibatide. At present only abciximab is licensed for indication 2 and none of the drugs are 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. Pilot studies for subsequently larger published trials were excluded.

As in the previous review, it was not considered appropriate to pool results from separate trials, given variations between trials in terms of patients enrolled settings and concurrent interventions. A Cochrane Review which does pool results has recently been published[2].

Searches for indications 1 and 2 commenced with publication dates at the end of the equivalent searches in the previous reviews (April/May 2000) and were terminated in August/September 2001; searches for indication 3 began at the start of the relevant database.

Results

The trial results (clinical effectiveness) are first considered by indication. The economics results (cost effectiveness) are then considered as a whole

Indication 1: Medical management

The previous review considered 7 trials of intravenous use, 3 of which have been excluded here because the drug involved (lamifiban) is not licensed in the UK. One additional study (GUSTO IV) was discovered from the update searches.

GUSTO-IV ACS differed from previous trials in this group in that it was designed specifically to address the issue of whether GP IIb/IIIa antagonists 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. There was a significantly impaired effect in women. Major bleeding was slightly more common in the treatment arms in line with previous studies.

Indication 2: Adjunct to PCI

The previous review considered 10 trials with abciximab; 1 trial with tirofiban, and 2 with eptifibatide, all against placebo.

The update search discovered 5 further trials, 2 of which were head to head comparisons of two separate agents, one a further placebo controlled trial of abciximab, and the other of eptifibatide.

ADMIRAL, the additional 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. This confirmed findings in smaller numbers of post-AMI patients included in previous trials.

ESPRIT assessed eptifibatide versus placebo in patients undergoing stenting who were not considered eligible for routine GP IIb/IIIa antagonist 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 48hours.

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

TARGET was a much larger head to head comparison, involving tirofiban rather than eptifibatide, and 198 hospitals as opposed to two. Designed to demonstrate the non-inferiority of tirofiban, in practice a 1.6% increase in the 30-day composite endpoint in the tirofiban group was observed, no difference in major bleeding, and a 1.5% reduction in minor bleeding.

An additional trial of early invasive versus conservative management of ACS (TACTICS) in which all patients received tirofiban has been included in the review because it is frequently referred to in the relevant company submission (was also identified in the update searches). A lower 30-day rate of death/MI was observed than in previous trials, suggesting that early GP IIb/IIIa antagonist treatment might offer particular benefit when PCI was planned.

Indication 3: Adjunct to thrombolysis

The searches discovered a total of 6 randomised 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. Of the remaining 2 studies, both compared abciximab + a reduced dose of thrombolytic versus a full dose of the thrombolytic.

In GUSTO V, the primary endpoint 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 to the control group. A third arm of the trial using low molecular weight heparin instead of abciximab was almost as effective (RD 4.0% compared to control), with much lower rates of major (RD 1.4%) and minor (RD 12.7%) bleeding.

Cost effectiveness

Relating to the use of glycoprotein IIb/IIIa antagonists in the medical management of ACS, a total of 7 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 6 were found in this update. For the new indication of the use of glycoprotein IIb/IIIa antagonists alongside thrombolysis in acute MI, no economic studies were located. Those studies which have been reviewed to date (including company submissions) exhibit a number of important limitations from the viewpoint of decision making in the UK. These include short-term time horizons; the use of condition-specific measures of effectiveness rather than generic measures of health gain such as QALY or life-years; and the estimation of costs and effects using data from clinical trials which are largely or wholly undertaken outside the UK. Particularly in the case of the use of glycoprotein 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.

Despite the shortcomings of existing economic evidence it is important to present the best estimates of cost per life-year/QALY gained in the literature. In the case of the use of Glycoprotein IIb/IIIa antagonists in ACS, the estimates of cost per life-year gained 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 £8,179 to £11,079 per life-year gained depending on the discount rate used for future survival. A separate report submitted alongside this update review provides preliminary results from a new cost-effectiveness model of alternative treatment strategies with Glycoprotein IIb/IIIa antagonists in ACS in a UK setting.

In the case of the use of Glycoprotein 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 gained to range between £3,554 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 Glycoprotein IIb/IIIa antagonists alongside thrombolysis in acute MI patients

represents a limitation of this review. These would be particularly helpful given the mixed results of the trials (potential small reductions in adverse outcomes versus increases in major and minor bleeding)

Conclusions

Notes on the generalisability of the findings

Most of the trials described in this report were conducted in the United States, or were multi-centre 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 reasons:

1 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 sub-group analysis of this type has been published and by the results from GUSTO-IV in ACS.
2 Age – the mean age of subjects enrolled in these trials (range 59 to 67 years) are notably lower than is generally seen in clinical practice

An additional difficulty with the extrapolation of these results is the rate of change of clinical practice and the publication of results of other treatments, which may reduce the frequency of occurrence or effects of plaque disruption. In particular, when all the reviewed studies were being undertaken, clopidogrel was not part of the routine management of ACS patients. The recent publication of the CURE study is likely to change this, and whether or not the conclusions of this review should apply in an environment in which clopidogrel is widely used is unknown.

Key changes arising from the update

The following conclusions may be drawn from the update:

1. The effectiveness of GP IIb/IIIa antagonists as adjuncts to PCI is further confirmed by additional large studies showing similar effect sizes and bleeding rates.
2. There is no evidence for the clinical superiority of tirofiban or eptifibatide over the original agent for this indication, abciximab. Drug costs of the newer agents are somewhat lower, however.
3. The evidence that GP IIb/IIIa antagonists 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 showed a small overall effect in such patients[3].
4. Based on current evidence, it may be considered that the extra benefits of GP IIb/IIIa antagonists adjunctive to thrombolysis in AMI are not justified by the risks of extra bleeding.

Need for further research

Further research is desirable:

1. To assess the benefits, if any, of GP IIb/IIIa antagonists in non-ST elevation ACS, in particular sub-groups such as women, and those not scheduled for PCI.
2. To assess the benefits, if any, of GP IIb/IIIa antagonists in Troponin patients, in particular sub-groups such as women, and those not scheduled for PCI.
3. To assess 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.
4. To assess 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

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 the review.

ACS: Acute Coronary Syndrome

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

AMI: Acute Myocardial Infarction

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)

Antagonist: a drug that nullifies the effect of another drug

Anticoagulant: a pharmaceutical that helps to stop the blood from clotting

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.

aPTT: activated partial thromboplastin time. Control measure in the treatment with heparin

ARR: Absolute relative risk

Arteriogram: A radiographic technique where a radio-opaque (shows up on X-ray) contrast material is injected into a blood vessel for the purpose of identifying its anatomy on X-ray

Atherosclerosis: a major disease of the arteries. Deposition of organised lipid and platelets at the intima of arteries. This 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).

CABG: (coronary artery bypass graft): A surgical procedure, known as a coronary artery bypass graft, which involves replacing disease (narrowed) coronary arteries with veins obtained from the patients lower extremities (autologous graft).

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 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

Cerebral Vascular Disease: Damage to the blood vessels in the brain, resulting in a stroke.

CHD: Coronary heart disease

CHF: Congestive heart failure

CI: Confidence interval; a measure of precision of statistical estimates.

CK-MB: Creatine Kinase Myocardial Band fraction

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.

Cointervention: In a randomised controlled trial, the application of additional diagnostic or therapeutic procedures to members of either or both the experimental and the reference groups.

Composite endpoint: Several different possible outcomes or events associated with individuals in a medical investigation.

Confounding: (1) mask an actual association or (2) falsely demonstrate an apparent association between the study variables where no real association between them exists.

Coronary Artery Disease (CAD): gradual blockage of the coronary arteries.

Cost-benefit analysis: an attempt is made to give the consequences of the alternative interventions a monetary value. In this way, the consequences can be more easily compared to 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 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 sub-type of cost-effectiveness analysis.

Cost-offset analysis: A special type of cost-benefit 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 to each other, and

the outcome (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.

Cox-regression: (also proportional hazard 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.

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 which 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

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

ECG: Electrocardiogram: a recording of the electrical signals from the heart.

Endpoint: A clearly defined outcome or event associated with an individual in a 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 not followed by an increase in oxygen consumption; this identifies the individual's maximal oxygen uptake. Allows the prescribing of exercise to the individual's actual, rather than estimated, heart rate or aerobic.

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.

Fixed effect model: The way in which results trials are combined in a meta-analysis. Fixed effects does not take account of the effects (results) from other trials when calculating the statistic and its confidence interval, a random effects model does.

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% CI s of the relative risk of the the intervention group compared to 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: genitourinary bleeding

Haematuria: The finding of blood in the urine.

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

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.

Hazard ratio: Measure of relative risk used in survival studies.

HDL: high density lipoprotein: These lipoproteins act to carry cholesterol in the blood

Hematemesis: The vomiting of blood.

Haematochezia: The passage of bright red blood per rectum.

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

Hemoptysis: The expectoration of blood or of blood stained sputum.
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 which measures the heart rhythm (ECG) over a 24 hour period of time while the patient records their symptoms and activities in adiary. 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: is the condition of one's blood pressure being lower than his normal.
ICD-9 coding system: International Classification of Diseases - 9th revision

ICER: Incremental cost-effectiveness ratio

ICU: intensive care unit

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 statistic 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.

Intravenous: Fluid injected into a vein.

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: (syn: product limit method) A nonparametric 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 (death, withdrawal) occurs and are therefore unequal.

Killip class: Classification for the severity of chronic heart failure.

LBBB: Left bundle branch block, a term used in ECG monitoring.

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

Melaena: The passage of dark stools containing blood, indicates bleeding from the lower intestine

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 to a specific number of the population.

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

nd: Not determined

NHS CRD: NHS Centre for Reviews & Dissemination

NICE: National Institute for Clinical Excellence

ns: Not statistically significant

NS: Not stated

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

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

NSAIDs: nonsteroidal anti-inflammatory drugs.

PCI: percutaneous coronary intervention

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

Percutaneous transluminal 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 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 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 that the specific and non-specific effects of the experimental treatment can be distinguished 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.

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 doesn't exist in the relevant population. Small p-values indicate stronger evidence to reject the null hypothesis of no difference.

QALY: Quality Adjusted Life Years; 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: is 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. Subjects 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) (Synonym: randomised clinical trial) These are designed to measure the efficacy and safety of particular types of health care 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 subjects 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 amongst those exposed to the relevant risk factor divided by the proportion of diseased people amongst 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.

Relative risk reduction (RRR): Alternative way of expressing relative risk (RR). It is calculated as follows: RRR=(1-RR) x100%
The RRR can be interpreted as the proportion of the initial or baseline "risk" which was eliminated by a given treatment or intervention, or by avoidance of exposure to a risk factor.

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: 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 which 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.

1. AIM OF THE REVIEW

The purpose of this report is to answer the following question: What is the clinical and cost-effectiveness of the glycoprotein IIb/IIIa antagonists in three indications: (i) the acute treatment of non-ST-elevation acute coronary syndromes; (ii) as an adjunct to percutaneous coronary interventions (PCI); and, (iii) for acute myocardial infarction, 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 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 identified through the literature search are reviewed excluding oral agents and agents for which no license applications are expected in the foreseeable future.

1.1 BACKGROUND

In 2000, two rapid reviews were undertaken for the National Institute for Clinical Excellence on the use of glycoprotein (GP) IIb/IIIa antagonists in cardiology. The first of these[4] focused on the role of these drugs in acute coronary syndrome and the second[5] looked at the use of GP IIb/IIIa antagonists alongside percutaneous coronary interventions (PCI) 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 acute myocardial infarction.

1.2 DESCRIPTION OF UNDERLYING HEALTH PROBLEM

1.2.1 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 under the age of 75[7]. 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[8].

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[7]. There remains a clear difference between the sexes in mortality from CHD, with lower rates in women[9].

The three indications covered in this report relate to several underlying health problems. The first indication relates to acute coronary syndrome, 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 acute myocardial infarction.

Acute coronary syndrome (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 acute coronary syndrome includes a spectrum of patients who may also be labelled as unstable angina or non-Q wave acute myocardial infarction. 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 myocardial infarction 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 acute myocardial infarction. 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-myocardial infarction. *Unstable angina* typically indicates significant coronary artery disease, although this is not always the case.

Non-Q-wave myocardial infarction is the term used when the cardiac enzymes are elevated to the range indicating that myocardial infarction has occurred, but a Q-wave does not develop on electrocardiogram 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 acute coronary syndrome that will or will not go on to develop acute myocardial infarction. It is only possible to differentiate between the two after 4 to 16 hours (at the earliest), when the cardiac enzymes can be tested. A definite diagnosis is often not possible until 2 to 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 coronary artery disease (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 to 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[10].

The risk is highest in the early stages of symptom presentation, but returns to baseline levels (the risk level of stable angina) within two months. The prognosis of a patient with an acute coronary syndrome 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 acute coronary syndrome are particularly important factors in predicting subsequent clinical course. Indicators of poor prognosis on physical exam include heart failure, mitral regurgitation (MR) murmur, or hypertension (particularly during pain). ECG findings that help identify high-risk patients include ST segment changes of >= 1mm, 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-T changes during symptoms. Rizik et al, have proposed a stratification system of unstable angina[11]. Class IA are patients with increasing exertional angina, without ECG changes, 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 one-month incidence proportions of death varied between 2 and 60%[6, 12-14]. Those studies using a definition of increasing angina showed one-month incidence proportions of death between 16 and 50%[15-19]. 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.

1.2.2 Patients undergoing percutaneous coronary intervention

PCI represents a key element of the therapeutic armamentarium available for the management of CHD. First used in the 1970's, 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[20, 21]. The development of new interventional coronary techniques as an addition or alternative to PTCA – particularly coronary stents[21] – 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[22], but these complications remain an increasing consideration in clinical decision making.

1.2.3 Patients undergoing thrombolysis

In patients with AMI, intravenous thrombolytic therapy to achieve myocardial reperfusion has become a mainstay of management since the late 1980s[23]. The effectiveness of thrombolysis was established in large randomised controlled trials 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[24, 25]. 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 reduction in mortality at 30-days compared to streptokinase[26]. 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[27]. 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[27].

One of the limitations 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[26]. This has led to research into the effectiveness of combining thrombolysis with agents which can inhibit platelet aggregation such as GP IIb/IIIa antagonists.

1.3 CURRENT SERVICE PROVISION

Estimating the current service provision and current costs in the areas relevant to this review is difficult due to a dearth of routine data. Regarding treatment of ACS, the ICD-9 coding system does not differentiate between stable and unstable angina. The number of people coded as having an acute MI, but who were admitted with

unstable angina is also not known. In addition, deaths due to acute coronary syndrome will often be classified as acute MI. The incidence of new cases of angina pectoris in the United Kingdom is conservatively estimated to be around 22,600 patients per annum[28]. The 1999 NHS Executive data show at least 129,458 cases of angina were seen by consultants, with cost per 'finished consultant episode' ranging from £156 to £1,123[29]. 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 US are 2-3 times greater, similar to the reported rates for AMI[30]. 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%[31.]

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)[32]. Table 1 shows the numbers of PCIs, rates per million and year-on-year increase between 1991 and 2000, as reported in 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.

Table 1. PCI rates in the UK 1991-2000. (Source: BCIS audit returns. http://www.bcis.org.uk/audit/oct01.html)[32]

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
2000	66	33,652	590	20

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 US[32].

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.

1.4 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 glycoprotein 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[33]. Thus abciximab may have wider effects than the small molecule GPAs. Abciximab also differs in its pharmacokinetics, in that its clearance from plasma its much slower. It binds to platelets for up to 2 weeks after infusion, and produces reduction in platelet aggregation for up to one week[34].

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[34]. 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 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 like 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[35]. The first clinical studies used a sequential approach, where abciximab was given after the thrombolytic[36]. 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 glycoprotein 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 70kg person is given In Table 2 below for each of the three drugs, as are details of their licensed indications. The information is taken from the British National Formulary[30].

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

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

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[32]. 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.

2.EFFECTIVENESS

2.1 METHODS FOR REVIEWING EFFECTIVENESS[1]

2.1.1 Search strategy

The following databases were searched for relevant literature (See Appendix 1 for full details of the search strategies)

- MEDLINE (WinSPIRS, 1966-2001/06)
- PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi Searched 7 Sept 2001)
- EMBASE (WinSPIRS, 1980-2001/08)
- Conference Papers Index (Dialog, 1973-2001/Sept.)
- Cochrane Library (CD-ROM, 2001/3)
- TRIP database (http://www.tripdatabase.com/ on the 5 Sept. 2001)
- DEC reports (http://www.doh.gov.uk/research/swro/rd/publicat/dec/index.htm on the 5 Sept. 2001)
- HTA database (http://www.york.ac.uk/inst/crd on the 5 Sept. 2001)
- DARE database (http://www.york.ac.uk/inst/crd on the 5 Sept. 2001)
- NHS EED database (http://www.york.ac.uk/inst/crd on the 5 Sept. 2001)
- NCCHTA website (http://www.hta.nhsweb.nhs.uk/ on the 7 Sept. 2001)
- National Guideline Clearinghouse (http://www.guideline.gov/index.asp on the 7 Sept 2001)
- National Research Register (CD-ROM Issue 2001/3)
- ScHARR Lock's Guide to the Evidence (http://www.shef.ac.uk/uni/academic/R
- Z/scharr/ir/scebm.html on the 7 Sept. 2001)
- SIGN guidelines (http://www.show.scot.nhs.uk/sign/index.html on the 7th Sept. 2001)

Search results were de-duplicated against previous results obtained for the HTA review and the Leeds update project. The Leeds update project is secondary research funded by the Health Technology Assessment 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 NRR were contacted by email initially followed by a follow up telephone call, for further information about their studies. Other contacts included the Cochrane Heart Group and researchers known to have

[1] According to the explicit Quality Standards agreed by InterTASC.

published economic analyses in the area of coronary artery diseases. 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.

2.1.2 Inclusion and exclusion criteria

Interventions

1. Glycoprotein 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 glycoprotein 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 glycoprotein 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. “Acute coronary syndrome” means any constellation of clinical signs or symptoms suggestive of AMI or UA 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

- Acute myocardial infarction (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

2.1.3 Study Designs

1. Randomised clinical trials.
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.

2.1.4 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.

2.1.5 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.

2.1.6 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 relative risk 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

2.2 SEARCH RESULTS

2.2.1 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, 6 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.

2.2.2 Studies included in the review

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

Table 3: Numbers of studies identified in the original review and in the update

	Update Search	McDonagh et al	Fischer et al*,**
Clinical Efficacy	22	4	12
Economics	6	5	12

*EXCITE excluded, as xemilofiban does not have a current UK license for this indication

** Papers on lamifiban were excluded, as the drug does not have a current UK license.

2.2.3 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 1st October 2001:

- American College of Cardiology, annual conference 2001, late breaking clinical trials
- American Heart Association, late breaking clinical trials 2001
- British Cardiac Society, annual conference 2001
- Cardiosource, ongoing & unpublished trials

IN addition to the 6 trials identified by the NRR, 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 + the low molecular weight heparin enoxaparin, and results are expected to be available late 2002.

2.3 Glycoproteins in the medical management of acute coronary syndrome.

2.3.1 Efficacy of intravenous glycoprotein IIb/IIIa antagonists

In addition to the 4 relevant trials identified in the previous NICE review (McDonagh et al[4]), one additional trial was identified in the update searches, GUSTO IV[37.] 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 sub-groups.

2.3.1.1 General details

The 5 trials all took place between 1996 and 2001 (Table 4), with 4 conducted in an international setting and 1 in the US (Schulman et al[38).] All studies were classified as randomised controlled trials, 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[39-42], PRISM[43], PRISM-PLUS[44] and GUSTO IV[37] studies were Phase III studies, looking at efficacy.

PRISM[43]and PRISM-PLUS[44,] studies evaluated the effectiveness of tirofiban, Schulman et al and PUSUIT looked at eptifibatide and GUSTO IV looked at abciximab. The intervention studied can be seen in Table 5. Duration of follow up varied from 24 hours (Schulman et al) to 6-months (PRISM-PLUS)

PRISM differed form 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 et al the smallest trial with 227 participants.

Table 4: Designs of included studies of intravenous glycoprotein IIb/IIIa antagonists in acute coronary syndromes

Study	Setting	Design/Phase	Treatment Arms	Number of participants	Follow-up time points
Schulman etal (1996) [38]	US	RCT Phase II	Low-dose eptifibatide High-dose eptifibatide Aspirin	77 76 74	24 hours
PURSUIT (1998) [39-42]	International	RCT Phase III	Eptifibatide Placebo	4722 4739	96 hours, 7 days, 30 days
PRISM (1998) [43]	International	RCT Phase III	Tirofiban Heparin	1616 1616	48 hours, 7 days, 30 days
PRISM-PLUS (1998) [44,]	International	RCT Phase III	Tirofiban Tirofiban + Heparin Heparin	345 773 797	48 hours, 7 days, 30 days 6 months
GUSTO IV (2001) [37]	International	RCT Phase III	24 hours abciximab 48 hour abciximab Placebo	2590 2612 2598	48 hours, 7 days, 30 days

Table 5: Interventions specified by study protocols

Study	Intervention 1	Intervention 2	Control
Schulman et al, 1996[38]	High dose eptifibatide bolus of 90 ug/kg, followed by 1.0 ug/kg/minute, plus placebo	Low dose eptifibatide, bolus of 45 ug/kg over 3 minutes, followed by 0.5 ug/kg/minute continuous infusion, plus placebo aspirin.	Aspirin, 325 mg/day, initiated immediately upon randomisation, plus placebo eptifibatide
	Study drug was given for 24-72 hours, but it was discontinued if cardiac catheterisation, angioplasty or cardiac bypass was performed. After termination of study drug, all patients received oral aspirin, 325 mg. All patients also received standard medical therapy, including heparin, 5000-unit bolus, followed by continuous infusion, with dose adjusted to maintain the aPTT between 1.5 and 2.5 times the control value.		
PURSUIT, 1998[39-42]	Eptifibatide bolus of 180 mcg/kg followed by infusion of 2.0 mcg/kg/min.	*Eptifibatide bolus of 180 mcg/kg followed by infusion of 1.3 mcg/kg/min	Placebo bolus and infusion
	Study drugs given for 72h or until discharge if earlier. Extended to 96h if PCI performed Subcutaneous or intravenous adjusted dose heparin was recommended, but not required. Aspirin (80 – 325mg per day) was given at the discretion of the treating physicians. If contraindicated or if intolerant to aspirin, ticlopidine could be given. * Low dose group stopped early. Data for high dose group only presented and analysed.		
PRISM, 1998[43]	Tirofiban 0.6 mcg/kg/min for 30 minutes, followed by 0.15 mcg/kg/min 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 per hour, adjusted at 6, and 24 hours to twice the aPTT.	
	Random alterations were made in the placebo heparin administration rate Aspirin (325mg daily) was administered to all patients before randomisation, and daily for 48 hours, and thereafter at the discretion of the physician. Other medication, except Non Steroidal Anti-inflammatory Drugs (NSAIDs), ticlopidine or warfarin could be prescribed.		
PRISM-PLUS, 1998[44]	Tirofiban 0.6 mcg/kg/min for 30 minutes, followed by 0.15 mcg/kg/min plus placebo heparin.	Tirofiban 0.4 mcg/kg/min for 30 minutes, followed by 0.1 mcg/kg/min 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 per 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 (325mg) was administered to all patients at the time of randomisation and daily thereafter		
GUSTO-IV, 2001[37]	Abciximab therapy for 24 hours (0.25 mg/kg bolus followed by a 0.125 ug/kg per min infusion up to a maximum of 10 ug/kg for 24 hours) followed by 24 hr 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 250-300mg 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 U/kg unfractionated heparin bolus (to maximum of 5000 U) followed by a continuous infusion of 10 U/kg per h (to maximum of 800 U/kg). Coronary angiography was not to be done during or within 12 h after completion of infusion.		

2.3.1.2 Patients characteristics and inclusion criteria

Although all trials included unstable and non-Q-wave MI patients, the definition of these patients varied (see inclusion criteria). Schulman et al was the only study to define the presence of unstable angina explicitly, defining it as "the recent onset of a changing pattern of cardiac ischemic symptoms at rest, with one episode lasting $\geq$ 10 minutes & occurring within 24 hours of randomisation". Inclusion and exclusion criteria used in each trial can be seen in Table 6 below.

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; 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. Troponin status was only known for all participants in GUSTO-IV (60% were positive). The comparable figure in the subgroup of PRISM in whom Troponin was measured was 29%.

Table 6: Inclusion and exclusion criteria from published texts.

Study/Drug	Inclusion criteria	Exclusion criteria
Schulman et al, 1996[38] **Eptifibatide**	Men and women aged 21 to 80 yrs 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 hrs 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 coronary artery disease on the basis of previous MI or cardiac catheterisation.	Suspected MI in evolution, prior coronary artery bypass graft surgery within 6 months, coronary angioplasty within 72 hrs, thrombolytic therapy within 7 days, major surgery within 6 weeks, a history of cerebral vascular disease, major GI or GU bleeding within 30 days, significant thrombocytopenia (<100,000 /mm3), coagulopathy (receiving coumadin or bleeding time > 20 minutes), and if they presented with severe hypertension (systolic blood pressure > 180 mmHg or diastolic blood pressure > 120 mmHg) or had renal insufficiency with a reatinine level > 4mg/dL.
PURSUIT, 1998[39-42] **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 creatine kinase MB isoenzyme (CK-MB) 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, systolic blood pressure above 200 mmHg or diastolic blood pressure above 110 mmHg, a history of major surgery within the previous 6 weeks, a history of non-hemorrhagic stroke within the previous 30 days or any history of hemorrhagic stroke, renal failure, pregnancy, the planned administration of a platelet glycoprotein IIb/IIIa inhibitor or thrombolytic agent or the receipt of thrombolytic therapy within the previous 24 hrs.
PRISM, 1998[43] **Tirofiban**	Patients who had their most recent episode of chest pain at rest or accelerating chest pain within 24 hours of randomisation. Coronary artery disease was defined as one of the following: 1) electrocardiographic evidence of myocardial ischemia 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; or 2) elevated cardiac enzyme levels consistent with the occurrence of non-Q wave MI 3) A history of MI, percutaneous revascularisation more than six months earlier, coronary surgery more than one 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 allergy to or intolerance of heparin; a serum creatinine level above 2.5 mg per decilitre (221 mmol per litre); and active bleeding disorder; a history of GI bleeding; hematuria, a positive faecal occult-blood test; known coagulopathy; a platelet disorder or a history of thrombocytopenia; persistent systolic blood pressure above 180 mmHg, diastolic blood pressure above 110 mmHg or both at the time of enrolment; a history of hemorrhagic cerebrovascular disease or an active intracranial pathologic process; a history of cerebrovascular disease or transient ischemic attack with in the previous year; a major surgical procedure within the previous month; active peptic ulceration within the previous 3 months; or an invasive procedure within 14 days before enrolment that would substantially increase the risk of haemorrhage
PRISM-PLUS, 1998[44,] **Tirofiban**	Prolonged anginal pain or repetitive episodes of or repetitive episodes of angina at rest or during minimal exercise in the previous 12 hours and new transient or persistent ST-T	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,

	ischemic changes on the electrocardiogram (ST-segment elevation or depression of 0.1mV 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 pseudonormal-isation of 0.1 mV or more) or an elevation of plasma levels of creatine kinase and of the creatine kinase MB fraction (CK-MB).	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 per cubic millimetre were also excluded.
GUSTO IV, 2001[37] **Abciximab**	Patients with ACS, without persistant ST-segment elevation. Aged 21 or over with more than one episode of angina lasting at least 5 min 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 history of MI 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 coronary artery disease, 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 gastro intestinal or genitourinary bleeding of clinical significance within the previous 6 wks; intracranial neoplasm or aneurysm, atrioventricular malformation, history of stroke within 2 yrs, 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/uL; 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.

Table 7: Baseline characteristics of participants in studies of intravenous drugs

Study	Prognostic indicators	Intervention 1	Intervention 2	Control
Schulman et al, 1998[38]	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, 1998[39-42]	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[43]	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, 1998[44,]	Mean age	63	63	63
	Diabetes (%)	25	22	24
	Previous MI (%)	46	45	39

	Previous PCI (%) Previous CABG (%) Previous heart failure (%) ST- depression (%) T wave changes (%)	13 17 11 57 58	9 16 11 57 52	9 13 8 60 52
GUSTO IV, 1998[37]	Mean age Diabetes (%) Previous MI (%) Previous PCI (%) Previous CABG (%) Previous heart failure(%) ST depression (%) Troponin I/T positive (%)	65 21 30 11 10 8 81 60	65 22 27 10 9 8 80 59	65 22 28 9 9 7 80 58

2.3.1.3 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 et al randomised patients to receive placebo or 325mg aspirin, with all patients given heparin. On termination placebo patients were then also give 325mg aspirin in conjunction with heparin. PRISM randomised patients to heparin or placebo, all patients received aspirin. GUSTO IV 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.

Table 8: Use of concomitant medication

Study	Treatment arm	Aspirin (%)	Heparin (%)	Nitrates (%)	Calcium channel blocker (%)	Beta blocker (%)
Schulman et al, 1996[38]	High-dose eptifibatide Low-dose eptifibatide Aspirin	86 88 88	- - -	60 64 57	40 46 38	33 38 40
PURSUIT, 1998[39-42]	-	-	-	-	-	-
PRISM, 1998[43]	Tirofiban Heparin	94.9 94.3	25.4 25.7	78 77	52 53	45 46
PRISM-PLUS, 1998[44,]	Tirofiban Tirofiban + Heparin Heparin	- - -	- - -	95 95 94	50 49 43	75 78 81
GUSTO IV, 2001[37]	24 hour abciximab 48 hour abciximab Placebo	- - -	- - -	59 60 61	22 23 22	78 76 76

2.3.1.4 Outcomes recorded & 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 CK above the upper limit of normal, whereas most other trials required twice the upper limit of normal. GUSTO-IV required CK-MB to be >upper limit of normal in 2 samples of which one was >3 times the upper limit of normal. All studies also defined a composite outcome, however this did not include the same types of events in each trial. PURSUIT and GUSTO IV only considered death or MI events. Schulman et al recorded refractory ischemia, MI, need for morphine, intra-aortic balloon pump, emergency catheterisation or PTCA and death. PRISM and PRISM-PLUS looked at death, MI or recurrent ischemia for the 48-hour and 30 days follow up, and included readmission for unstable angina in the 30-day composite outcome (PRISM-PLUS also looked at this outcome at 6-month follow-up).

Table 9: Definitions of outcomes in trials of intravenous drugs

Study	Acute MI	Severe recurrent angina/refractory ischemia	Composite end-point
Schulman et al, 1996[38]	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 catheter-isation or PTCA, or death.
PURSUIT (1998) [39, 40, 41, 42]	*< 18 h after enrolment:* chest pain with ST-T changes (depression or elevation) in 2 continuous leads for more than 30 minutes. *>18 h 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) [43]	New episode of chest pain with: 1. new ST-T changes 2. new pathologic Q waves >0.03 sec 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 2 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 mins, or two episodes lasting ≥ 10 mins each within a 1 hour period, despite full medical therapy. 2. Haemodynamic instability attributed to ischaemia as evidenced by pulmo-nary oedema (new rales over one third of the lung fields or tachypnoea lasting > 30 mins), systolic blood pressure < 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 UA.
PRISM-PLUS[44] **(1998)**	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 two times the upper limit of normal or higher (three times the upper limit of normal when infarction was related to coronary angioplasty) and elevated CK-MB values. An evolving MI at study entry was defined as a new increase in CK and CK-MB levels to more than 50% above the previous	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	Death from any cause, new MI or refractory ischaemia within 7 days after randomisation. Rehospitalisation for unstable angina was included at 7 days, 30 days and 6 months.

	value after an initial peak. A perioperative MI was defined as new Q-waves.	hypotension. 3. Repetitive chest pain (three or more episodes each lasting 5 minutes or more) necessitating intra-aortic counterpulsation, urgent intervention or both within 12 hours.	
GUSTO IV (2001) [37]	New Q-wave > 0.04 sec or ¼ R 2 leads or, CK-MB > ULN in 2 samples of which ≥ 3x ULN in 1 sample. MI post PCI: as above Post CABG MI: Q-wave only	Not defined	Death or MI at 30-days

2.3.1.5 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 sub-group papers can be seen below in Table 10.

Table 10: Separate sub-group analysis undertaken on medical management trials

Study	Trial	High-risk group	Patients enrolled	Outcomes reported
Heeschen et al (1999) [45]	PRISM	Troponin positive patients.	222 patients in PRISM of which 629 had troponin concentrations higher than 1.0 μg/L and 644 with concentrations higher than 0.1 μg/L.	Death, MI, Death/MI and refractory ischaemia reported for troponin positive versus troponin negative patients.
Theroux et al (2000) [46]	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[47]	PURSUIT	Elderly	9722 patients in PURSUIT were divided into 5 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 myocardial infarction. Risk of events in sub-groups calculated.

Heeschen et al (1999)[45] looked at outcomes in the PRISM trial by Troponin-I status; an indication of high risk. Theroux et al (2000)[46] looked at patients with a diagnosis of diabetes mellitus at enrolment. Hasdai et al, 2000[47] and Boersma et al, 2000[48] looked at the impact of age, ST-depression and diabetes on the outcomes of patients in 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 et al did not undertake any analysis on high-risk sub-groups.

Table 11:Outcomes of high-risk groups reported in trials

Trial	Diabetics	Troponin T positive	ST depression	Elderly patients
Schulman[38]	-	-	-	-
PURSUIT[39, 40, 41, 42]	Odds ratios reported for death/MI	-	Odds ratios reported for death/MI	Odds ratios reported for death/MI
PRISM[43]	Risk ratios reported for composite of death/MI/refractory ischaemia within 48-hours.	-	Risk ratios reported for composite of death/MI/refractory ischaemia within 48-hours.	Risk ratios reported for composite of death/MI/refractory ischaemia within 48-hours.
PRISM-PLUS[44]	Numbers of patients in tirofiban + heparin or heparin only group experiencing composite outcomes at 7 days reported.	-	-	Numbers of patients in tirofiban + heparin or heparin only group experiencing composite outcomes at 7 days reported.
GUSTO-IV[37]	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.

2.3.1.6 Assessment of internal validity

The assessment of the internal validity of the studies included in the review is presented below 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 homogenous. Pre-stratification on variables known to be prognostically important would involve stratifying at randomisation in smaller trials, or stratifying by centre in multi-centre 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 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, multi-centre 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 endpoint composition, timing of endpoint 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 et al trial all studies used blinded end points committees 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.

Table 12: Assessment of internal validity

Internal validity					
Study	**Schulman**	**PURSUIT**	**PRISM**	**PRISM PLUS**	**GUSTO IV**
Selection of prognostic ally homogenous study population	?	?	?	?	+
Pre-stratification on prognostic ally 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 bear on 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 confidence intervals (or dispersion)	+	+	+	+	+
The statistical methods	+	+	+	+	+
The way missing values were dealt with	?	?	?	?	-
Intention to treat analysis	+	+	+	+	+
Distributions of baseline characteristics	+	+	+	+	+
The way any imbalances in prognostic variables were accounted for	±	±	+	+	+

+	Item properly addressed	-	Item not properly addressed or not stated
?	Unclear	+/-	Item partially addressed
N/A	Not applicable		

2.3.2 Results of trials

The results of the trials are presented below by drug. In the plots of relative risk, 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 relative risk estimates at 30-days and later were considered more relevant than those at 48 and 96 hours and at 7 days.

2.3.2.1 Eptifibatide

The Schulman study (Table 13) refers to the study drug as Integrilin, which is now the brand name of eptifibatide. This Phase II study appeared to have lower internal validity than the Phase III studies reviewed because in addition to the items that were not addressed in all studies, random sequence allocation and blinding of persons assessing outcomes were not 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, subjects not included in the primary endpoint.

