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Abciximab

An Updated Review of its Therapeutic Use in Patients with Ischaemic Heart Disease Undergoing Percutaneous Coronary Revascularisation

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Data Selection

Sources: Medical literature published in any language since October 1998 on abciximab, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: Medline search terms were 'abciximab' or 'C7E3'. EMBASE search terms were 'abciximab'. AdisBase search terms were 'abciximab' or 'C7E3'. Searches were last updated 11 April 2003.

Selection: Studies in patients with ischaemic heart disease who received abciximab. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Abciximab, percutaneous coronary revascularisation, angioplasty, ischaemic heart disorders, unstable angina pectoris, myocardial infarction, pharmacodynamics, therapeutic use, tolerability, pharmacoeconomics.

Contents

Summary

Abstract

Abciximab (Reopro®) is an antibody fragment that dose-dependently inhibits platelet aggregation and leucocyte adhesion by binding to the glycoprotein (GP) IIb/IIIa, vitronectin and Mac-1 receptors.

Abciximab (0.25 mg/kg bolus plus infusion of 0.125 μg/kg/min for 12 hours) showed greater efficacy than tirofiban in reducing the 30-day composite endpoint of death, nonfatal myocardial infarction (MI) or urgent target-vessel revascularisation in the randomised, double-blind TARGET study in patients scheduled for stent placement. In addition, the beneficial effects of treatment with abciximab previously observed in the randomised, multicentre, placebo-controlled EPILOG and EPISTENT studies have been maintained to 1 year, with a significantly reduced incidence of ischaemic complications relative to placebo consistently observed across a range of subgroups including age, sex, bodyweight and indication for revascularisation.

The incidence of the composite endpoint was reduced in patients presenting with acute MI of <48 hours' duration in comparison with either fibrinolytic therapy or stenting alone in the randomised STOPAMI and ADMIRAL trials, primarily because of a reduced requirement for urgent repeat revascularisation and reduced incidence of mortality. In the randomised, nonblind, multicentre CADILLAC trial in patients with acute myocardial infarction (MI), stenting alone was superior to percutaneous transluminal coronary angioplasty (PTCA) and stenting alone was not inferior to PTCA plus abciximab.

Recent large randomised, multicentre studies (ASSENT-3 and GUSTO-V) have shown higher efficacy (on various ischaemic endpoints) of abciximab in combination with either a reduced dose of tenecteplase or reteplase compared with the fibrinolytic drug alone. TIMI grade 3 flow rates at 60 and 90 minutes in the TIMI-14 and SPEED trials were higher in patients who received abciximab in combination with either alteplase or reteplase than abciximab alone and were similar to that seen with the full-dose fibrinolytic alone.

In the randomised, multicentre GUSTO IV-ACS study, no significant differences in any of the ischaemic endpoints at either 7 or 30 days in patients with acute coronary syndromes who were not scheduled to undergo early revascularisation (within 12 hours of end of infusion) were apparent between those who received abciximab (bolus and either 24- or 48-hour infusion) and those who received placebo in addition to aspirin and heparin.

The most common adverse events associated with the use of abciximab are bleeding complications and thrombocytopenia, although the risk of major bleeding can be limited through adhering to current administration protocols.

Treatment costs are generally higher in both stent plus abciximab and angioplasty plus abciximab groups than stent plus placebo, primarily because of the acquisition cost of abciximab. Abciximab appeared most cost beneficial in high-risk patients undergoing elective percutaneous coronary revascularisation; among lower risk patients, abciximab therapy has been associated with higher total in-hospital and 6-month medical costs than eptifibatide.

Conclusion: The GP IIb/IIIa receptor antagonist abciximab, when used with aspirin and heparin, has demonstrated efficacy in reducing the short- and long--term risk of ischaemic complications in patients with ischaemic heart disease undergoing percutaneous coronary intervention, when used with aspirin and heparin. High-risk patients (including those with diabetes mellitus) derive particular benefits from abciximab treatment. Abciximab remains an important therapeutic option for the prevention of complications in patients with ischaemic heart disease.

Overview of Pharmacology

Abciximab is an antibody fragment that inhibits platelet aggregation by binding to the glycoprotein (GP) IIb/IIIa receptor. Abciximab also binds to the vitronectin and Mac-1 receptors. Inhibition of platelet aggregation is correlated with the degree of GP IIb/IIIa receptor blockade. An intravenous (IV) bolus of abciximab 0.25 mg/kg blocks >80% of GP IIb/IIIa receptors and produces the maximum antiplatelet effect (>80% inhibition of ADP-induced platelet aggregation) at 10 minutes after treatment initiation. Continuous infusion (0.125 μg/kg/min or 10 μg/min) after the bolus maintains near maximal platelet inhibition. However, marked interindividual variability has been observed in the degree of platelet inhibition in patients undergoing revascularisation.

Ex vivo, administration of abciximab (0.25 mg/kg bolus then 10 μg/min for 12 hours) to patients undergoing percutaneous coronary revascularisation has shown generally equivalent inhibition of platelet aggregation in response to ADP or thrombin receptor-activating peptide (TRAP) as tirofiban or eptifibatide, although dosage regimens of tirofiban and eptifibatide varied between some studies.

Platelet aggregation was significantly increased relative to baseline following fibrinolytic therapy with either alteplase or reteplase in patients with acute myocardial infarction (MI; n = 51) enrolled in the dose-finding TIMI-14 trial, but no significant differences in platelet aggregation at 90 minutes or 24 hours were evident between patients who received abciximab (0.25 mg/kg bolus) with either reduced doses of reteplase (a 5U bolus and either 5 or 10U bolus) or alteplase (dose range 35 to 65mg); all patients receiving combination abciximab/fibrinolytic therapy achieved >80% inhibition of platelet aggregation at 90 minutes which was sustained for ≥24 hours after initiation of abciximab treatment. The addition of ticlopidine to treatment maintained the platelet inhibition achieved with abciximab therapy during the first 24 hours.

In addition to inhibition of platelet aggregation, abciximab has shown potentially antithrombotic effects which are independent of heparin administration. Abciximab inhibits platelet-dependent thrombin generation, most likely through blockade of both GP IIb/IIIa and vitronectin receptors. Blockade of vitronectin receptors prevents smooth muscle cell adhesion and migration, thus reducing intimal proliferation. Moreover, abciximab may inhibit activated Mac-1 receptors, thus reducing monocyte and polymorphonuclear leucocyte recruitment at the site of vascular injury.

Abciximab binds rapidly to platelets after administration and has an initial half-life of > 10 minutes and a second phase half-life of about 30 minutes. Platelet function generally recovers within 48 hours, although platelet-bound abciximab is still detectable 15 days or more after administration in a platelet-bound state.

Therapeutic Use in Percutaneous Coronary Intervention

In General Patient Populations: Abciximab (0.25 mg/kg bolus plus infusion of 0.125 μg/kg/min for 12 hours) has been investigated as an adjunct to aspirin and heparin in patients undergoing percutaneous coronary intervention. Large well designed studies have shown abciximab prevents acute ischaemic complications (death, MI or urgent revascularisation).

Abciximab demonstrated greater efficacy at 30 days than tirofiban treatment (10 μg/kg bolus then 0.15 μg/kg/min IV infusion for 18 to 24 hours) in the randomised, double-blind, multicentre TARGET study in patients scheduled for stent placement. At 30 days, the composite endpoint of death, nonfatal MI or urgent target-vessel revascularisation occurred in significantly fewer patients who received abciximab than received tirofiban (6.0 and 7.6%, respectively), mainly because of a greater number of MI events in patients treated with tirofiban (5.4 vs 6.9%).

The beneficial effects of treatment with abciximab previously observed in the randomised, multicentre, placebo-controlled EPILOG and EPISTENT studies have been maintained to 1 year, with a significantly reduced incidence of ischaemic complications relative to placebo which was consistently observed across a range of subgroups (including age, sex, bodyweight and indication for revascularisation). Factors which were significantly and independently associated with improved survival at 1 year in multivariate analysis in EPISTENT were use of abciximab in combination with stenting (versus placebo and stenting alone), and preprocedural percentage diameter stenosis, whereas worse survival was associated with previous congestive heart failure, type 1 diabetes mellitus, age >70 years and postprocedural TIMI grade 0 flow. Nonetheless, abciximab has demonstrated efficacy, reducing the composite endpoint of death, MI or target-vessel revascularisation, in a prospectively defined subset of patients with diabetes mellitus undergoing percutaneous coronary intervention in the EPISTENT study.

In Acute Myocardial Infarction: Five randomised comparative studies (ADMIRAL, CADILLAC, STOPAMI, STOPAMI-2, and ISAR-2) have investigated the use of abciximab in combination with stent placement in patients with acute MI. Both STOPAMI and ADMIRAL studies reported that patients receiving abciximab plus stent showed a significantly reduced composite endpoint compared to either fibrinolytic therapy or stent alone at 30 days. In STOPAMI-2 patients receiving abciximab plus stent showed a greater myocardial salvage index than those receiving abciximab plus alteplase. Results of the CADILLAC study suggest that stent plus abciximab, angioplasty plus abciximab and stent alone each leads to significantly better outcomes at 30 days compared to angioplasty alone. Patients receiving stent plus abciximab showed a significantly lower rate of revascularisation than those receiving angioplasty either alone or in combination with abciximab.

In the ADMIRAL study, blood flow was greater in patients who received abciximab than in placebo recipients immediately following revascularisation (TIMI grade 3 flow achieved in 95.1% vs 86.7% of patients; $p = 0.04$) and at 6 months with (94.3% vs 82.8%).

Recent large randomised, nonblind, multicentre studies (ASSENT-3 and GUSTO-V) have shown higher efficacy with abciximab in combination with either a

reduced dose of tenecteplase or reteplase than the full-dose fibrinolytic drug alone.