The primary endpoint for this study was ischemia 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 (4), missing data (2), abnormal baseline ST-segment on Holter (27), Holter malfunction (13), received wrong study drug (7), wrong infusion rate (4), and eligibility violation, such as MI (4) or anaemia (1).

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

Table 13: Results of study by Schulman at al[38]: Outcomes at 24-hours

Treatment Arm	MI		Recurrent ischaemia		Death		Composite	
	n	%	n	%	N	%	n	%
Low-dose eptifibatide (n=77)	1	0.8	1	0.8	0	0.0	1	0.8
High-dose eptifibatide (n=76)	0	0.0	0	0.8	0	0.0	2	1.5
Placebo (n=74)	1	0.7	1	0.7	0	0.0	4	3.0

PURSUIT evaluated eptifibatide versus placebo while recommending intravenous or subcutaneous heparin for all patients. All patients received aspirin (80 to 325 mg per day). The primary endpoint was MI, death or composite endpoint (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 journals editors, later reported these). Use of anti-anginal medications before or after enrolment were 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 less events occurred in eptifibatide patients compared to those that received placebo, this occurred at all time points.

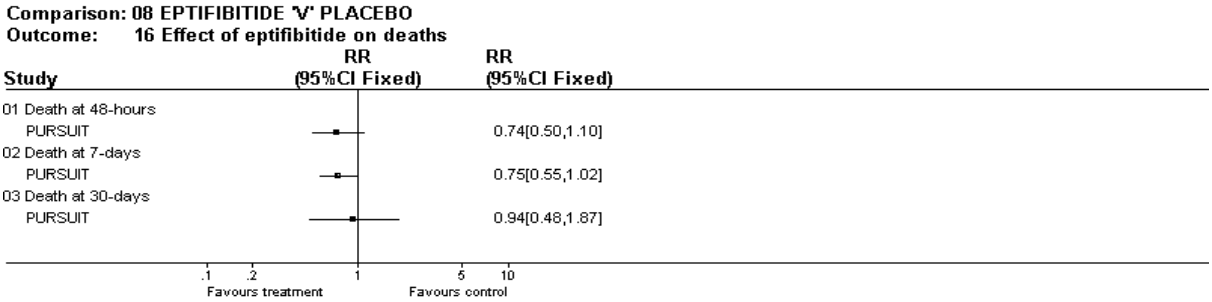
Table 14: Results of PURSUIT[39-42] study

Treatment Arm	Time-point	MI		Death		PTCA		CABG		Composite	
		n	%	n	%	n	%	n	%	n	%
Eptifibatide (n= 4722)	96 hours	335	7.1	42	0.9	-	-	-	-	359	7.6
	7 days	439	9.3	71	1.5	-	-	-	-	476	10.1
	30 days	595	12.6	16	3.5	1100	23	656	14	670	14.2
	6 months					-		-	-	836	17.7
Placebo (n= 4739)	96 hours	393	8.3	57	1.2	-	-	-	-	431	9.1
	7 days	493	10.4	95	2.0	-	-	-	-	550	11.6
	30 days	640	13.5	17	3.7	1175	25	678	14	744	15.7
	6 months	-	-	-	-	-	-	-	-	896	18.9

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.

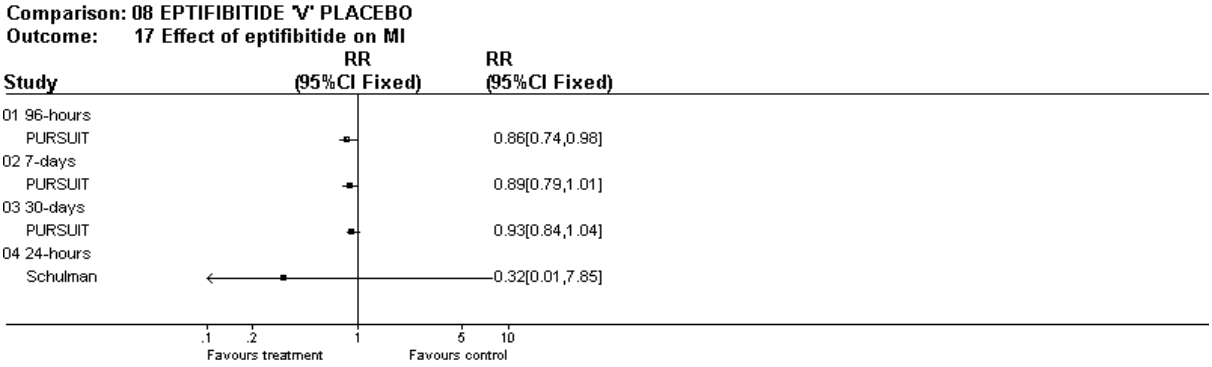
Figure 1: Effect of eptifibatide on the death in the PURSUIT trial



Myocardial infarction

The effect of eptifibatide on non-fatal 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 Schulman et al, although large was not statistically signifiant. PURSUIT did show a statistically significant effect at 7-days.

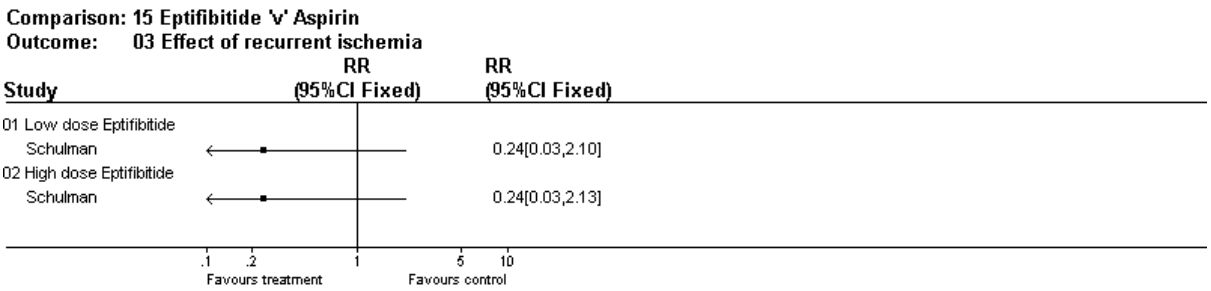
Figure 2: Effect of eptifibatide on myocardial infarction for patients receiving glyoproteins as part of medical management



Recurrent ischemia

Schulman et al reported on the effect of eptifibatide on recurrent ischemia at 24-hours. This can be seen below in the forest plot in Figure 3. PURSUIT did not report refractory ischemia as a separate endpoint.

Figure 3: Effect of eptifibatide on recurrent ischemia in the Schulman trial



Revascularisation

The effect of eptifibatide on revascularisation (CABG and PTCA) can be seen in the forest plots in Figures 4 and 5.

Figure 4: Effect of eptifibatide on rates of PTCA for patients receiving glycoproteins as part of medical management

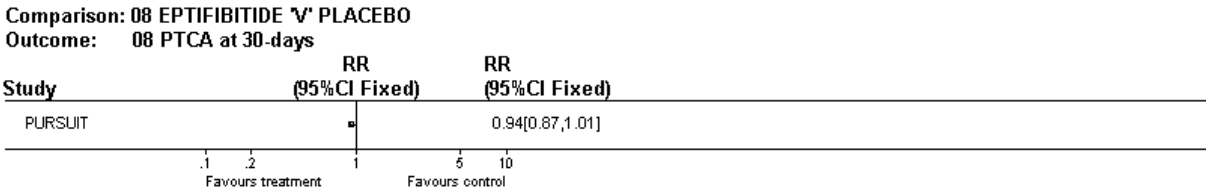
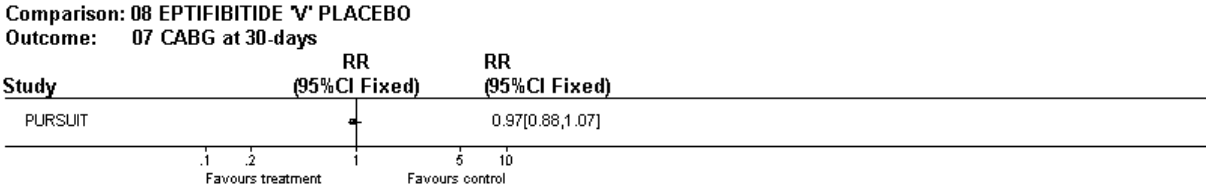


Figure 5: Effect of eptifibatide on rates of CABG for patents receiving glycoproteins as part of medical management



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 [49] trial as a primary endpoint, and the definitions from the GUSTO[50] trial as a secondary endpoint. 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.

Figure 6: Effect of eptifibatide on minor bleeding episodes for patients receiving glycoproteins as part of medical management.

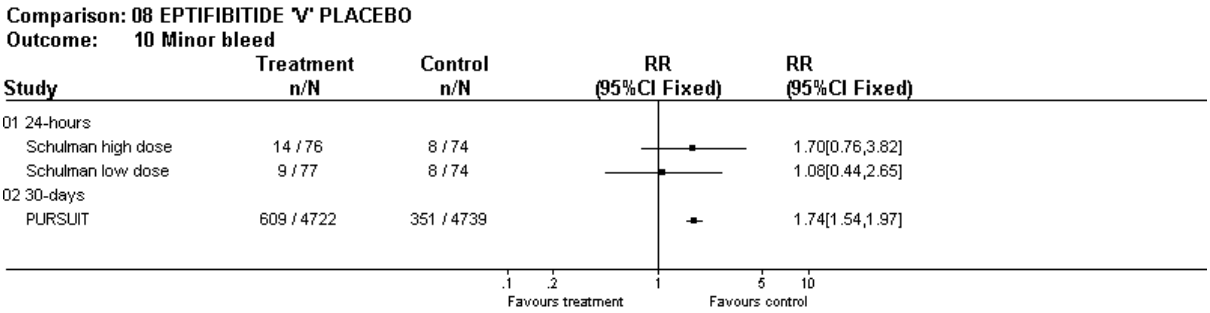
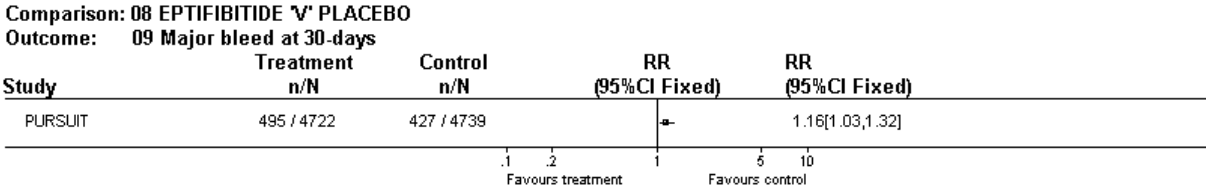


Figure 7: Effect of eptifibatide on episodes of major bleeding for patients receiving glycoproteins as part of medical management.



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

Table 15: Definitions of bleeding used in eptifibatide medical management studies

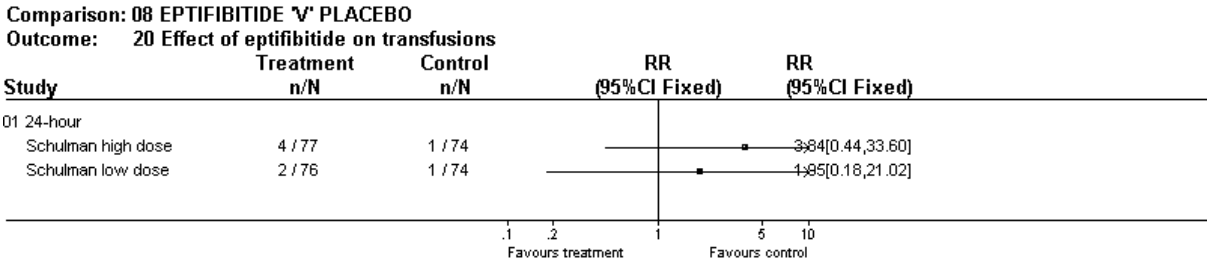
Study	Major/Minor bleeding
PURSUIT[51]	Primary According to TIMI trial criteria Major bleeding = intracranial haemorrhage or bleeding associated with a drop of 15% or more in the hematocrit or of 5 g/dL or more in haemoglobin. Minor bleeding = a drop of 12% in hematocrit or 4g/dL in haemoglobin (with 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. Moderated was bleeding that required blood transfusion without causing hemodynamic compromise.
Schulman et al[38]	Not defined, but petechiae, ecchymoses, haematomas, hemoptysis, hematemesis, hematuria 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 PURSUIT 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/mm3) was 0.2% vs. 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 is much greater in the eptifibatide group the number of patients experiencing an event is small, as can be seen in Figure 8 (5.2% 'v' 1.3%).

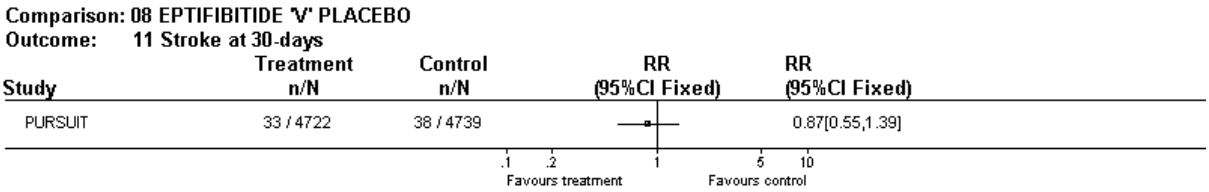
Figure 8: Effect of eptifibatide on RBC transfusions, for patients receiving glycoproteins as part of medical management



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 relative risk is however small (<0.001 (0.00)).

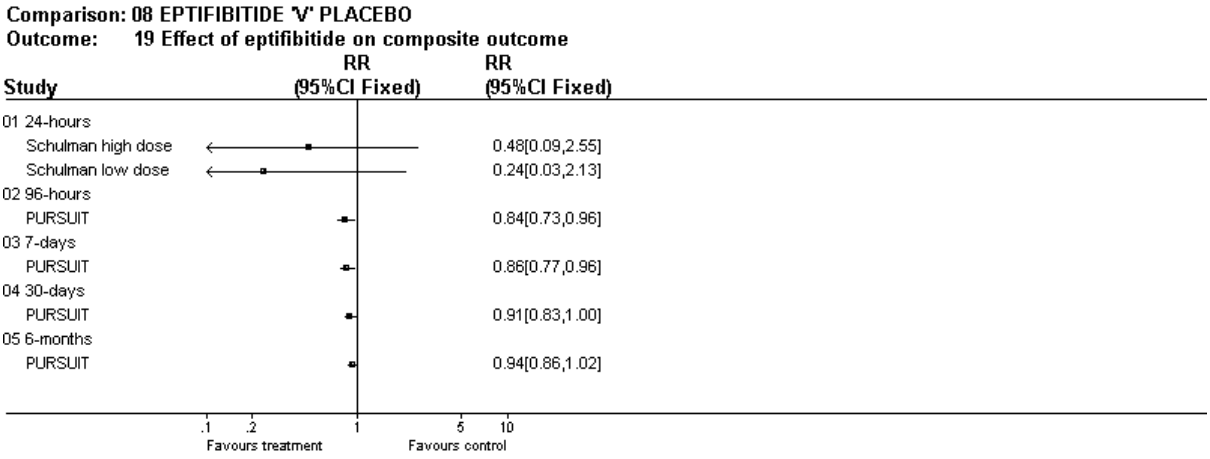
Figure 9: Effect of eptifibatide on incidences of stroke, for patients receiving glycoproteins as part of medical management



Composite endpoint

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 endpoint identified in PURSUIT.

Figure 10: Effect of eptifibatide on the composite outcome, for patients receiving glycoproteins as part of medical management



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 et al[40]. Small variations in the risk difference were seen using various definitions of MI

2.3.2.2 Tirofiban

The two studies assessing tirofiban were PRISM and PRISM-PLUS. PRISM[43] 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 PRISM the primary endpoints were MI, recurrent ischemia, death and the composite endpoint 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 endpoint was 0.67 (95% CI 0.48 to 0.92) and refractory ischemia was 0.65 (95% CI 0.46 to 0.91). None of the other outcomes, primary or secondary, were significant at any time point.

Table 16: Results of PRISM[43] study

Treatment Arm	Time-point	MI		Recurrent ischaemia		Death		PTCA		CABG		Composite	
		n	%	n	%	n	%	n	%	n	%	N	%
Tirofiban (n= 1616)	48 hours	15	0.9	57	3.5	6	0.4	-	-	-	-	61	3.8
	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 (n= 1616)	48 hours	23	1.4	86	5.3	3	0.2	-	-	-	-	90	5.6
	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

PRISM-PLUS 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 endpoint 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 risk difference for death or MI 3.0% (95% CI -0.4 to 6.4; NNT = 33).

Table 17: Results of PRISM-PLUS[44] study[φ]

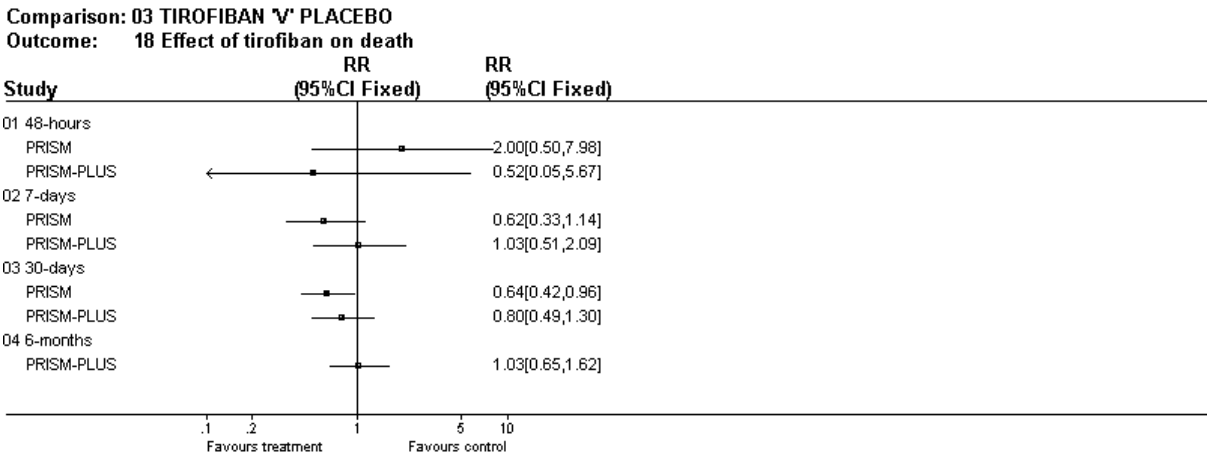
Treatment Arm		**MI**		**Recurrent Ischemia**		**Death**		**PTCA**		**CABG**		**Composite**	
		n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Tirofiban (n=345)	48-hours	2	0.6	-	-	2	0.6	-	-	-	-	26	7.5
	7-days	16	4.6	-	-	16	4.6	-	-	-	-	59	17.1
	30-days	21	6.1	-	-	21	6.1	-	-	-	-	81	23.5
	6-months	25	7.2	-	-	25	7.2	-	-	-	-	105	30.4
Tirofiban + heparin (n=773)	48-hours	6	0.8	37	4.8	1	0.1	-	-	-	-	44	5.7
	7-days	30	3.9	72	9.3	15	1.9	-	-	-	-	100	12.7
	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 (n=797)	48-hours	19	2.4	47	5.9	2	0.3	-	-	-	-	62	8
	7-days	56	7.0	101	12.7	15	1.9	-	-	-	-	143	18
	30-days	73	9.2	107	13.4	36	4.5	236	29.6	20	2.5	178	22
	6-months	84	10.5	107	13.4	56	7.0	-	-	-	-	256	32

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

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 relative risk. The results for PRISM-PLUS relate to the comparison of tirofiban + heparin 'v' 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.

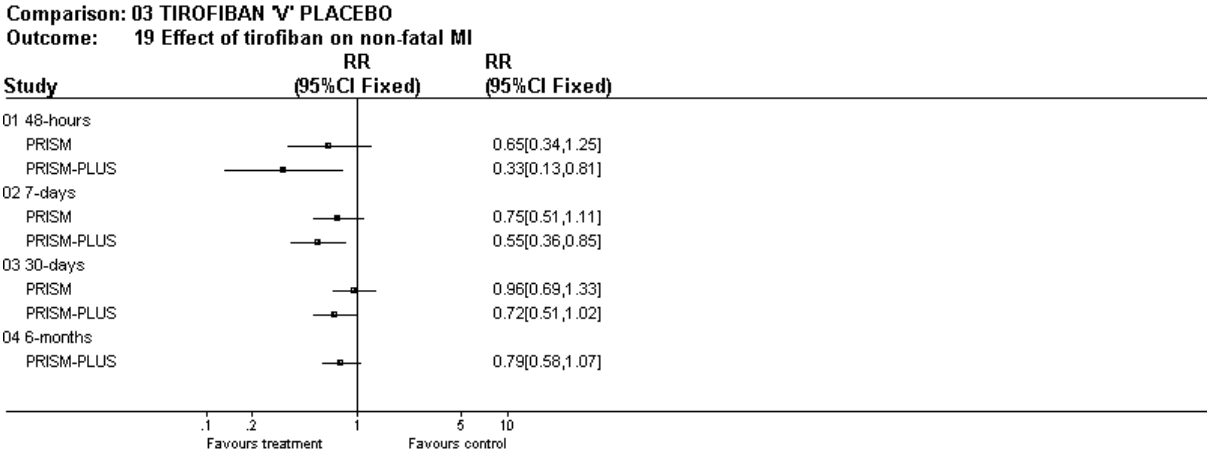
Figure 11: Effect of tirofiban on death for patients receiving glycoproteins as part of medical management



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 risk difference, results for multiple comparisons can be seen in McDonagh et al. The results show a statistically significant positive effect of tirofiban on MI at various follow-up points.

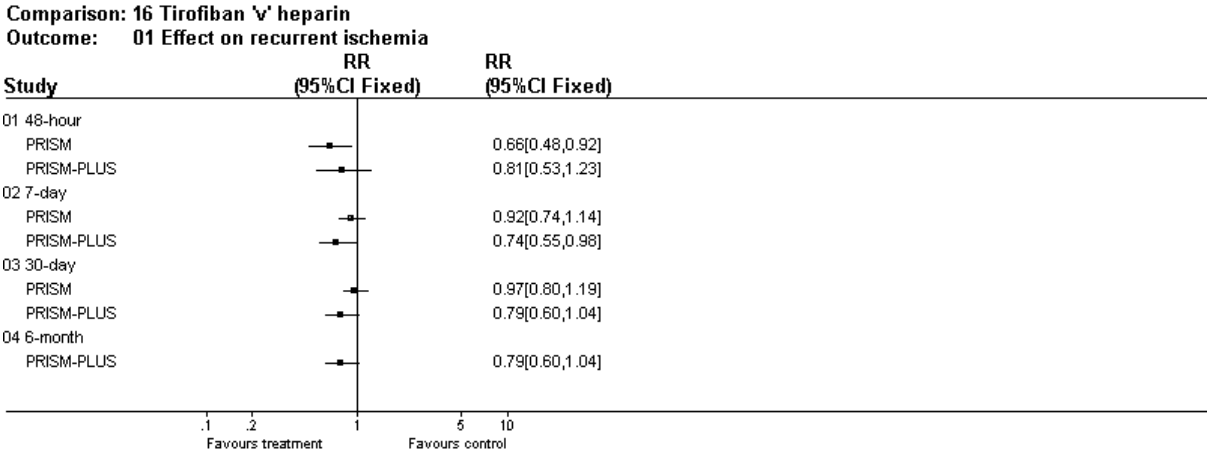
Figure 12: Effect of tirofiban on MI for patients receiving glycoproteins as part of medical management



Recurrent Ischemia

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

Figure 13: Effect of tirofiban on recurrent ischemia for patients receiving glycoproteins as part of medical management



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.

Figure 14:Effect of tirofiban on rates of PTCA, for patients receiving glycoproteins as part of medical management.

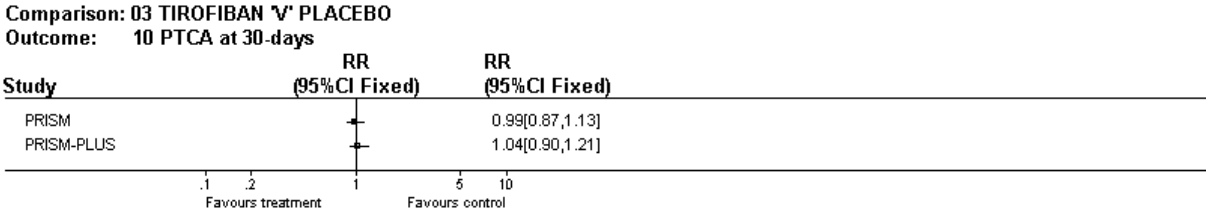
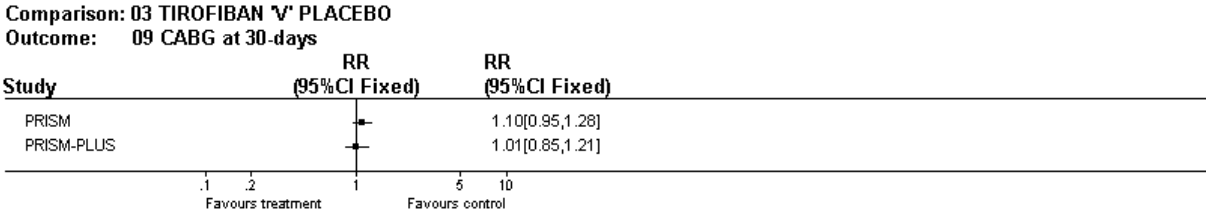


Figure 15: Effect of tirofiban on rates of CABG, for patients receiving glycoproteins as part of medical management



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 2 trials can be seen in Table 18. PRISM used the TIMI 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 appriximately the same in the PRISM study (32/1616 ‘v’ 31/1616) for tirofiban and placebo respectively. The PRISM study also showed no differences in major bleeding, with 6 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 to the heparin alone group (RR = 1.33 (0.79, 2.25).

Figure 16: Effect of tirofiban on minor bleeding for patients receiving glycoproteins as part of medical management

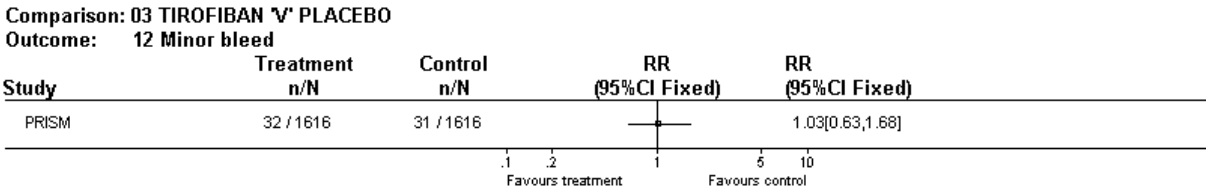


Figure 17: Effect of tirofiban on major bleeding, for patients receiving glycoproteins as part of medical management

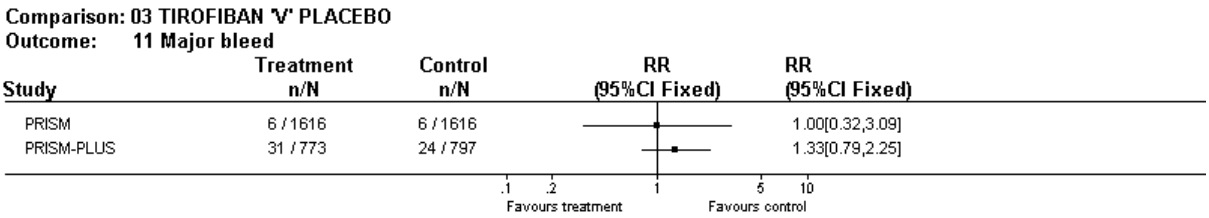


Table 18: Definitions of bleeding in tirofiban trials

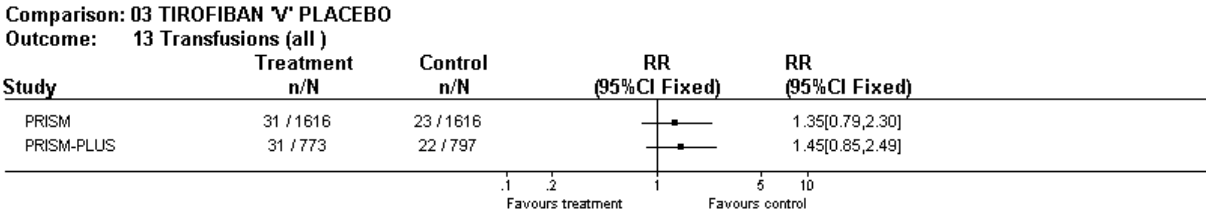
Study	Major/minor bleeding
PRISM[43]	According to the TIMI trial criteria: Major bleed is a decrease in the haemoglobin level of 50 g per litre, intracranial haemorrhage, or cardiac tamponade. Minor bleeding was defined as a decrease in the haemoglobin level of more than 30 g per litre from an identified site, spontaneous gross hematuria, hematemesis, or hemoptysis.
PRISM-PLUS[44]	Decrease in blood haemoglobin level of more than 4.0 g per decilitre, 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.

Thrombocytopenia:
Both studies showed an increased rate of thrombocytopenia in the treatment groups (1.1 'v' 0.49% in the PRISM trial and 1.9 'v' 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 was however 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)

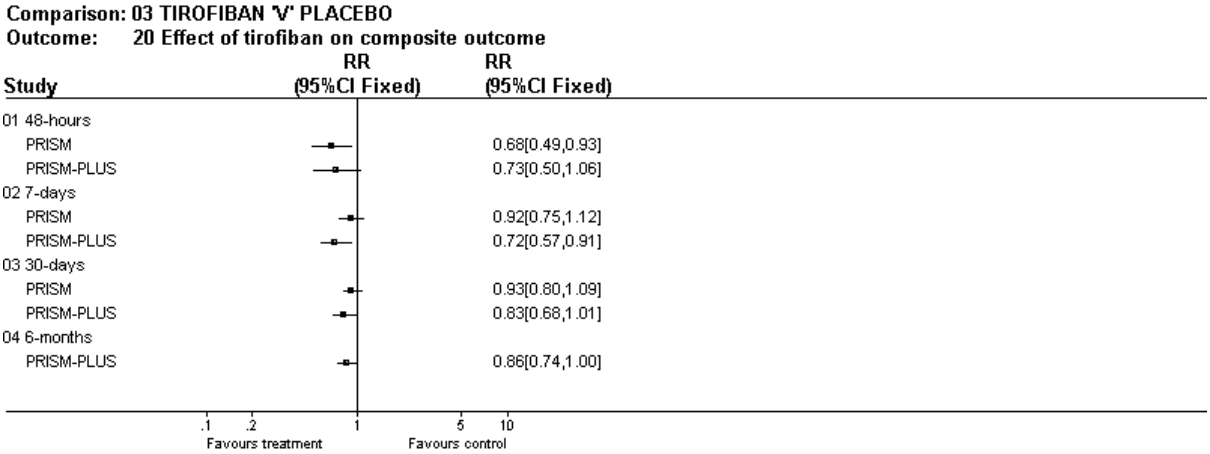
Figure 18: Effect of tirofiban on all transfusions, for patients receiving glycoproteins as part of medical management



Composite endpoint

The effect of tirofiban on the composite endpoint can be seen in Figure 19. The composite endpoint used in PRISM and PRISM-PLUS was death from any cause, non-fatal MI and refractory ischemia. Rehospitalisation for unstable angina is also included at 7 days, 30 days, and 6 months in PRISM-PLUS.

Figure 19: Effect of tirofiban on the composite outcomes, for patients receiving glycoproteins as part of medical management.



2.3.2.3 Abciximab

The use of abciximab in the medical management of ACS patients has been studied in just one trial, GUSTO IV. 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. The results of GUSTO IV are summarised in Table 19. Small differences were observed between the three groups.

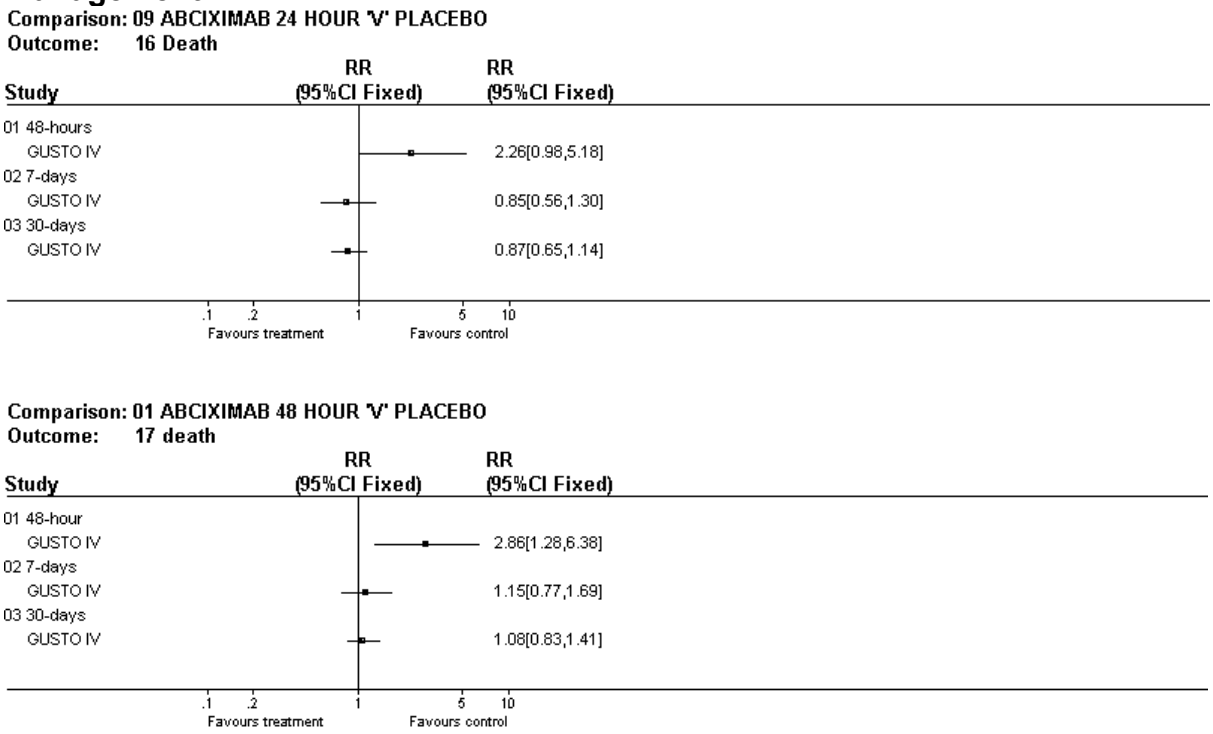
Table 19: Results from GUSTO-IV[37]

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

Death

The effect of abciximab on death, using 24 and 48 hr infusion times can be seen in Figure 20. The NNT to avert one death in the GUSTO IV 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 3 time points, and the difference at 48 hours was statistically significant.