The effect of abciximab in combination with fibrinolytic therapy (either alteplase, streptokinase or reteplase) on reperfusion after acute MI was investigated in the TIMI-14 and SPEED trials. More patients who received abciximab in combination with fibrinolytic therapy in TIMI-14 and SPEED achieved TIMI grade 3 flow rates at 60 and 90 minutes than those who received abciximab alone. In TIMI-14, at both 60 and 90 minutes TIMI grade 3 flow rates were significantly greater in patients receiving abciximab plus fibrinolytic therapy than than in those receiving full-dose fibrinolytic alone ($p = 0.0009$ and 0.02, respectively). In the multicentre SPEED study, the percentage of patients achieving TIMI grade 3 flow rates 60 to 90 minutes after reperfusion treatment was greatest in patients who received two 5U boluses reteplase plus abciximab (62%).

Pooled Analyses: Pooled analysis of large, randomised, placebo-controlled trials involving abciximab (>9000 patients) showed a decrease in mortality of approximately 30% compared with placebo at 1 year; mortality was also reduced to a similar extent with either angioplasty or stenting (both approximately 30%). Analyses from the EPIC, EPILOG and EPISTENT trials showed that the overall treatment benefit (as indicated by 30-day and 6-month ischaemic outcomes) with abciximab was observed irrespective of sex or smoking status.

In meta-analyses of prospective, randomised placebo-controlled trials GP IIb/IIIa antagonists reduced the need for urgent revascularisation but had no effect on mortality compared to placebo. Abciximab but not eptifibatide or tirofiban significantly reduced the incidence of acute MI compared to placebo.

In Patients Without Early Revascularisation: In the randomised, multicentre GUSTO IV-ACS study, no differences were apparent between groups of patients with ACS who were not scheduled to undergo early revascularisation (within 12 hours of end of infusion) who had received abciximab (bolus and either 24- or 48-hour infusion) in addition to aspirin and heparin in any of the ischaemic endpoints at either 7 or 30 days (primary endpoint) compared with placebo.

Tolerability

The most common adverse events associated with the use of abciximab are bleeding complications and thrombocytopenia, although the risk of major bleeding can be limited through careful selection of patients, use of a low-dose, bodyweight-adjusted regimen of heparin, discontinuation of heparin immediately following revascularisation, early removal of the vascular sheath and femoral artery access site care.

In recent large, randomised clinical trials (ADMIRAL, GUSTO IV-ACS and TARGET), the incidence of major bleeding with a standard dose of abciximab (0.6–0.7% of patients) was similar to that seen with placebo (0% and 0.3%) and tirofiban (0.9%), although extension of the abciximab infusion to 48 hours significantly increased the incidence of major bleeding complications relative to placebo in one arm of the GUSTO IV-ACS trial (1% vs 0.3%). Rates of minor

bleeding were significantly greater (3–12.1%) than with either placebo (2% and 3.3%) or tirofiban (2.8%).

Thrombocytopenia (platelet count $<100 \times 10^9$/L) developed in 2.4–7% of abciximab-treated patients (the higher value was recorded in patients receiving a 48 hour infusion of abciximab in GUSTO IV-ACS) compared with ≈1% of placebo and 0.5% of tirofiban recipients in the ADMIRAL, GUSTO IV-ACS and TARGET clinical trials. Severe thrombocytopenia (platelet count $<50 \times 10^9$/L) was observed in 0.9–2% of patients who received abciximab, 0.04% and 1.3% of placebo recipients and 0.1% of tirofiban recipients. 2.1% of patients treated with abciximab were identified as having pseudothrombocytopenia in pooled data from the CAPTURE, EPIC, EPILOG and EPISTENT trials compared with 0.6% of patients who received placebo.

In the ASSENT-3 trial, rates of major and minor bleeding were significantly higher in patients receiving abciximab plus tenecteplase than in those receiving tenecteplase alone or plus enoxaparin. Similarly, in GUSTO-V rates of major and minor bleeding were significantly higher in patients receiving abciximab plus reteplase than in those receiving reteplase alone. In both studies, the rates of intracranial haemorrhage were similar for each treatment group. No cases of anaphylactic, allergic or other hypersensitivity reactions have been reported in 500 patients enrolled in the ReoPro Readministration Registry.

Pharmacoeconomic Considerations

Cumulative treatment costs from a prospectively defined subset of patients in the US who participated in the EPISTENT study at 1 year were significantly higher in both the stent plus abciximab (by $US932) and angioplasty plus abciximab ($US581) groups than in the stent plus placebo group, primarily because of the acquisition cost of abciximab.

The addition of abciximab to stenting also significantly increased the estimated mean costs per patient after 6 months' treatment when results of the EPISTENT trial were extrapolated to a European setting based on an economic evaluation from the BElgian NEtherlands Stent (BENESTENT)-II study.

Cost savings associated with abciximab in a prospectively defined economic substudy of EPILOG were for the most part attributed to a reduced requirement for repeat revascularisation, bailout stenting and shorter hospital stays. Over a 6-month follow-up period, hospitalisation costs remained increased in the abciximab groups because of an increase in the number of patients undergoing nonurgent revascularisation.

Increased costs in the abciximab group were primarily because of drug acquisition costs.

Two nonrandomised studies (based in the US and Netherlands) showed a reduced incidence of ischaemic complications with abciximab and stenting; however, overall treatment costs were similar or increased in these patients compared with those who underwent only percutaneous coronary intervention.

Among lower risk patients undergoing elective percutaneous coronary revascularisation, abciximab has been associated with higher total in-hospital and

6-month medical costs than eptifibatide in the prospective PRICE cost analysis study. Abciximab appeared most cost beneficial in high-risk patients in a retrospective cost analysis; the estimated cost to prevent one event was $US39 201 compared with $US74 047 for tirofiban. Patients treated with abciximab spent fewer days in hospital than patients who received either tirofiban or eptifibatide according to a retrospective analysis.

An incremental cost of $US932, or cost-effectiveness ratio of $US6213 per added life-year, was seen in the stent plus abciximab group compared with stent and placebo in EPISTENT. Patients who received abciximab plus stent had an incremental cost of $US581 and a cost-effectiveness ratio of $US5291 per added life-year in comparison with the abciximab and angioplasty group. One Italian-based analysis has evaluated the cost effectiveness of abciximab based on 6-month results from the EPILOG, EPIC (not including patients who received only abciximab bolus) and CAPTURE studies. Cost-effectiveness ratios for patients in the abciximab and placebo groups were L16.6 and L15.4 million Lire per event-free patient (approximately $US7543 and $US6998; 2002 values), resulting in an incremental cost-effectiveness ratio of L34.3 ($US15 587) per event avoided at 6 months after intervention.

Dosage and Administration

The recommended dosage of abciximab is a 0.25 mg/kg IV bolus administered 10 to 60 minutes before the start of percutaneous coronary intervention, followed by a continuous IV infusion of 0.125 μg/kg/min (up to a maximum of 10 μg/min) for 12 hours. For patients with refractory unstable angina pectoris in whom percutaneous coronary revascularisation is planned within 24 hours, the recommended dosage is an IV bolus of 0.25 mg/kg followed by an infusion of 10 μg/min for 18 to 24 hours before the procedure and finishing 1 hour (US recommendation) or 12 hours (UK recommendation) after the procedure. Abciximab should be used in combination with aspirin and heparin.

Abciximab is contraindicated in patients at high risk for bleeding complications or in whom bleeding complications would have serious consequences, those requiring IV dextran and those with known hypersensitivity to the drug.

Haemostatic parameters should be measured before administration. Caution is required in patients receiving other drugs that affect haemostasis. Infusion of abciximab and heparin should be stopped if uncontrollable serious bleeding occurs or if emergency surgery is required.

To reduce the risk of bleeding, careful femoral artery access site care, use of a low-dose, bodyweight-adjusted regimen of heparin, discontinuation of heparin immediately after the procedure, early removal of the arterial sheath and careful patient management are recommended.

Platelet counts should be monitored before and during treatment. If the platelet count decreases by ≥25% and to $<100 \times 10^9$/L, abciximab should be discontinued and appropriate treatment initiated.

1. Introduction

In 2000, ischaemic heart disease was one of the most significant contributors to morbidity and mortality worldwide, responsible for an estimated 12.4% of all deaths.[1] An estimated 1.3 million coronary revascularisation procedures were performed in the US in 1998[2] and 20 500 in the UK in 1996.[3] The acute coronary syndromes (ACS) are a group of clinical conditions including unstable angina pectoris (UAP), non-ST-segment elevation myocardial infarction (MI), ST-segment elevation MI and sudden ischaemic death.[4] Among these, UAP and MI without ST-segment elevation are among the most commonly observed clinical manifestations.[5]

Platelet aggregation is a key step in thrombus formation both on the ruptured atherosclerotic plaque and after percutaneous coronary intervention. A conformational change in glycoprotein IIb/IIIa (GP IIb/IIIa) results from the activation of a specific platelet membrane receptor. GP IIb/IIIa then becomes an active receptor for fibrinogen-mediated platelet aggregation. At high shear stress, von Willebrand factor also binds to GP IIb/IIIa and contributes to platelet aggregation (see figure 1).[6]

Medical management of ACS often involves revascularisation of the underlying disease process with either percutaneous coronary intervention or coronary artery bypass grafting (CABG) in conjunction with pharmacological therapy. As the GP IIb/IIIa receptor is critical to the process of thrombus formation, it is an attractive target for pharmacological intervention.

Abciximab (Reopro®[1]), a chimeric human-murine monoclonal antibody Fab (fragment antigen binding) fragment which inhibits platelet aggregation through antagonism of GP IIb/IIIa, was first reviewed in *Drugs* in 1994,[7] and an update was subsequently published in 1998.[8] A further review detailing the pharmacoeconomics of its use in percutaneous coronary revascularisation was published in *PharmacoEconomics* in 1999.[9] This review primarily provides an update on the therapeutic use of abciximab in patients with ischaemic heart disease undergoing percutaneous coronary revascularisation, and also reviews its use in patients without early revascularisation and in MI.