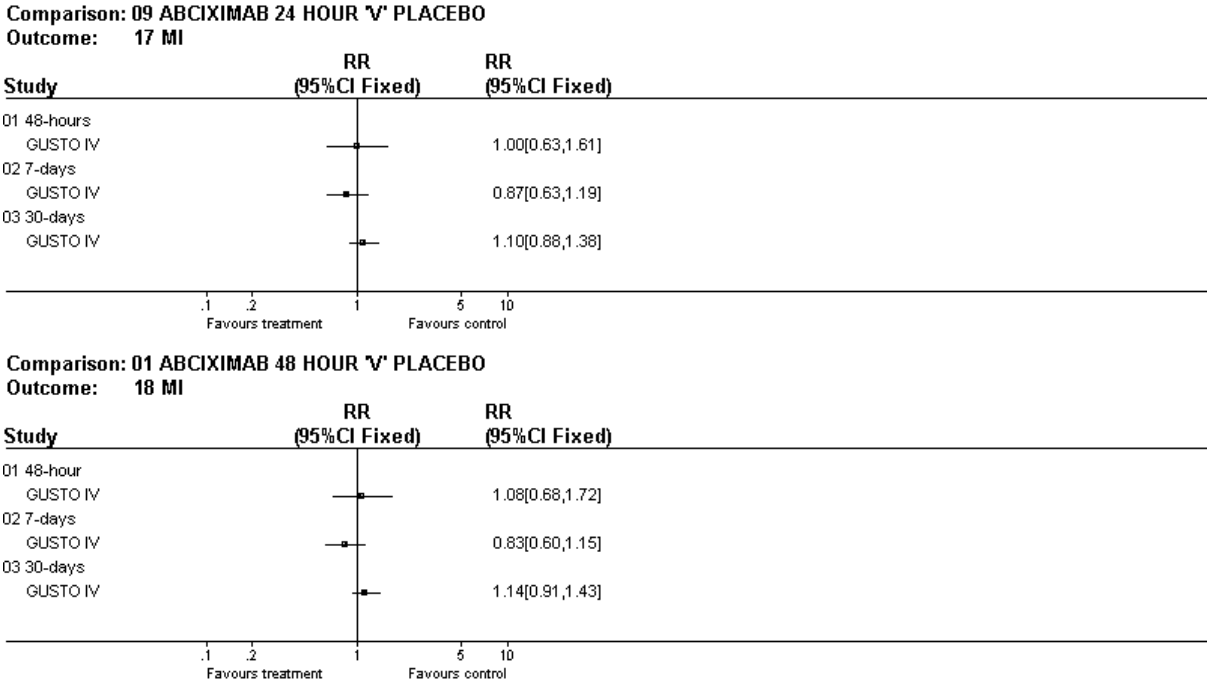
Figure 20: Effect of abciximab on death, for patients receiving glycoproteins as part of medical management.



Myocardial infarction

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

Figure 21: Effect of abciximab on MI, for patients receiving glycoproteins as part of medical management.



Recurrent ischemia

Rates of recurrent ischemia were not reported in the GUSTO IV trial.

Revascularisations

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.

Figure 22: Effect of abciximab on PTCA, for patients receiving glycoproteins as part of medical management

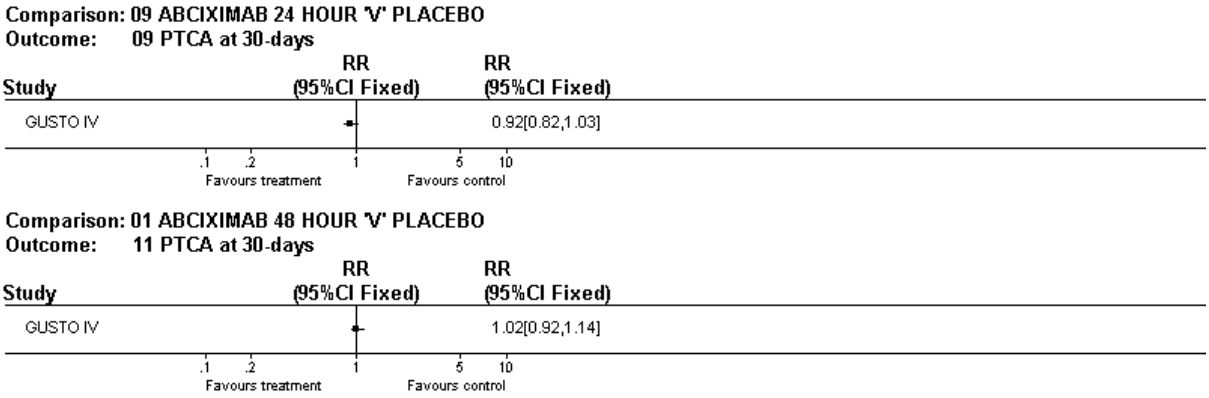
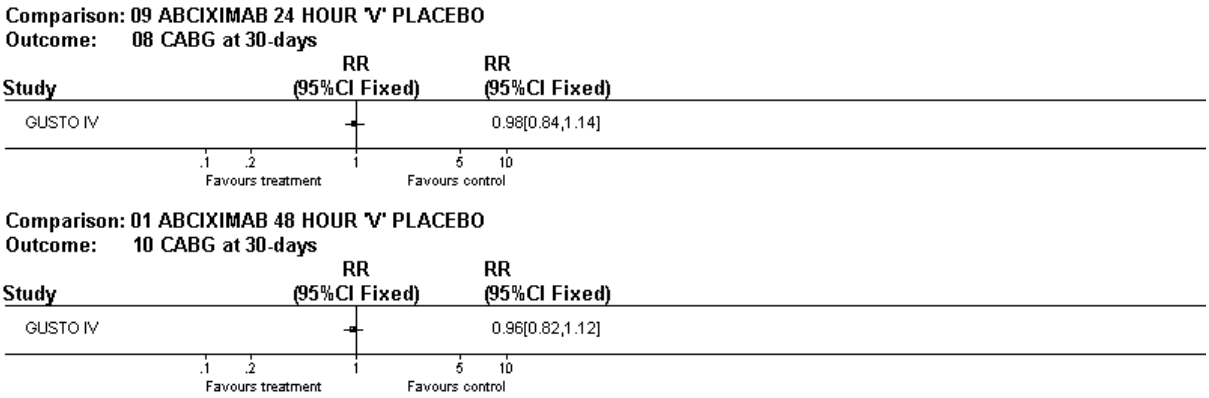


Figure 23: Effect of abciximab on CABG, for patients receiving glycoproteins as part of medical management



Adverse events

The main concerns for adverse effects in the GUSTO IV 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 major and minor bleeding episodes can be seen in Figures 24 and 25. 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 but less than or equal to 50 g/L; or decrease in haemoglobin concentration of more than 30, 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 to placebo. 2.5% of 24-hour infusion, 3.6% of 48-hour infusion and 1.5% of placebo patients experianced 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, at 0.6%, 0.9% and 0.2% in the 24-hour infusion, 48-hour infusion and placebo groups respectively. Relative to placebo, the excess major bleeding in the 48-hour infusion arm was statistically significant

Figure 24: Effect of abciximab on minor bleed, for patients receiving glycoproteins as part of medical management

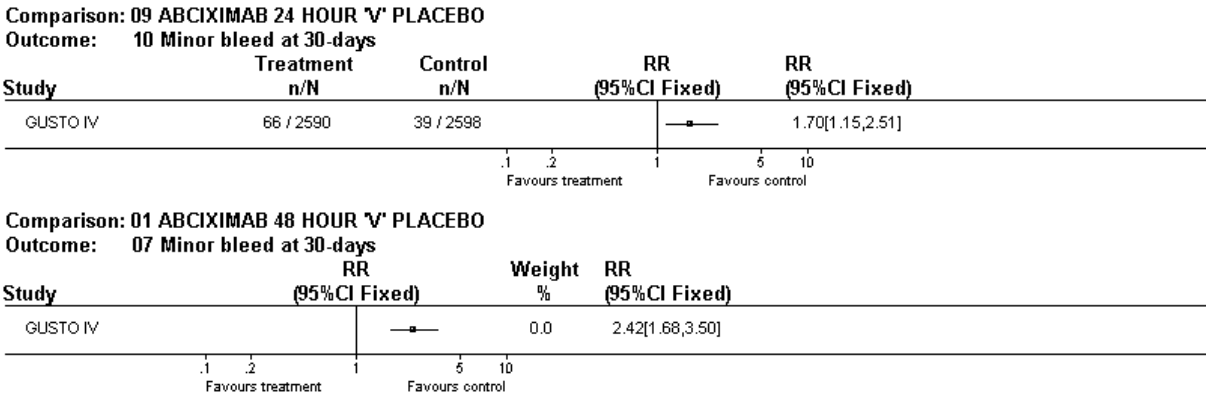
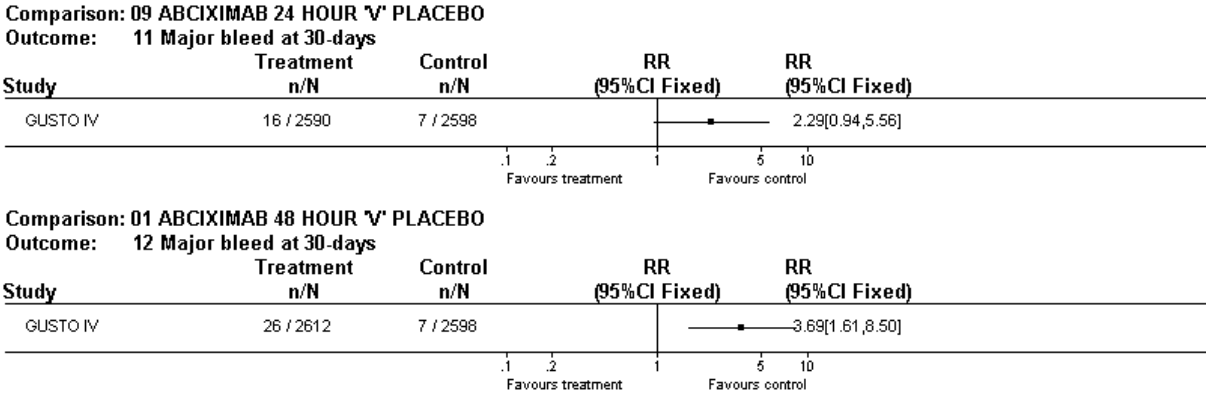


Figure 25: Effect of abciximab on major bleed, for patients receiving glycoproteins as part of medical management



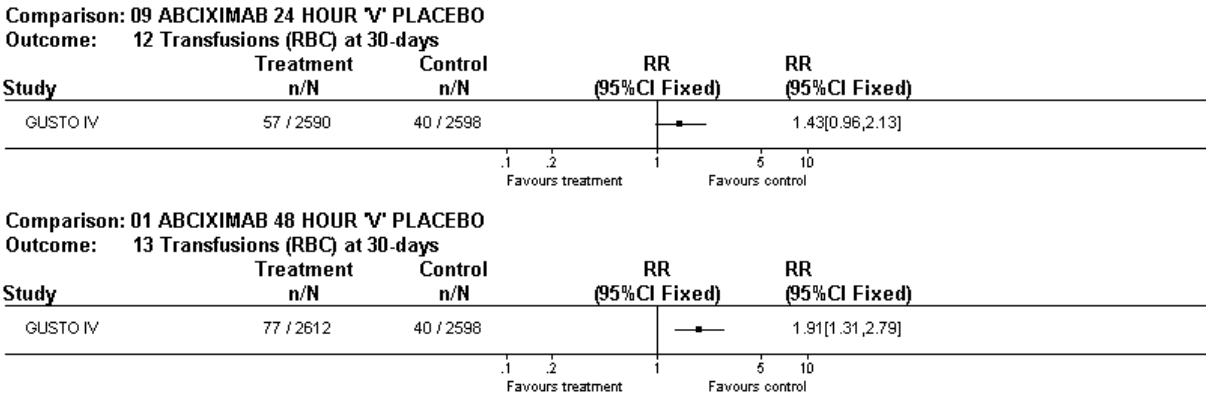
Thrombocytopenia:

Thrombocytopenia (platelet count <50 000/μL) was seen in 78 (1.5%) of abciximab patients compared to 1 placebo patient.

Transfusions:

The effect of abciximab on red blood cell (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 (1.31, 2.13)). The 24-hour infusion group were also more likely to require a RBC transfusion compared to the placebo group, but this excess rate was not statistically significant (RR=1.43(0.96, 2.13)).

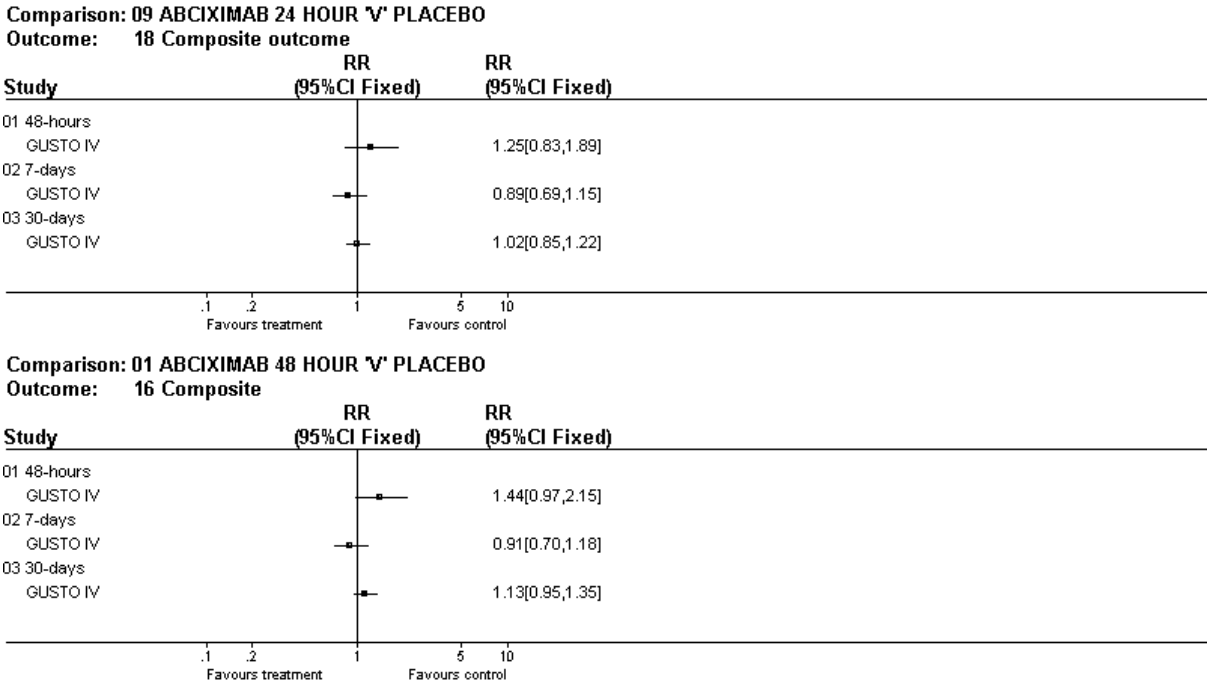
Figure 26: Effect of abciximab on RBC transfusions, for patients receiving glycoproteins as part of medical management



Composite

The effect of abciximab on the composite endpoint 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 endpoint is more common in treatment than control arms at 48-hours and 30-days follow-up. At 7-days, 24-hour and 48-hour infusion groups were less likely to experience a death or MI. The RR at 7-days was 0.89 (0.69, 1.15) for the 24-hour infusion group compared to placebo and 0.91 (0.70, 1.18) for the 48-hour infusion group compared to placebo. None of the differences in the composite outcome was statistically significant.

Figure 27: Effect of abciximab on the composite outcome, for patients receiving glycoproteins as part of medical management



2.3.2.4 Results for high-risk groups

Outcomes for the four high-risk groups identified (elderly, ST-depression, troponin positive and diabetics) are presented in Tables 20-23 below. Boersma et al looked at the relationship between baseline characteristics, including ST-depression, diabetes and age on 30-day outcomes. Rates and odds ratios for the relationship were presented for all the baseline characteristics in combination and not those specified as relevant for this review, therefore it has not been possible to extract relevant results from this paper.

Table 20: Outcomes for diabetic patients, receiving glycoproteins as part of medical management.

Trial	Death	MI	Death/MI	Composite	Bleeding
PURSUIT	-	-	Odds ratio approx. 0.95 (eptifibatide better)	-	
PRISM	-	-	-	Diabetics = RR 0.4 (approx)	
PRISM-PLUS	-	-	-	Tirofiban + heparin = 25/169 (14.8%) Heparin = 42/193 (21.8%)	
GUSTO IV	-	-	Abciximab 24 hour = 9.6% Abciximab 48-hour = 11.0% Placebo = 11.4%	-	
PRISM-PLUS (sub-group analysis by Theroux et al)	-	-	-	Tirofiban + heparin: 48-hours = 7.7%, 7-days = 14.8%, 30-days = 20.1%, 6-months = 32.0% Heparin: 48-hours = 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%

The analysis of diabetics included in the PRISM-PLUS trial undertaken by Theroux et al showed little difference in ARR of the primary endpoint of death, new MI or refractory ischaemia 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% repsectively, 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.

Table 21: Outcomes for elderly patients, receiving glycoproteins as part of medical management.

Trial	Death	MI	Death/MI	Composite
PURSUIT	-	-	Odds ratio approx 0.98 (eptifibatide better) in age ≥65	-
PRISM	-	-	-	>75 years = RR 0.6 (approx)
PRISM-	-	-	-	Tirofiban +

PLUS				heparin = 66/371 (17.8%) Heparin = 93/395 (23.5%)
GUSTO IV	-	-	Abciximab 24 hour = 10.6% Abciximab 48-hour = 12.4% Placebo = 11.1%	
PURSUIT (sub-group analysis by Hasdai et al)	Eptifibatide: < 50=5 (0.8%) 50-59=15 (1.4%) 60-69=45 (3%) 70-79=71 (5.8%) >80 =29 (11.7%) Placebo: < 50 =6 (0.9%) 50-59 =16 (1.5%) 60-69 =54 (3.5%) 70-79 =78 (6.6%) >80 =23 (9%)	Eptifibatide: < 50 =54 (8.2%) 50-59 =100 (9%) 60-69 =188 (12.6%) 70-79 =194 (15.9%) >80 =57 (22.9%) Placebo: < 50 =63 (9.5%) 50-59 =138(12.8%) 60-69 =203(13.0%) 70-79= 194(16.5%) >80 =46(17.9%)	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 =64(9.6%) 50-59 =148(13.8%) 60-69 =235(18.6%) 70-79=237 (20.1%) >80 =61 (23.7%)	-

The analysis of PURSUIT data by age group by Hasdai et al 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.

GUSTO IV 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.

Table 22: Outcomes for troponin positive patients, receiving glycoproteins as part of medical management.

Trial	Death	MI	Death/MI	Composite
GUSTO IV	-	-	Abciximab 24 hour = 10.0% Abciximab 48-hour = 11.6% Placebo = 10.0%	-
PRISM (Sub-group analysis by Heeschen et al)	Tirofiban: 48-hours =0 7-days =2(0.7%) 30-days =5(1.6%) Heparin: 48-hours =2(0.6%) 7-days =12(3.7%) 30-days =20(6.2%)	Tirofiban: 48-hours=1 (0.3%) 7-days =4(1.3%) 30-days =8(2.6%) Heparin: 48-hours=9(2.8%) 7-days =18(5.6%) 30-days =22(6.8%)	-	Tirofiban: 48-hours =1 (0.3) 7-days =6 (2.0) 30-days =13 (4.3) Heparin: 48-hours =11 (3.4) 7-days =30 (9.3) 30-days =42 (13.0)

The sub-group analysis of troponin status by Heeschen et al 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% amd 17.1% for tirofiban and heparin arms respectively. GUSTO IV was the only other trial to report any results in

troponin positive patients. There was no difference in the number of deaths or MI's in the abciximab 24-hour infusion group and placebo group, whereas a negative effect of abciximab was found in the 48-hour infusion compared to placebo groups (11.6% versus 10.0%). These results were similar to those for all patients in the trial.

Table 23: Outcomes for patients with ST-depression, receiving glycoproteins as part of medical management.

Trial	Death	MI	Death/MI	Composite
PRISM	-	-	-	RR 0.5 (approx)
PRISM-PLUS				Tirofiban plus Heparin = 16.6% Heparin = 21.7%
GUSTO IV	-	-	Abciximab 24 hour = 8.5% Abciximab 48-hour = 9.9% Placebo = 8.4%	-

PRISM, PRISM-PLUS and GUSTO IV 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 endpoint 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 endpoint occurred in 16.6% of trreated 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 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 = 9.9%, placebo = 8.4%) and little difference between the 24-hour infusion group and placebo.

In summary sub-group 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.

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

Five trials of three intravenous glycoprotein 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 to other interventions for acute coronary syndromes. For aspirin the 30-day reduction in mortality is 2.4% (1.6-3.2%) (NNT 41(32-62)[52]. For thrombolysis, equivalent figures are 1.9% (NNT 56)[52]. Equivalent absolute risk reductions in mortality in these trials are 0.2% (PURSUIT); 1.3% in PRISM, 0.9% in PRISM-PLUS (tirofiban and heparin v heparin). In GUSTO-IV 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 0.98,5.18, RR 48-hour infusion = 2.86, 95% CI 1.28,6.30). The increased risk of death continued for longer follow up periods in the 48-hour infusion (RR at 7-days = 1.15, 95% CI 0.77,1.69, RR at 30-days = 1.06, 95% CI 0.83, 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, 1.30, RR at 30-days = 0.87, 95% CI 0.65, 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[3] (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 were significant at the 5% level, although this is a function of the size of the trials as well as the drugs' effectiveness.

Sub-group 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 endpoints for subgroup defined by Troponin. In the PURSUIT study, with regard to age, the ARR for death was 2.7% in those >80 yrs 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:

1 Such analyses are rarely pre-specified in published protocols, so those published may be selected post hoc;
2 Randomisation is not stratified by sub-groups so there may be imbalances in prognostic factors resulting in spurious differences in endpoints.[53]

Differences between the baseline characteristics of subjects enrolled in PRISM and PRISM-PLUS may partially explain the opposing findings with tirofiban alone. In PRISM-PLUS more than 90 percent of patients had baseline ST-T ECG changes, whereas only 39 percent 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[54]. 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 subjects 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 to placebo, 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 endpoints, and patients could have received an intervention (possibly in combination with a glycoprotein IIb/IIIa antagonist) during these studies, then the result would be an underestimate of the real effects of the glycoprotein IIb/IIIa antagonists. The treatment effect may also be understated if the patients who are already receiving 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 be recieve PCI and to be Troponin-positive[3]. 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 glycoprotein IIb/IIIa antagonists among patients not going on to receive PCI may be much smaller than is reported in these trials. Sub-group analysis in patients not receiving early revascularisation shows effect in some trials but not 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 [55]. These sub-group 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 glycoprotein antagonists) 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 endpoint at 96 hours are slightly less at 6 months, but the confidence intervals overlap. The effects seen with tirofiban plus heparin for the composite endpoint appear to be the greatest at 7 days, and were slightly less at 6 months. However, the confidence intervals again overlap. The precision of the estimates of effect is relatively low, with wide confidence intervals for all trials except for PURSUIT. Many of the confidence intervals cross the no effect mark.

The results of GUSTO-IV, 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[56]. Abciximab may differ in this way from the small molecule GP. Alternatively all three GP IIb/IIIa inhibitors may be of limited effectiveness in patients not undergoing early invasive management. A recent editorial in Heart[55] argued that none of the trials had demonstrated benefits in patients not having early intervention.

However, an alternative retrospective re-analysis of PURSUIT and PRISM-PLUS[57] 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 2 trials excluded from this review[3] 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 sub analysis of cases of stroke revealed that most of the strokes were non-hemorrhagic (83.5% of all strokes), and this was not higher in the eptifibatide treated patients[58]. 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. PURSUIT defined thrombocytopenia as <100,000/m3, while PRISM and PRISM-PLUS defined it as <90,000/m3.

In reaching an overall conclusion about 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. NNH (Number treated resulting in one adverse event) from major bleeding ranges from 66 in PURSUIT to 250 in GUSTO-IV. There are too few such events to assess whether adverse effects are more common in those sub-groups, 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 whose major bleed or stroke may have been caused in this way. A recent case report published by the Lancet illustrates this[59].

Although there is evidence from all 5 trials of a reduction in composite outcome at some time point for ACS patients overall, given the uncertainty of sub-group analysis, there remains doubt about the effectiveness in specific sub-groups, such as those patients not undergoing early intervention. With regard to the latter, the Chairman of the ACC/AHA 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[60]- He states “The totality of evidence with GPIIb/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/AHA 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.

2.4 Glycoproteins alongside PCI

2.4.1 Efficacy of intravenous glycoprotein IIb/IIIa antagonists

The earlier review by Fischer et al[5] reviewed 13 trials looking at the use of glycoproteins alongside PCI. The Excite trial[61] was not included in this updated review as it considered the use of xemilofiban, which is not licenced in the UK. In addition to these 12 trials, the update searches identified another 5 trials (PRICE[62,] ADMIRAL[63], TACTICS-TIMI[64], TARGET[65] and ESPRIT[66]). A sixth trial, CADILLAC[67] 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 et al review.

2.4.1.1 General details

The 17 trials all took place between 1992 and 2001, with 4 conducted in an international setting, 8 took place in the US, 2 in the US and Canada, and 1 each in Taiwan, Italy, France and Germany. All trials were classified as randomised placebo controlled trials apart from Galassi et al, TARGET and PRICE which did not include placebo as a comparator and TACTICS-TIMI in which all patients received Tirofiban (Table 24).

Abciximab was evaluated in 10 of the trials, with similar doses used between studies. Eptifibatide was assessed by IMPACT-II[68], ESPRIT and Harrington et al[49]. Tirofiban was assessed in the RESTORE[69,70] and TARGET and TACTICS-TIMI 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[71] (although longer follow up was also assessed) to 7 years in EPIC[72-74] (7 year data submitted as part of company submission).

Table 24: Details of included studies of intravenous glycoprotein IIb/IIIa antagonists

Study	Setting	Design/phase	Treatment arms	Number of participants	Follow up times
EPIC, 1992[72-74]	US	Multi-centre, double blind, placebo RCT.	Abciximab + infusion Abciximab + placebo Placebo + placebo infusion	1695 2708 696	30-days 6-months 3-years 7-years *
IMPACT II, 1994[68]	US	Double blind, placebo RCT	Eptifibatide high dose Eptifibatide low dose Placebo	1349 1333 1328	30-days 6-months
CAPTURE, 1995[71]	12 Countries	Double blind, placebo RCT	Abciximab Placebo	630 635	≤36 hours before PTCA ≤72 hours after randomisation 30-day 6 month

EPILOG, 1995[75 76]	US & Canada	Double blind, placebo RCT	Abciximab + high dose Heparin Abciximab + standard dose Heparin Placebo	935 918 939	30-day 6-month 4.5 years*
RESTORE, 1995[69]	International	Double blind, placebo RCT.	Tirofiban Placebo	1071 1070	30-days 6-months
RAPPORT, 1997[77]	US	Double blind, placebo RCT	Abciximab Placebo	241 242	7-days 30-days 6-months
EPISTENT, 1997[78]	US & Canada	Double blind RCT	Abciximab + stent Abciximab + Balloon Placebo + stent	794 796 809	30-days 6-months 1-year (some) 3-year *
ERASER, 1997[79]	US	Multi-centre, double blind, placebo RCT	Abciximab 12-hour Abciximab 24-hour Placebo	79 75 71	6-months
Galassi et al, 1998[80]	Italy	Randomised trial, not placebo	No abciximab Abciximab	52 54	30-days
Harrington et al[49]	US	RCT, some double blinding	Eptifibatide placebo	54 19	Until discharge
Chen et al, 1997 [81]	Tiawan	Double blind, placebo RCT	Abciximab Placebo	22 20	30-days
ISAR-II [82]	Germany	Single blind, RCT	Abciximab Heparin	201 200	30-days 1 year *
TACTICS-TIMI[64]	US	Double blind RCT	Invasive Conservative (all patients received tirofiban)	1114 1106	30-days 6-months
TARGET[65]	US	Multi-centre, double-blind, double-dummy trial	Tirofiban Abciximab	2398 2411	30-days
ESPRIT[66]	US & Canada	Multi-centre, randomised, placebo-controlled, parallel-group trial.	eptifibatide Placebo	1040 1024	48-hours 30-days 6-months 1-year
PRICE, 2000[62]	US	Randomised, double-blind study	Abciximab Eptifibatide	163 157	30-days
ADMIRAL, 2001[63]	France	Randomised, placebo-controlled trial.	Abciximab Placebo	149 151	30-days 6-months

2.4.1.2. Patient characteristics and inclusion criteria

The inclusion criteria used in the trials were heterogeneous: 9 trials included a broad cross section of patients undergoing elective or emergency PCI (IMPACT II, EPISTENT, ERASER, Galassi et al, Harrington et al, TARGET, ESPRIT, PRICE, EPILOG); 1 trial focused on ACS patients (RESTORE); 2 trials concentrated solely on unstable angina patients (CAPTURE, TACTICS-TIMI); 3 on primary PCI after MI (RAPPORT, ADIMIRAL, ISAR II); and 2 selected patients at high risk of cardiac

complications (EPIC, Chen et al). Inclusion and exclusion criteria used in each trial can be seen in Table 25 below.

Table 25: Inclusion and exclusion criteria from published texts

Study	Inclusion criteria	Exclusion criteria
EPIC, 1992[72-74]	Patients needing coronary angioplasty or directional atherectomy, with an evolving or recent MI, UA, or high risk angiographic lesion morphology or clinical characteristics.	Tendency to bleed, > 80 yrs, stroke within last 2 yrs or major surgery ≤ 2 weeks prior to study entry.
IMPACT II, 1994[68]	Scheduled for elective, urgent, or emergency coronary intervention with a device approved by the FDA (balloon angioplasty, Directional coronary atherectomy, rotational atherectomy, or excimer laser ablation); representative cross-section of patients undergoing percutaneous revascularisation.	1. History of bleeding diathesis 2. Severe hypertension (SBP > 200 mm Hg or DBP > 100 mm Hg on therapy) 3. Major surgery <=6 weeks 4. History of stroke or other disorders of the CNS 5. Pregnancy 6. GI or GU bleeding <=30 days 7. Other major illness
CAPTURE, 1995[71]	Patients with refractory unstable angina undergoing PTCA. Refractory UA 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 both. Latest episode of ischaemia within the last 48 hours before enrolment. Patients undergone angiography and had significant CAD with a culprit lesion suitable for angioplasty. Patients enrolled within 24h of angiography.	Recent MI, unless creatine kinase values had returned to below two times 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, 1995[75 76]	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 UA with ECG changes in last 24hr))	1. AMI or UA with associated ECG changes < 24 hours 2. Planned stent implantation or rotational atherectomy 3. PCI performed <=3months 4.Left-main-CA stenosis >50% not protected by collateral vessels 5. Concurrent warfarin therapy or a base- line prothrombin time > 1.2 times the control value 6. CVE <=2 years or a residual neurologic deficit Intracranial neoplasm 7. Aneurysm Arteriovenous malformation 8. History of vasculitits 9. Known hemorrhagic diathesis or active internal bleeding 10. SBP > 180 mm Hg or DBP >100 mm Hg 11. Major surgery Gastrointestinal bleeding or genitourinary bleeding <=6 weeks inability to give written consent.
RESTORE, 1995[69]	Patients undergoing coronary	1. Received thrombolytic therapy <= 24 hrs 2.

	interventions (balloon angioplasty or directional colour angiography) within 72 hr of presentation of ACS (UA or acute MI). Also included if MI occurred in last 72hrs.	Contraindication to anticoagulation History of platelet disorder or thrombocytopenia 3. History of stroke or other intracranial pathology likely to predispose to bleeding 4. Scheduled for elective stent placement or if angioplasty using a rotablator or transluminal extraction catheter device was planned
RAPPORT, 1997[77]	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. percutaneous coronary intervention within <=3 months
EPISTENT, 1997[78]	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 3) patient did not have bleeding diathesis, intracrnial neoplasm, history of stroke in previous 2 years, uncontrolled hypertension or PCI within last 3 months.	1. Bleeding diathesis, intracranial neoplasm, history of stroke in the previous 2 years, 2. Uncontrolled hypertension (systolic blood pressure > 180 mm Hg, diastolic > 100 mm Hg), 3. Recent surgery, or percutaneous coronary intervention within <=3 months 4. Concurrent warfarin therapy of an INR > 1.5 at baseline
ERASER, 1997[79]	Patients required to have a de novo target coronary stenosis of ≥50% in vessel of diameter 2.75-3.5mm, 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, 1998[80]	Patients with demonstrable ischemia and a target de novo complex lesion stenosis ∫70% in a native vessel	Acute MI; bleeding diathesis thrombocytopenia, history of stroke in previous two years, internal bleeding; hypertension; major trauma/surgery within 6 weeks.
Harrington et al[49]	Patients undergoing elective coronary intervention.	Bleeding disorders; recent gastrointestinal 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; hemoatocrit <30%; platelet count <100,000/ ∝l or creatinine >40mg/dl.
Chen et al, 1997 [81]	Patients undergoing angioplasty at high risk for cardiac complications, not at high risk of bleeding.	>80 years of age; bleeding diatheses; major surgery within six preceding weeks; stroke within preceding 2 years; not patients who were to undergo planned stent implantation, directional atherectomy or rotational atherectomy.
ISAR-II, 2000[82]	AMI patients undergoing revascularisation by stent placement within 48 hours after onset of pain, and typical anginal pain lasting >30 min; ST segment elevation of a least 1 mm in two or more contiguous leads; elevation in creatine kinase to at least 3 times the upper limit of normal; coronary artery occlusion with angiographic appearance of fresh thrombus	1. Inability to give informed consent 2. Contraindications to one of the study drugs.

TACTICS-TIMI[64]	18 years of age with accelerating pattern, prolonged or recurrent anginal pain at rest or minimal effort < 24 hours and at least 1 of 1) Ischemic electrocard iogram changes 2) Elevated cardiac markers and a history of MI 3) Coronary artery disease4) PCI or CABG. AMI patients excluded.	Persons excluded for any of the following reasons: persistent ST-segment elevation, secondary angina, a history of percutaneous coronary revascularisation or coronary artery bypass grafting within the preceding 6 months, factors associated with an increased risk of bleeding, left bundle-branch block or paced rhythm, severe congestive heart failure or cardiogenic shock, serious systemic disease, a serum creatine level of more than 2.5 mg per deciliter (221 umol per litre), or current participation in another study. Patients also excluded if they were taking warfarin or had received ticlopidine or clopidogrel for more than 3 days before enrolment.
TARGET[65]	Patients undergoing PCI. Anatomy appropriate for stenting, elective or ACS (except primary PCI_MI), and creatinine < 2.5 mg/dL. AMI patients excluded	Patients with cardiogenic shock or an acute myocardial infarction with electrographic evidence of ST-segment elevation; serum creatine levels $\geq$ 2.5 mg/dl; and ongoing bleeding or a bleeding diathesis, including platelet count < 120,000 mm2.
ESPRIT[66]	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	Myocardial infarction 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 a thienopyridine 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 systolic blood pressure greater than 200 mm Hg or a diastolic greater than 110 mm Hg; documented thrombocytopenia with a platelet count less than 100 x 10/L; or a serum creatine > 350 umol/L.
PRICE, 2000[62]	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 (ACC)/American Heart Association (AHA) type C lesions, 5) history of haemorrhagic diathesis or major surgery or trauma < 6 weeks before randomisation, 6) known baseline platelet count < 100,000 mm3, 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, and 11) participation in other clinical research studies within 30-days of

		randomisation.
ADMIRAL, 2001[63]	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 anticoagulant therapy, limited life expectancy, childbearing potential, and contraindications to therapy with aspirin, ticlopidine, or heparin

The number of participants in each trial varied quite significantly, PURSUIT was the largest trial with 9461 participants and Chen et al 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 et al. 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 et al 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 et al. 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 below.