2. Overview of Pharmacology

The pharmacodynamic and pharmacokinetic properties of abciximab have been reviewed extensively elsewhere[7,8] and are summarised in table I. This section provides an overview of the *in vitro* and *ex vivo* properties of the drug, with emphasis on recently published reports of the effect of various platelet GP IIb/IIIa antagonists or their combination with fibrinolytic therapy on platelet function.

2.1 Inhibition of Platelet Aggregation

The effect of abciximab on platelet function in *ex vivo* studies was primarily measured by inhibition of adenosine diphosphate (ADP)- or 11-amino acid thrombin receptor-activating peptide (TRAP)-induced platelet aggregation. A schematic representation of the factors involved in platelet aggregation and the points of action of various antithrombotic and anticoagulant drugs (including abciximab) is presented in figure 1.

Inhibition of platelet aggregation is correlated with the degree of GP IIb/IIIa receptor blockade.[8] An intravenous (IV) bolus of abciximab 0.25 mg/kg blocks >80% of GP IIb/IIIa receptors and produces the maximum antiplatelet effect (>80% inhibition of ADP-induced platelet aggregation) at 10 minutes after treatment initiation.[28] Continuous infusion (0.125 μg/kg/min or 10 μg/min) after the bolus maintains near maximal platelet inhibition.[8] Marked interindividual variability has been observ-

1 Use of tradenames is for product identification purposes only and does not imply endorsement.

Table I. Summary of the pharmacodynamic properties of abciximab. *Ex vivo* studies were conducted with whole blood or plasma samples taken ≤2 hours after abciximab treatment in patients (pts) undergoing percutaneous coronary revascularisation. Most studies stated that pts also received heparin and aspirin

Ex vivo
Inhibition of platelet aggregation is correlated with the degree of GP IIb/IIIa receptor blockade[8] (also seen after coronary stenting in pts with angina pectoris[10]) although substantial interindividual variability is seen[11-14]
Almost complete inhibition of platelet aggregation during treatment[15,16]
Inhibits platelet aggregation in combination with either reteplase or alteplase in pts with acute MI similar to that reported in elective settings[17]
Degree of platelet function inhibition similar between pts with and without diabetes mellitus[11]
Receptor blockade not significantly altered by heparin, although platelet aggregation inhibition was lower 24 hours after treatment[18]
Decreases Mac-1 expression on monocytes in pts with acute MI[19]
Did not induce stable fibrinogen binding nor platelet aggregation in response to ADP 20 μmol/L in healthy volunteers[20]
Significantly reduces serum levels of CRP and IL-6 following angioplasty compared with placebo[21] and in pts with UAP[22]
Combination of abciximab and ticlopidine has a prolonged inhibitory effect on *ex vivo* thrombus formation with respect to either treatment alone[23]
In vitro
Binds to and inhibits GP IIb/IIIa, vitronectin and Mac-1 receptors[8]
No significant effect on platelet P-selectin expression (marker of platelet secretion) *in vitro*[24] or *ex vivo* in pts undergoing PTCA[25]
Inhibits fibrinogen binding;[14,24] effect in combination with aspirin and clopidogrel greater than aspirin and clopidogrel alone[24]
Heterozygotes for the PLA2 (GP IIb/IIIa) polymorphism may benefit from longer abciximab infusions or earlier treatment with a GP IIb/IIIa antagonist than homozygotes[26]
Modulates platelet and leucocyte activation and interaction after PTCA; also reduces platelet-dependent Mac-1 upregulation in monocytes and neutrophils[27]
Decreases number of platelet-neutrophil aggregates after PTCA but increases P-selectin-mediated leucocyte adhesion[23]

ADP = adenosine diphosphate; **CRP** = C-reactive protein; **GP** = glycoprotein; **IL** = interleukin; **MI** = myocardial infarction; **PTCA** = percutaneous transluminal coronary angioplasty; **UAP** = unstable angina pectoris.

ed in the degree of platelet inhibition in patients undergoing revascularisation.[11-14]

However, platelet aggregation in response to TRAP (25 μmol/L) was inhibited to a lesser extent than that induced by ADP (20 μmol/L) in patients treated with abciximab (0.25 mg/kg bolus then 10 μg/min for 12 hours) undergoing coronary stenting. *In vitro*, TRAP- and ADP-induced platelet aggregation was inhibited in a concentration-dependent manner when platelets were incubated with abciximab 1–100 mg/L.[15]

In addition to inhibiting platelet aggregation, recent *in vitro* data suggests that abciximab may also facilitate the dispersal of newly formed platelet aggregates.[29] ADP-induced aggregation of platelets from healthy, non-medicated volunteers was completely reversed by concentrations of abciximab which produced partial displacement of platelet bound fibrinogen. The ability of abciximab to disperse aggregates was inversely proportional to the interval between aggregation and addition of abciximab, and the concentration of ADP. This suggests that only newly-formed aggregates whose formation does not involve granule secretion are susceptible to dissaggregation by abciximab (TRAP-induced platelet aggregation was not reversed by abciximab).[29]

2.1.1 Comparison with Other Platelet Glycoprotein IIb/IIIa Antagonists

Ex vivo, administration of abciximab to patients undergoing percutaneous coronary revascularisation has generally shown equivalent inhibition of platelet aggregation in response to ADP or TRAP to that of tirofiban or eptifibatide (table II), although some exceptions exist and dosage regimens of tirofiban and eptifibatide varied between some studies.

At 2 hours post-infusion, all three drugs inhibited TRAP-induced platelet aggregation by >80% in

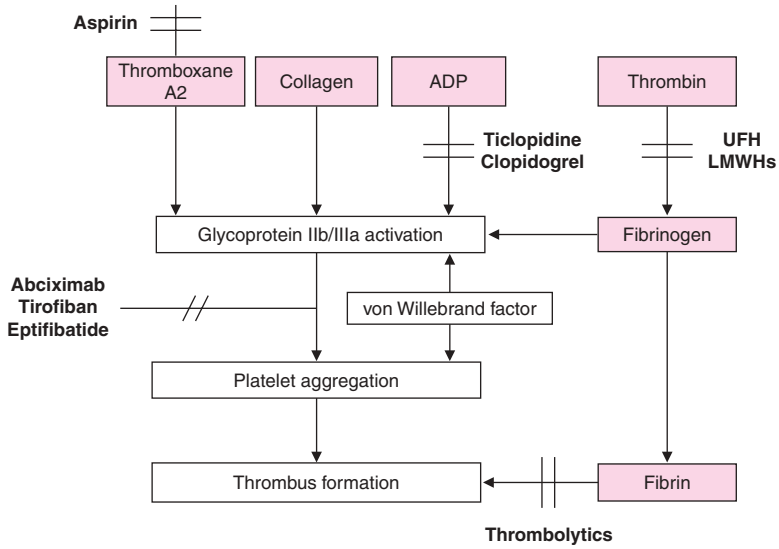

Fig. 1. Schematic representation of the factors involved in platelet aggregation and points of action for various antithrombotic and anticoagulant drugs, including abciximab. **ADP** = adenosine diphosphate; **LMWH** = low-molecular-weight heparin; **UFH** = unfractionated heparin.

small, randomised trials (table II). Inhibition with eptifibatide was significantly greater than with either abciximab or tirofiban at the end of the infusion in a trial in patients with UAP[31] and significantly less (at 2 hours) than with these two drugs in another study in patients with ACS, reported as an abstract.[30] Abciximab ($p = 0.041$) and eptifibatide ($p = 0.002$) both produced greater inhibition at patient discharge than tirofiban in the trial in patients with UAP.[31] Where used, the ADP assay produced generally similar results (table II).

Any differences, however, may relate to study design rather than any true disparaties in the magnitude of *ex vivo* inhibitory effect, which, in the case of eptifibatide, is influenced by the anticoagulant used in the assay.[33] Some studies used hirudin[32] or P-PACK[31] rather than citrate as an anticoagulant which gives misleading results for eptifibatide; one trial showing inferior results for eptifibatide did not state which aggregatory agent was used.[30] Also, the seemingly lower inhibitory effect of tirofiban in one trial[31] may have resulted from the extended delivery time of the tirofiban bolus (30 minutes) compared to that used in other trials (≤3 minutes).[30,31] Lastly, heparin dosages varied among the three treatment arms.[31,32]

Recovery of platelet aggregatory function is delayed after cessation of abciximab therapy, compared with eptifibatide or tirofiban.[31,32]

Continuous platelet inhibition was achieved when full-dose abciximab (0.25 mg/kg bolus then 0.125 μg/kg/min IV infusion for 12 hours) was given to 50 patients with UAP or acute MI scheduled to undergo percutaneous coronary intervention within 14 days who were already receiving treatment with either full-dose tirofiban (0.4 μg/kg/min for 30 minutes then 0.1 μg/kg/min over 20–24 hours) or eptifibatide (180 μg/kg bolus then 2.0 μg/kg/min IV infusion over 20–24 hours).[34] Platelet inhibition (ADP- [20 μmol/L] and TRAP- [15 μmol/L] stimulated) following administration of abciximab was equivalent to or greater than that seen when the drugs were given alone in this non-randomised trial.

Shear-force mediated platelet adhesion is also inhibited by the glycoprotein IIb/IIIa antagonists. In

Table II. *Ex vivo* effects of abciximab (ABC), tirofiban (TBN) and eptifibatide (EPT) given intravenously in patients undergoing percutaneous coronary interventions (PCI). All studies were randomised and parallel group in design

Reference	Type of CAD	Patient numbers	Aggregatory agent[c]	Regimen[a]	Platelet inhibition (%)[b]		
					at 2h	at infusion end[d]	at discharge
Jain et al.[30] [abstract]	ACS (ND)	10	Iso-TRAP (ND)	ABC 0.25 mg/kg bolus then 0.125 μg/kg/min for 12h	96.7*		
		11		TBN 10 μg/kg over 1 min then 0.15 μg/kg/min for 20h	97.01*		
		11		EPT 180 μg/kg bolus then 2 μg/kg/min for 20h	92.77		
Kereiakes et al.[31]	UAP	10	Iso-TRAP (ND), ADP	ABC 0.25 mg/kg bolus then 0.125 μg/kg/min for 12h	97.5 (90.1)	76* (82.5*)	59.5** (49)
		10		TBN 0.4 μg/kg/min bolus for 30min then 0.1 μg/kg/min for 20–24h	91 (73.8)	91.7 (86.4)	41 (22.9)
		9		EPT 180 μg/kg bolus then 2.0 μg/kg/min for 20–24h	96.5 (91.7)	100 (95.9)	75 (40)
Neumann et al.[32]	Symptomatic CAD	20	Iso-TRAP 4 μmol/L, ADP	ABC 0.25 mg/kg bolus then 10 μg/min for 12h	>80%; ABC = others[e]		
		20		TBN 10 μg/kg bolus then 0.15 μg/kg/min for 72h	>80%		
		20		EPT 180 μg/kg bolus then 2 μg/kg/min for 72h	>80%		

a Patients also received aspirin 325 mg/day and heparin in various regimens before undergoing PCI (not stated in Jain et al.[30]).

b Results are for the TRAP assay; ADP results are in brackets.

c ADP 20 μmol/L. Where stated, the anticoagulant used was P-PACK[31] or hirudin[32] for all EPT samples, and either P-PACK[31] or citrate[32] for the other drugs. All results for TRAP used the Rapid Platelet Function Assay (RPFA).

d 12h for abciximab, 19.4h for tirofiban and 19.8h for eptifibatide.

e There were no differences between treatments; ADP results were similar.

ACS = acute coronary syndrome; **CAD** = coronary artery disease; **ND** = no further data available; **TRAP** = thrombin receptor activating peptide; **UAP** = unstable angina pectoris; * $p < 0.05$, ** $p \leq 0.006$ vs EPT.

a recent study using blood samples from healthy volunteers, abciximab, tirofiban and eptifibatide each inhibited shear-induced platelet adhesion in a concentration-dependent manner with IC_{50} values of 43, 430 and 5781nm, respectively.[35]

2.1.2 In Combination with Fibrinolytic Therapy

In patients with acute MI, high levels of platelet aggregation and activation may limit the success of fibrinolytic therapy.[17,36]

Platelet aggregation was evaluated in the dose-finding TIMI-14 trial (see section 3.2.3 for further study details) in 51 patients with acute MI who received either full-dose alteplase or reteplase alone, or a reduced dose of the fibrinolytic drug with full-dose abciximab.[17] ADP-induced platelet aggregation was increased relative to baseline at 90 minutes following fibrinolytic therapy ($p = 0.02$). No differences in platelet aggregation at 90 minutes or 24 hours were evident between patients who received abciximab (0.25 mg/kg bolus) with either reduced dosages of reteplase (a 5U bolus and either 5 or 10U bolus) or alteplase (dose range 35–65mg). All patients receiving combination abciximab/fibrinolytic therapy achieved >80% inhibition of platelet aggregation at 90 minutes and this was sustained for ≥24 hours after initiation of abciximab treatment.[17]

The effect of combination therapy with abciximab, reteplase and ticlopidine on platelet function and GP IIb/IIIa blockade was also evaluated in 46 patients with MI as part of the SPEED trial (see section 3.2.2 for further study details).[36] The degree of GP IIb/IIIa blockade (measured by inhibition of

fibrinogen binding) was inversely correlated to abciximab binding ($r = -0.72$; $p < 0.0001$). In addition, ADP-induced platelet aggregation was maximally inhibited at 10 minutes and recovered within 48 hours, although the majority of GP IIb/IIIa receptors were still blocked with abciximab. Reteplase treatment alone did not increase platelet aggregation. Abciximab binding was not influenced by concomitant administration of reteplase as indicated by measures of P-selectin expression, fibrinogen binding and platelet aggregation. However, platelet inhibition achieved with abciximab therapy during the first 24 hours was maintained by additional treatment with ticlopidine ($p < 0.001$ vs without ticlopidine for all timepoints).[36]

2.2 Effect on Measures of Thrombosis

The effects of abciximab on glycoprotein IIb/IIIa are well documented; however recent *ex vivo* data using monocytes from healthy volunteers suggest that abciximab may also directly modulate the coagulation cascade through binding to the leucocyte integrin Mac-1.[37] Binding of various ligands including fibrinogen and coagulation factor X to Mac-1 was inhibited by abciximab (10 μg/mL) *in vitro*. This in turn resulted in the impairment of the conversion of factor X to Xa and of fibrinogen-mediated cell aggregation. The clinical relevance of these anti-leucocyte and anticoagulative effects of abciximab are unclear; however, these data extend the molecular understanding of abciximab beyond the blockade of glycoprotein IIb/IIIa.[37]

Treatment with abciximab results in a significant decrease in thrombus formation which is independent of heparin administration. The addition of standard-dose abciximab to heparin and aspirin therapy showed significant decreases in thrombin generation (despite increased thrombin generation and activity in the abciximab group at baseline) in 32 consecutive patients undergoing revascularisation for ACS in a nonrandomised study.[38] A significant increase in the activated clotting time (ACT) and decrease in prothrombin fragment F1.2 before and during coronary intervention were seen in patients treated with heparin and either abciximab (0.25 mg/kg bolus then 0.125 μg/kg/min IV infusion for 12 hours)[39,40] or tirofiban (10 μg/kg over 3 minutes, then 0.15 μg/kg/min).[39] However, in the GUSTO IV-ACS trial, prothrombin activation was unaffected in 167 patients with ACS not undergoing revascularisation who received abciximab (see section 3.5 for further study details).[41]

When porcine aortic segments were perfused with blood from 23 patients with UAP who had received abciximab (0.25 mg/kg bolus followed by an IV infusion 10 μg/min for 12 hours, *ex vivo* thrombus formation was reduced by 58% ($p < 0.001$ vs baseline) and this was not further reduced following treatment with heparin.[42]

Similarly, in 14 patients receiving abciximab (0.25 mg/kg bolus before angioplasty then 10 μg/min IV infusion for 12 hours) in combination with ticlopidine (500mg 12–36 hours before angioplasty then 250mg twice daily for 30 days), *in vitro* mural thrombosis measured 3 days following angioplasty was reduced by approximately 50% compared with baseline values; treatment with abciximab alone inhibited mural thrombus formation for 1 day. However, while the number of circulating platelet-neutrophil aggregates was decreased with abciximab therapy, P-selectin-mediated leucocyte adhesion was significantly increased.[23]

In the ADMIRAL study, 23 patients with acute MI receiving abciximab (see section 3.2.1 for further study details) showed a 65% reduction in platelet aggregate size ($p = 0.0007$) and a 63% decrease in the viscoelastic properties ($p = 0.0001$) compared with placebo. This was independent of previous heparin administration. These changes to the architecture of platelet-rich clots may contribute to the improved artery patency observed in patients treated with abciximab.[43]

2.3 Other Effects

Abciximab prevents the adhesion and migration of smooth muscle cells via inhibition of the vitronectin integrin receptor[44,45] and through this mechanism abciximab may also prevent other vitronectin-mediated effects such as thrombin generation and clot formation (see section 2.2).

For example, the chemotactic and invasive potential of human coronary smooth muscle cells *in vitro* was significantly inhibited by the addition of abciximab 24 hours prior to and during smooth muscle cell migration (mean concentration required to achieve 50% inhibition [IC_{50}] = 33.0 mg/L for chemotaxis and 0.5 mg/L for invasion).[46] Migration was similarly inhibited if abciximab was administered only during migration (IC_{50} = 32.6 mg/L), although the drug affected invasion to a lesser extent in this phase.[46]

2.4 Pharmacokinetic Properties

Abciximab binds rapidly to platelets following IV administration and the unbound drug is rapidly cleared from the plasma. It has an initial half-life of >10 minutes and a second phase half-life of about 30 minutes. Following IV infusion, free plasma concentrations decline rapidly for 6 hours; the decline is slower thereafter.[28] Less than 4% of the total dose was present as free plasma antibody after 2 hours.[8]

Platelet function generally recovers within 48 hours, although platelet-bound abciximab is still detectable 15 days or more after administration in a platelet-bound state. Abciximab is continually redistributed among circulating platelets, including newly released cells.[8] Thus, the drug is uniformly distributed on all platelets and there is no drug-free platelet population.

3. Therapeutic Use in Percutaneous Coronary Intervention

At the time of the previous review in *Drugs*,[8] large, well designed studies showed that administration of abciximab (as an adjunct to heparin and aspirin) during percutaneous coronary revascularisation significantly reduced the incidence of ischaemic complications occurring in the 30 days after the procedure. Significant benefit, particularly in the incidence of MI, was still evident at 6 months in two of the four major trials.[47-50]

Abciximab was particularly effective in high-risk patients with acute MI and UAP. Subsequent studies which have investigated the therapeutic use of abciximab in these patient groups alone are described in sections 3.3 and 3.4. Moreover, abciximab showed additive benefits to coronary stenting. Preliminary data also suggested that abciximab may improve coronary blood flow after MI, as well as achieving reperfusion in conjunction with reduced doses of fibrinolytic agents,[8] and new data in this area are presented in sections 3.3.2 and 3.3.3.

Unless otherwise specified, abciximab was administered as a 0.25 mg/kg bolus followed by a 0.125 μg/kg/min IV infusion (up to a maximum of 10 μg/min) for 12 hours. All patients also received aspirin (usually 150–325mg) and weight-adjusted heparin; a lower dose of heparin was generally given to patients receiving either abciximab or a fibrinolytic agent.

The primary endpoint in large, randomised, multicentre trials was generally a composite of death, MI and target-vessel revascularisation and/or stroke at 30 days or 6 months. In studies involving patients with acute MI who received abciximab and fibrinolytic therapy, primary endpoints were the time to reperfusion and TIMI blood flow rates. Analyses were intent-to-treat. A summary of the acronyms used to describe the major trials in this area is presented in table III.