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 et al which had a relatively small percentage of patients included who had a prior CABG (3%)

Table 26: Baseline characteristics of participants in trials of intravenous drugs

Study	Prognostic indicators	Intervention 1	Intervention 2	Control
EPIC, 1992[72-74]	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, 1994[68]	Median age	62	60	60
	Diabetes (%)	23	23	22
	Hypertension (%)	54	55	54
	Hypercholesterohaemia (%)	53	66	53
	Smokers	65	65	66
CAPTURE, 1995[71]	Median age	61		61
	Diabetes (%)	15		18
	Hypertension (%)	43		41.4
	Current smoker (%)	37		40.8
EPILOG, 1995[75] [76]	Median age (%)	60	60	60
	Diabetes (%)	23	22	24
	Previous bypass (%)	13	12	13
RESTORE, 1995[69]	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, 1997[77]	Median age	62		65
	Hypertension (%)	46		50
	Current smoker (%)	41		41
	Diabetes (%)	23		22
	Previous MI (%)	17		21
	Prior revascularisation (%)	14		14
EPISTENT, 1997[78]	Median age	59	59	60
	Hypertension (%)	47	55	55
	Diabetes (%)	20	19	21
	Smoker (%)	37	34	39
ERASER, 1997[79]	Median age	58	62	58
	Diabetes (%)	12	18	11
	Hyper tension (%)	46	52	50
	Smoker (%)	29	36	28
	Prior PCI (%)	12	12	16
Galassi et al, 1998[80]	Median age	63	61	
	Family history of CAD (%)	40	44	
	Diabetes (%)	26	27	
	Hypertension (%)	34	33	
	Smoking (%)	67	72	
	Hypercholesterolemia (%)	26	22	
Harrington et al[49]	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
Chen et al, 1997 [81]	Median age	70		70

[81]	Current smoker (%) Diabetes (%) Hypertension (%) Hypercholesterolemia (%) Prior MI (%) Previous angioplasty (%) Prior CABG (%)	36 36 68 18 41 9 5		55 35 65 15 50 15 0
ISAR-II, 2000[82]	Median age Active smoker (%) Diabetes (%) Previous PTCA (%) Previous CABG (%)	60 42.8 17.4 7.5 4.0	64 43.5 2.25 6.0 4.5	
TACTICS-TIMI[64]	Median age Diabetes (%) ST segment or T wave changes (%) Prior MI (%) Elevated Troponin T (%)	62 28 48 39 56	62 27 47 39 52	
TARGET[65]	Median age Diabetes (%) Hypertension (%) Smoker (%) CABG (%) MI (%)	62 23 64 65 17 40	62 23 65 64 17 39	
ESPRIT[66]	Median age Diabetes (%) Hyper-tension (%) Smoker (%) Stable Angina (%) UA/NQWMI (2-180 days) UA/NQWMI (within 2-days) ST elevated MI (7 days) Prior PCI (%) Prior MI (%) Prior CABG (%)	62 20 59 24 39 32 13 4 23 32 10		62 21 59 23 38 33 14 5 24 31 10
PRICE, 2000[62]	Mean age Hypertension (%) Diabetes (%) CHF (%) Smoker (%) Prior CABG (%) Prior PCI (%)	63 68 25 9 63 22 37	63 71 33 9 71 20 37	
ADMIRAL, 2001[63]	Mean age Diabetes (%) Current smoker (%) History of hypertension (%) History of MI (%) History of unstable angina(%) History of stable angina (%) History of heart failure (%) CHF (%)	59.6 15.4 45.0 34.2 14.1 8.7 12.1 2.0 0.7	62.1 19.9 39.7 41.1 7.3 14.6 12.0 2.0 9.3	

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

Only 5 trials gave the timing of administration of the intervention drug before PCI, but those that did indicate another source of heterogeneity. Chen et al, EPISTENT and EPILOG 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 4-48 hours before PCI. ESPRIT patients were given eptifibatide immediately before PCI.

Only 2 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.

2.4.1.4 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 units/kg or 10000 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 et al, CAPTURE, RESTORE, TACTICS-TIMI, TARGET, ESPRIT and IMPACT-II. Continued use 12-hours after PTCA was recommended in EPIC and Chen et al, Harrington, PURSUIT and ERASER did not specify timing but stated that heparin was given to patients. EPISTENT, RAPPORT, ESPRIT, ISAR, PRICE, ADMIRAL and EPILOG did not recommend the use of heparin during the procedure.

Table 27: Use of concomitant medications

Study	Treatment arm	Aspirin	Heparin	Nitrates	Calcium channel blockers	Beta blocker
EPIC, 1992[72-74]	Abciximab + infusion Abciximab + placebo Placebo + placebo infusion	325mg oral aspirin at least two hours before procedure. At discharge patients given 325mg 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.	-	-	-
IMPACTII, 1994[68]	Eptifibatide high dose Eptifibatide low dose Placebo	325mg Aspirin orally before intervention.	100 U/kg bolus of heparin, additional heparin given during procedure	-	-	-
CAPTURE, 1995[71]	Abciximab Placebo	Aspirin at minimum daily dose of 50mg. If not on aspirin previously first dose at least 250mg.	Heparin until at least 1 hr after PTCA	All patients received these-percentages and amounts not reported.		
EPILOG, 1995[75,76]	Abciximab + high dose Heparin Abciximab + standard dose Heparin Placebo	325 oral Aspirin two hours before PCI, and daily thereafter.	-	-	-	-
RESTORE, 1995[69]	Tirofiban Placebo	325mg Aspirin within 12 hr before PTCA	Preprocedure heparin 150 μg/kg for patients weighing < 70kg. Heparin as required during procedure	-	-	-
RAPPORT, 1997[77]	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 investigators discretion.		
EPISTENT, 1997[78]	Abciximab + stent Abciximab +	325mg oral aspirin at	-	-	-	-

	Balloon Placebo + stent	least 2hr before PCI				
ERASER, 1997[79]	Abciximab 12-hour Abciximab 24-hour Placebo	200mg ≥oral Aspirin ≥2 hours before procedure. Aspirin continued for ≥6 months	Patients received Heparin	Patients received nitrates	-	-
Galassi et al, 1998[80]	No abciximab Abciximab	Aspirin 325 mg orally before intervention, and then daily.	-	-	-	-
Harrington et al[49]	Eptifibatide placebo	Aspirin 375mg oral before administration of study drug. Aspirin 325mg daily continued until discharge	Patients received heparin	-	-	-
Chen et al, 1997 [81]	Abciximab Placebo	Aspirin 325mg daily continued until discharge	Heparin administered in an initial bolus of 70 U/kg (max 7,000 U), additional bolus given	-	-	-
ISAR-II, 2000[82]	Abciximab Heparin	500 mg Aspirin, IV before catheterisation.	500 U heparin, IV before catheterisation.	-	-	-
TACTICS-TIMI[64]	Invasive Conservative (all patients received abciximab)	325 mg aspirin daily	IV unfractionated Heparin initial dose 5000 U (bolus	-	-	-
TARGET[65]	Tirofiban Abciximab	All patients received 250-500 mg aspirin before the procedure	<70 U/kg administered at the start of the procedure	-	-	-
ESPRIT[66]	Eptifibtide Placebo	Patients received aspirin	Heparin: Initial bolus of 60 units/kg, not exceeding 6000 units.	-	-	-
PRICE[62]	Abciximab Eptifibatide	325 mg administered at least 2 hours before PCI and daily	All patients received weight adjusted Heparin (70	-	-	-

		thereafter.	U/kg) before the procedure			
ADMIRAL[63]	Abciximab Placebo	Aspirin plus heparin, initial bolus 70 U/kg (max 7000 U).		-	-	-

2.4.1.5 Outcomes recorded and definition of outcomes

All studies except Harrington et al 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, 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 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 x2 in Harrington to x5 in EPISTENT.

Table 28: Outcomes recorded and definition of outcomes

Study	Acute MI	Severe recurrent angina/ refractory ischaemia	Composite end-point
EPIC, 1992[72-74]	Patients entering trial within 24hr of an MI: MB isoenzyme at least 3x upper normal limit, or activity of CB or MB isoenzyme increased by at least 100% and remained 3xupper limit of normal after a 50% decrease from a previous peak level. During the follow up period: new significant Q-wave of 0.04 second or more in duration or with a depth above ¼ of the corresponding R wave amplitude in 2 or more contiguous leads, or CK-MB > 2x the upper limit of normal.	Interventions resulting from recurrent ischemia recorded.	At 30 days: Composite endpoints of death from any cause, non-fatal MI, unplanned revascularisation, unplanned repeat PCI, unplanned stenting or insertion of balloon pump for refractory ischemia. 6-month: as 30 day but not including stenting or balloon insertion. 3 year: death, MI or coronary revascularisation.
IMPACT II, 1994[68]	If no history of MI or enrolled more than 24hr after infarction, endpoint	-	Occurrence within 30 days of: death, MI,

	MI during hospital admission defined as any rise in total creatine kinase MB concentration to 3+ times upper normal limit + development of new Q-waves. Patients with MI within 24hr before intervention reinfarction based on 1or 2 criteria (MB isoenzyme, previous peak)		urgent or emergency CABG or repeat coronary intervention, or index placement of a stent.
CAPTURE, 1995[71]	*During hospital stay:* Values of creatine kinase or its MB isoenzyme more than 3x the upper limit of normal in at least 2 samples, increased by 50% over the previous value, BCG with new Q-waves in 2+ contiguous leads. *After discharge:* concentration of creatinine kinase or its MB isoenzyme above 2x 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,1995[75,76]	In Hospital: New clinically significant Q-waves in 2+ contiguous leads or elevation in CK or its MB isoenzyme to at least 3x upper normal limit. After discharge: occurrence of Q-waves or elevation of CK or its MB isoenzyme to more than 2x upper normal limit.	-	Composite of death from any cause, MI or reinfarction, severe myocardial ischemia requiring urgent CABG or repeat PCI within 30 days. Secondary endpoint same outcomes at 6-months.
RESTORE, 1995[69]	***Before hospital discharge:*** UA patients with normal CK/CK-MB values without history of MI within 72 hr 1) typical chest pain with new ST-T changes or new pathological Q waves and an elevated CK-MB level 2) CK-MB ≥ 3x normal upper limit. Patients entering study within 72hr after an acute MI 1)CK-MB level ≥ 3x 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 ≥2x upper limit of normal or 3) CK-MB level ≥2x upper limit of normal with elevated CK-MB level, unaccompanied by chest pain and/or ECG changes	Refractory ischemia resulting in CABG or repeat angioplasty.	Occurrence of any of these: death, MI, CABG surgery owing to angioplasty failure or recurrent ischemia, repeat angioplasty for recurrent ischemia or insertion of stent
RAPPORT, 1997[77]	Ischemic chest pain lasting more than 20 mins, accompanied by significant ST elevation in 2 contiguous leads or by new complete left bundle-branch block pattern. Reinfarction with 24 hours defined as re-elevation of CK-MB by at least 33% or 100% from preceding nadir, reaching at least 3x normal value in addition to ischemic symptoms. Reinfarction after 24 hours defined as new Q-waves or re-elevation of	Urgent revascularisation defined as repeat PTCA or CABG performed within 24hours of recurrent ischemia.	Measured as occurrence of death, re-infarction or urgent target vessel revascularisation.

	CK-MB to > 3x normal (24 hours to discharge) or >2 x normal if after hospital discharge.		
EPISTENT, 1997[78]	New pathological Q waves or a value of creatine kinase or its MB isoenzyme at least 5x upper laboratory limit.	-	Combination of death from any cause, MI, re-infarction or severe myocardial ischaemia requiring urgent coronary-artery bypass surgery or revascularisation within 30 days.
ERASER, 1997[79]	1) New significant Q-wave of ≥0.04 seconds or depth of ≥25% of the corresponding R wave amplitude in ≥2 contiguous leads 2) Creatine kinase MB ≥3 times the upper limit of normal	-	Percent in-stent volume obstruction of target lesion measured at 6-months by IVUS.
Galassi et al, 1998[80]	*Q-wave MI*: occurrence of new pathologic Q waves in conjunction with an elevation of creatine kinase levels greater than 3x the upper limit of normal. Non-Q wave: elevation of cardiac enzymes greater than 3x the normal value without pathologic Q waves.	-	Cardiac events: MI, death, and revascularisation.
Harrington et al[49]	Appearance of new pathological Q-waves on ECG, creatine kinase MB isoenzyme fraction elevation of 3x local laboratory limit, or total creatine kinase elevation of 2x upper limit of normal.	Not stated	Composite outcome not reported
Chen et al, 1997 [81]	*In hospital MI:* New clinically significant Q-waves in 2 or more contiguous leads. Elevation in creatine kinase or its MB isoenzyme to at least 3x the upper limit of normal. *After discharge MI:* Occurrence of Q-waves or elevation of creatine kinase 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, 2000[82]	Not stated	Not stated	Death, recurrent non-fatal MI and target lesion revascularisation (TLR)
TACTICS-TIMI[64]	Not stated in original see New Eng J Med 22/11/01 for definition later submitted.	-	Death, MI or re-hospitalisation for ACS.
TARGET[65]	Levels of the MB isoform of creatine kinase that were at least 3 times the upper limit of the normal range in 2 separate blood samples or by the finding of abnormal Q waves in 2 or more contiguous leads.	-	Death, non-fatal MI, urgent target revascularisation within 30-days.

ESPRIT[66]	Enzymatic MI: 2 or more values of CK-MB isoenzyme, for the first 24h after PCI, were at least 3x the upper limit of normal. Clinical MI: Reported by investigator and adjudicated as an endpoint 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 @ 30 days.
PRICE[62]	Not defined, but measures of creatine phosphokinase (CPK) and CPK-myocardial band (MB) isoenzyme levels were obtained from patients	Not stated	Not stated
ADMIRAL[63]	Defined according to clinical symptoms and new electrographic changes with a new elevation of the creatine kinase or creatine kinase MB isoenzyme levels.	Not stated	Primary outcome: Death, reinfarction, or urgent revascularisation of the target vessel at 30 days. Secondary outcome: As above at 30-days and 6-months

2.4.1.6 Assessment of internal validity

The assessment of the internal validity of the studies included is presented below 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 homogenous sub-populations and pre-stratification on prognostically relevant variables to avoid heterogeneity was discussed for the previous indication in Section 2.3. All of the trials included tables of baseline characteristics of patients enrolled but again, it is difficult to determine if the groups are truly homogenous. 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 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 Section 2.3, 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 endpoint composition, timing of endpoint assessment, and study validity.

Table 29: Assessment of internal validity

Internal validity																	
Study	**EPIC**	**IMPACT II**	**CAPTURE**	**EPILOG**	**RESTORE**	**RAPPORT**	**EPISTENT**	**ERASER**	**Galassi**	**Harrington**	**Chen**	**TARGET**	**TACTICS-TIMI**	**ISAR II**	**ESPRIT**	**ADMIRAL**	**PRICE**
Selection of prognostically homogenous study population	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
Blinding of persons to assess inclusion criteria	?	?	?	?	?	?	?	?	?	?	?	+	-	?	?	?	?
Pre-stratification 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 bear on outcome for each group	-	-	-	-	-	-	-	-	-	-	-	-	?	-	+	-	-
Blinding of persons assessing treatment effects	+	+/-	+/-	+	+/-	+	+	?	?	?	?	?	-	?	?	?	?
Check to what extent blinding was successful	?	?	?	?	?	?	?	?	?	?	?	-	na	-	-	-	-
Data description and analysis																	
Measures of central tendency and their CI's (e.g. SE or SD)	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+/-
The statistical measures	+	+	+	+	+	+	+	+	+	+	+/-	+	+	+	+	+	+
The way missing values were dealt with	?	?	?	?	?	?	?	?	?	?	?	?	+/-	-	?	-	?
Intention to treat analysis	+	+	+	+	+	+	+	+	?	?	?	+	?	+	+	+	+
Distributions of baseline characteristics	+	+	+	+	+	+	+	+	+	+	+	+	?	+/-	+	+/-	+/-
Accounting for imbalances	+	?	+	+	?	?	?	?	-	?	-	+	+	-	?	+	-

+ Item properly addressed - Item not properly addressed or not stated
? Unclear +/- Item partially addressed

N/A Not applicable

2.4.2 Results of trials

The results of the trials are presented below by drug. In the plots of relative risk, the vertical line (at 1) indicates the 'no-effect' line. PRICE, TACTICS-TIMI and TARGET have not been included in the plots of relative risk, as they are "head to head" comparisons of 2GP IIb/IIIa antagonists which are included for information only.

2.4.2.1 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 below.

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.

Table 30:Results from the CAPTURE[71] study

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	193	31.0
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	7	193	30.8

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

Table 31:Results from the Chen [81] study

Treatment Arm	Time point	MI		Death		Urgent PTCA		Urgent CABG		Composite	
		n	%	n	%	n	%	n	%	n	%
Abciximab (n= 22)	**30-day**	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 shows the results of the EPIC trial, which showed 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 32: Results from the EPIC[72-74] study

Treatment Arm	Time point	MI		Death		PTCA		CABG		Composite	
		n	%	n	%	n	%	N	%	n	%
Abciximab + infusion (n= 695)	**30-day**	37	5.2	12	1.7	-	-	-	-	59	8.3
	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 (n= 708)	**30-days**	43	6.2	9	1.3	-	-	-	-	79	11.4
	6-months	57	8.0	18	2.6	102	14	66	9	231	32.6
	1-year	-	-	29	4.2	-	-	-	-	251	36.3
	2-years	-	-	40	5.8	-	-	-	-	290	42.4
	3-years	-	-	54	6	-	-	-	-	321	47.4
	7-years	-	-	-	-	-	-	-	-	-	-
Placebo + infusion (n= 696)	**30-days**	60	8.6	12	1.7	-	-	-	-	89	12.8
	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	42.3
	3-years	-	-	59	-	-	-	-	-	319	47.2
	7-years	-	-	-	20. 1	-	-	-	-	-	-

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

Table 33:Results from the EPILOG[75 76] study

Treatment Arm	Time point	MI		Death		Urgent PTCA		Urgent CABG		Composite	
		n	%	n	%	n	%	n	%	n	%
Standard dose abciximab	**30-day**	35	3.8	4	0.4	14	1.5	8	0.8	49	5.4
	6-month	48	5.3	13	1.4	-	-	-	-	76	8.3

abciximab (n= 918)	**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-month	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	-	-	-	-	-	-

Table 34 shows the results of the EPISTENT trials. 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.

Table 34: Results from the EPISTENT[78] study

Treatment Arm	**Time point**	**MI**		**Death**		**PTCA**		**CABG**		**Composite**	
		N	%	n	%	n	%	N	%	n	%
Abciximab + stent (n= 794)	**30-day**	-	4.5	-	0.3	-	0.6	-	0.8	42	5.3
	6-month	-	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-month	-	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-month	-	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 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.

Table 35:Results from the ERASER[79] study

Treatment Arm	Time point	MI		Death		PTCA		CABG		Composite	
		N	%	n	%	n	%	N	%	n	%
Abciximab 12 hour infusion (n= 79)	**30-day**	4	5.1	0	0	0	0	0	0	4	5.1
	6-month	6	7.6	0	0	1	0.79	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-month	7	9.3	0	0	10	7.5	0	0	16	22.7
Placebo (n= 71)	**30-days**	8	11.3	0	0	1	0.71	0	0	8	11.3
	6-month	9	12.7	2	2.8	11	7.81	0	0	16	25.4

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 36:Results from the Galassi[80] study

Treatment Arm	Time point	MI		Death		Urgent PTCA		Urgent CABG		Composite	
		N	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Abciximab (n= 54)	**30-day**	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 summarises the results of the RAPPORT trial, which shows similar quality limitations to ther other trials including a failure to describe the randomisation procedure. Limited details of the individual results of the trial were presented, but the composite outcomes were similar in the two groups.

Table 37:Results from the RAPPORT[77] study

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

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.

Table 38: Results from ADMIRAL study[63]

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

The results of the PRICE study are shown in Table 39. This was a head-to-head study comparing abciximab and eptifibatide, which is presented just for information. This study showed similar results in terms of the composite endpoint.

Table 39: Results from PRICE[62] study

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

The results of the ISAR II study are shown in Table 40. Showing similar weaknesses as other studies (Table 29), composite event rate was lower in the abciximab arm than the heparin arm, but this is based on a small number of events.

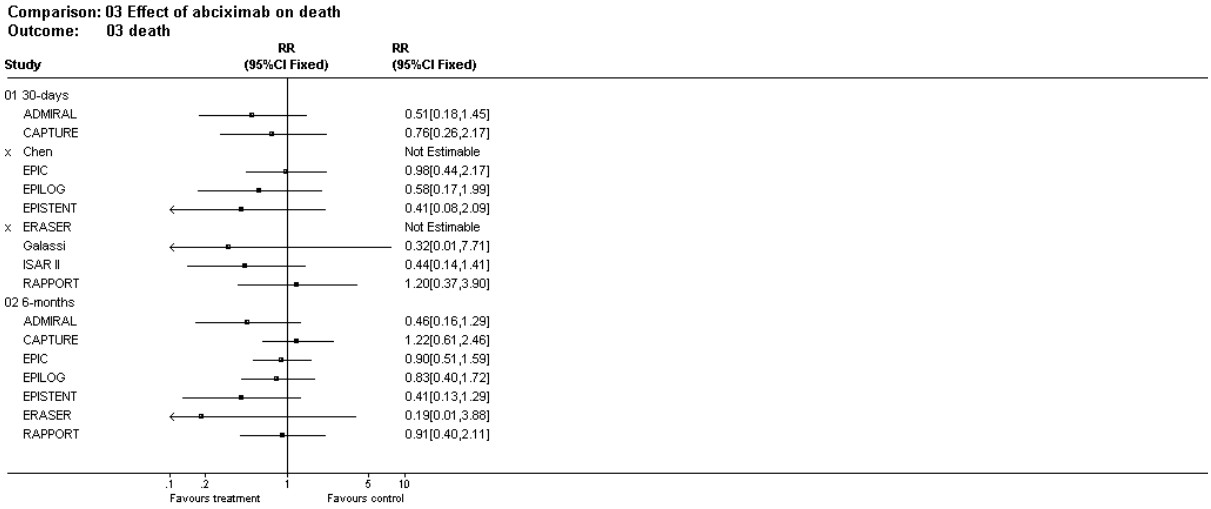
Table 40: Results from ISAR II[82]

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

Death

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.

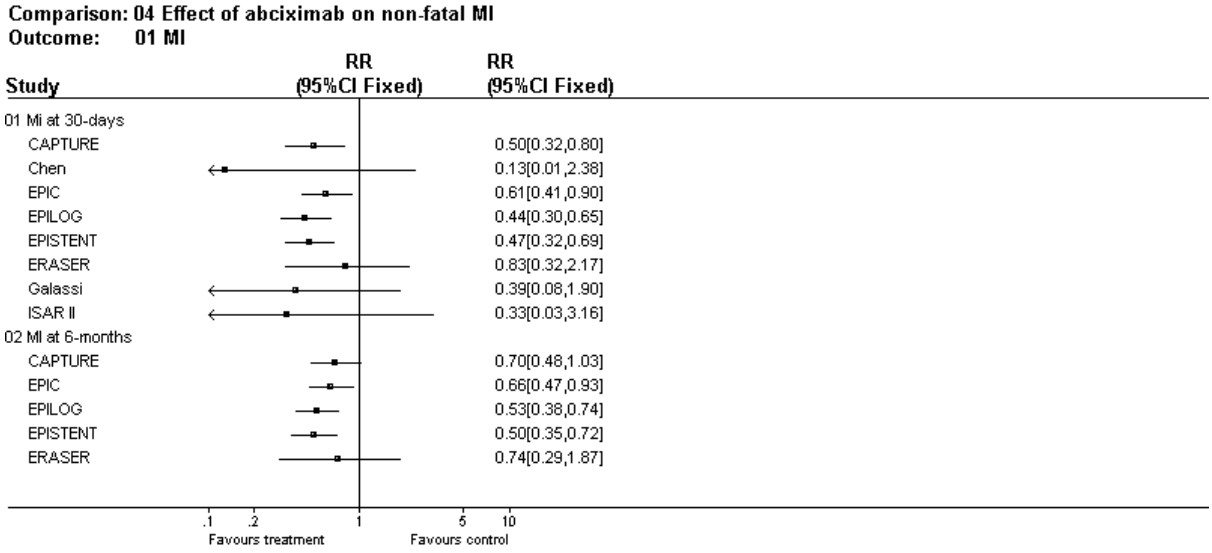
Figure 28: The effect of abciximab on death, for patients taking glycoproteins alongside PCI.



Myocardial infarction

The effect of abciximab on non-fatal MI can be seen in Figure 29. These relative risks 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 relative risk of about a 50% reduction.

Figure 29: The effect of abciximab on MI, for patients taking glycoproteins alongside PCI



Recurrent ischemia

The majority of trials do not report on recurrent ischemia 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 reinfarction.

In both AMI studies, reinfarction was less common in the abciximab group. In RAPPORT, at 7-days reinfarction 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.

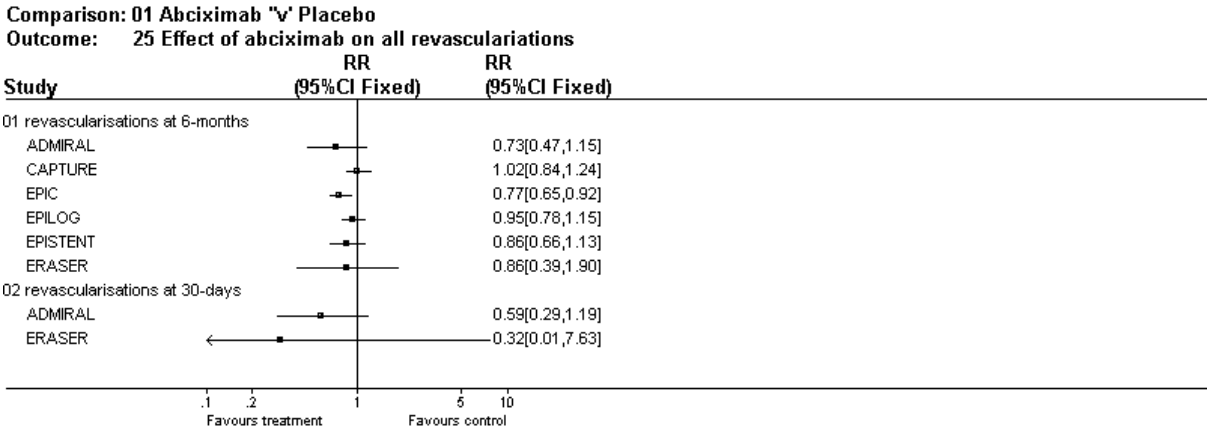
In ADMIRAL rates were 1.3% and 2.6% at 30 days and 2.0% and 4.0% at 6 months in the abciximab and placebo groups respectively.

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 (TVR), 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.

Figure 30: The effect of abciximab on revascularisations, for patients taking glycoproteins alongside PCI



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 major and minor bleeding can be seen in Figures 31 and 32. All trials except the smallest (Chen) show an 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 (1.39, 9.57 for minor bleeding and RR = 3.04 (0.12, 74.04) for major bleeding episodes)

Figure 31: Effect of abciximab on incidence of minor bleeding, for patients taking glycoproteins alongside PCI.

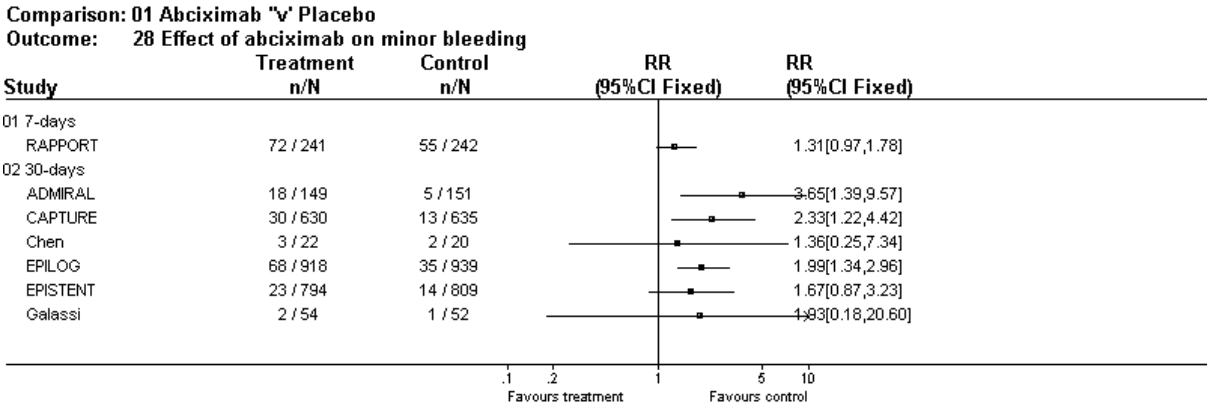
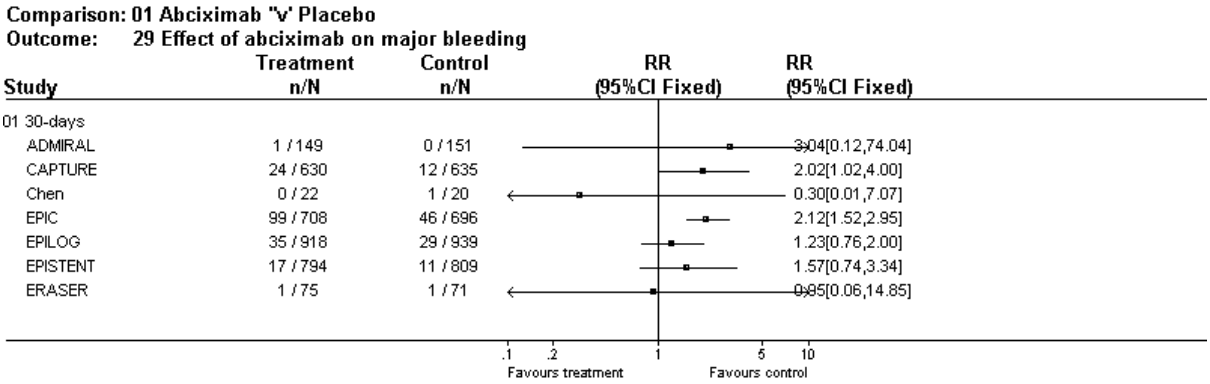


Figure 32: Effect of abciximab on incidence of major bleeding, for patients taking glycoproteins alongside PCI.



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 (platelet and red blood cell (RBC)) 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 red blood cell transfusions in EPIC (RR = 2.19 (1.59, 3.01)). Chen et al showed 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 (0.29, 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 (1.23, 3.69)).

CAPTURE and EPISTENT reported on total transfusions and both found a significant increase in the risk of transfusions in the abciximab group (RR = 2.11 (1.27, 3.51) in CAPTURE; RR = 1.25 (0.67, 2.30) in the EPISTENT trial).

Figure 33: Effect of abciximab on RBC transfusions, for patients receiving glycoproteins alongside PCI.

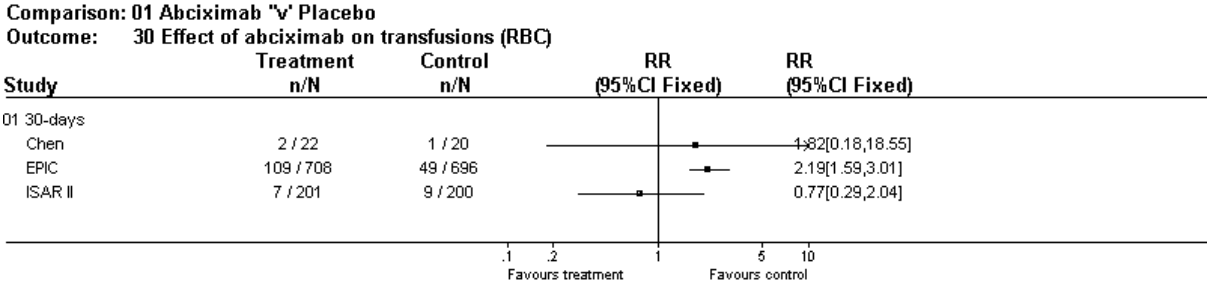
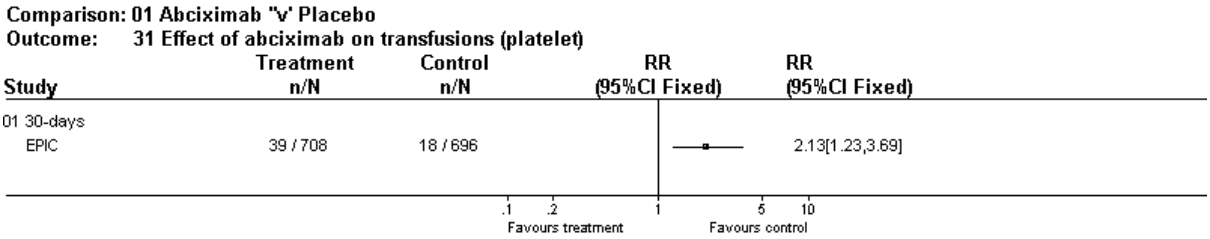
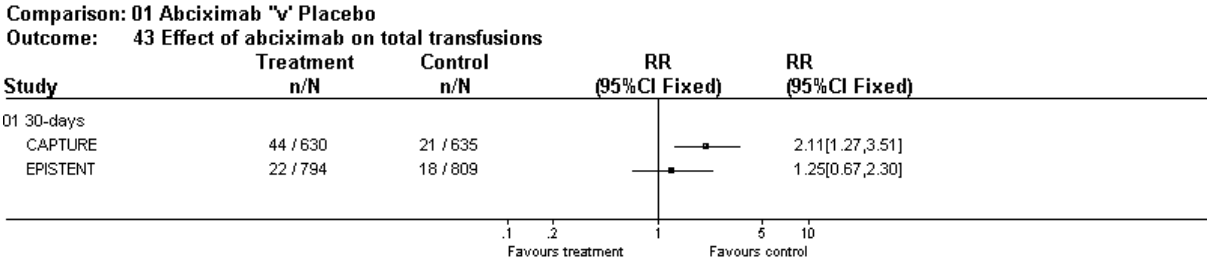


Figure 34: Effect of abciximab on platelet transfusions, for patients receiving glycoproteins alongside PCI.



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.