Table III. Summary of acronyms for major trials which have investigated the use of abciximab in patients with ischaemic heart disease

ADMIRAL	Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long-term follow-up
ASSENT-3	ASsessment of the Safety and Efficacy of a New Thrombolytic agent
CADILLAC	Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications
CAPTURE	C7E3 AntiPlatelet Therapy in Unstable Refractory Angina
EPIC	Evaluation of 7E3 for the Prevention of Ischaemic Complications
EPILOG	Evaluation in PTCA to Improve Long-term Outcome with abciximab Glycoprotein IIb/IIIa blockade
EPISTENT	Evaluation of glycoprotein IIb/IIIa Platelet Inhibitor for STENTing
ERASER	Evaluation of Reopro and Stenting to Eliminate Restenosis
GRAPE	Glycoprotein Receptor Antagonist Patency Evaluation
GUSTO	Global Utilization of Streptokinase and Tissue plasminogen activation for Occluded coronary arteries
ISAR-2	Intracoronary Stenting and Antithrombotic Regimen-2
NICE	National Investigators Collaborating on Enoxaparin
PRICE	Prairie Reopro versus Integrilin Cost Evaluation trial
RAPPORT	ReoPro And Primary Percutaneous transluminal coronary angioplasty Organization and Randomized Trial
SPEED	Strategies for Patency Enhancement in the Emergency Department
STOPAMI	Stent versus Thrombolysis for Occluded coronary arteries in Patients with Acute Myocardial Infarction
TARGET	Do Tirofiban And Reopro Give similar Efficacy Trial
TIMI	Thrombolysis In Myocardial Infarction

PTCA = percutaneous transluminal coronary angioplasty.

3.1 In General Patient Populations

The use of abciximab in reducing the incidence of MI in patients undergoing percutaneous coronary intervention had been well established at the time of the previous review.[8] One large study (TARGET) has subsequently investigated the comparative efficacies of the platelet GP IIb/IIIa antagonists abciximab and tirofiban in patients without ST-segment elevation scheduled to undergo elective or urgent coronary stenting or CABG.[51] One-year follow-up data from the previously reported EPISTENT[52] and EPILOG[53] studies are also presented in this section (table IV).

3.1.1 The TARGET Study

The multicentre TARGET study randomised patients in a double-blind fashion to receive either abciximab (n = 2411) or tirofiban (10 μg/kg bolus then 0.15 μg/kg/min IV infusion for 18–24 hours; n = 2398) prior to coronary revascularisation.[51] All patients were also treated with aspirin and clopidogrel after revascularisation.

At 30 days, death, nonfatal MI or urgent target-vessel revascularisation (the primary endpoint) occurred in 6.0% and 7.6% of patients who received abciximab or tirofiban, respectively (p = 0.038) [figure 2]. The larger beneficial effect of abciximab was predominantly due to a greater number of MI events in patients treated with tirofiban (6.9% vs 5.4% with abciximab; p = 0.04).[51] This was also observed when the analysis was restricted to patients with ACS (9.3% vs 6.3%; p = 0.002).[54]

At 6-months the incidence of death, repeat revascularisation and the combined endpoint were similar between treatment groups, but the incidence of MI remained significantly lower in patients who received abciximab compared to those who received tirofiban (figure 2).[55] In patients with ACS, abciximab showed significantly greater efficacy than tirofiban in the combined endpoint (14.7% vs 17.2%; p = 0.05). The incidence of MI and death/MI was significantly lower in ACS patients who received abciximab than those who received tirofiban (7.2% vs 9.8% and 8.1% vs 10.4%, respectively; p = 0.013 and 0.03).[54,55]

Of the 4809 randomised patients, 1117 had diabetes mellitus and these were stratified evenly be-

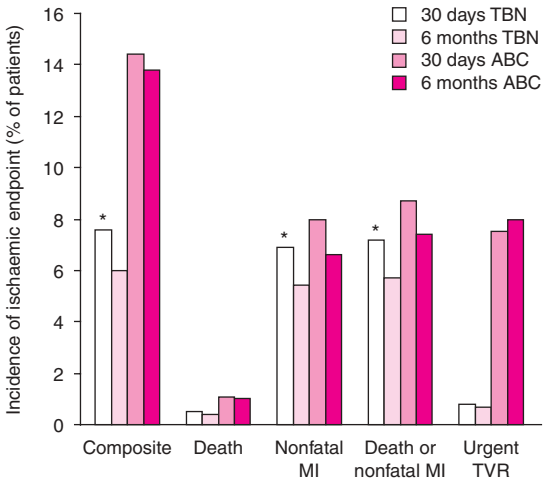

Fig. 2. Effects of abciximab (ABC) or tirofiban (TBN) on 30-day (primary endpoint) and 6-month ischaemic outcomes in patients undergoing coronary revascularisation. Patients without ST-segment elevation were treated with either abciximab (0.25 mg/kg bolus then 0.125 μg/kg/min intravenous (IV) infusion for 12 hours; n = 2411) or tirofiban (10 μg/kg bolus, then 0.15 μg/kg/min IV infusion for 18 to 24 hours; n = 2398) in this randomised, double-blind, multicentre study (TARGET).[51,55] The composite endpoint consisted of death, myocardial infarction (MI) and target-vessel revascularisation (TVR); * $p < 0.05$ vs TBN.

tween treatment groups (tirofiban n = 560, abciximab n = 557).[56] These groups were similar in their baseline and procedural characteristics. In these patients, the composite endpoint of death, nonfatal MI or urgent target-vessel revascularisation at 6 months was similar between treatment groups (15.7% vs 16.9%). One year following the initial procedure, mortality rates in patients with diabetes mellitus were also similar between treatment groups (2.1% vs 2.9%).[56]

3.1.2 The EPISTENT and EPILOG Studies

One-year outcomes have been reported from the two large randomised, multicentre, placebo-controlled EPISTENT and EPILOG trials.[53,57] EPILOG included patients of all risk levels (excluding patients with acute ischaemic syndromes) undergoing elective or urgent revascularisation primarily with balloon angioplasty (85%);[48] EPISTENT included all patients with ischaemic heart disease requiring elective or urgent intervention.[50] Previously reported 30-day outcomes from these studies demonstrated that the beneficial effect of abciximab in high-risk patients shown in EPIC was extended to a patient population with different risk levels; an approximate 50–55% reduction in ischaemic complications was seen compared with placebo.[48,50]

Table IV. Effect of abciximab (ABC) on 1-year ischaemic event rates in patients (pts) undergoing percutaneous coronary revascularisation in the placebo-controlled EPILOG and EPISTENT trials. Abciximab was given as a 0.25 mg/kg bolus followed by an intravenous (IV) infusion of 0.125 μg/kg/min for 12 hours. All pts received aspirin and heparin in addition to study treatment. Analyses were intent-to-treat

Study	No. of pts	Treatment regimen[a]	Percentage of pts experiencing:			
			composite endpoint[b]	death	MI	TVR
EPILOG[53]	918	ABC and std-dose heparin	9.5**	1.8	5.5**	4.2*
	935	ABC and low-dose heparin	9.6**	1.7	5.1**	3.8**
	939	PL and std-dose heparin	16.1	2.6	10.4	7.2
EPISTENT[57]	794	ABC plus stent plus low-dose heparin[c]	20.1*	1.0*	5.9**	15.2
	796	ABC plus PTCA and low-dose heparin	25.3	2.1	7.7*	20.0*
	809	PL plus stent and std-dose heparin[c]	24.0	2.4	11.3	15.6

a Abciximab was administered as a 0.25 mg/kg bolus followed by an IV infusion of 0.125 μg/kg/min (up to 10 μg/min) for 12h. Std-dose heparin was given as an initial loading dose of 100 U/kg, then a continuous infusion adjusted to achieve target ACT ≥300 sec; low-dose heparin was given as an initial loading dose of 70 U/kg, then a continuous infusion adjusted to achieve target ACT ≥200 sec.

b Death, reinfarction or TVR.

c Pts undergoing stenting also received ticlopidine.

ACT = activated clotting time; **MI** = myocardial infarction; **PL** = placebo; **PTCA** = percutaneous transluminal coronary angioplasty; **std** = standard; **TVR** = target-vessel revascularisation; * $p \leq 0.05$, ** $p < 0.001$ vs PL.

The beneficial effects of treatment with abciximab have been maintained for up to 1 year, with a significantly lower incidence of MI, target-vessel revascularisation and composite of death, MI and target-vessel revascularisation compared with placebo (table IV).[53,57] This effect was consistent across a range of subgroups including age, sex, bodyweight or indication for revascularisation.[53] Factors independently associated with improved survival at 1 year in multivariate analysis in EPISTENT were use of abciximab in combination with stenting (versus placebo and stenting alone) and preprocedural percentage diameter stenosis; whereas those associated with worse survival were previous congestive heart failure, type 1 diabetes mellitus, age >70 years and postprocedural TIMI grade 0 flow (all $p < 0.05$).[57]

In Patients with Diabetes Mellitus

Patients with diabetes mellitus are at increased risk of ischaemic complications following percutaneous revascularisation; in addition, mortality rates are approximately twice those in patients without diabetes mellitus.[58] In the EPILOG study, abciximab plus standard-dose heparin was associated with a reduction in death or MI (4.1% vs 14.8%), but not target-vessel revascularisation (19.1% vs 15.5%) compared with placebo at 6 months in patients with diabetes mellitus undergoing percutaneous coronary intervention.[59] The effect of treatment with abciximab on mortality in a pooled analysis of patients with diabetes mellitus enrolled in the EPIC, EPILOG and EPISTENT trials is presented in section 3.3.1. This section reports results from a prospectively defined subset of patients enrolled in the EPISTENT study.[60,61]