Figure 35: Effect of abciximab on total transfusions, for patients receiving glycoproteins alongside PCI



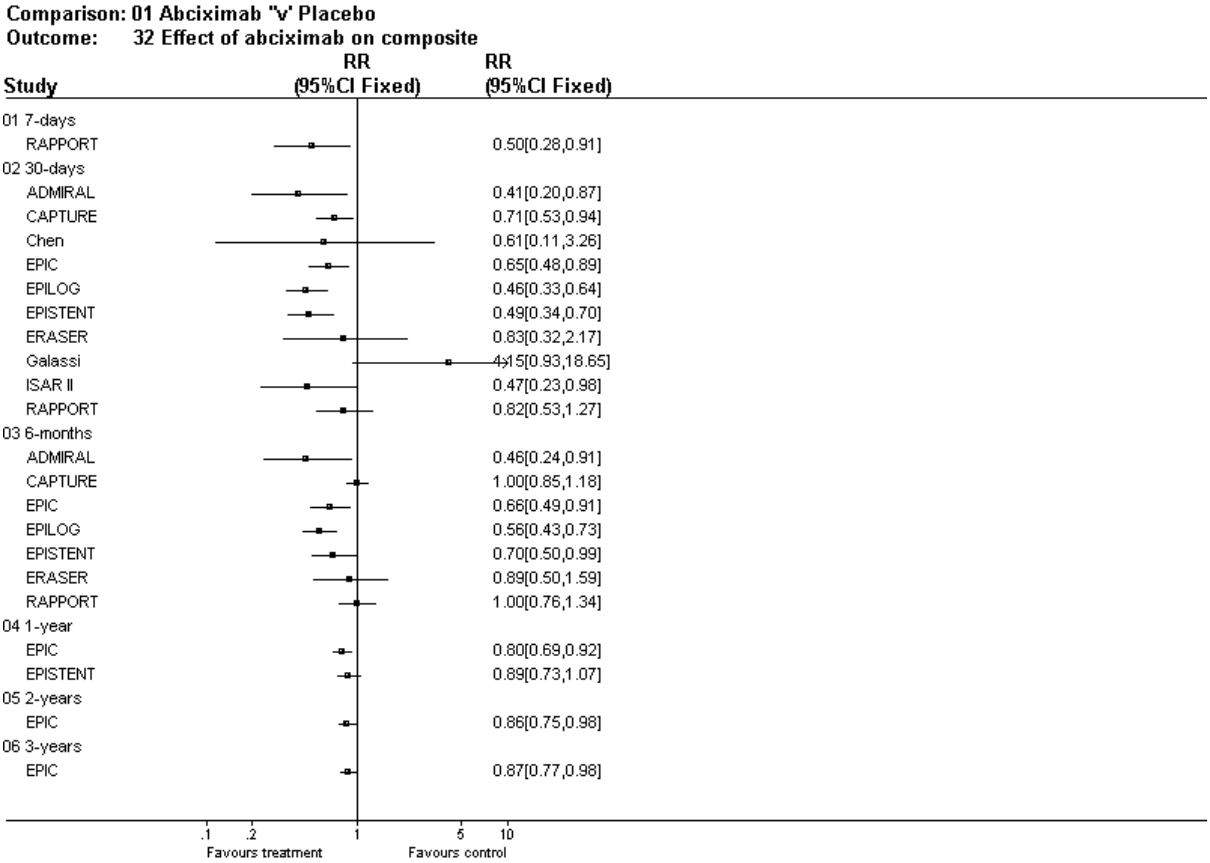
Stroke:

Only CAPTURE collected data on all strokes. Only one stroke occurred during the trial, 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; and 1/918 versus 0/939 in those two groups respectively, in EPILOG. Haemorrhagic strokes occurred in 0/794 abciximab patients versus 0/809 control patients in EPISTENT; and 1/918(0.1%) versus 0/939 in those two groups respectively in EPILOG. The overall incidence of stoke in all three trials was very low.

Composite

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), 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 (see Table 28).

Figure 36: Effect of abciximab on the composite outcome, for patients receiving glycoproteins alongside PCI.



2.4.2.2 Eptifibatide

Three studies (ESPRIT, Harrington et al 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 lack of pre-stratification (Table 29). In addition, ESPRIT suffers from the lack of a prognostically homogenous study population. In terms of the results, there is a favourable effect of eptifibatide on the composite outcome at all time periods ((48 hours to 12 months). This appears to have been driven by the MI rate.

Table 41: Results from ESPRIT[66] study

Treatment Arm	Time point	MI		Death		Composite	
		n	%	N	%	n	%
Eptifibatide (n= 1040)	**48 hours**	56	5.4	1	0.1	69	0.07
	30-days	64	6.2	4	0.4	71	0.07
	6-months	73	7.0	8	0.8	146	14.3
	12-months	74	7.2	14	1.4	178	17.5
Placebo (n= 1024)	**48-hours**	92	9.0	2	0.2	108	0.11
	30-days	99	9.7	6	0.6	107	0.10
	6-months	106	10.4	14	1.4	187	18.5
	12-months	109	10.7	20	2.0	222	22.1

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.

Table 42:Results from Harrington[49] study

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	1.8	-	-

The results of IMPACT II are shown in Table 42. 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 shows improved composite outcomes at 30 days (the only point of follow-up). This appears to be driven mainly through a lower MI rate.

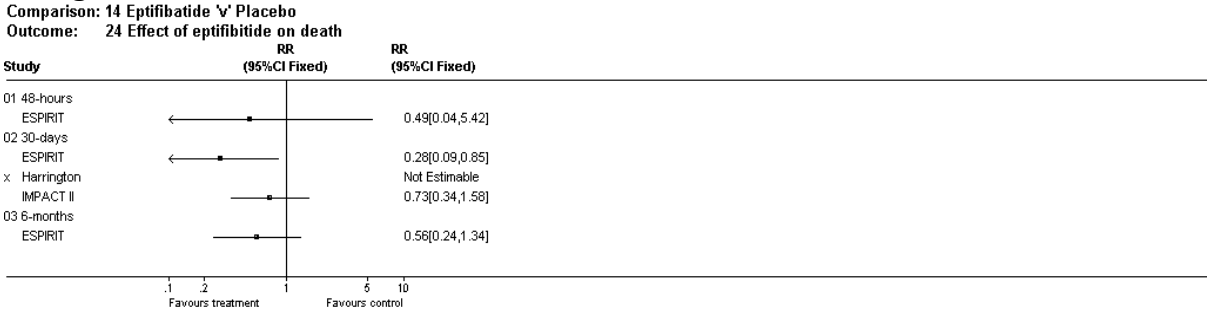
Table 43:Results from IMPACT II[68] study

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	0.8	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

Death

The effect of eptifibatide on death can be seen below in Figure 37. All trials showed a trend in favour of eptifibatide. However, only ESPRIT showed a statistically significant effect at 30 days, and this was no longer statistically significant at 6 months.

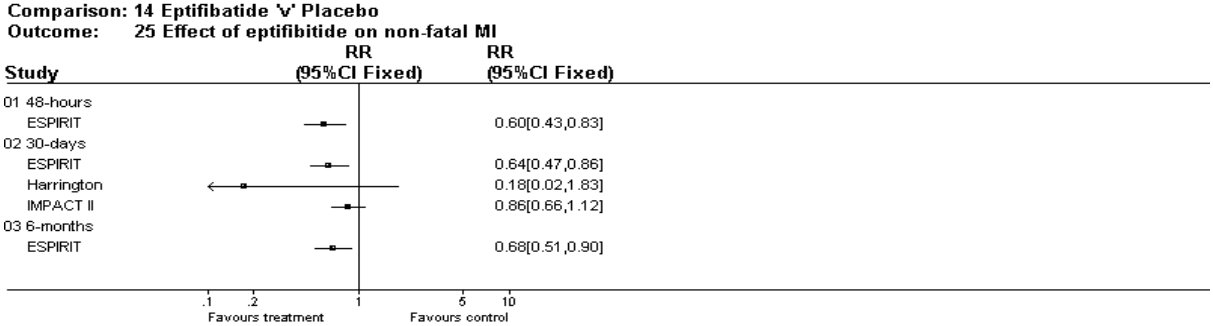
Figure 37: Effect of eptifibatide on death, for patients receiving glycoproteins alongside PCI



Myocardial infarction

The effect of eptifibatide on non-fatal MI can be seen in Figure 38. There is a consistent effect across all 3 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 relative risk is fairly similar to the short-term results and remains statistically significant.

Figure 38: Effect of eptifibatide on MI, for patients receiving glycoproteins alongside PCI



Recurrent ischemia

Only Harrington et al reported on the effect of eptifibatide on recurrent ischemia. Three patients (6%) in the eptifibatide groups suffered from recurrent ischemia, compared to 2 (11%) patients in the placebo group.

Revascularisations

The effect of eptifibatide on repeat revascularisations was reported in ESPRIT alone at six 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.

Figure 39: Effect of eptifibatide on PTCA, for patients receiving glycoproteins alongside PCI.

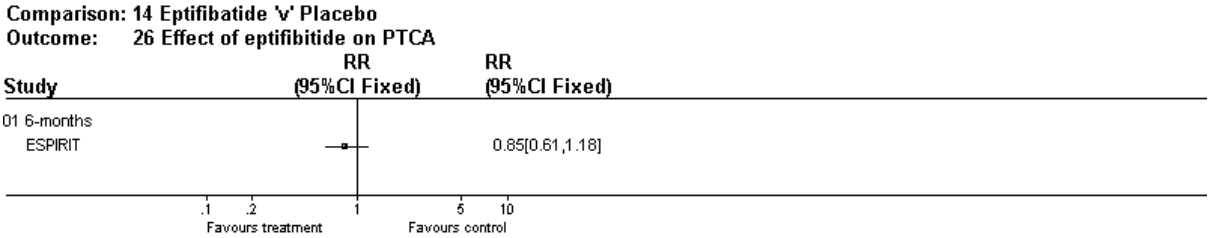
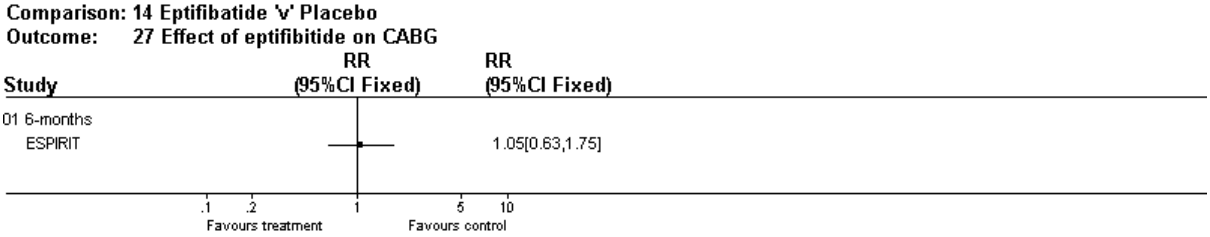


Figure 40: Effect of eptifibatide on CABG, for patients receiving glycoproteins alongside PCI.



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 major and minor bleeding episodes can be seen in Figures 41 and 42. IMPACT II did not report on the incidence of major or minor 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 (1.05, 9.78))

Figure 41: Effect of eptifibatide on incidence of minor bleeding, for patients receiving glycoproteins alongside PCI

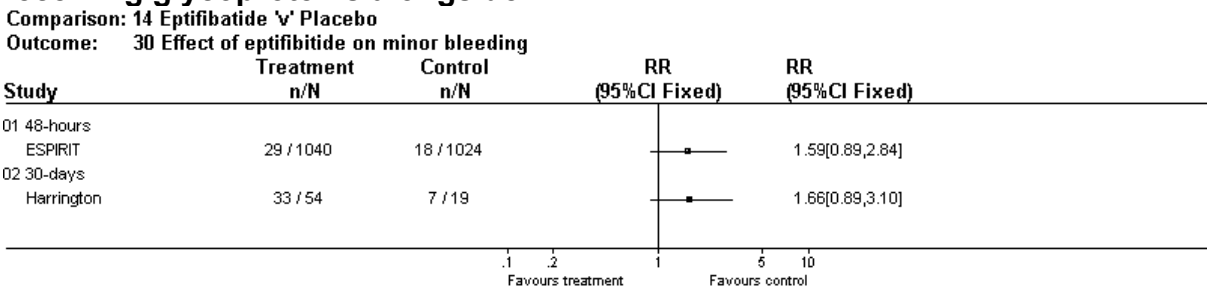
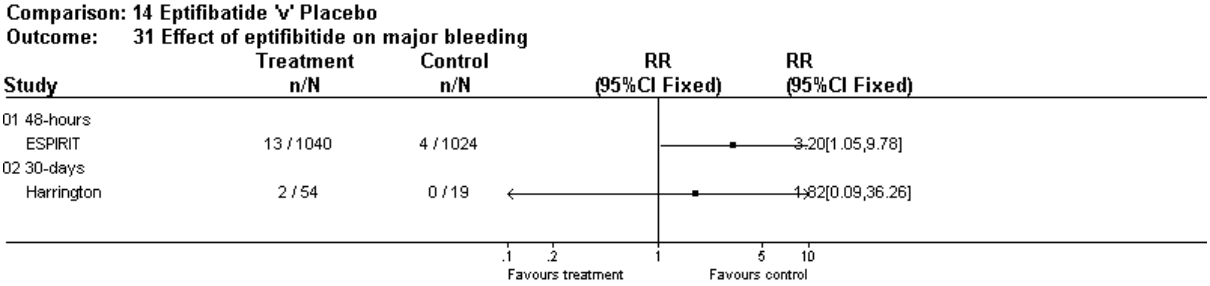


Figure 42: Effect of eptifibatide on incidence of major bleeding, for patients receiving glycoproteins alongside PCI



Transfusions:
The effect of eptifibatide on transfusions can be seen in Figures 43 and 44. Harrington et al did not report on transfusions and ESPRIT only reported on red blood cell (RBC) transfusions. In line with increased bleeding, an increased requirement for transfusion is reported in the eptifibatide groups, but this is not statistically significant.

Figure 43: Effect of eptifibatide on RBC transfusions, for patients receiving glycoproteins alongside PCI

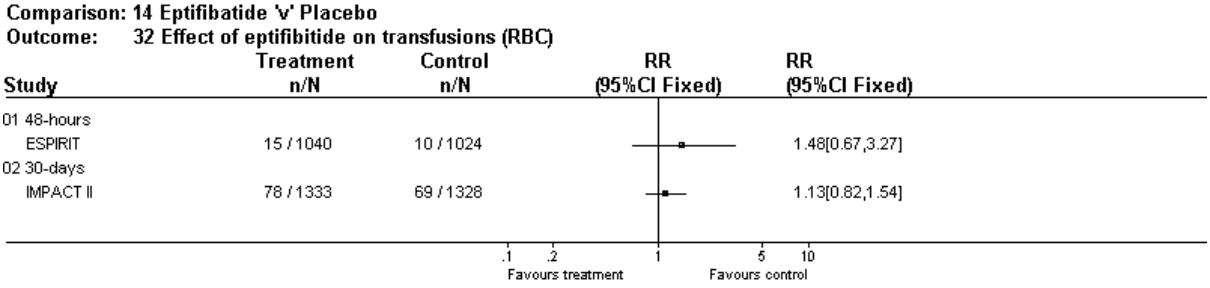
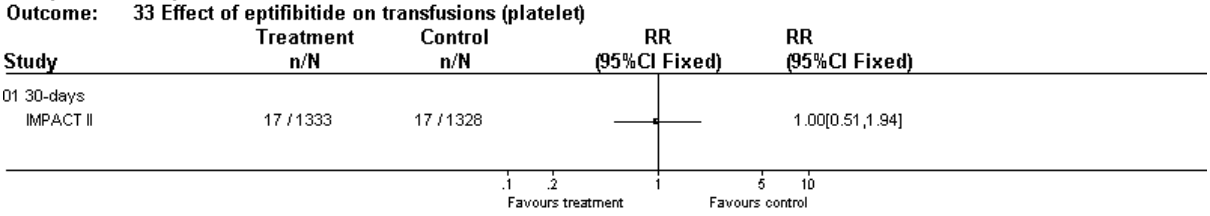


Figure 44: Effect of eptifibatide on platelet transfusions, for patients receiving glycoproteins alongside PCI

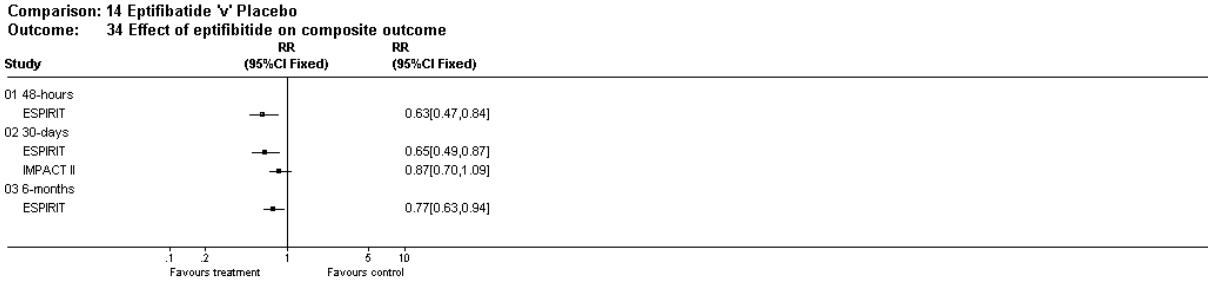


Stroke:
The two studies that reported data on strokes - Harrington et al and IMPACT II - defined strokes as either haemorrhagic or non-haemorrhagic. Harrington et al reported no strokes in patients randomised. In IMPACT II, the number of strokes occurring was low: 6/1349 (0.4%) and 7/1328(0.5%) non-haemorrhagic strokes in the abciximab and placebo groups, respectively, and 1/1349 (0.007%) and 1/1328 (0.007%) haemorrhagic strokes in the abciximab and placebo groups, respectively.

Composite

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, CI = 0.66, 0.94).

Figure 45: Effect of eptifibatide on the composite outcome, for patients receiving glycoproteins alongside PCI



2.4.2.3 Tirofiban

The effectiveness of tirofiban for use alongside PCI was studied in 3 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 relative risk 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 relative risk. The results of all three trials are extracted and discussed in the tables below.

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 RESTORE[69] study

Treatment Arm	Time point	MI		Death		PTCA		CABG		Composite	
		N	%	N	%	n	%	n	%	N	%
Tirofiban (n= 1071)	**7-day**	22	2.1	13	1.2	29	2.7	13	1.2	67	6.3
	30-day	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	59	5.5	258	24.1
Placebo (n= 1070)	**7-day**	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

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

Table 45:Results from TARGET[65] study

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

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.

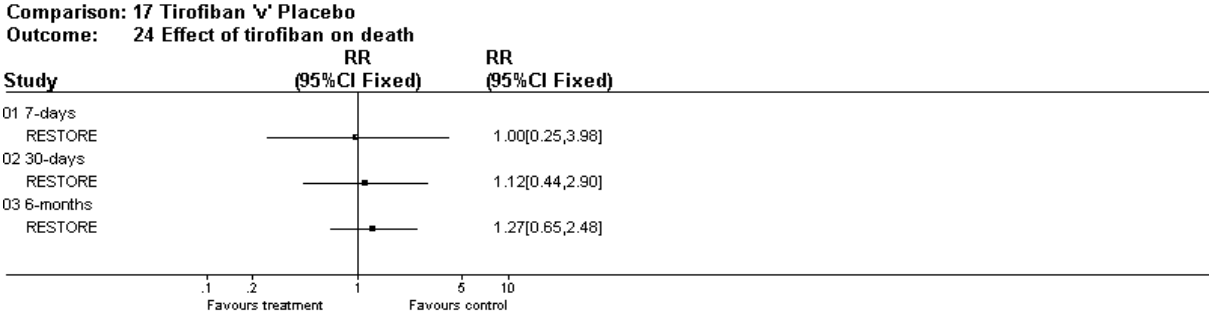
Table 46:Results from TACTICS-TIMI[64]

Treatment Arm		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-month	-	-	-	-	75 (14.8)
	Conservative	**30-day**	-	-	-	-	78 (16.2)
		6-month	-	-	-	-	116 (24.2)
Troponin-negative	**Invasive**	**30-days**	-	-	-	-	25 (6)
		6-month	-	-	-	-	69 (16.7)
	Conservative	**30-days**	-	-	-	-	24 (5.6)
		6-month	-	-	-	-	63 (14.8)

Death

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.

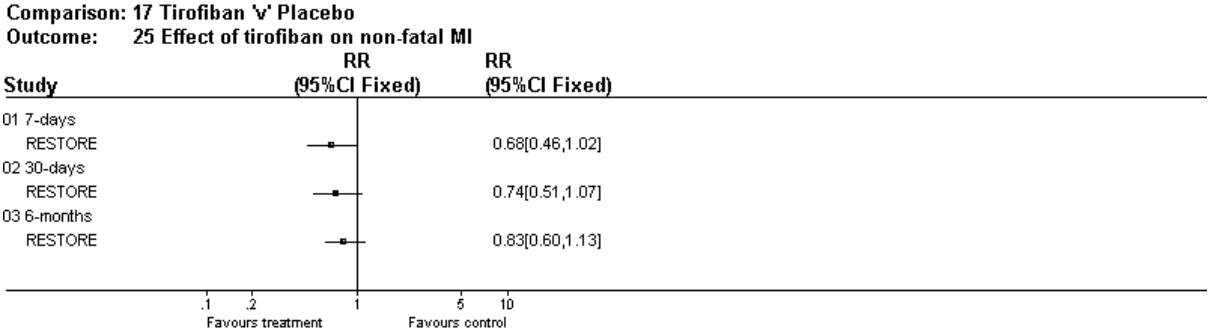
Figure 46: Effect of tirofiban on death in the RESTORE trial



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.

Figure 47: Effect of tirofiban on MI in the RESTORE trial



Recurrent ischemia

None of the three trials reported on the rates of recurrent ischemia.

Revascularisation

The effect of tirofiban on rates of repeat revascularisation (repeat PTCA and CABG) in RESTORE can be seen in Figures 48 and 49. There is a non-significant reduction in both CABG and PTCA.

Figure 48: Effect of tirofiban on PTCA rates in the RESTORE trial

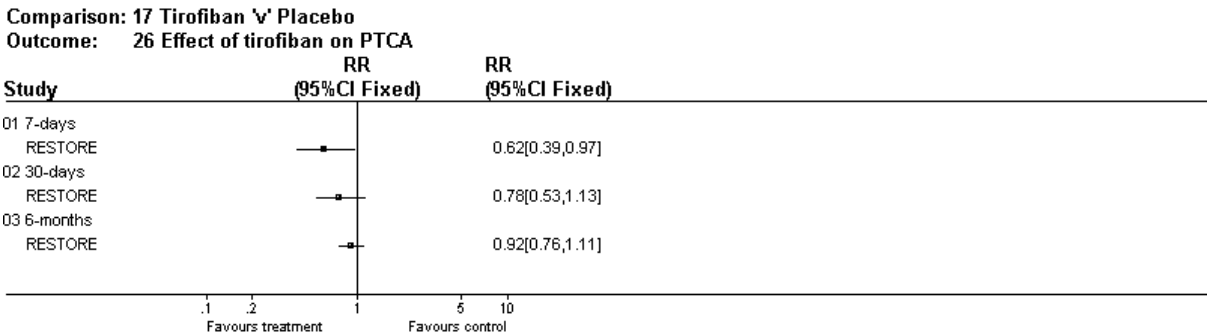
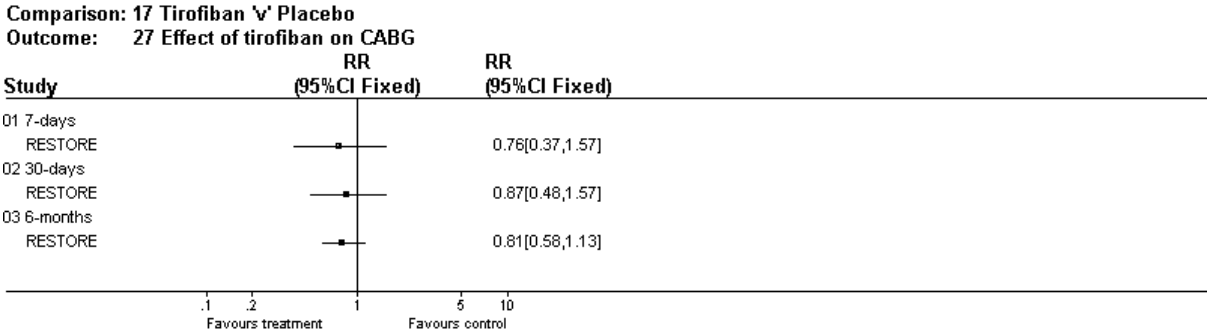


Figure 49: Effect of tirofiban on CABG rates in the RESTORE trial



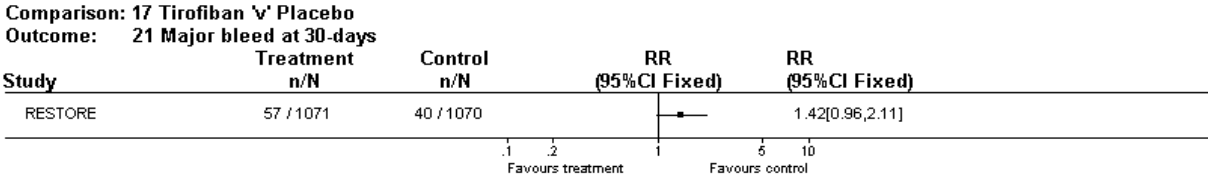
Adverse events

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 (0.96, 2.11).

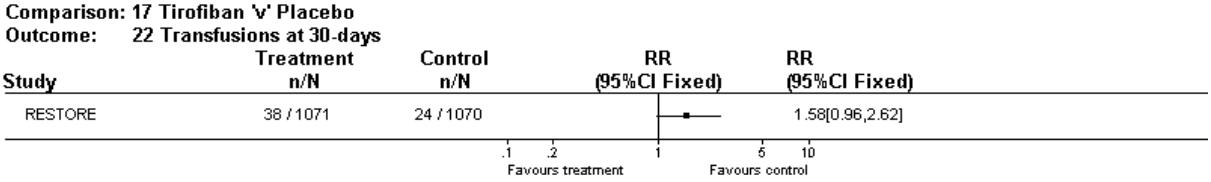
Figure 50: Effect of tirofiban on the incidence of major bleeding in the RESTORE trial



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 (0.96, 2.62).

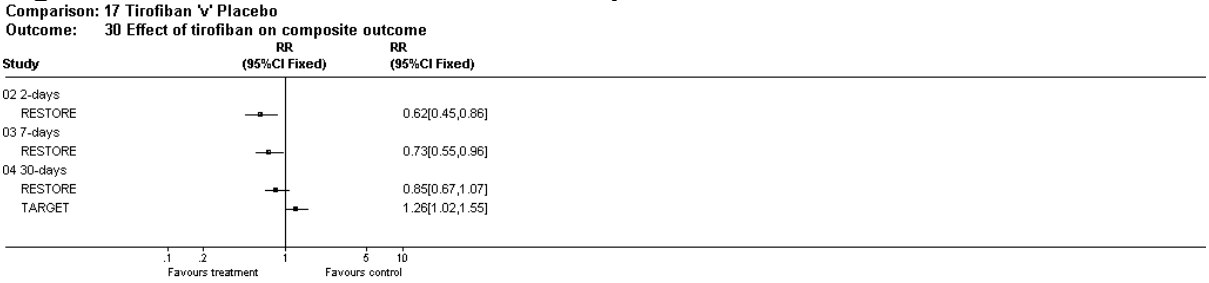
Figure 51: Effect of tirofiban on transfusions in the RESTORE trial



Composite

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

Figure 52: Effect of tirofiban on the composite outcome in the RESTORE trial



2.4.3 Conclusions regarding effectiveness of glycoproteins alongside PCI

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

1 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 heterogenous also.
2 Uncertainty in the clinical significance of an important type of measured endpoint, namely peri-procedural infarction which is detected by a rise in cardiac enzymes alone. The inclusion of such endpoints 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 health care costs is unknown/ ambiguous.
3 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, e.g. ESPRIT, stenting is routine.
4 Differences between the outcomes in the trials and those in routine UK populations.

Despite these caveats, abciximab has shown a clear benefit, particulalry 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 (Absolute risk reduction = 0.05 (95% 0.03, 0.07)) NNT = 18 (95% CI 13, 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, which 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 sub-groups, which receive a particular benefit from abciximab, or conversely if there are subgroups in whome there is little effect. A subgroup analysis of the EPIC trial for patients with unstable angina suggested a 8.0% ARR (NNT 12) for a composite endpoint of death, myocardial infarction, and urgent or repeat revascularisation[83]. As with the trials of GPAs without PCI, such analyses should be interpreted with caution for the reasons stated in Section 2.3:

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.

2.5 Use of thrombolytics alongside glycoproteins

The two existing earlier reviews (McDonagh et al and Fischer et al) did not consider the use of glycoproteins alongside thrombolytics in patients with acute MI. The update searches therefore sought to identify relevant studies dating back to the original search period.

2.5.1 Efficacy of intravenous glycoproteins alongside thrombolytics.

The searches identified 5 trials (ASSENT-3[84], TIMI-14[85], IMPACT-AMI[86], GUSTO V[87] and Ronner et al[88] 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.

2.5.1.1 General details

Three of the five trials were conducted in the US (ASSENT 3, IMPACT-AMI and GUSTO V), TIMI 14 was conducted in the US, Canada, UK, Belgium, Netherlands, France and Germany and Ronner et al 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 efect on mortality. ASSENT-3 was designed to test the effectiveness of a low molecular weight heparin adunct to thrombolysis as well as a GP IIb/IIIa antagonists 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 16588 patients to receive treatment.

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

Table 47:Designs of included studies of intravenous glycoprotein IIb/IIIa antagonists

Study	Setting	Design/ Phase	Treatment Arms	Number of participants	Follow-up time points
ASSENT –3[84]	US	Randomised open-label trial	Enoxparin + tenecteplase Abciximab + tenecteplase + heparin Heparin + tenecteplase	2040 2017 2038	30-days
TIMI-14[85]	International	Multi-centre randomised trial	Abciximab + reteplase (5 + 5 U) Abciximab + reteplase (10 + 5 U) Reteplase + heparin	105 92 102	30-days
IMPACT-AMI[86]	US	Placebo-controlled dose ranging trial (only dose confirmation phase randomised-phase 2)	Phase 2: Eptifibatide + Alteplase Placebo + Alteplase	35 13	24-hours
GUSTO V[87]	US	Randomised multicentre study	Reteplase Abciximab + half dose reteplase	8260 8328	30-days 1-year
Ronner et al[88]	Netherlands	Phase 3 dose escalation, randomised, double-blind study.	Eptifibatide 0.75 ug/kg bolus + streptokinase Eptifibatide 1.33 ug/kg bolus + streptokinase Eptifibatide 2.00 ug/kg bolus + streptokinase Placebo + streptokinase	44 45 30 62	30-days

2.5.1.2 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 48:Inclusion and exclusion criteria from published texts

Study	Inclusion criteria	Exclusion criteria
ASSENT-3[84]	Age 18 years or older, onset of symptoms less than 6 h before	Exclusion criteria on admission: systolic blood pressure of more than 189 mm Hg, diastolic

	randomisation, ST segment elevation of at least 0.1mV in two or more limb leads or at least 0.2mV in in two or more contiguous precordial leads, or left bundle-branch block.	blood pressure of more than 110 mm Hg, 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 central nervous system; current treatment with oral anticoagulants; treatment with unfractionated heparin of more than 5000 U or a therapeutic subcutaneous dose of low molecular-weight heparin within 6 h; known thrombocytopenia; known renal insufficiency; sustained cardiopulmonary resuscitation in previous 2 weeks; pregnancy; lactation,or parrturution 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[85]	Aged 18 to 75; qualifying episode of ischemic discomfort of at least 30 min duration within previous 12 h; and at least 0.1mV 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[86]	Patient 18 to 65 years; within 6 h of acute of acute myocardial infarction onset, defined as >30 min of angina and ST-segment depression in leads V_1 to V_6 with posterior current of injury; ST-segment elevation $\geq$ 0.1 mV in at least two inferior leads (II, III or a VF), precordial leads (V_1 through V_6), or leads I and aVL; or primary ST-segment change in the inferior or anterior leads with left bundle-branch block.	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 noncompressible vascular punctures; comorbid conditions likely to alter prognosis; prolong cardiopulmonary resuscitation within 2 wks; severe trauma within 6 mths; known or suspected vasculitis; or participation in another study of an experimental drug within 7 days before enrolment.
GUSTO V[87]	Continuous symptoms of chest discomfort for at least 30-min and fewer than 6 h from onset to the time of randomisation, along with electrocardiographic criteria of ST-elevation myocardial infarction or new left-bundle branch block	Age less than 18 years, planned catheter-based reperfusion, active bleeding or a non-compressible vascular puncture site, blood pressure higher than 180mm Hg systolic and 110 mm Hg diastolic, warfarin therapy, stroke within the past 2-years, weight more than 120 kg, or platelet count less than 100,000 cells/uL.
Ronner et al[88]	Evolving myocardial infarction and onset of chest pain within 6h, ST-elevation of 0.1 mV in two or more standard leads r	Previous cerebrovascular disease; previous CABG; current anticoagulant therapy; recent GI or urinary tract bleeding; severe trauma or major surgery; known thrombocytopenia;

	0.2 mV in two or more precordial leads. Patients >75 years had to weigh >50 kg.	known liver and kidney function abnormalities; and suspected streptokinase intolerance, < 18 years old.

Table 49:Baseline characteristics of participants in trials of intravenous drugs

Study	Prognostic indicators	Intervention 1	Intervention 2	Intervention 3	Control
ASSENT –3[84]	Mean age Hypertension (%) Diabetes (%) Previous MI (%) Prior CABG (%) Prior PCI (%) Current smoker (%)	61 41 19 14 3.6 6.2 44	61 41 18 13 3.3 6.0 47		61 41 18 14 2.6 6.4 47
TIMI-14[85]	Mean age Diabetes (%) Smoker (%) Prior MI (≤ 30 days) (%) Prior MI (> 30-days) (%)	59 13%) 50 0 8	60 12 30 53 1		60 15 29 40 0
IMPACT-AMI[86]	Mean age Hypertension (%) Diabetes (%) Prior angina (%) Prior infarction (%) Prior angioplasty (%) Prior CABG (%)	55 40 17 23 23 11 11	61 42 15 69 8 15 0		
GUSTO V[87]	Mean age (SD) Diabetes (%) Smoker (%) Previous MI (%) Previous CHF (%) Prior CABG (%) Prior PTCA (%)	61.1 16 46 15 3 3 7	61.6 6 45 16 3 3 7		
Ronner et al[88]	Mean age Hypertension (%) Diabetes (%) Smoking (%) Previous infarct PTCA (%)	63 27 7 73 5 5	60 20 18 71 16 7	62 20 3 63 7 10	58 23 16 66 5 2

2.5.1.3 Concomitant medication

Only the 2 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 below.

Table 50:Use of concomitant medications

Study	Treatment arm	Aspirin	Heparin	Nitrates	Calcium channel blockers	Beta-blocker
ASSENT –3[84] **(n =**	**Arm 1** **Arm 2**	96% 95%	-	73% 71%	11% 10%	84% 84%

6095)	**Arm 3**	95%		73%	11%	83%
TIMI-14[85] **(n = 299)**	**Arm 1** **Arm 2** **Arm 3**	150-325 mg orally or 250-500 mg intravenously	-	-	-	-
IMPACT-AMI[86] **(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/h.	-	-	-
GUSTO V[87] **(n = 16588)**	**Arm 1** **Arm 2**	150-325 mg orally or 250-500mg intravenously, at time of randomisation and then 75-325 orally daily for remainder of study.	Arm 1 received 5000 U bolus followed by 1000 u/h infusion, for those less than 80 kg or 800 u/h infusion for those more than 80kg. Arm 2 received a 60 U/kg bolus followed by infusion of 7 U/kg per h.	-	-	-
Ronner et al[88]	**All**	-	-	-	-	-

2.5.1.4 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 to trials for the other indications.

Table 51: Outcomes recorded and definition of outcomes

Study	Acute MI	Severe,recurrent angina/ refractory ischaemia	Composite end-point
ASSENT –3[84]	Not defined	Not defined	Primary endpoint: Mortality, in-hospital reinfarction, or refractory ischaemia. Primary endpoint + safety endpoint: As above + in-hospital intracranial haemorrhage or in-hospital major bleed.
TIMI-14[85]	Standardised definitions – not reported	As before	Not assessed
IMPACT-AMI[86]	Not defined	Not defined	Death, reinfarction, stroke, percutaneous or surgical coronary revascularisation, or new in-hospital heart failure or pulmonary oedema.
GUSTO V[87]	Not defined	Not defined	Listed as endpoint but not defined (included death)

Ronner et al[88]	Listed as endpoint but not defined	Not defined	Listed as endpoint but not defined (included death)

2.5.1.5 Assessment of internal validity

The assessment of the internal validity of the studies included is presented below 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 2 of the 5 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) endpoints (except neurological endpoints in GUSTO-V) were determined by the investigators themselves. The importance of blinding was discussed in section 2.4.