One hundred and seventy-three patients with diabetes mellitus were randomised to receive stent plus placebo, 162 to stent and abciximab and 156 to angioplasty with abciximab.[61] Abciximab showed greater efficacy than placebo in combination with stenting; a significant reduction was observed in the incidence of the composite endpoint of death, MI or target-vessel revascularisation at 6 months (13.0% vs 25.2%; $p = 0.005$), but not the separate endpoints of death or MI (0.6% vs 1.7% and 6.2% vs 11.0%, respectively) [figure 3]. An approximate 50% reduction in target vessel revascularisation with stent plus abciximab compared with stent plus placebo was also seen (8.1% vs 16.6%; $p = 0.021$). The combination of stenting and abciximab in patients with diabetes mellitus also resulted in significantly decreased rates of death, MI and target vessel revascularisation compared with angioplasty plus abciximab. When the analysis was restricted to include only patients with type 1 diabetes mellitus ($n = 250$), the composite event rates for patients treated with stent-abciximab and stent-placebo were 14.6% and 26.1%, respectively ($p = 0.026$). Factors which were significant predictors of the composite endpoint at 6 months were stenting with abciximab ($p = 0.008$), hypertension ($p = 0.015$), recent history of smoking ($p = 0.006$), prior percutaneous coronary intervention ($p = 0.003$) and type B2 or C lesions ($p = 0.029$). At 1 year, mortality rates were 4.1% for

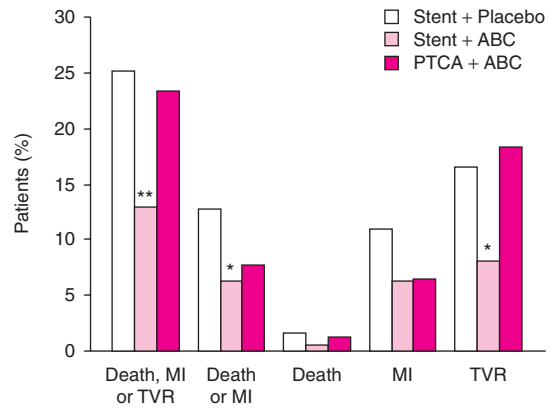

Fig. 3. Effect of abciximab (ABC; 0.25 mg/kg bolus followed by an intravenous infusion 0.125 μg/kg/min for 12 hours) on 6-month event rates in patients with diabetes mellitus undergoing percutaneous coronary intervention who were enrolled in the multicentre, placebo-controlled EPISTENT study. Patients were randomised to receive either stent and placebo (n = 173), stent and ABC (n = 162) or angioplasty and ABC (n = 156) in this prospectively defined subset of patients.[61] **MI** = myocardial infarction; **PTCA** = percutaneous transluminal coronary angioplasty; **TVR** = target-vessel revascularisation; * $p < 0.05$, ** $p = 0.005$ vs stent plus placebo.

stent-placebo and 1.2% for stent-abciximab (p = 0.11). Patients receiving angioplasty-abciximab had a 1-year mortality rate of 2.6%.[61]

The incidences of the 30-day or 6-month composite secondary endpoint of death, MI or urgent target-vessel revascularisation were not significantly different between groups of women with diabetes mellitus (n = 143) who received stenting with placebo or abciximab, or angioplasty with abciximab.[60] However, stenting plus abciximab was more effective than stenting plus placebo at reducing the incidence of the composite endpoint of death, MI or target-vessel revascularisation (34.5% vs 13.3%; p = 0.02); angioplasty plus abciximab was similarly effective (28.9%). The incidence of target-vessel revascularisation was similar between groups at 30 days, but significantly fewer patients receiving abciximab and stent required target-vessel revascularisation at 6 months (2.3% vs 15.7% and 23.1%; p ≤ 0.03) and 1 year (4.5% vs 21.1% and 26.7%; p ≤ 0.02) than either patients who received placebo and stent or angioplasty plus abciximab.[60]

3.2 In Acute Myocardial Infarction

At the time of the previous review, abciximab was reported to produce a significant reduction in the incidence of acute ischaemic complications (death, reinfarction or urgent target-vessel revascularisation) in patients with acute MI undergoing primary percutaneous revascularisation (relative reduction 48% compared with placebo).[62] Subsequent large randomised studies which have investigated the use of abciximab in this indication are presented in table V.

In addition, preliminary results had been reported from the TIMI-14 trial, which suggested that adequate reperfusion was achieved when abciximab was combined with a reduced dosage of a fibrinolytic drug.[8] This has since been expanded upon and recent studies in this area are presented in the following sections. Patients involved in these studies usually presented within 12 hours of onset of symptoms and had ST-segment elevation.

3.2.1 In Addition to Coronary Stenting

Five randomised comparative studies (ADMIRAL,[63] CADILLAC,[64] STOPAMI,[65] STOPAMI-2,[66] and ISAR-2[67]; table V) have investigated the use of abciximab in combination with stent placement in patients with acute MI. Both STOPAMI and ADMIRAL studies reported that patients receiving abciximab plus stent showed a reduced requirement for urgent repeat revascularisation leading to a reduction in the composite endpoint compared to either fibrinolytic therapy or stent alone. The use of abciximab plus stent is also supported by the findings to the STOPAMI-2 study in which patients receiving abciximab plus stent showed a greater myocardial salvage index than those receiving abciximab plus alteplase. Results of the CADILLAC study suggest that stent plus abciximab, angioplasty plus abciximab and stent alone each leads to significantly better outcomes at 30 days compared to angioplasty alone. As in STOPAMI and ADMIRAL, the differences in the rates of revascularisation of the target vessel between treatment groups may account for the difference in the composite endpoint in CADILLAC. Patients receiving stent plus abciximab showed a significantly lower rate of revascularisation than those receiving angioplasty either alone or in combination with abciximab.

The beneficial effects of using abciximab with stent placement in patients with acute MI compared to stent alone were demonstrated in the double-blind ADMIRAL study (table V[63]). After 30 days, the incidence of the composite endpoint was significantly lower in patients receiving stent plus abciximab than in those receiving stent plus placebo (6.0% vs 14.6%, p = 0.01). This difference in the primary endpoint was largely due to a requirement for significantly fewer target vessel revascularisations in patients receiving abciximab than those

Table V. Effect of abciximab (ABC) in conjunction with a percutaneous coronary intervention on 30-day ischaemic event rates in patients (pts) with acute myocardial infarction (MI) of <12 hours' duration in randomised trials. All pts received aspirin and heparin in addition to the study treatment. ABC was administered as a standard bolus followed by a 12-hour infusion unless otherwise specified and analyses were intent-to-treat

Study (design)	Intracoronary device	No. of pts	Treatment regimen	Percentage of pts experiencing event [event rates at 6mo]			
				composite endpoint[a]	death	MI	urgent repeat revascularisation
STOPAMI[65]	Stent	71	ABC	7.0 [8.5*][b]	4.2 [4.2]	2.8 [NR]	1.4 [10.0*]
(nb)	None	69	Alteplase 15mg then 0.75 mg/kg (30min infusion) then 0.5 mg/kg (60min infusion)	13.0 [23.2]	7.2 [13.0]	5.8 [NR]	1.4 [34.9]
ADMIRAL[63]	Stent[c]	149	ABC[d]	6.0** [7.4*]	3.4 [3.4]	1.3 [2.0]	1.3* [2.0*]
(db, pc, mc)	Stent	151	Placebo[d]	14.6 [15.9]	6.6 [7.3]	2.6 [4.0]	6.6 [6.6]
CADILLAC[64]	Stent	524	ABC	10.2†[e]	4.2	2.2	5.2‡
(mc, nb)	Stent	512	None	11.5††	3.0	1.6	8.3‡‡
	PTCA	528	ABC	16.5	2.5	2.7	13.8
	PTCA	518	None	20.0	4.5	1.8	15.7
ISAR-2[67][f]	Stent	201	ABC[dg]	5.0*	2.0	0.5	3.0
(nb)	Stent	200	IV heparin 10 000U then 1000 U/h for 12h[d]	10.5	4.5	1.5	5.0

a Death, reinfarction or target vessel revascularisation, unless otherwise specified.

b Death, reinfarction or stroke.

c Stent implanted if diameter of artery exceeded 2.5mm and was without extensive calcification.

d All patients received ticlopidine (250mg twice daily) for 28–30 days after stent implantation.

e Death, MI, target-vessel revascularisation and stroke.

f Pts presented with MI within 48 hours of undergoing stenting.

g Pts also received heparin 2500U.

db = double-blind; **IV** = intravenous; **mc** = multicentre; **nb** = nonblind; **NR** = not reported; **pc** = placebo-controlled; **PTCA** = percutaneous transluminal coronary angioplasty; * $p < 0.05$, ** $p \leq 0.01$ vs comparator; † $p < 0.001$ vs PTCA and $p = 0.004$ versus PTCA plus ABC, ‡ $p < 0.001$ vs PTCA, and PTCA plus ABC, †† $p < 0.001$ vs PTCA and $p = 0.03$ vs PTCA plus ABC, ‡‡ $p < 0.001$ vs PTCA and $p = 0.006$ vs PTCA plus abciximab.

receiving placebo (1.3% vs 6.6%, $p = 0.02$). Thus, patients receiving abciximab plus stenting showed relative risk reductions of 59% for the composite endpoint at 30 days and this was maintained at 6 months (53%, $p = 0.02$) compared to placebo.[63] Furthermore, in patients with diabetes mellitus, treatment with abciximab resulted in a significant reduction in 6-month mortality (0% vs 16.7%; $p = 0.02$) and in the 6-month composite endpoint (20.7% vs 50.0%; $p = 0.02$) compared to placebo.[63]

More patients receiving abciximab had grade 3 blood flow before the procedure compared to those receiving placebo (16.8% vs 5.4%; $p = 0.01$); this was due to the early randomisation of 26% of patients who received treatment before and during transportation to the catheterisation laboratory.[63] Blood flow was greater in patients who received abciximab than in placebo recipients immediately following revascularisation (TIMI grade 3 flow achieved in 95.1% vs 86.7% of patients; $p = 0.04$). This difference remained at 6 months with 94.3% and 82.8% of patients who received abciximab or placebo achieving TIMI grade 3 blood flow. TIMI grade 3 blood flow was a strong predictor of clinical outcomes at both day 30 and 6 months; 7.4% of patients with grade 3 blood flow experienced either death, reinfarction or urgent revascularisation compared with 35.3% of patients with blood flow grades 0–2 ($p < 0.001$).