None of the trials reported how missing values where dealt with which, as previously discussed in section 2.3, 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 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 endpoint. 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.

Table 52: Assessment of internal validity

Internal validity					
Study	**ASSENT –3**	**TIMI-14**	**IMPACT-AMI**	**GUSTO V**	**Ronner et al**
Selection of prognostically homogenous study population	+	+	+	+	+
Blinding of persons to assess inclusion criteria	?	?	?	?	?
Pre-stratification 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 bear on outcome for each group	+	-	-	+	-
Blinding of persons assessing treatment effects	-	?	+	-	?
Check to what extent blinding was successful	N/A	-	-	N/A	-
Data description and analysis					
Measures of central tendency and their CI's (e.g. SE or SD)	+	+/-	+/-	+	-
The statistical measures	+	+/-	+	+	-
The way missing values were dealt with	?	?	?	?	-
Intention to treat analysis	+	-	+	+	?
Distributions of baseline characteristics	+	+	+	+	+
Accounting for imbalances	-	-	-	-	-

+ Item properly addressed +/- Item partially addressed
- Item not properly addressed or not stated ? Unclear

2.5.2 Results of trials

Results of published trials are presented below, according to the glycoprotein used with a 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 at al) looked at eptifibatide in conjunction with a thrombolytic agent.

2.5.2.1 Abciximab

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

Table 53: Results from ASSENT 3[84]

Treatment Arm	Time point	Recurrent MI		Death		Revascularisations		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	353	314	15.4

Table 54 Results from GUSTO V[87]

Treatment Arm	Time point	Recurrent MI		Death		PTCA		CABG		Composite	
		n	%	n	%	n	%	n	%	N	%
Reteplase (n = 8260)	**6-hour** **24-hour**	- -	- -	- 188	- 3.2	710 -	8.6 -	83 -	0.1 -	-	-

	7-days	289	3.5	368	4.5	-	-	-	-	1701	20.6
	30-days	-	-	488	5.9	2304	27.9	306	3.7	-	-
Abciximab + Reteplase (n = 8328)	**6-hours**	-	-	-	-	466	5.6	83	0.1	-	-
	24-hour	-	-	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 TIMI-14[85]

Treatment Arm	Time point	Recurrent MI		Death		PTCA		CABG		Composite	
		n	%	N	%	n	%	n	%	N	%
Abciximab+ reteplase (5 + 5U) (n = 105)	30-days	4	4	3	3	63	62	12	12	-	-
Abciximab + reteplase (10 + 5U) (n = 92)	30-days	1	1	-	-	72	73	3	3	-	-
Placebo (n = 102)	30-days	2	2	2	2	49	53	8	9	-	-

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

Death

The effect of glycoprotein + thrombolytic combination therapy, reported in each trial, on the incidence of death can be seen in Figures 53, 54 and 55. None of the trials showed a significant treatment effect. The abciximab 5+5U arm as 10+5U in TIMI-14 had no events. In ASSENT-3 death was more common in the abciximab than the enoxaparin arm.

Figure 53: Effect of abciximab + half-dose reteplase on death

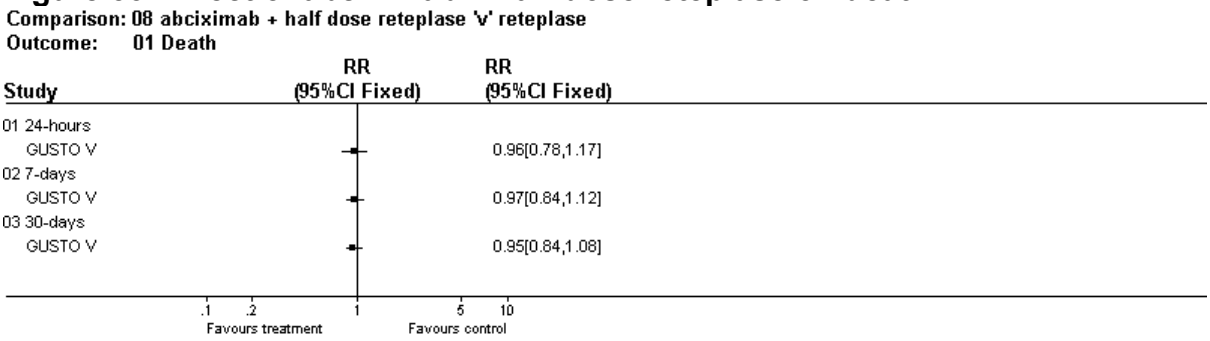


Figure 54: Effect of abciximab + teneceplase on death

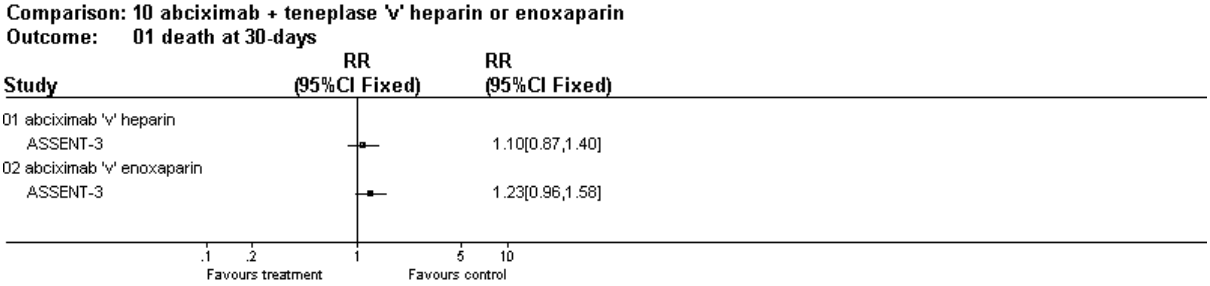
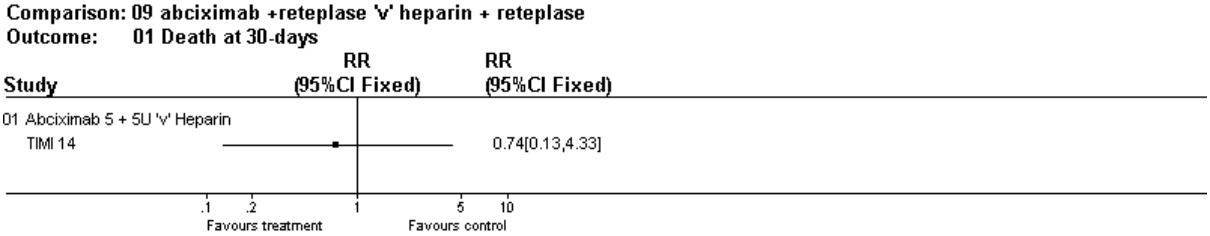


Figure 55: Effect of abciximab + reteplase on death



Recurrent Myocardial Infarction

All three trials reported on the number of repeat acute myocardial infarctions. The forest plots can be seen below in Figures 56-58.

Figure 56: Effect of abciximab + reteplase on repeat MI

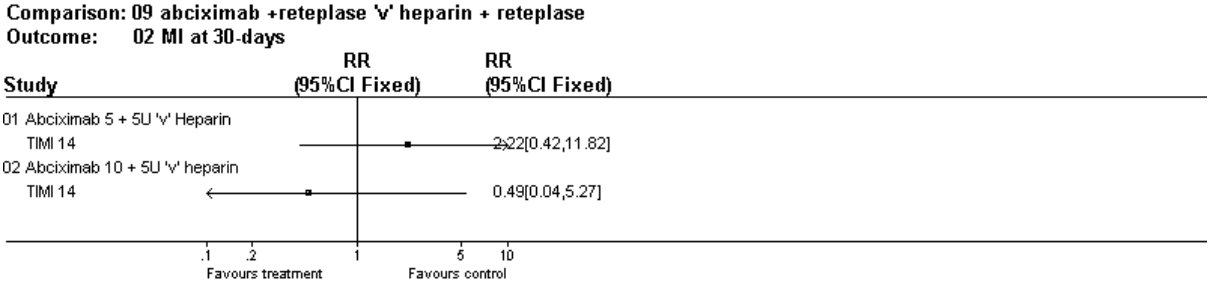


Figure 57: Effect of abciximab + half-dose reteplase repeat MI

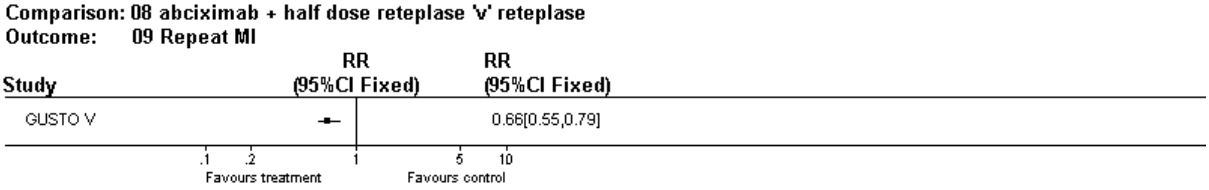
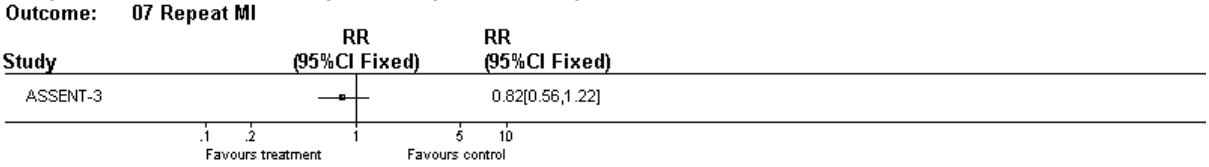


Figure 58: Effect of abciximab + teneceplase on repeat MI



Recurrent ischemia

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

Table 56: Effect of abciximab + thrombolytics on recurrent ischemia

Study	Time Point	Recurrent ischemia	Re-infarction
GUSTO V	7-days	Reteplase = 12.8% Abciximab + reteplase ½ dose = 11.3%	-
ASSENT-3	In-hospital	Enoxaparin + tenecteplase =	Enoxaparin + tenecteplase = 2.7%

		4.6% Abciximab + tenecteplase = 3.2% Heparin + tenecteplase = 6.5%	Abciximab + tenecteplase = 2.2% Heparin + tenecteplase = 4.2%

TIMI-14 reported the number of patients experiencing severe ischemia 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 +5U abciximab and 10+5U abciximab groups respectively.

Revascularisations

The effect of combination therapy with abciximab on the rates of revascularisations can be seen below in Figures 59-64. 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, 7 & 30 days; and for PTCA and CABG at 7 & 30 days.

Figure 59: Effect of abciximab + half dose reteplase on PTCA

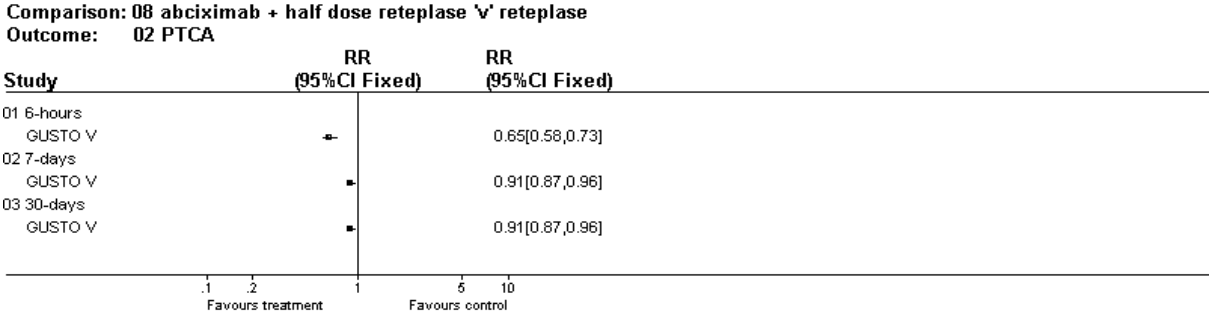


Figure 60: Effect of abciximab + half dose reteplase on CABG

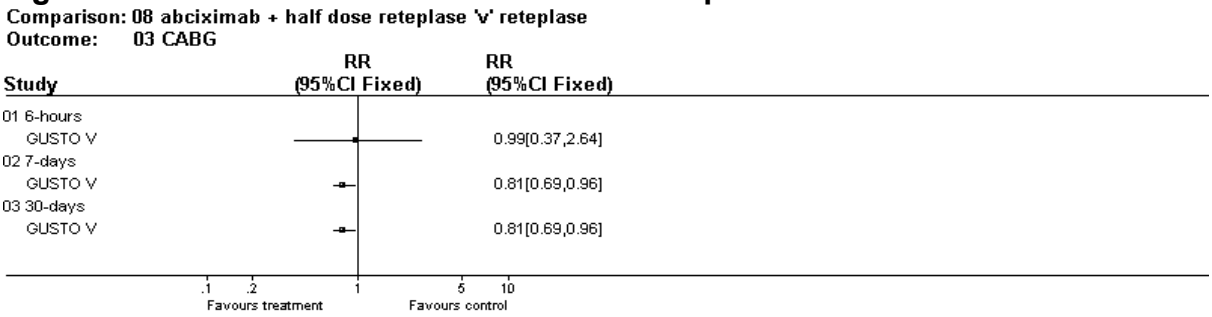


Figure 61: Effect of abciximab + teneceplase on all revascularlations at 30-days

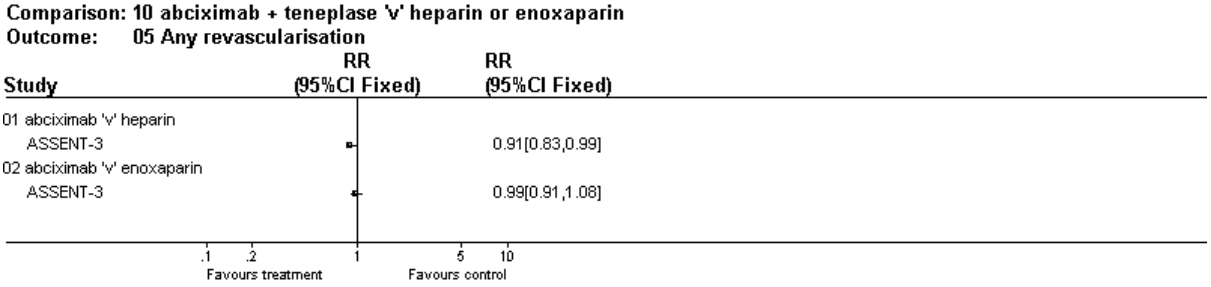


Figure 63: Effect of abciximab + reteplase on PTCA

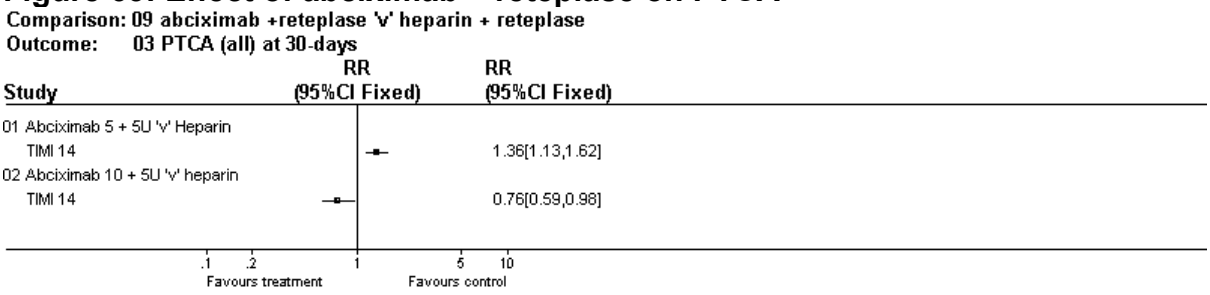
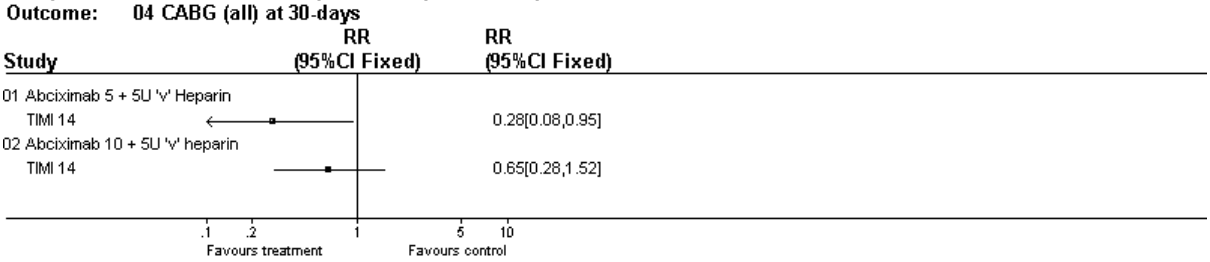


Figure 64: Effect of abciximab + reteplase on CABG



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 and major bleeding, can be seen below in Figures 65- 68, TIMI-14 did not report on bleeding events. The definitions of bleeding used in the two trials can be seen in Table 57. In ASSENT-3 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 and diabetic patients, the rates in the abciximab and enoxaparin arms being 13.3% versus 4.1%, and 7.0% versus 2.2% repsectively. All analyses showed a statistically significant increase associated with combination treatment.

Figure 65: Effect of abciximab + half dose reteplase on moderate bleeding

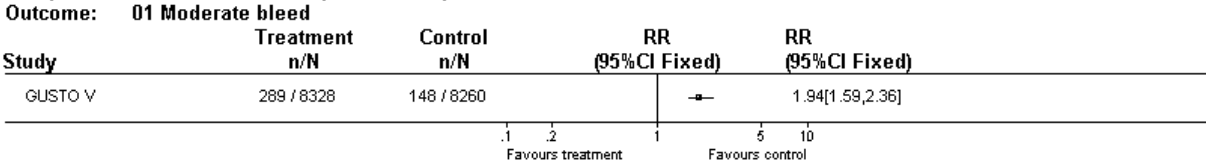


Figure 66: Effect of abciximab + reteplase on severe bleeding

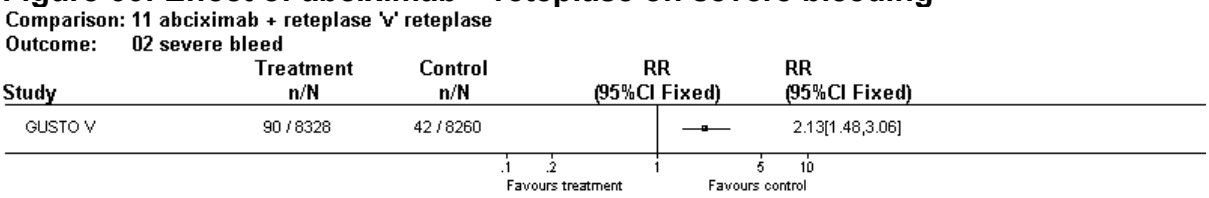


Figure 67: Effect of abciximab + tenecteplase on minor bleeding

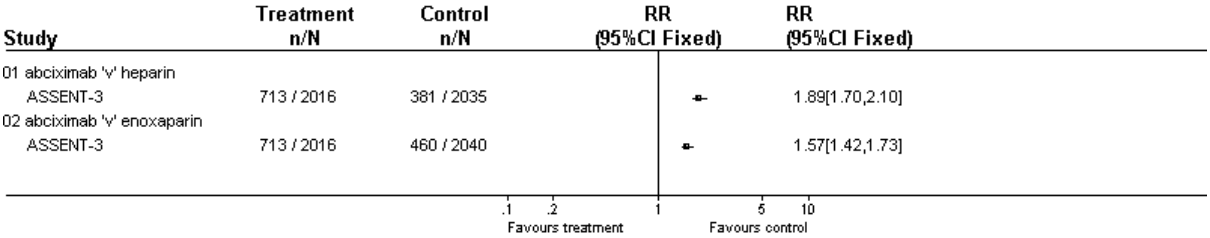


Figure 68: Effect of abciximab + tenecteplase on major bleeding

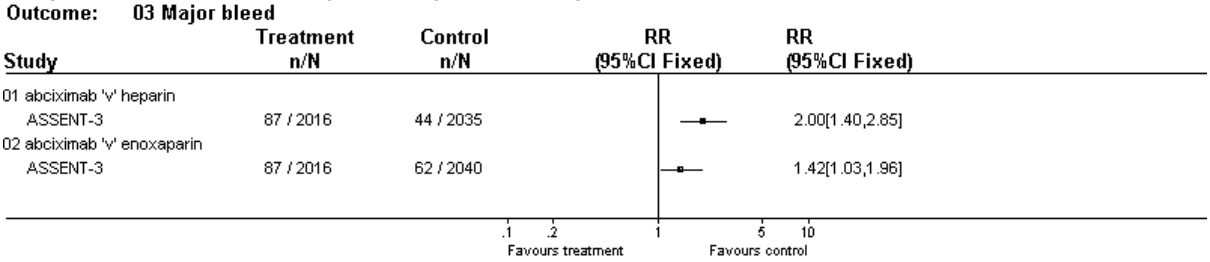


Table 57: Definitions of bleeding used in trials of combination therapy with abciximab

Study	Minor/Moderate/major bleeding
GUSTO V	Classified as severe when associated with haemodynamic compromise, moderate when requiring transfusion without haemodynamic compromise, and mild without transfusion or haemodynamic compromise.
ASSENT-3	Non cerebral bleeding complications were defined as major (requiring transfusion, intervention because of haemodynamic compromise, or both) or minor

Stroke:

The effect of combination therapy on incidences of stroke can be seen in Figures 69 and 70. TIMI 14 did not report on stroke. There are no significant differences in the risk of stroke in the interventions arms compared to control arms of the trials.

Figure 69: Effect of abciximab + half dose reteplase on stroke (any)

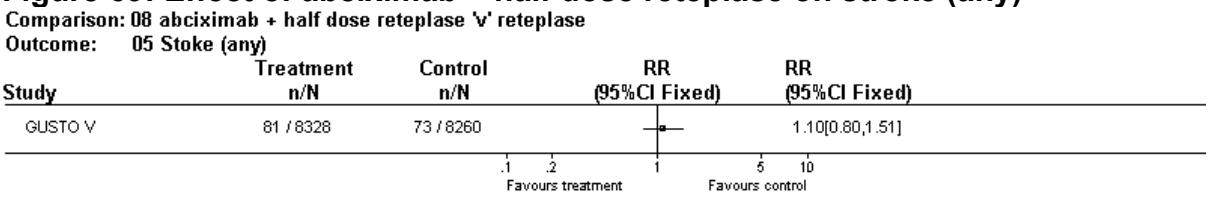
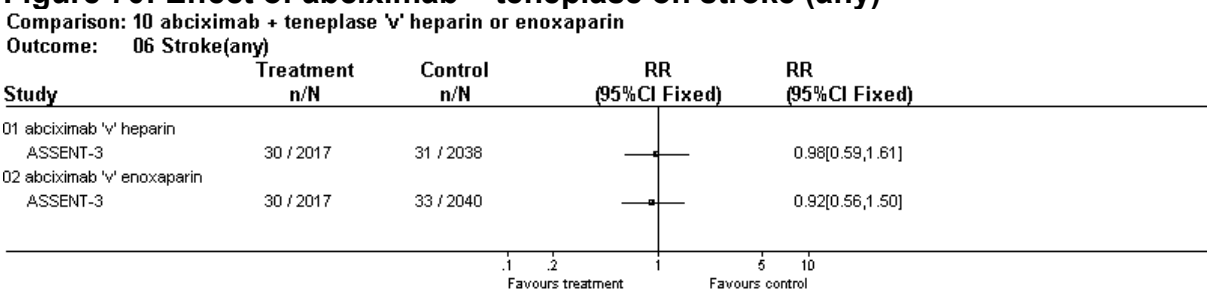


Figure 70: Effect of abciximab + teneplase on stroke (any)



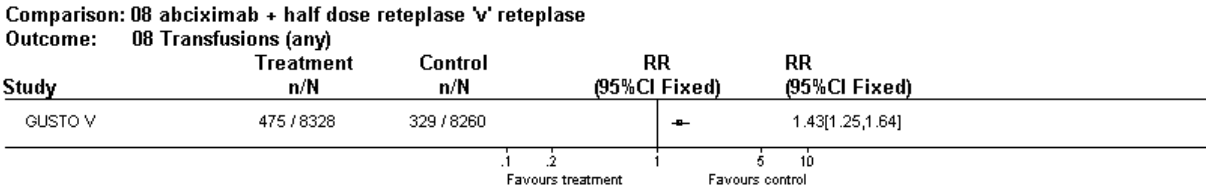
Thrombocytopenia:
TIMI-14 did not report on the incidence of thrombocytopenia. GUSTO V and ASSENT 3 did report these events. However, the platelet count used to describe an episode of thrombocytopenia differed between the 2 trials. The effect of abciximab combination therapy on thrombocytopenia can be seen in Table 58. Increased thrombocytopaenia with abciximab is observed throughout.

Table 58: Effect of abciximab combination therapy on thrombocytopenia

Study	Definition of thrombocytopenia				
	< 20 cell/μL	20-50 cells/μL	<50 cell/μL	50-100 cell/μL	<100 cell/μL
GUSTO V	-	-	Reteplase = 0.7% Abciximab + reteplase = 2.9%	-	Reteplase = 0.1% Abciximab + reteplase = 1.2%
ASSENT-3	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%	-

Transfusions:
The effect of abciximab + reteplase on the number of patients requiring transfusions can be seen in Figure 71. Only the GUSTO IV 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 (1.25, 1.64))

Figure 71: Effect of abciximab + half-dose reteplase on transfusions in the GUSTO V trial



Composite

The effect of combination therapy on the composite outcomes can be seen in Figures 72 and 73. GUSTO V showed a statistically significant benefit of abciximab + reteplase on the composite outcome. Less favourable results were observed comparing abciximab to enoxaparin: the efficacy endpoint was 0.3 % less frequent (NNT 300) and the safety plus efficacy endpoint (incorporating bleeding as well as death and reinfarction) was 0.4% more common. The TIMI-14 trial did not report a composite.

Figure 72: Effect of abciximab + half dose reteplase on the composite outcome

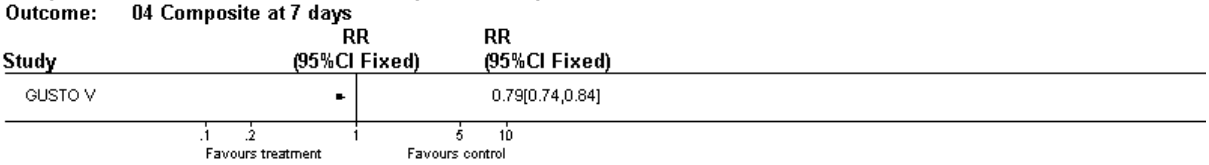
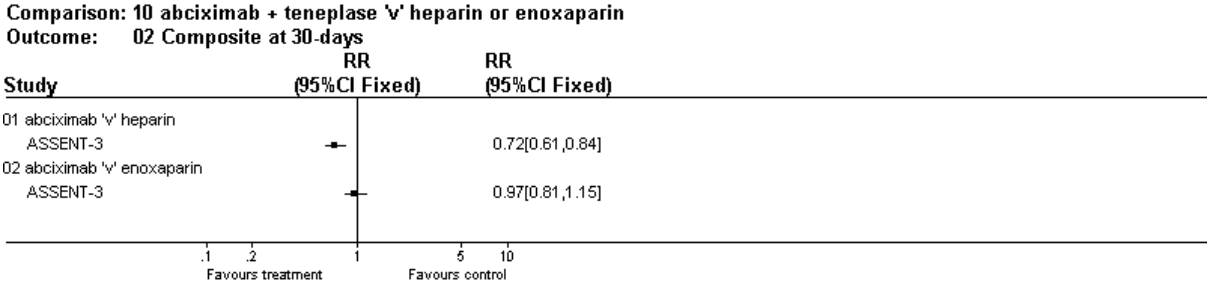


Figure 73: Effect of abciximab + teneceplase on the composite outcome



2.5.2.2 Eptifibatide

The two small trials (IMPACT-AMI and Ronner et al) looked at the use of the glycoprotein eptifibatide in combination with thrombolytics. Ronner et al looked at the thrombolytic alteplase in combination with different doses of eptifibatide and IMPACT-AMI looked at streptokinase in combination with one dose of eptifibatide. Less than 200 patients were included in the two trials, hence results lack statistical power and should be interpreted with caution.

Table 59: Results from IMPACT- AMI[86]

Treatment Arm	Time point	Recurrent MI	Death	PTCA	CABG	Composite

		n	%	n	%	n	%	n	%	N	%
Eptifibatide (n = 35)	**24-hours**	0	0	4	11 (1-22)	6	16	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 Ronner et al[88]

Treatment Arm	Time point	Recurrent MI		Death		PTCA		Composite	
		n	%	n	%	n	%	N	%
Eptifibatide low dose infusion (n = 44)	**30-days**	Listed as endpoint, but not reported		1	2.2	8	18	-	-
Eptifibatide medium dose infusion (n = 45)	**30-days**			2	4.4	2	4	-	-
Eptifibatide high dose infusion (n = 30)	**30-days**			2	6.6	4	13	-	-
Placebo (n = 62)	**30-days**			4	6.4	0	0	-	-

Death

The effect of eptifibatide + alteplase (IMPACT-AMI) or eptifibatide + streptokinase (Ronner et al) on the number of deaths recorded can be seen in Figures 74 and 75. A benefit of eptifibatide + streptokinase was seen in the low-dose versus placebo and medium-does 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.

Figure 74: Effect of eptifibatide + streptokinase on death, as reported in Ronner et al.

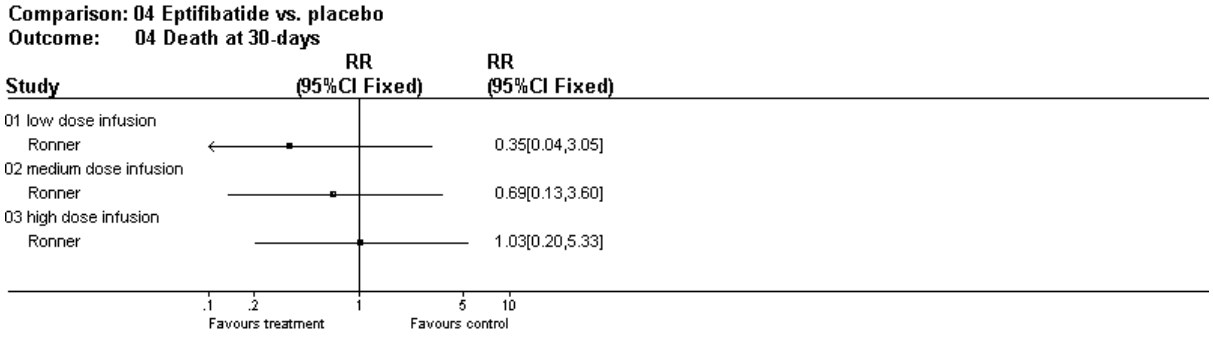
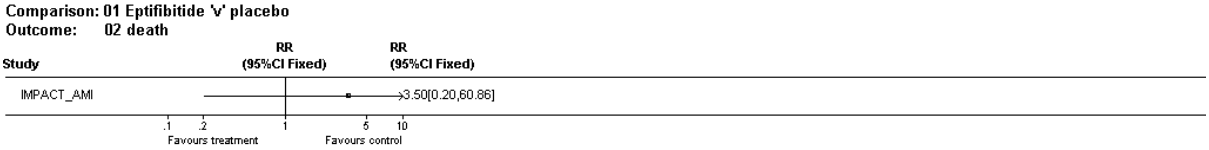


Figure 75: Effect of eptifibatide + alteplase on death, as reported in IMPACT-AMI



Recurrent myocardial infarction

Ronner et al did not report on recurrent MI's, and no events occurred in the IMPACT-AMI trial.

Recurrent ischemia

Only Ronner et al reported on recurrent ischemia, and found that low dose combination group (eptifibatide + streptokinase) were the combination group most likely to suffer from recurrent ischemia, 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 PTCA's performed can be seen in Figure 76. The effect of eptifibatide + alteplase on the number of PTCA's and CABG's can be seen Figures 77 and 78.

Figure 76: Effect of eptifibatide + streptokinase on PTCA

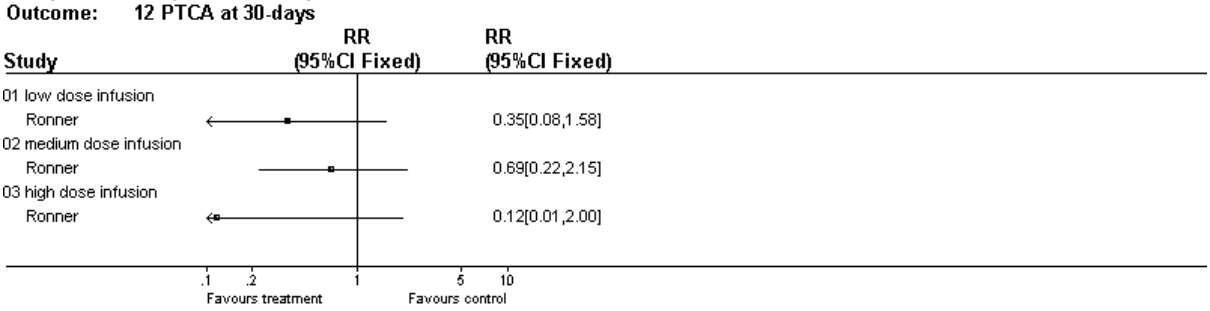


Figure 77: Effect of eptifibatide + alteplase on PTCA

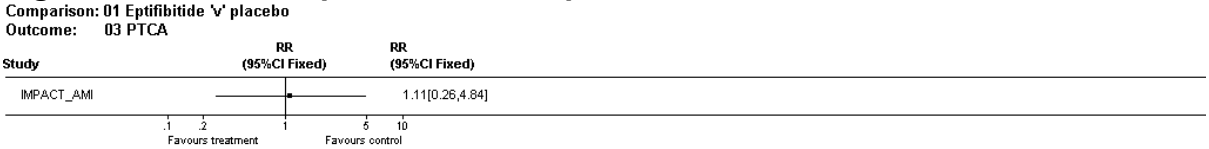
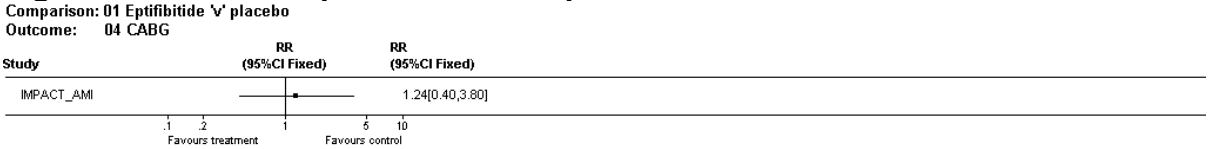


Figure 78: Effect of eptifibatide + alteplase on CABG



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 79 and 80. As in the large trials of abciximab, a substantial increase in both major and minor bleeding is associated with eptifibatide + thrombolytic treatment.

Figure 79: Effect of eptifibatide + streptokinase on minor bleeding

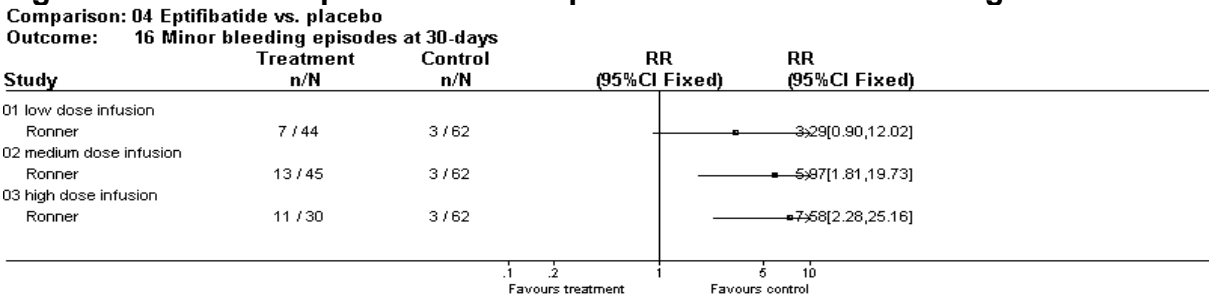
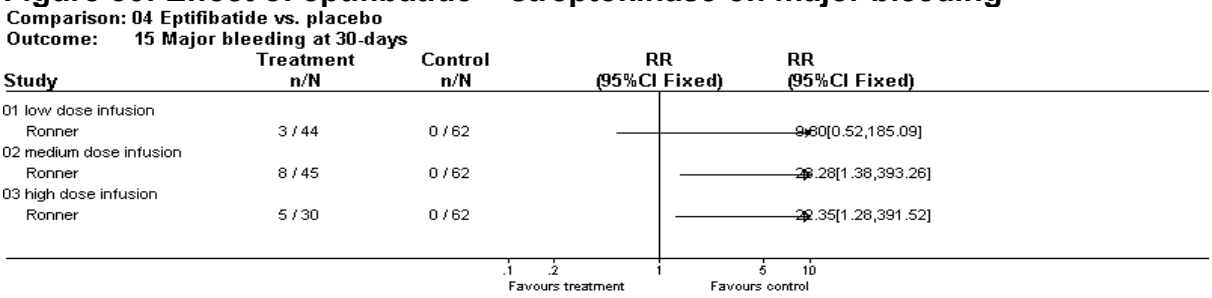


Figure 80: Effect of eptifibatide + streptokinase on major bleeding

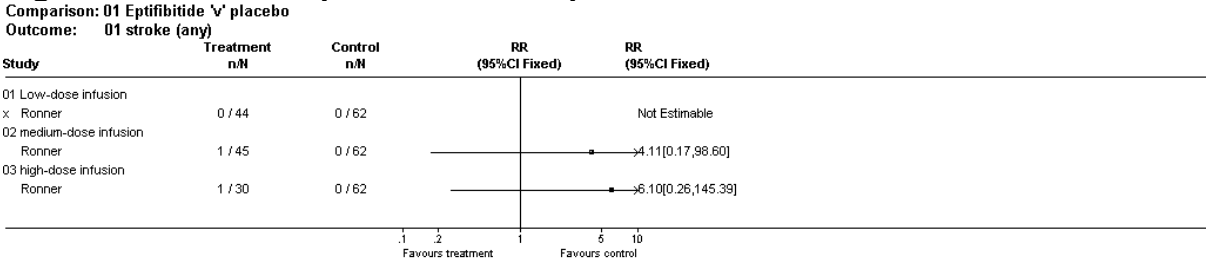


IMPACT-AMI also reported on the number of bleeding episodes occurring. Bleeding was classified as mild, moderate or severe. Although more common in the eptifibatide + thrombolytic arm, no statistically significant differences between groups were found.

Stroke:

The effect of eptifibatide + streptokinase on incidences of stroke can be seen below in Figure 81. 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.

Figure 81: Effect of eptifibatide + streptokinase on incidences of stroke

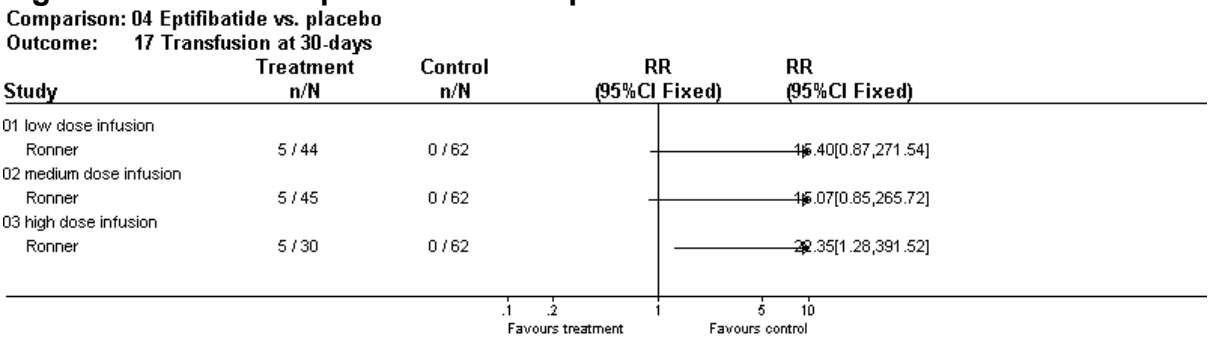


IMPACT-AMI also reported on the incidence of stroke, and categorised these as embolic or intracranial haemorrhagic. Only 1 intracranial stroke occurred in the eptifibatide + alteplase group.

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

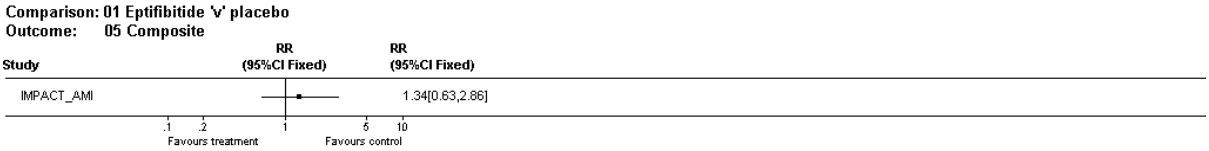
Transfusions:
The effect of eptifibatide + streptokinase on transfusions can be seen below in Figure 82. Only Ronner et al reported on transfusions. A significant increase in risk of transfusion is associated with all three intervention arms compared to control. The biggest difference was seen in the high dose infusion group (RR = 16.07 (0.87, 271.54) for the low dose compared to placebo, RR = 16.07 (0.85, 265.72) for the medium dose compared to placebo and RR = 29.35 (1.28, 391.52) for the high dose infusion group).

Figure 82: Effect of eptifibatide + streptokinase on transfusions



Composite
The effect of eptifibatide + alteplase on the composite outcome, as defined, can be seen in Figure 83. Ronner et al 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.

Figure 83: Effect of eptifibatide + alteplase the composite outcome



2.5.3 Conclusions regarding effectiveness of thrombolytics alongside glycoproteins, for the treatment of acute myocardial infarction.

Five trials have been described concerning the use of GPAs in conjunction with thrombolytics for ST elevated AMI first use of acronym covering about 23000 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 enoxaprain 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. (26, 86) for PTCA and 142 (80, 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 trial which was regarded as significant.

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

In summary evidence published to date does not convincingly demonstrate that benefits outweigh harms. There may be a sub-group of AMI patients, e.g. 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.

3. ECONOMIC ANALYSIS

Full economic evaluations for the use of glycoproteins alongside PCI and in the medical management of ACS patients are discussed below. 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.

3.1 METHODS FOR ECONOMIC ANALYSIS

3.1.1 Search methods

The two earlier reviews of glycoproteins[4, 5] 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 Appendix 1 and 2. These are the same search strategies used by NHS CRD for their earlier review of GP IIb/IIIa antagonists[4, 5]. Hence, the inclusion criteria for the present searches was designed not to repeat but to up-date the searches.

3.1.2 Inclusion criteria

As detailed in Section 2.1.3, 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).

3.1.3 Data extraction and quality assessment

The data extraction tables set out in the earlier review was used to extract the majority of data from the studies. However, it was felt that, for the purposes of this project, additional information regarding sub-group 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.

3.1.4 Search results

The update review identified 6 papers in addition to the 16 studies identified in the two previous reports.[4, 5]

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

3.2.1. Studies identified

The earlier review identified (see NICE report for search strategy) 5 published (Mark et al, 2000[89], McElwee, 1997[90], Bell, 1999[91], Hillegass, 1999[54] and Szucs et al, 1999[92]), plus an additional 2 economic analyses which were part of industry submissions from Schering Plough and MSD [93, 94] 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. Quality of economic evaluations was evaluated using a validity assessment tool. Results of the quality assessment can be seen below in Table 61.

Table 61: Quality of cost-effectiveness studies, for glycoproteins in the medical management of ACS patients.

	Mark (2000)	McElwee (1997)	Bell (1999)	Hillegass (1999)	Szucs (1999)
Well- defined question posed?	+	+	+	+/-	+
Comprehensive descriptions of alternatives given?	+	-	+	+	+
Effectiveness established?	+	+/-	+	+/-	+
Important/relevant costs + 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 & discussion include all the issues of concern to users?	+	-	+	-	+

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[90] analysis looked at the cost-effectiveness of GP IIb/IIIa antagonists both as medical management and alongside PCI in ACS patients.

Of the 5 published studies, 4 were conducted in the US, and Szucs was conducted using Swiss data. Costs were all reported as US Dollars, apart from Szuchs (1999) [92] which reported Swiss francs and also converted cost results to Euros.

From the perspective of UK decision making, the papers by McElwee[90], Hillegrass[54] and Szuchs[92] are of limited relevance. This is because they focused on the cost-effectiveness of GP IIb/IIIa antagonists in health care systems outside the UK. Given that UK practice with respect to the management of ACS differs from other developed countries, particularly regarding the rate of PCI, studies primarily focused on other systems will generate unreliable estimates of cost-effectiveness. Furthermore, the papers by Hillegrass and Szuchs use condition-specific measures of effect rather than the generic measures of health gains such as life-years and quality-adjusted life-years gained favoured by NICE[95].

The paper by Mark et al[89] is focused on the US system but it worth further consideration for two reasons. Firstly, it was the only prospective economic analysis undertaken alongside a randomised trial. Secondly, it was used as a basis of the Schering Plough UK analysis.

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

3.2.1.1 Mark et al

Only PURSUIT was planned with a prospective economic analysis. The Mark et al[89] 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 et al 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 quality adjusted life year (QALY) gained. This is based on the risk difference in all-cause death or non-fatal MI at 30 days found in the North American subgroup, 3.5%. If the overall 1.5% risk difference found in PURSUIT was used the cost per life year saved was US$ 33,619. It should be noted that the risk difference for the Western European patients was smaller, 1.0%. Further sensitivity analyses resulted in $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 $20,768 per life year saved and at 7% this was further increased to $25,460. The ICER without applying any discount rate was $10, 954 per life year gained.

Although the methods used in the Mark et al 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[93].

3.2.1.2 Schering Plough submission

The Schering-Plough study is closely related to the Mark et al, 2000 analysis in that it uses the PURSUIT trial as its main data source. The study used resource use data from both UK patients (n=429) and all Western European (n=3697) 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% risk difference for all-cause survival and a 1.01% risk difference for MI-free survival at 6 months favouring eptifibatide Using the modelling approach and life expectancy data detailed in the Mark et al paper, years of life gained (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 £8,179 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 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.

3.2.1.3 MSD submission

The cost-effectiveness analysis in the MSD submission focuses on the use of tirofiban as used in the PRISM-PLUS trial. This trial is used as the source of effectiveness data, and the composite measure of effect (all cause mortality, new MI, refractory ischaemia 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 £8,760 using the 7-day effects and £9,995 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 refractory ischaemia are estimated based on data from PRAIS-UK[96] 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 £6,820 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 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.

3.3 Cost effectiveness of glycoproteins alongside PCI

3.3.1 Studies identified

From the literature searches for the original review (see appendix for search strategy) 17 published studies were identified (Dunn (1999)[97], Mark (1996)[98], Van Hout (1995)[99], Van Hout (1998)[100], Anderson (1999)[101], Sacristan (1996)[102], Zed (1998)[103], Aristides (1998)[104], Goklaney (1998)[105], Lorenzoni (1999)[106], Hillegass (1999)[54], McGregor (1999)[107], Bell (1999)[91], Mark (2000)[89], Topol (1999)[108], Weintraub (1999)[109] and Hermiller (1999)[110]). The update searches identified an additional 6 studies, Reed (2000)[111], Weintraub (2000)[112], Hermiller & Kereiakes (1999)[110], Kereiakes et al (1999)[113], Zwart-van Rijkon (2001)[114] & Van-Hout (2001) and the PRICE trial (2000)[62]. In addition, an economic analysis submitted to the 2000 review is included here as it is not now commercial in confidence[123]. The data extracted from the included economics papers can be seen in Appendix 8.

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

Table 62: Quality of cost-effectiveness studies, for glycoproteins alongside PCI.

	Dunn (1999)	Mark (1996)	Van Hout 1995)	Van Hout 1998)	Anderson 1999)	Sacristan (1996)	Zed (1998)	Aristides (1998)	Goklaney (1998)	Lorenzoni (1999)	Hillegass (1999)	McGregor (1999)	Bell (1999)	Mark (2000)	Topol (1999)	Weintraub (1999)	Handerson (1999)	Reed (2000)	Weintraub (1999)	Hermiller (1999)	Kereiakes (1999)	PRICE (2000)	Zwart-van-Rijon (2001)
Well- defined question posed?	+	+	+	+	-	+	+	+	?	+	-	+	?	+	+	+	+	+	+	-	+	+	+
Comprehensive descriptions of alternatives given?	+	na	+	+	-	+	+	+	-	?	?	+	?	?	+	+	?	+ / -	+	-	-	+	+
Effectiveness established?	+	+	+	+	na	+	+	+	?	?	+/ ?	+	?	-	+	-	-	+	-	+	+	+	+
Important/relevant costs + 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	n a	na	na	n a	?	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 & discussion include all the issues of concern to users?	+	+	+	+	?	+	+	+	?	?	-	+	-	?	+	?	?	+	?	?	?	?	?

3.3.2 Overall results

A number of cost-effectiveness studies were undertaken to assess the cost-effectiveness of abciximab compared to standard therapy in the EPIC trial. With the exception of the early Mark et al cost analysis[98], most studies have concluded that, although abciximab may 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[104], Spain[102]the Netherlands[99] and Canada[115]. The general conclusion of these studies was the abciximab was cost-effective in this indication, although cost-effectiveness has been shown to be superior in high-risk patients such as those with acute MI or unstable angina[99-102].

Some studies have also sought to extrapolate the short-term results of EPIC over a longer time period using simple extrapolation methods[100, 104]. However, only Aristedes estimated a cost per life-year gained 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 trial are important to consider. Using 6-month outcome data from the trial, Zwart van Rijkon 2001 and van Hout 1998, estimated cost per additional MI free survivor of adding abciximab to stents at 12876 Euros; the incremental cost per major adverse event avoided was 14198 Euros. Topol et al[108] used EPISTENT data to estimate long-term cost-effectiveness using similar extrapolation methods to Mark et al(2000) referred to in the previous section on ACS patients. They estimated the cost per life-year gained of US$6213 per life-year gained.

Several studies have sought to synthesise the results of a number of trials looking at GP IIb/IIIa antagonists alongside PCI[54, 91, 107]. Bell 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, and US$25,201 using EPILOG effectiveness data.

Of the studies looking at the small molecule GP IIb/IIIa antagonists. Weintraub et al[109] using data collected in the RESTORE 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 data, Bell estimated the cost per event avoided of eptifibatide to be $10,695.

3.3.3 Cost-effectiveness for UK decision-making

Although most studies generally conclude 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 to 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 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 life-years gained, it was assumed that those patients in the trial surviving the first year would live for a further 15 years. No differential costs were assumed as part of this longer-term extrapolation. QALYs were estimated assuming a quality-adjustment factor of 0.8 for all living patients. These assumptions generated estimates of cost per life-year gained from abciximab of £3,554 for EPISTENT, £6,247 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 range between £6,941 and £9,053 for EPILOG and £3,949 and £5,151 for

EPISTENT. The authors consider two specific sub-groups – acute coronary syndrome 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. Firstly, 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 maybe 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 to 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.

3.4 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 relative risks associated with GP IIb/IIIa antagonists, may be different to those in the UK. Some sub-group 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 life year gained ranging between £8,179 and £11,079. The cost-effectiveness of tirofiban for the UK are estimated based on PRISM-PLUS, but no estimate of cost per life-year or QALY gained are provided.

4. Company submissions

For the update review evidence relating to the use of glycoproteins was submitted from each of the three manufacturers, Merck Sharp & Dolme, 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.

5. DISCUSSION

5.1 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 acute coronary syndrome
- Adjunctive to PCI (urgent or elective)
- In combination with intravenous thrombolytics for ST elevation acute myocardial infarction

Specific discussion of the clinical effectiveness for each indication is included elsewhere: section 2.3.3 for medical management; section 2.4.3 for use with PCI; and section 2.5.3 for use with thrombolytics. Here we consider over-arching issues and summarise how our conclusions have developed from those of the previous rapid reviews conducted for NICE.

5.1.1 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 subjects 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 endpoints may be a concern where the relative risk between treatment and reference groups in the components (i.e. MI, death) of the composite endpoint are very small, but when added together the effect becomes clinically important. With the intravenous glycoprotein IIb/IIIa antagonists, this appears to be the case. The survival analyses presented in the studies suggest a significant benefit that is consistent over time, when using composite endpoints. In examining the forest plots of the relative risk, 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.

5.1.2 Generalisability of trial results

Most of the trials described in this report were conducted in the United States, or were multi-centre 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:

1. 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[39-42]) where a geographical sub-group analysis of this type has been published and by the results from GUSTO-IV[37] in ACS.
2. Age – the mean age of subjects enrolled in these trials (range 59 to 67 years) are 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 trial[116], 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[117]. 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.

5.1.3 Variations in effectiveness by sub-group

An important issue with any new technology is whether there are specific sub-groups 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 2.3.3 for further details). If greater effectiveness in a given sub-group 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 Section 1.2.1 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[118]. In the case of PCI, recent unstable angina or AMI, diabetes, and complex coronary morphology are associated with more complications [72]. For AMI, hypotension congestive heart failure and continuing ischaemia suggest a poor prognosis[119]. Together these suggest a large number of sub-groups where there might be important differences in clinical effectiveness.

The evidence from which conclusions about differential effectiveness between sub-groups, can be drawn is limited. As has been already pointed out in the discussion for specific indications, most sub-group analyses of trial results are retrospective. Furthermore the numbers of patients in sub-groups 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[120], 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[3]. 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 sub-groups, 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 sub-groups are:

1. What is the effectiveness, if any, of GP IIb/IIIa antagonists in high risk ACS in the absence of early PCI? As described in Section 2.3.3, the recent GUSTO-IV trial showed no effect in this situation. Retrospective analyses of other trials which 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.[45]

2. Is there a low-risk sub-group 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 sub-group analyses which address this question. Although NICE recommended 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% (McLenechan J – 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.

5.1.3 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 are:

- As part of the medical (non-interventional) management of ACS, 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 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 sub-group of PRISM: RR 0.30(0.10-0.81) in medically-managed patients compared to RR 0.37(0.15-0.93) 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[121]. 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.
- No evidence for the clinical superiority of small molecule GP IIb/IIIa antagonists over the more widely used agent, abciximab, as 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.

5.2 Cost-effectiveness

For two of the three indications considered in this report – the use of glycoprotein 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 manufactures. 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 health care systems other than 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 effect 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 glycoprotein 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 glycoprotein 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 glycoprotein 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 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 report to this details the results of a modelling exercise which has sought to assess the cost-effectiveness of the three strategies described above, also in comparison with standard care without glycoprotein IIb/IIIa antagonists[122]. 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.

Despite the shortcomings of existing economic evidence it is important to present the best estimates of cost per life-year/QALY gained in the literature. In the case of the use of the use of glycoprotein IIb IIIa antagonists in ACS, the estimates of cost per life-year gained 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 £8,179 to £11,079 per life-year gained depending on the discount rate used for future survival. In the case of the use of glycoprotein 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 £3,554 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 glycoprotein IIb/IIIa antagonists alongside thrombolysis in acute MI 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.

APPENDICES
Appendix 1: Search strategy

The following databases were searched for trials of the named glycoproteins

MEDLINE (WinSPIRS, 1966-2001/06)
PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi Searched 7 Sept 2001)
EMBASE (WinSPIRS, 1980-2001/08)
Conference Papers Index (Dialog, 1973-2001/Sept.)
Cochrane Library (CD-ROM, 2001/3)
TRIP database (http://www.tripdatabase.com/ on the 5 Sept. 2001)
DEC reports (http://www.doh.gov.uk/research/swro/rd/publicat/dec/index.htm on the 5 Sept. 2001)
HTA database (http://www.york.ac.uk/inst/crd on the 5 Sept. 2001)
DARE database (http://www.york.ac.uk/inst/crd on the 5 Sept. 2001)
NHS EED database (http://www.york.ac.uk/inst/crd on the 5 Sept. 2001)
NCCHTA website (http://www.hta.nhsweb.nhs.uk/ on the 7 Sept. 2001)
National Guideline Clearinghouse (http://www.guideline.gov/index.asp on the 7 Sept 2001)
National Research Register (CD-ROM Issue 2001/3)
ScHARR Lock's Guide to the Evidence (http://www.shef.ac.uk/uni/academic/RZ/scharr/ir/scebm.html on the 7 Sept. 2001)
SIGN guidelines (http://www.show.scot.nhs.uk/sign/index.html on the 7th Sept. 2001)

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

The search strategies to be used are listed below:

1. MEDLINE (Silverplatter)

explode "Angina-Pectoris"/ all subheadings
explode "Myocardial-Infarction"/ all subheadings
explode "Atherectomy"/ all subheadings
"Catheter-Ablation"/ all subheadings
explode "Angioplasty-Balloon"/ all subheadings
explode "Myocardial-Revascularization"/ all subheadings
"Stents"/ all subheadings
#1 or #2 or #3 or #4 or #5 or #6 or #7
myocardi*
infarct*
myocardi* infarct* in ti,ab
heart attack* in ti,ab
coronary syndrome* in ti,ab
crescendo in ti,ab
unstable angina in ti,ab

percutaneous coronary intervention* in ti,ab
percutaneous transluminal coronary angioplasty in ti,ab
ptca in ti,ab
balloon angioplasty in ti,ab
#8 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
"Platelet-Glycoprotein-GPIIb-IIIa-Complex"/ all subheadings
(abciximab or reopro) in ti,ab
(eptifibatide or integrilin or integrelin) in ti,ab
(tirofiban or aggrastat) in ti,ab
((gp* or glycoprotein*) near (iib* or 2b*)) in ti,ab
(gpiib* or gp2b* or glycoproteiniib* or glycoprotein2b*) in ti,ab
#21 or #22 or #23 or #24 or #25 or #26
#20 and #27
exact{CLINICAL-TRIAL} in PT
"Randomized-Controlled-Trials"/ all subheadings
"Random-Allocation" in MIME,MJME
"Double-Blind-Method" in MIME,MJME
"Single-Blind-Method" in MIME,MJME
explode "Clinical-Trials"/ all subheadings
"Placebos"/ all subheadings
"Research-Design"/ all subheadings
explode "Evaluation-Studies"/ all subheadings
"Follow-Up-Studies" in MIME,MJME
"Prospective-Studies" in MIME,MJME
#30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39
(clin* near trial*) in ti,ab
((singl* or doubl* or treble* or tripl*) near (blind* or mask*)) in ti,ab
random* in ti,ab
placebo* in ti,ab
exact{COMPARATIVE-STUDY} in TG
(control* or prospectiv* or volunteer*) in ti,ab
#40 or #41 or #42 or #43 or #44 or #45 or #46
explode "Economics"/ all subheadings
explode "Costs-and-Cost-Analysis"/ all subheadings
explode "Economics-Hospital"/ all subheadings
explode "Economics-Medical"/ all subheadings
"Economics-Nursing"/ all subheadings
"Economics-Pharmaceutical"/ all subheadings
#48 or #49 or #50 or #51 or #52 or #53
(cost effect*) in ti,ab
(cost benefit*) in ti,ab
(economic evaluation*) in ti,ab
(technology assessment*) in ti,ab
pharmacoeconomic* in ti,ab
cost util* in ti,ab
#54 or #55 or #56 or #57 or #58 or #59 or #60
#28 and (#47 or #61)
exact{ANIMAL} in TG
exact{HUMAN} in TG

#63 not (#63 and #64)
#62 not #65

2. EMBASE (Silverplatter)

explode "Angina-Pectoris"/ all subheadings
explode "Heart-Infarction"/ all subheadings
"Artery-Catheterization"/ all subheadings
"Percutaneous-Transluminal-Angioplasty"/ all subheadings
"Transluminal-Coronary-Angioplasty"/ all subheadings
"Heart-Muscle-Revascularization"/ all subheadings
"Coronary-Stent"/ all subheadings
"Heart-Muscle-Ischemia"/ all subheadings
myocardi* infarct* in ti,ab
heart attack* in ti,ab
coronary syndrome* in ti,ab
crescendo in ti,ab
unstable angina in ti,ab
percutaneous coronary intervention* in ti,ab
percutaneous transluminal coronary angioplasty in ti,ab
ptca in ti,ab
balloon angioplasty in ti,ab
#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
"Glycoprotein-IIb"/ all subheadings or "glycoprotein-IIIa"/ all subheadings
"abciximab"/ all subheadings
"eptifibatide"/ all subheadings
"tirofiban"/ all subheadings
(abciximab or reopro) in ti,ab
(eptifibatide or integrilin or integrelin) in ti,ab
(tirofiban or aggrastat) in ti,ab
((gp* or glycoprotein*) near (iib* or 2b*)) in ti,ab
(gpiib* or gp2b* or glycoproteiniib* or glycoprotein2b*) in ti,ab
#19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27
#18 and #28
explode "Clinical-Trial"/all subheadings
"crossover-procedure"/ all subheadings
"Randomization"/ all subheadings
"Double-Blind-procedure"/ all subheadings
"Single-Blind-procedure"/ all subheadings
explode "Clinical-Trials"/ all subheadings
"Evaluation"/ all subheadings
explode "Comparative-study"/ all subheadings
"Placebo"/ all subheadings
"Follow-Up"/ all subheadings
"Controlled-Study"/ all subheadings
"Prospective-Study"/ all subheadings
((intervention or clinical) near (trial* or study or studies)) in ti,ab
((singl* or doubl* or treble* or tripl*) near (blind* or mask*)) in ti,ab

(random* or placebo or rct) in ti,ab
((controlled or uncontrolled) near (trial* or study or studies)) in ti,ab
((multicentre* or multicenter*) near (trial* or study or studies)) in ti,ab
((cross over or crossover or evaluation or prospective) near (trial* or study or studies)) in ti,ab
((follow up or followup) near (trial* or study or studies)) in ti,ab
#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
"cost-benefit-analysis"/ all subheadings
"Cost-effectiveness-analysis"/ all subheadings
"Cost-minimization-analysis"/ all subheadings
"Cost-utility-analysis"/ all subheadings
"Economic-Evaluation"/ all subheadings
(cost effect*) in ti,ab
(cost benefit*) in ti,ab
(economic evaluation*) in ti,ab
(technology assessment*) in ti,ab
pharmacoeconomic* in ti,ab
cost util* in ti,ab
#50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60
#29 and (#49 or #61)

3. Conference Papers Index (Dialog)

S angina()pectoris
S Myocardial()Infarct?
S Atherectomy
S Catheter()Ablation
S balloon()angioplasty
S Myocardial()Revascularization
S coronary()Stent?
S heart()attack?
s coronary()syndrome?
s crescendo
s unstable()angina
s percutaneous()coronary()intervention?
S percutaneous()transluminal()coronary()angioplasty
S ptca
S s1:s14
S Glycoprotein()GPIIb?
S abciximab or reopro
S eptifibatide or integrilin or integrelin
S tirofiban or aggrastat
S (gp? or glycoprotein?)(w)(iib? or 2b?)
S gpiib? or gp2b? or glycoproteiniib? or glycoprotein2b?
S s16:s22
S s15 and s22

4. Cochrane Library (2001/3)

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

5. TRIP Index (5 Sept. 2001)

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.

Glycoprotein
GpII not glycoprotein
Abciximab not glycoprotein
Reopro not glycoprotein
eptifibatide not glycoprotein
integrilin not glycoprotein
integrelin not glycoprotein
tirofiban not glycoprotein
aggrastat not glycoprotein
integrin not glycoprotein

6. DEC reports (searched 5 Sept. 2001)

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

7. DARE/NHS EED/HTA database search (searched 5 Sept. 2001)

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

Glycoprotein or gpii or abciximab or reopro or eptifibatide or intrifiban or integrilin or integrilenOr tirofiban or integrin or aggrastat

8. NCCHTA website (searched 7 Sept. 2001)

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

Glycoprotein
Gpiib
gpiiia
abciximab
reopro
eptifibatide
intrifiban
integrilin
integrilen
tirofiban
integrin
aggrastat

9. National Guideline Clearinghouse (searched 7 Sept. 2001)

The web site was searched using the keywords individually:

Glycoprotein
glycoproteins
Gpiib
Gpiiia
abciximab
reopro
eptifibatide
intrifiban
integrilin
integrilen
tirofiban
integrin
aggrastat

10. National Research Register (issue 2001/3)

Angina-Pectoris*:ME
Myocardial-Infarction*:ME
Atherectomy*:ME
Catheter-Ablation:ME

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

11. Scharr-Lock's Guide to the Evidence (searched 7 Sept. 2001)

This resource does not seem to have been updated recently.
The following headings were searched:

Angina
Myocardial Infarction
Atherectomy
Catheter Ablation
Angioplasty Balloon
Myocardial Revascularization
Stents

12. SIGN guidelines (searched 7 Sept. 2001)

The list of published guidelines were scanned.

13. PubMed (searched 7 Sept. 2001)

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

Appendix 2: Original search strategy for previous glycoprotein review

1. CD-ROM Resources

The Cochrane Library

Search Strategy for Licensed Glycoprotein Antagonists (searched 19/02/00)
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:

#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 05/04/00)
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 extra two hits. The numerical drug identities are excluded from the search strategy since 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)

2. EMBASE: Silverplatter Version.

Search Strategy for Licensed Glycoprotein Antagonists (searched 19/02/00)
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 trial studies relating to unstable angina.

The search strategy used to find cost effectiveness studies was:

No.	Records	Request
1	1660	"fibrinogen-receptor"/ all subheadings
2	1014	"fibrinogen-receptor-antagonist"/ all subheadings
3	1082	"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	2296	((glycoprotein* or gp*) near (iib* near iiia*)) or GPII*
16	20428	explode "angina-pectoris"/ all subheadings
17	18875	angina in ti ab
18	52760	explode "heart-infarction"/ all subheadings

19 45660 myocard* infarct*
20 943 heart attack*
21 1154 coronary syndrome*
22 155 crescendo
23 34164 explode "economic-evaluation"/ all subheadings
24 27117 cost effect*
25 12041 cost benefit*
26 1528 economic evaluation*
27 1555 technology assessment*
28 7119 pharmacoeconomic*
29 600 cost util*
30 4134 #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 82173 #16 or #17 or #18 or #19 or #20 or #21 or #22
32 48160 #23 or #24 or #25 or #26 or #27 or #28 or #29
33 107 #30 and #31 and #32
34 28572 explode "animal"/ all subheadings
35 3438241 explode "human"/ all subheadings
36 23537 #34 not (#34 and #35)
37 107 #33 not #36

The search strategy used to find trial studies was as follows;

No.	Records	Request
1	1660	"fibrinogen-receptor"/ all subheadings
2	1014	"fibrinogen-receptor-antagonist"/ all subheadings
3	1082	"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	2296	((glycoprotein* or gp*) near (iib* near iiia*)) or GPIIB*
16	20428	explode "angina-pectoris"/ all subheadings
17	18875	angina in ti ab
18	52760	explode "heart-infarction"/ all subheadings
19	45660	myocard* infarct*
20	943	heart attack*
21	1154	coronary syndrome*
22	155	crescendo
23	174982	explode "Clinical-Trials"/ all subheadings
24	51540	(clin* near trial*) in ti ab
25	54877	((singl* or doubl* or trebl* or tripl*) near (blind* or mask*)) in ti ab
26	564	Placebos
27	58244	placebo* in ti ab
28	42369	random in ti ab
29	42725	"randomized-controlled-trial"/ all subheadings
30	4134	#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	82173	#16 or #17 or #18 or #19 or #20 or #21 or #22
32	295390	#23 or #24 or #25 or #26 or #27 or #28 or #29
33	574	#30 and #31 and #32
34	28572	explode "animal"/ all subheadings
35	3438241	explode "human"/ all subheadings
36	23537	#34 not (#34 and #35)
37	574	#33 not #36

Search Strategy for Unlicensed Glycoprotein Antagonists (searched 05/04/00)
After it was decided that the review should include unlicensed Glycoprotein Antagonists a second set of searches were conducted. This search strategy was designed to exclude all papers already retrieved and yielded no extra hits.

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

No.	Records	Request
1	1660	"fibrinogen-receptor"/ all subheadings
2	1014	"fibrinogen-receptor-antagonist"/ all subheadings
3	1082	"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	2296	((glycoprotein* or gp*) near (iib* near iiia*)) or GPII*
16	20428	explode "angina-pectoris"/ all subheadings
17	18875	angina in ti ab
18	52760	explode "heart-infarction"/ all subheadings
19	45660	myocard* infarct*
20	943	heart attack*
21	1154	coronary syndrome*
22	155	crescendo
23	34164	explode "economic-evaluation"/ all subheadings
24	27117	cost effect*
25	12041	cost benefit*
26	1528	economic evaluation*
27	1555	technology assessment*
28	7119	pharmacoeconomic*
29	600	cost util*
30	4134	#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	82173	#16 or #17 or #18 or #19 or #20 or #21 or #22
32	48160	#23 or #24 or #25 or #26 or #27 or #28 or #29
33	107	#30 and #31 and #32
34	28572	explode "animal"/ all subheadings
35	3438241	explode "human"/ all subheadings
36	23537	#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 trial studies was as follows:

No.	Records	Request
1	1660	"fibrinogen-receptor"/ all subheadings
2	1014	"fibrinogen-receptor-antagonist"/ all subheadings
3	1082	"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	2296	((glycoprotein* or gp*) near (iib* near iiia*)) or GPIIB*
16	20428	explode "angina-pectoris"/ all subheadings
17	18875	angina in ti ab
18	52760	explode "heart-infarction"/ all subheadings
19	45660	myocard* infarct*
20	943	heart attack*
21	1154	coronary syndrome*
22	155	crescendo
23	174982	explode "Clinical-Trials"/ all subheadings
24	51540	(clin* near trial*) in ti ab
25	54877	((singl* or doubl* or trebl* or tripl*) near (blind* or mask*)) in ti ab
26	564	Placebos
27	58244	placebo* in ti ab
28	42369	random in ti ab
29	42725	"randomized-controlled-trial"/ all subheadings
30	4134	#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	82173	#16 or #17 or #18 or #19 or #20 or #21 or #22
32	295390	#23 or #24 or #25 or #26 or #27 or #28 or #29
33	574	#30 and #31 and #32
34	28572	explode "animal"/ all subheadings
35	3438241	explode "human"/ all subheadings
36	23537	#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 Version.

Search Strategy for Licensed Glycoprotein Antagonists (searched 19/02/00)
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 trial studies relating to unstable angina.