The large CADILLAC study (table V[64]) endorsed the use of stent versus angioplasty. In this study, both primary objectives were met; stenting alone was superior to percutaneous transluminal coronary angioplasty (PTCA) and stenting alone was not inferior to PTCA plus abciximab (table V). The incidence of MACE at 30 days was significantly higher in patients receiving angioplasty alone, compared to patients receiving angioplasty plus abciximab (8.3% vs 4.8%, $p < 0.02$); the difference in MACE between angioplasty and stent plus abciximab also approached statistical significance at 30 days (8.3% vs 4.4%, $p = 0.08$).[64] These differences were largely due to the increased rates of target vessel revascularisation required by patients undergoing angioplasty. Significantly fewer patients receiving abciximab plus stent required revascularisation of the ischaemic target vessel than those undergoing angioplasty either alone (1.6% vs 5.6%, $p < 0.001$) or plus abciximab (1.6% vs 3.4%, $p < 0.05$). There was no statistical difference between patients undergoing stent alone and those undergoing stent plus abciximab, either in the composite endpoint at 30 days (5.7% vs 4.4%) or in the rates or target vessel revascularisation (1.6% vs 3.2%, $p = 0.08$).[64] However, CADILLAC differed from ADMIRAL[63] and ISAR-2[67] in that it was not powered to examine differences between stent alone and stent plus abciximab, but to examine differences between angioplasty plus abciximab and early discharge, and angioplasty plus placebo. In ADMIRAL,[63] abciximab was administered either before arrival at the hospital or in the emergency department, the intensive care unit or in the catheterisation laboratory and always before sheath insertion and coronary angiography; in CADILLAC, abciximab was administered only in the catheterisation laboratory.[64] Also, patient selection differed between CADILLAC (where patients lacked many high-risk characteristics) and ADMIRAL. This is evidenced by the difference in the incidence of the primary composite endpoint in patients receiving stent plus placebo in these two trials (ADMIRAL 14.6% vs CADILLAC 5.7%).

Six months after treatment in CADILLAC, the effect of stent placement remained evident. The composite endpoint (the primary endpoint) was significantly lower in patients with stent either with abciximab or alone compared to those patients undergoing angioplasty (table V).[64] The incidence of MACE and target vessel revascularisation was not statistically different between patients undergoing stent alone and those receiving stent plus abciximab (11.5% vs 10.2% and 8.9% vs 5.7%).

CADILLAC study subgroup analyses indicate that stenting lowered the rate of target-vessel revascularisation and MACE compared to PTCA in patients with diabetes mellitus.[68] Elderly patients (aged ≥75 years) showed significantly higher mortality and rates of MACE than nonelderly patients, irrespective of treatment at 30 days, 6 months and 1 year.[69] The number of patients achieving TIMI grade 3 blood flow after intervention was similar between all four groups (94.5–96.9%).[64]

Three smaller studies also support the use of abciximab plus stent in patients with acute MI (table V). In the prospective ISAR-2 study[67] cardiac-related events and event-free survival were significantly higher in patients receiving heparin plus stent compared to those receiving abciximab plus stent after 30 days (absolute reduction in cardiac events of 5.5%; $p < 0.05$). The between-group difference in event-free survival was maintained at 1-year but did not reach statistical significance. The myocardial salvage index (percentage of the left ventricle that was salvaged divided by the percentage compromised by the initial perfusion defect), the primary endpoint in STOPAMI, was significantly greater with stent plus abciximab than alteplase alone (0.57 vs 0.26; $p < 0.001$).[65] Finally, in the nonblind randomised STOPAMI-2 study, a reperfusion strategy with stent plus abciximab produced a higher myocardial salvage index than a combination of

Table VI. Effect of abciximab (ABC) compared with fibrinolytic therapies on 30-day event rates in randomised studies involving patients with acute myocardial infarction (MI). Patients presented within 12 hours of onset of symptoms and all analyses were intent-to-treat

Study (design)	No. of pts	Treatment regimen[a]	Pts experiencing endpoint event (%)			
			composite endpoint[b]	death	MI	intracranial haemorrhage
ASSENT-3[72] (mc, nb)	2017	ABC plus TEN 15–25mg (bodyweight-dependent) + HEP	11.1†[c]	6.6	2.2†[d]	0.9[d]
	2040	TEN 30–50mg (bodyweight-dependent) plus ENX 30mg bolus then 1 mg/kg sc (repeated every 12h for up to 7 days)	11.4†	5.4	2.7†	0.9
	2038	TEN 30–50mg (bodyweight-dependent)	15.4	6.0	4.2	0.9
GUSTO-V[73]	8328	ABC plus RET 2 5U boluses, 30min apart	16.2*[e]	5.6[f]	3.5*[e]	0.6
(mc, nb)	8260	RET 2 10U boluses, 30min apart	20.6	5.9	2.3	0.6
SPEED[74]	63	ABC	9.5	3.2	0	0
(mc)	76	ABC plus RET 2 5U boluses, 30min apart	11.8	3.9	2.6	1.3
	241	ABC plus RET (either 5, 7.5, 10, 5 + 2.5 or 5 + 5U)	10.8	3.3	3.7	0.8
	109	RET 2 10U boluses, 30min apart	11.0	5.5	2.8	0.9

a In all studies ABC was administered as a 0.25 mg/kg bolus, then as a 0.125 μg/kg/min intravenous (IV) infusion for 12 hours. Dosages of heparin, where specified, ranged between 40 and 70 U/kg, followed in ASSENT-3[72] and GUSTO-V[73] by an IV infusion of 7–12 U/kg/h or 800–1000 U/h; heparin was given to target aPTT of 50–70 seconds; a lower dose was given to pts when heparin was coadministered with abciximab. In SPEED,[74] heparin was given to achieve and maintain an ACT of ≥200 seconds.

b Unless otherwise specified this was composed of death, reinfarction or target vessel revascularisation.

c Mortality, in-hospital reinfarction or refractory ischaemia.

d In-hospital.

e At 7 days.

f Death was the primary endpoint.

ACT = activated clotting time; **aPTT** = activated partial thromboplastin time; **ENX** = enoxaparin; **HEP** = heparin; **mc** = multicentre; **nb** = nonblind; **pts** = patients; **RET** = reteplase; **sc** = subcutaneously; **TEN** = tenecteplase; * $p < 0.0001$ vs comparator; † $p < 0.001$ vs TEN and ENX.

fibrinolysis plus abciximab (0.60 vs 0.41, $p = 0.001$).[66]

3.2.2 In Combination with Fibrinolytic Therapy

Reperfusion with fibrinolytic therapy, aspirin and heparin is hindered by high reocclusion rates and dose-limiting intracranial haemorrhage. Reocclusion following initial reperfusion occurs in 5–15% of patients and is associated with increased mortality.[70] In addition, approximately 50% of patients present more than 12 hours after the onset of symptoms, do not show ST-segment elevation or are at increased risk for bleeding and, therefore, are not suitable for fibrinolytic therapy.

At the time of the previous review, preliminary results from the TIMI-14 trial suggested that abciximab was effective in combination with a reduced dose of a fibrinolytic agent, improving blood flow rates in patients with acute MI.[71] The effect of abciximab in combination with a reduced-dose fibrinolytic on the incidence of various cardiac events had only been investigated in dose-finding studies. This has since been an area of considerable interest and recent randomised studies have evaluated the therapeutic use of abciximab in combination with reduced-dose tenecteplase,[72] reduced- or full-dose reteplase[73-75] or alteplase[75] compared with the use of a full-dose fibrinolytic agent alone (table VI).

An earlier study showed similar ischaemic outcomes in patients who received either abciximab therapy or abciximab in combination with a reduced dose of reteplase (SPEED).[74] However, recent large multicentre, nonblind studies have shown higher efficacy of abciximab in combination with either a reduced dose of tenecteplase or reteplase

than with the full-dose fibrinolytic agent alone. There may also be an increased propensity for bleeding with combined abciximab plus fibrinolytic therapy relative to fibrinolytic therapy alone and this is discussed in greater detail in section 4.2.

In the ASSENT-3 study, patients were randomised within 6 hours of onset of symptoms to receive tenecteplase 30–50mg (depending on bodyweight) with enoxaparin (30mg IV followed by 1 mg/kg subcutaneously, then subcutaneously every 12 hours up to discharge, revascularisation or for a total of 7 days; n = 2040), unfractionated heparin (60 U/kg bolus then 12 U/kg/h to maintain activated partial thromboplastin time (aPTT) of 50–70 seconds, then as needed; n = 2038) or abciximab (n = 2017).[72] Patients treated with abciximab received a reduced weight-adjusted dose of tenecteplase (range 15–25mg).