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

No.	Records	Request
1	1252	"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	2144	((gp* or glycoprotein*) near (iib* near iiia*)) or GPIIB*
10	246	integrin* near (iib* near iiia*)
11	3015	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
12	24547	explode "Angina-Pectoris"/ all subheadings
13	33440	angina
14	77507	explode "Myocardial-Infarction"/ all subheadings
15	90173	myocard* infarct*
16	1132	heart attack*
17	1047	coronary syndrome*
18	202	crescendo
19	114387	#12 or #13 or #14 or #15 or #16 or #17 or #18
20	482	#11 and #19
21	16712	cost effect*
22	19914	cost benefit*
23	923	economic evaluation*
24	2613	technology assessment*
25	475	pharmacoeconomic*
26	366	cost util*
27	156887	explode "Economics"/ all subheadings
28	168135	#21 or #22 or #23 or #24 or #25 or #26 or #27

* 29 29 #20 and #28

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

No.	Records	Request
1	1252	"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	2144	((gp* or glycoprotein*) near (iib* near iiia*)) or GPIIB*
10	246	integrin* near (iib* near iiia*)
11	3015	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
12	24547	explode "Angina-Pectoris"/ all subheadings
13	33440	angina
14	77507	explode "Myocardial-Infarction"/ all subheadings
15	90173	myocard* infarct*
16	1132	heart attack*
17	1047	coronary syndrome*
18	202	crescendo
19	114387	#12 or #13 or #14 or #15 or #16 or #17 or #18
20	482	#11 and #19
21	80314	explode "Clinical-Trials"/ all subheadings
22	53706	(clin* near trial*) in ti ab
23	56340	((singl* or doubl* or treble* or tripl*) near (blind* or mask*)) in ti ab
24	19407	"Placebos"/ all subheadings
25	180594	random* in ti ab
26	58647	placebo* in ti ab
27	310381	#21 or #22 or #23 or #24 or #25 or #26
* 28	230	#20 and #27

Search Strategy for Unlicensed Glycoprotein Antagonists (searched 05/04/00)
After it was decided that the review should include unlicensed Glycoprotein Antagonists a second set of searches were conducted. This search strategy was designed to exclude all papers already retrieved and yielded no extra hits.

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

No.	Records	Request
1	1347	"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	2215	((gp* or glycoprotein*) near (iib* near iiia*)) or GPIIB*
10	250	integrin* near (iib* near iiia*)
11	3155	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
12	24766	explode "Angina-Pectoris"/ all subheadings
13	33794	angina
14	78253	explode "Myocardial-Infarction"/ all subheadings
15	91184	myocard* infarct*
16	1142	heart attack*
17	1136	coronary syndrome*
18	204	crescendo
19	115672	#12 or #13 or #14 or #15 or #16 or #17 or #18
20	533	#11 and #19
21	17212	cost effect*
22	20415	cost benefit*
23	966	economic evaluation*
24	2681	technology assessment*
25	499	pharmacoeconomic*
26	382	cost util*
27	159145	explode "Economics"/ all subheadings
28	170713	#21 or #22 or #23 or #24 or #25 or #26 or #27
29	34	#20 and #28
30	106636	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 trial studies was as follows:

SilverPlatterASCII 3.0WINNSelected Databases
"Platelet-Glycoprotein-GPIIb-IIIa-Complex"/ all subheadings
abciximab*
reopro*
aggrastat*
eptifibatide*
intrifiban*
integrelin*
tirofiban*
(gp* or glycoprotein*) near (iib* near iiia*)
integrin* near (iib* near iiia*)
#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
explode "Angina-Pectoris"/ all subheadings
angina
explode "Myocardial-Infarction"/ all subheadings
myocard* infarct*
heart attack*
coronary syndrome*
crescendo
#12 or #13 or #14 or #15 or #16 or #17 or #18
#11 and #19
explode "Clinical-Trials"/ all subheadings
(clin* near trial*) in ti ab
((singl* or doubl* or treble* or tripl*) near (blind* or mask*)) in ti ab
"Placebos"/ all subheadings
random* in ti ab
placebo* in ti ab
#21 or #22 or #23 or #24 or #25 or #26
#20 and #27
ud>200001
#29 and #28
lamifiban or ro 44-9883
sibrafiban or xubix or ro 44-3888 or ro 48 3657
fradafiban or bibu
lefradafiban
xemilofiban or sc-54701A or sc-54684A
orbofiban or sc-57099b
#31 or #32 or #33 or #34 or #35 or #36
#19 and #27 and #37
#38 not #28

4**. National Research Register CD-ROM (searched 19.1.00)**

NRR Issue 1:2000 was searched with the following strategies.

Search Strategy for Licensed Glycoprotein Antagonists (searched 19/02/00)
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 05/04/00)
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 extra 26 hits. The numerical drug identities are excluded from the search strategy are excluded since all numbers are ignored by the NRR 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)

Appendix 3: Assessment of internal validity tool

Internal validity					
Study					
Selection of prognostic ally homogenous study population					
Pre-stratification on prognostic ally 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 bear on 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 confidence intervals (or dispersion)					
The statistical methods					
The way missing values were dealt with					
Intention to treat analysis					
Distributions of baseline characteristics					
The way any imbalances in prognostic variables were accounted for					

Appendix 4: Included and excluded studies

INCLUDED

1. Neumann, F. J., A. Kastrati, et al. (2000). Effect of glycoprotein IIb/IIIa receptor blockade with abciximab on clinical and angiographic restenosis rate after the placement of coronary stents following acute myocardial infarction. *J Am Coll Cardiol* 35(4): 915-21.

2. Anonymous. (1997). Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis-II. *Lancet* 349: 1422-8.

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

4. Anonymous. (1997). PURSUIT (Platelet IIb/IIIa in unstable angina: Receptor suppression using Integrelin(TM) therapy). *Clin Cardiol* 20(11): 967.

5. Anonymous. (1997). Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE Study. *Lancet* 349: 1429-35.

6. Bazzino, O., C. Barrero, et al. (1998). Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. *N Engl J Med* 338(21): 1488-1497.

7. Brener, S. J., L. A. Barr, et al. (1998). Randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. *Circulation* 98(8): 734-741.

8. Ronner, E., H. A. M. Van Kesteren, et al. (2000). Safety and efficacy of eptifibatide vs placebo in patients receiving thrombolytic therapy with streptokinase for acute myocardial infarction: A phase II dose escalation, randomized, double-blind study. *Eur Heart J* 21(18): 1530-1536.

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

10. Cannon, C. P., W. S. Weintraub, et al. (1998). Invasive versus conservative strategies in unstable angina and non-Q- wave myocardial infarction following treatment with tirofiban: Rationale and study design of the international TACTICS-TIMI 18 trial. *Am J Cardiol* 82(6): 731-736.

11. Gibson, C. M., M. Goel, et al. (1998). Six-month angiographic and clinical follow-up of patients prospectively randomized to receive either tirofiban or placebo during angioplasty in the RESTORE trial. Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis. *J Am Coll Cardiol* 32(1): 28-34.

12. Harrington, R. A. (1997). “Design and methodology of the PURSUIT trial: Evaluating eptifibatide for acute ischemic coronary syndromes.” AM J CARDIOL. American Journal of Cardiology 80(4): 34b-38b.

13. Hanrath, P., J. Vom Dahl, et al. (1997). Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. *Circulation* 96(5): 1445-1453.

14. Harrington, R. A., N. S. Kleiman, et al. (1995). Immediate and reversible platelet inhibition after intravenous administration of a peptide glycoprotein IIb/IIIa inhibitor during percutaneous coronary intervention. *Am J Cardiol* 76(17): 1222-1227.

15. Lincoff, A. M., J. E. Tcheng, et al. (1999). Sustained suppression of ischemic complications of coronary intervention by platelet GP IIb/IIIa blockade with abciximab. One-year outcome in the EPILOG trial. *Circulation* 99(15): 1951-1958.

16. Mahaffey, K. W., R. A. Harrington, et al. (1999). Stroke in patients with acute coronary syndromes: Incidence and outcomes in the platelet glycoprotein IIb/IIIa in unstable angina: Receptor suppression using integrilin therapy (PURSUIT) trial. *Circulation* 99(18): 2371-2377.

17. Schulman, S. P., P. J. Goldschmidt Clermont, et al. (1996). Effects of integrelin, a platelet glycoprotein IIb/IIIa receptor antagonist, in unstable angina. A randomized multicenter trial. *Circulation* 94(9): 2083-9.

18. Topol, E. J., R. M. Califf, et al. (1994). Randomised trial of coronary intervention with antibody against platelet IIb/IIIa integrin for reduction of clinical restenosis: results at six months. The EPIC Investigators. *Lancet* 343(8902): 881-6.

19. Topol, E. J., J. J. Ferguson, et al. (1997). Long-term protection from myocardial ischemic events in a randomized trial of brief integrin beta3 blockade with percutaneous coronary intervention. EPIC Investigator Group. Evaluation of Platelet IIb/IIIa Inhibition for Prevention of Ischemic Complication. *JAMA* 278(6): 479-84.

20. Montalescot, G., P. Barragan, et al. (2001). Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Engl J Med* 344(25): 1895-903.

21. O'Shea, J. C., G. E. Hafley, et al. (2001). Platelet glycoprotein IIb/IIIa integrin blockade with eptifibatide in coronary stent intervention: the ESPRIT trial: a randomized controlled trial. *JAMA* 285(19): 2468-73.

22. Topol, E. J., D. J. Moliterno, et al. (2001). Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. *N Engl J Med* 344(25): 1888-94.

23. Topol, E. J., A. M. Lincoff, et al. (1998). Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. *Lancet* 352(9122): 87-92.

24. Anonymous (1994). Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. The EPIC Investigation. *N Engl J Med* 330(14): 956-61.

25. Ohman, E. M., N. S. Kleiman, et al. (1997). Combined accelerated tissue-plasminogen activator and platelet glycoprotein IIb/IIIa integrin receptor blockade with Integrilin in acute myocardial infarction. Results of a randomized, placebo-controlled, dose-ranging trial. IMPACT-AMI Investigators. *Circulation* 95(4): 846-54.

26. Lam, W., J. B. Gill, et al. (2001). Comparative 30-day economic and clinical outcomes of platelet glycoprotein IIb/IIIa inhibitor use during elective percutaneous coronary intervention: Prairie ReoPro Versus Integrilin Cost Evaluation (PRICE) trial. *AM HEART J* 141(3): 402-409.

27. Topol, E. J. (2001). Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: The GUSTO V randomised trial. *Lancet* 357(9272): 1905-1914.

28. Simoons, M. L. (2001). Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularisation: The GUSTO IV-ACS randomised trial. *Lancet*. 357(9272): 1915-1924.

29. Antman, E. M., C. M. Gibson, et al. (2000). Combination reperfusion therapy with abciximab and reduced dose reteplase: Results from TIMI 14. EUR HEART J. *European Heart Journal* 21(23): 1944-1953.

30. Anonymous (1997). Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. The EPILOG Investigators. *N Engl J Med* 336(24): 1689-96.

31. Van de Werf, F., P. W. Armstrong, et al. (2001). Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. *Lancet* 358(9282): 605-13.

32. Ellis, S. G., M. B. Effron, et al. (1999). Acute platelet inhibition with abciximab does not reduce in-stent restenosis (ERASER study). *Circulation* 100(8): 799-806.

33. Galassi, A. R., G. Russo, et al. (1999). Usefulness of platelet glycoprotein IIb/IIIa inhibitors in coronary stenting for reconstruction of complex lesions: procedural and 30 day outcome. *Cardiologia* 44(7): 639-45.

34. Reed, S. O., C. D. Mullins, et al. (2000). Cost effectiveness of abciximab during routine medical practice. *Pharmacoeconomics* 18(3): 265-274.

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Appendix 5: Outcomes for high-risk groups: Medical management indication

Heeschen et al (1999): *PRISM* Sub Group Analysis by Troponin-I status

Study Details

Study (Author, Year)		Number subjects enrolled (total and high risk)	*Number subjects lost to follow up*	Median age *range, and standard deviation*	Prognosis indicators n (%) & standard deviation for continuous variables, e.g. blood pressure, heart rate						
					History of MI	History of PCI	History of CABG	History of CHF	Hyper-tension	Hypercol-esterolaemia	Diabetes
Heeschen, 1999	Troponin-I positive	629	Not stated	62.5 (11.1)	274 (43.5%)	58 (9.3%)	96 (15.2%)	78 (12.4%)	320(50.9 %)	281 (44.6%)	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*)

Study (author, year)		Selected anti-anginal medication before randomisation (%)		Selected anti-anginal medication after randomisation (%)	
		Aspirin	Heparin	Aspirin	Heparin
Heeschen, 1999	Troponin-I positive	592 (94.1%)	155 (24.7%)	608 (96.6%)	Not stated
	Troponin-I negative	1509 (94.7%)	336 (21.1%)	1537 (96.5%)	Not stated

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

Study (Author, Year)		Time Point	Acute Myocardial Infarction n (%)		Severe Recurrent Angina/Refractory Ischaemia n (%)		Death n (%)		Measurement of Quality of Life n (%)	Composite Outcome (Death, MI), n (%)		Other
			Troponin-I positive	Troponin-I negative	Troponin-I positive	Troponin-I negative	Troponin-I positive	Troponin-I negative		Troponin-I positive	Troponin-I negative	
Heeschen, 1999	**Arm 1: tirofiban (n = 1097)**	**48 hours** **7 days** **30 days**	1 (0.3) 4 (1.3) 8 (2.6)	4 (0.5) 17 (2.1) 27 (3.6)	10 (3.3) 26 (8.5) 31 (10.2)	17 (2.1) 59 (7.4) 72 (9.1)	0 2 (0.7) 5 (1.6)	3 (0.4) 7 (0.9) 18 (2.3)		1 (0.3) 6 (2.0) 13 (4.3)	7 (0.9) 24 (3.0) 45 (5.7)	
	Control: heparin (n = 1125)	**48 hours** **7 days** **30 days**	9 (2.8) 18 (5.6) 22 (6.8)	5 (0.6) 14 (1.8) 21 (2.6)	30 (9.3) 47 (14.5) 48 (14.8)	24 (3.05) 53 (6.6) 60 (7.5)	2 (0.6) 12 (3.7) 20 (6.2)	0 3 (0.4) 18 (2.3)		11 (3.4) 30 (9.3) 42 (13.0)	5 (0.6) 18 (2.2) 39 (4.9)	

Theroux et al, 2000: Subgroup analysis on diabetic patients in PRISM-PLUS

Study Details

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

Characteristics of participants

Study (Author, year)		Number subjects enrolled (total and high risk)		Number subjects lost to follow up		Mean age *range, and standard deviation*		Prognosis indicators (%) and standard deviation 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
Theroux et al, 2000	Arm 1: Tirofiban + Heparin	169	604	Not stated. Only patients from 2 of the treatment arms included in sub-study		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

Study (Author, year)		Selected anti anginal medication** before enrolment (%)				Selected anti-anginal medication* after enrolment n (%)
		Nitrates	B-blocker	Channel calcium blocker	Insulin	
Theroux et al, 2000	**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- Not stated for sub-group
	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; enoxaprin;daltrepin)**

Outcomes: Results (for diabetic patients only)

Study (Author, year)	Time point	MI/Death (%)	Severe recurrent angina/Refractory Ischaemia (%)	Death (%)	Measurement of Quality of Life (%)	Composite Outcome (%)
Theroux et al, 2000	48-hours 7-days 30-days 6-months	0 1.2 4.7 11.2	- - - -	- - - -	- - - -	7.7 14.8 20.1 32.0
	48-hours 7-days 30-days 6-months	3.1 9.3 15.5 19.2	- - - -	- - - -	- - - -	8.3 21.8 29.0 39.9

Adverse Effects (specify separately for high risk patients)

Study (Author, year)		TIMI major bleeding (%)		TIMI minor bleeding (%)		All TIMI bleeding (%)		Other Adverse Effects Requiring Treatment
				DM	No DM	DM	No DM	
Theroux et al, 2000	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	

Boersama et al (2000): Sub-groups analysis on PURSUIT

Study Details

Study (Author, year)	Study design; *any subgroup analyses?*	Definition of High Risk Group *(if any)*	Inclusion Criteria	Interventions (specified by protocol)	Follow up duration
Boersma et al, 2000	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 min) and had either transient ST-segment elevation (>0.5mm), transient or persistent ST-segment depression (>0.5mm), T-wave inversion (>1.0mm), or elevation of creatine kinase-MB fraction above the upper limit of normal (ULN). Exclusion: Persistent (>30 min) ST-segment elevation. For full inclusion criteria see PUSUIT.	see PURSUIT.	30-days

Characteristics of participants (specify separately for high risk patients)

Study (Author, year)		Number subjects enrolled (total and high risk)	Number subjects lost to follow up	Median age *range, and standard deviation*	Prognosis indicators n (%) and standard deviation for continuous variables e.g. blood pressure, heart rate
Boersma et al, 2000	Arm 1: Eptifibatide	See PURSUIT for full demographic data			
	Arm 2: Placebo				

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

Study (Author, year)		Selected anti anginal medication** before enrolment n (%)	Selected anti-anginal medication* after enrolment n (%)
Boersma et al, 2000	Arm 1: Eptifibatide	See PURSUIT for data	
	Arm 2: Placebo		

Outcomes: Definitions and measures

Study (Author, year)	Acute myocardial infarction	Death	Composite Outcome
Boersma et al, 2000	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 ULN. For patients undergoing PCI or CABG; CK-MB elevation above 3 or 5 times the ULN.	See PURSUIT for definition.	Death and MI at 30 days.

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

Study (Author, year)	*High risk or all?*	Death		Composite Outcome	
		Rate %	OR (95% CI)	Rate %	OR (95% CI)
Boersma et al, 2000	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

Study (Author, year)	*High risk or all?*	Death OR (95% CI)	Composite Outcome OR (95% CI)
Boersma et al, 2001	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

*** Selected anti-anginal drugs to be considered: anti-platelet agents (aspirin,ticlodipine, clopidogrel); anticoagulants (unfractionated heparin; low molecular weight heparin; enoxaprin;daltrepin)**

Hasdai et al: Sub-group analysis on PURSUIT

Study Details

Study (Author, year)	**Study design;** *any* ***subgroup analyses?***	Definition of High Risk Group *(if any)*	**Inclusion Criteria/Exclusion criteria**	**Interventions (specified by protocol)**	**Follow up duration**
Hasdai et al, 2000	Study looking at impact of age on clinical outcomes of patients in PURSUIT trial.	-	See PURSUIT	Eptifibatide 'v' placebo	30-days

Characteristics of participants

Study (Author, year)		**Number subjects enrolled (total and high risk)**	**Number subjects lost to follow up**	**Prognosis indicators - n (%)**						
				Current smoker	Previous MI	History of CAD	History of CHF	History of hypertension	History of diabetes	Prior CABG
Hasdai et al, 2000	**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 (29%)	395 (16%)	1466 (61%)	692 (29%)	347 (14%)
	Age ≥ 80	506	Not stated	32 (6%)	198 (40%)	88 (18%)	106 (21%)	314 (62%)	123 (24%)	53 (10%)

Other medication

Study (Author, year)		**Selected anti anginal medication** before enrolment (%)**	**Selected anti-anginal medication* after enrolment n (%)**
Hasdai et al, 2000		See PURSUIT	See PURSUIT

*** Selected anti-anginal drugs to be considered: anti-platelet agents (aspirin,ticlodipine, clopidogrel); anticoagulants (unfractionated heparin; low molecular weight heparin; enoxaprin;daltrepin)**

Outcomes: Definitions and measures

Study (Author, year)		Time point	Death – n(%)		MI – n(%)		Death or MI – n(%)		Bleeding	
			Eptifibatide	Placebo	Eptifibatide	Placebo	Eptifibatide	Placebo	Eptifibatide	Placebo
Hasdai et al, 2000	**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)

Appendix 6: Validity assessment tool for economic evaluations

Validity Assessment

	Study						
1	**Well defined question**						
2	**Comprehensive description of alternatives**						
3	**Effectiveness established**						
4	**All important and relevant costs and consequences for each alternative identified**						
5	**Costs and consequences measured accurately**						
6	**Costs and consequences valued credibly**						
7	**Costs and consequences adjusted for differential timing**						
8	**Incremental analysis of costs and consequences**						
9	**Sensitivity analyses to allow for uncertainty in estimates of cost or consequences**						
10	**Study results/discussion include all 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.

McElwee (1997)

What question(s) does the study address	Country/Currency	Comparator(s)	Study population	Sub-group 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's 'v' placebo.	Unstable angina patients with non-Q wave MI	Patients with Unstable angina compared with those that 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 acute MI 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 acute MI (non-fatal) estimated from regression analysis of IMPACT II and other sources (?)	-	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 YLS) at treatment effects of 30 and 40% and in the range considered acceptable. (≤$50,000 per YLS) at treatment effect of 20%. Primary therapy is wise in unstable angina patients, compared with treating only patients who undergo PCI.

Hillegass.WB (1999)

What question(s) does the study	Country/Currency	Comparator (s)	Study population	Sub-group analysis	Length of follow up

address?					
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 'v' 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	Non 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 will likely 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.

Bell.DM (1999)

What question(s) does the study address?	Country/ Currency	Comparator(s)	Study population	Sub-group 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	None reported	30 days

			North American cohort.		

Methods/type of study	Effectiveness data	Cost data	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 absolute RR and wholesale costs. 95% CI used for max and min 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

Szuchs.TD (1999)

What question(s) does the study address?	Country/ Currency	Comparator (s)	Study population	Sub-group 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. CHf (Swiss) European Currency at a rate of 1 ECU to CHF 1.64	Tirofiban plus heparin plus aspirin 'v' heparin plus aspirin	100 patients with acute unstable angina pectoris and/or non-Q 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 unstable angina pectoris and/or non-Q wave MI.	Clinical efficacy data from PRISM-PLUS. Unstable angina defined as prolonged repetitive angina at rest with 12hr prior to randomisation and ECG evidence of ischaemia or elevated cardiac enzymes	Costs of managing ischemic complications based on typical practice patterns in Swiss hospitals. Revas from secondary sources.	-	Univariate sensitivity analyses performed: Unit cost resource +/- 50%, threshold analysis for drug costs, 95% CI for RD reported in PRISM-	Tirofiban is cost saving in ACS and improves the economics of managing these patients during initial hospitalisation. Tirofiban saved CHF 549 per patient.

				PLUS	

Mark.DB (2000)

What question(s) does the study address?	Country/ Currency	Comparator (s)	Study population	Sub-group 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.	-	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 c/e 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 endpoint 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 endpoint 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 addition of eptifibatide to standard care for non-ST elevation ACS patients is economically attractive by conventional standards.

Schering-Plough

What question(s) does the study address?	Country/ Currency	Comparator(s)	Study population	Sub-group analysis	Length of follow up
The cost effectiveness of Eptifibatide for patients with coronary artery disease undergoing planned, elective PCI with stenting.	Focus on Western European patients in multi-national trial. Costs reported in UK pounds.	Eptifibatide Placebo	2,000 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	PURSUIT trial: Western	PURSUIT trial. Costs reported for	6-month survival and 30 day non-	Sensitivity analysis	Cost per YOLG for eptifibatide

controlled.	European patients increase in life expectancy data.	UK and all Western European patients. Hospital rates from 3 cardiovascular centres (UK), hospital admin costs from accounting system, procedures based on actual consumables and equipment, PTCA & CABG costs from Mckenna (1997), MRI costs from charge data, stroke follow up costs from PSSRU & HRG and drug costs from the BNF.	fatal MIs modelled to estimate life expectancy. 4 models developed by Mark (2000) integrated to obtain survival estimates. Life expectancy estimated using follow-up data from DUKE database.	conducted on unit costs, discount rate and resource use.	versus placebo in UK patients, at all 3 discount rates Eptifibatide dominates. Using all Western European data. No discounting £8,179, 1.5% = £9,749, 3% = 11,079 per YOLG

Merck Sharp and Dohme

What question(s) does the study address?	Country/ Currency	Comparator(s)	Study population	Sub-group analysis	Length of follow up
Cost efficacy analysis of tirofiban as compared to placebo in patients with unstable angina or non-Q wave MI.	UK Pounds. Effect data taken from US trial.	Tirofiban + heparin 'v' Heparin	PRISM-PLUS patients. Unstable angina and non-Q wave MI.	None reported	180 days for primary C/E analysis. 7 days for secondary C/E 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 1,046 UK patients in PRAIS-UK. Case mix data used to assign	Not used	95% CI provided for effects, costs and ICER's.	ICER of tirofiban over placebo for 7-day timeframe = £8,760. ICER for 180-day time frame = £9,955

		costs.			

Appendix 8: Economic evaluations of glycoproteins used alongside PCI.

Dunn & Foster (1999)

What question(s) does the study address	Country/ Currency	Comparator(s)	Study population	Sub-group 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, which projected 10-year survival for those surviving initial period.	As individual trials. Descriptions not clear.	Abciximab was cost saving in patients with unstable angina, and other less high-risk groups.

Mark.DB (1996)

What question(s) does the study address	Country/ Currency	Comparator(s)	Study population	Sub-group 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 ischemic events and increased bleeding rates. Cost minimisation analysis	EPIC trial	Hospital charges converted to costs- charge to cost ratios from Medicare cost report of hospital.	-	Standard deviations 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 net cost of £25, with bleeding included.

Van Hout (1995)

What question(s) does the study	Country/	Comparator(s)	Study population	Sub-group analysis	Length of follow up

does the study address	Currency		population	analysis	follow up
The cost effectiveness of abciximab in high-risk patients undergoing PCI.	Netherlands DFL, 1995	Abciximab bolus and 12h infusion. Abciximab bolus and placebo infusion. Placebo bolus and placebo infusion.	2099 patients enrolled in EPIC.	Results for UA or MI patients reported, also for different weight sub-groups.	EPIC looked at outcomes after 30 days, and then after 6-months 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 US.	Taken from Dutch patients in HELVETIC A 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 (1998)

What question(s) does the study address	Country/ Currency	Comparator(s)	Study population	Sub-group 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 hr 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 acute MI or high risk coronary morphologic characteristics	Unstable angina sub-group 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 endpoint: 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 (1995)	Probabilistic sensitivity analysis. Uncertainties in CE 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%.

Anderson (1999)

What question(s) does the study address	Country/ Currency	Comparator(s)	Study population	Sub-group analysis	Length of follow up
Review of two study designs, for trials with abciximab.	USA US Dollars	Placebo bolus followed by 12 hr placebo infusion, abciximab bolus followed by 12-hr placebo infusion, abciximab bolus followed by 12-hr abciximab infusion.	Patients in EPIC trial	Subset of patients with unstable angina. Separate costs/outcomes reported.	See EPIC
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	Not undertaken	Standard deviations reported.	Abciximab appears to be particularly cost

		and subsequent treatment in study. Cost to charge ratios calculated from Medicare Cost reports.			effective in unstable angina patients undergoing PTCA.

Sacristan (1996)

What question(s) does the study address	Country/ Currency	Comparator(s)	Study population	Sub-group analysis	Length of follow up
The cost effectiveness of abciximab compared to standard therapy in high-risk patients undergoing PCI.	Spanish cost data- Pesetas	Abciximab. Standard care: Heparin + Aspirin.	Patients enrolled in EPIC trial. High-risk patients scheduled for PCI or directional atherectomy.	Sub-group of patients with MI and UA. Effectiveness data and cost effectiveness results reported separately. UA 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 NHS perspective used. Additional cost for each patient who did not have ischaemic complications or need to repeat PCI, CABG or both, calculated	EPIC	Published Spanish data.	-	Sensitivity analysis performed on cost of ischaemic complications and revascularization.	Incremental cost effectiveness of abciximab compared with standard therapy was $5804 for each patient without ischaemic complications or repeat RP at 6-months post PTCA.

Zed (1998)

What question(s) does the study address	Country/ Currency	Comparator(s)	Study population	Sub-group 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 mins prior to PTCA followed by abciximab infusion 12 hours after 'v' 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 RV 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 VHHSC.	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 $29700 Cost per event free patient.

Goklaney (1998)

What question(s) does the study address	Country/ Currency	Comparator(s)	Study population	Sub-group analysis	Length of follow up
Review of the economic evidence of abciximab during PCI	US Dollars	Abciximab Standard therapy	As in three trials	None reported	As in three 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	No stated	Not undertaken	95% CI on EPIC cost difference.	Evidence shows cost savings in high risk groups

Lorenzoni (1999)*

What question(s) does the study address	Country/ Currency	Comparator(s)	Study population	Sub-group analysis	Length of follow up
-	Italian Lira		As described in 3 trials	None reported	As in 3 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 DRG's	-	Not reported	ICER 34.3 mill lire per event prevented. Cost of a life year saved 32.3 mill lire.

Hillegass (1999)

What question(s) does the study address	Country/	Comparator(s)	Study population	Sub-group analysis	Length of follow up

	Currency				
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	Analysis of uncertainty	Methods of extrapolation	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.

McGregor (1999)

What question(s) does the study address	Country/ Currency	Comparator (s)	Study population	Sub-group 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 + acute MI, EPILOG: MI or unstable angina, CAPTURE: Refractory unstable angina. Combined study had more patients with UA and evolving MI, than stable angina	None reported	As in 4 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 and RAPPORT trials.	Personal communication, S.Grover. Costs for a Vancover hospital from Zed (1998)	Not undertaken	One way sensitivity analysis on MI and revascularisation rate, gives range $C15,500-$C56,600. Monte Carlo on same inputs, gives range $C12,000-$C91,000	Costs of preventing one MI at time of PCI with abciximab in high risk populations is $44,073. When MI and revascularisation taken together cost = $26,933.

Bell (1999)

What question(s) does the study address	Country/ Currency	Comparator(s)	Study population	Sub-group analysis	Length of follow up
Comparison of acquisition costs and outcomes of	US Dollars	Abciximab, Eptifibatide	As in trials	None reported	As in trials

GPAs in patients undergoing PCI.	Dollars	Eptifibatide Tirofiban			

Methods/type of study	Source of effectiveness data	Source of cost data	Methods of extrapolation	Analysis of uncertainty	Main conclusions
Retrospective review Number needed to treat 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

Mark.DB (2000)[2]

What question(s) does the study address	Country/ Currency	Comparator(s)	Study population	Sub-group 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 'v' 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 wholesale 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 endpoint, definition of primary endpoint, need to account for end-point MI size) subjected to sensitivity analysis. Discount rates, incremental costs and health state values also varied.	Incremental cost effectiveness ratio for Eptifibatide versus placebo was $16,491 per year of life saved. ICER not calculated for 6 months trial data, authors felt study not powered to detect difference in life expectancy.

Topol.EJ (1999)

What question(s) does the study address	Country/	Comparator(s)	Study population	Sub-group analysis	Length of follow up

[2] Mark et al, 2000 featured in both McDonagh et al and Fischer et al reviews, table refers to data extracted in Fischer et al.

the study address	Currency		population		follow up
Outcomes for potent antiplatelet therapy at the time of stenting.	US Dollars.	Abciximab+ stenting Stenting + placebo PCI + abciximab	EPISTENT : Patients about the 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 US cost data and overall survival data from the trial. Societal perspective used. Cost per additional life year saved calculated.	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, 1995,2000)	Sensitivity analysis not reported.	Compared with stent + placebo, stent + abciximab had C?E ratio of $6213 per added life year. Compared with PCI + abciximab, stent + abciximab had a C?E ratio of $5291 per added life year.

Weintraub.WS (1999)

What question(s) does the study address	Country/ Currency	Comparator(s)	Study population	Sub-group 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 'v' 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.

Aristides (1998)

What question(s) does the study address	Country/ Currency	Comparator(s)	Study population	Sub-group 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 six 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 endpoint 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% CI's. Eliminating survival benefit for single vessel disease patients and halving the number of event free years gained analysed in sensitivity analysis.	Cost per additional life year gained = $5547 and cost per additional year event free = $4285.

Reed (2000)

What question(s) does the study address	Country/ Currency	Comparator(s)	Study population	Sub-group 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 'V' no abciximab	Patients at high risk for ischaemic events. Including patients who underwent a PCI.	Numbers of unstable/stable angina, Post MI angina and acute MI 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,	Non random matched cohort study	Hospital billing data. Cost to charge ratio used	-	Confidence ellipses using Fiellers theorem, used to	Abciximab patients had an ICER of $21,789- 95% CI= -infinity to -

diabetes mellitus and stenting). Third party payer perspective. Variability in results presented as ellipses.				assess variability in results.	$115,461 and $391 to +infinity.

Weintraub (2000)

What question(s) does the study address	Country/ Currency	Comparator(s)	Study population	Sub-group 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's 'v' no GP IIb/IIIa's.	4962 patients at Emory University Hospitals, Atlanta. All underwent coronary intervention procedures. Study included patients having procedures for UA.	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 21535 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.

Hermiller & Kereiakes (1999)

What question(s) does the study address	Country/ Currency	Comparator(s)	Study population	Sub-group analysis	Length of follow up

Review to determine how cost effective is GP IIb/IIIa receptor blockade in comparison with other frequently used accepted therapeutic modalities.	US Dollars	As in trials	Patients from EPIC, EPILOG and CAPTURE trials.	Subgroup analysis of EPIC UA population described	As in trials.

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 trails	-	-	Overall the available data suggest that the clinical benefit of abciximab is worth the net increment in the cost of therapy.

Kereiakes et al, 1999

What question did the study address	Country/ Currency	Comparators	Study population	Sub-group 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 'v' 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% confidence intervals.	Cost per life year gained for adjunctive abciximab during PCI ranged from 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 Rijkon & Van-Hout, 2001

What question did the study address?	Country/ Currency	Comparators	Study population	Sub-group 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 US. Dutch cost data. Costs expressed in 1998 Euros.	As in EPISTENT	ACS patients undergoing PTCA. Also looks at a sub-group of diabetic patients.	Diabetic patients	30-days

Methods/ type of study	**Source of effectiveness data**	**Source of cost data**	**Methods of extra-polation**	**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 BENEST ENT II trial.	-	Confidence ellipses and 95% confidence intervals for incremental ratios presented. Results for diabetic patients appeared to be more uncertain.	*ICER adding abciximab*: All patients (MI free survival) = 12876, All patients (MACE-free survivor) = 14198, Diabetic patients (MI-free survival) = 3695, Diabetic patients (MACE-free survival) = 2167 *ICER adding stents:* All patients (MI-free survival) = 39463, All patients (MACE-free survival) = 12228, Diabetic patients (MI-free survival) = 33219, Diabetic patients (MACE-free survival) = 8040.

MACE = Major adverse cardiac events

PRICE, 2000

What question did the study address?	**Country/ Currency**	**Comparators**	**Study population**	**Sub-group analysis**	**Length of follow up**
-	US dollars	Abciximab 'v' 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 trial	Patient specific resource use. Costs collected from participating hospitals in PRICE trial.	-	Bootstrapping to give 95% confidence intervals 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 Submission, 2000

What question did the study address?	Country/ Currency	Comparators	Study population	Sub-group analysis	Length of follow up
Cost effectiveness of ReoPro (abciximab) in a UK setting.	UK	Abciximab + aspirin + heparin 'v' aspirin + heparin	As in 3 trials	UA sub-group 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 life year gained 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 life year gained using EPIC = £12,421, EPILOG = £6,247, EPISTENT = £3,554. Cost per QALY (basecase): EPILOG =£7,808, EPISTENT = £4,443. Cost-effectiveness may be enhanced in US sub-group.

Appendix 9: Company submissions

Manufacturers & Drug	Relevant trial evidence included in review	Relevant economics evidence included in the review	Additional evidence
Merck, Sharp & Dolme	TACTICS-TIMI, TARGET, RESTORE, PRISM, PRISM-PLUS, GUSTO-IV.	-	ACUTE II (Not published),
Schering Plough	ESPRIT (including 12-month data)	-	
El Lilly	EPISTENT, GUSTO – IV, TARGET, ASSENT III, ESPRIT, TACTICS-TIMI, GUSTO V, TARGET, ESPRIT, EPIC, RAPPORT, ISAR II, ADMIRAL, CAPTURE.	Kereiakes et al, 2000, Zwart-van-Rijkan et al, 2001, Lincoff et al, 2000, PRICE, 2000.	-

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