At 30 days, the primary efficacy endpoint of mortality, in-hospital reinfarction or in-hospital refractory ischaemia was reduced to a significant extent (≈30%) in patients who received either abciximab or enoxaparin compared with unfractionated heparin (table VI).[72] In addition, this was seen for the combined endpoint which also included in-hospital intracranial haemorrhage or in-hospital major bleeds for the three treatment groups (14.2% vs 13.8% vs 17.0%, respectively; p = 0.0081), in-hospital reinfarction (2.2% vs 2.7% vs 4.2%; p = 0.0009) and in-hospital refractory ischaemia (3.2% vs 4.6% vs 6.5%; p < 0.0001), although mortality did not differ significantly (6.6% vs 5.4% vs 6.0%). Both enoxaparin and abciximab showed greater efficacy than unfractionated heparin on the overall event rate and in various subgroups (males, age ≤75 years, patients without diabetes mellitus and in all infarct locations), but showed similar efficacy in female patients, those aged over 75 years and patients with diabetes mellitus.[72]

The large GUSTO-V study investigated the comparative efficacy of reteplase versus half-dose reteplase with abciximab.[73] Patients received either full-dose reteplase alone (n = 8260) or combination abciximab plus half-dose reteplase (n = 8328) within 6 hours of presentation with an acute ST-segment elevation MI. All-cause mortality at 30 days, the primary endpoint, was similar between the two groups (5.9% vs 5.6%; table VI) and did not differ with sex, age (greater or less than 75 years), the presence of diabetes mellitus, location of MI or time to treatment. Early percutaneous coronary intervention (within 6 hours) was performed more often in the reteplase than combination group (8.6% vs 5.6%; p < 0.0001); this difference remained after 7 days (27.9% vs 25.4%; p < 0.0001). In addition, the composite of death, reinfarction or urgent percutaneous revascularisation was lower in the abciximab and reteplase group than in the group receiving reteplase alone (16.2% vs 20.6%; p < 0.0001).[73]

3.2.3 Reperfusion during Acute Myocardial Infarction

The use of abciximab alone or in combination with fibrinolytic therapy on reperfusion during acute MI has been investigated in the TIMI-14,[76,77] SPEED[74] and GRAPE trials.[78] At the time of the previous review only preliminary results were available; these suggested that abciximab together with alteplase or streptokinase allowed reperfusion to be achieved with reduced doses of the fibrinolytic drug.[8] Myocardial perfusion was evaluated according to TIMI myocardial perfusion grade.

The TIMI-14 trial compared therapy with alteplase or reteplase, either with or without concomitant abciximab and/or revascularisation.[79] The alteplase arm consisted of two phases: dose-finding (n = 677) and dose-confirmation (n = 888).[76] During the dose-finding phase, patients with acute MI of <12 hours' duration were randomised to receive a standard dose of alteplase (15mg bolus followed by an initial infusion of 0.75 mg/kg up to 50mg over 30 minutes, then 0.50 mg/kg up to 35mg over 60 minutes), abciximab alone or in combination with a

reduced dose of streptokinase (total dose range 500–1500U × 10^3) or alteplase (total dose 20 or 35mg). In the dose-confirmation phase, all patients who received abciximab also received alteplase (15mg bolus then 35mg IV infusion over 60 minutes) and then either low-dose (60 U/kg bolus then 7 U/kg/h infusion [to target activated partial thromboplastin time of 50–70 seconds]) or very low-dose heparin (30 U/kg bolus then 4 U/kg/h infusion). Coronary angiography was performed within 90 minutes of thrombolysis and before percutaneous coronary revascularisation.[76]

At 90 minutes, TIMI grade 3 flow rates (the primary efficacy endpoint) in patients who received abciximab alone were lower than in those treated with alteplase alone (32% and 57%); flow rates were significantly higher in the alteplase 50mg plus abciximab group than in the group receiving alteplase alone at both 60 minutes (72% vs 43%; p = 0.0009) and 90 minutes (77% vs 62%; p = 0.02).[76]

In addition, TIMI grade 3 flow rates at 60 and 90 minutes in patients treated with full-dose reteplase were similar to those seen with full-dose abciximab plus a reduced dose of reteplase (≈70–75%; figure 4). Patients were randomised to receive either reteplase given as two 10U boluses 30 minutes apart (n = 102), or abciximab in combination with a reduced dose of reteplase (either two 5U boluses [n = 105] or 10U then 5U [n = 92]) in this arm of the TIMI-14 trial.[77]

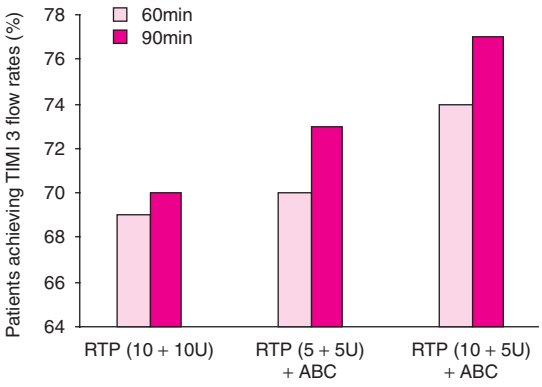

Fig. 4. Effect of abciximab in combination with fibrinolytic therapy on TIMI grade 3 blood flow rates at 60 and 90 minutes after percutaneous coronary intervention. Patients enrolled into the reteplase (RTP) arm of the TIMI-14 trial were randomised to receive either RTP alone (two 10U boluses given 30 minutes apart; n = 102), or abciximab (ABC; 0.25 mg/kg bolus then 0.125 μg/kg/min for 12 hours) in combination with RTP (either two 5U boluses, or a 10U and 5U bolus given 30 minutes apart; n = 105 and 92, respectively).[77]

In the multicentre SPEED study, 294 patients with acute MI were randomised to receive either abciximab or reteplase alone (two 10U boluses 30 minutes apart), or abciximab together with varying doses of reteplase (from 5–10U total) within 12 hours of onset of chest pain.[74] Angiographic measurements were taken 60 and 90 minutes after initiation of reperfusion therapy. TIMI grade 3 flow 60–90 minutes after reperfusion treatment (the primary endpoint) was achieved in 27% of patients treated with abciximab alone (n = 48) and was highest in 60 patients who received abciximab and reteplase 5 + 5U (62%; p = 0.001 vs abciximab alone). Overall, 30-day event rates were low and did not differ appreciably between groups (table VI).[74] In the second phase of this study, patients treated with abciximab and reteplase 5 + 5U (n = 100) showed similar rates of TIMI grade 3 flow 60–90 minutes after reperfusion treatment to patients who received reteplase 10 + 10U alone (n = 98; achieved in approximately 50% of patients in either group).[74]

The GRAPE study investigated the use of abciximab in 60 patients who showed onset of symptoms within 6 hours and were to undergo angioplasty. No significant difference was seen between the number of patients who received abciximab (0.25 mg/kg bolus then 10 μg/min IV infusion for 12 hours) within 2.5 hours of onset of symptoms achieving grade 2 and 3 flow rates and those who did not (33% vs 46%). Similarly, no differences were apparent between patients who underwent angioplasty within 45 minutes of receiving abciximab and those who did not.[78]

Therefore, overall these results confirm earlier results, which suggest that although the use of abciximab alone may not be effective in achieving reperfusion, abciximab in combination with a reduced-dose fibrinolytic drug is as effective as a full-dose fibrinolytic drug alone.

3.3 Pooled Analyses

The largest of the pooled analyses reported in this section involved >9000 randomised patients enrolled in the EPIC, EPILOG, EPISTENT, ISAR-2, RAPPORT, ERASER, ADMIRAL and CADILLAC trials.[80] All studies were randomised, double-blind and placebo-controlled except for ISAR-2 and CADILLAC, where treatment was nonblind. Patients received abciximab as a 0.25 mg/kg bolus 60 minutes before undergoing percutaneous coronary intervention followed by a 12-hour infusion (24-hour infusion in one of the arms in the ERASER study); all patients received aspirin and heparin. Follow-up was available for between 6 months and 3 years. The studies included in these analyses were performed in a variety of patient types and used differing heparin dosage regimens.

Mortality at 1 year decreased with abciximab treatment in all studies and mortality was also significantly reduced with abciximab plus stenting in the EPISTENT study ($p = 0.043$). Overall, mortality was reduced ≈30% with abciximab compared with placebo (hazard ratio 0.71; $p = 0.003$). Mortality was reduced to a similar extent when abciximab was combined with either angioplasty or stenting (both ≈30%).[80]

Variables associated with increased mortality identified by survival regression in patients who received abciximab or placebo were increasing age ($p < 0.001$), female sex ($p = 0.047$), low bodyweight ($p = 0.013$), previous CABG ($p < 0.001$), history of chronic heart failure ($p < 0.001$), diabetes mellitus ($p = 0.004$), history of cancer ($p < 0.001$), history of hypertension ($p < 0.001$), no previous percutaneous coronary intervention ($p = 0.018$), history of peripheral vascular disease ($p < 0.001$), no percutaneous coronary intervention attempted ($p = 0.003$), multiple vessels attempted ($p < 0.001$) and treatment with placebo ($p = 0.011$).[80]

In addition, several pooled analyses are available from the EPIC, EPILOG and EPISTENT trials.[81-84] These showed that the treatment benefit with abciximab was similar between men and women, as indicated by 30-day and 6-month mortality outcomes (composite death, MI or urgent revascularisation), although increased rates of bleeding (both minor and major) were observed in women (see also section 4.1.1).[82] A decrease in combined death/MI was seen in patients with ACS (UAP with chest pain within 48 hours, evolving MI or acute MI within 7 days) compared with stable angina pectoris ($p = 0.05$), but not in mortality alone ($p = 0.63$).[83]

There was no statistically significant difference between the 30-day or 6-month composite endpoint (death, MI or urgent revascularisation) rates between smokers ($n = 2236$) and nonsmokers ($n = 4283$) who received abciximab. Smoking was an independent predictor of poor outcome at 30 days (odds ratio 1.22; $p = 0.03$), but not at 6 months. In contrast, abciximab therapy was predictive of improved outcome at both 30 days and 6 months (odds ratios 0.52 and 0.59, respectively; both $p < 0.001$).[81]

Mortality at 1 year was reduced in 888 patients with diabetes mellitus who received abciximab compared with 574 who received placebo (2.5% vs 4.5%; $p = 0.031$); mortality was also lower in patients with type 1 diabetes mellitus treated with abciximab than in those receiving placebo ($n = 265$ and 197, respectively), although this did not achieve statistical significance (4.2% vs 8.1%).[84] A reduction in the combined endpoint of death, MI or target-vessel revascularisation (29.1% vs 34.3%; $p = 0.022$) and MI alone (4.0% vs 9.7%; $p < 0.001$) was seen in patients who received abciximab compared

with patients who received placebo. Predictors of 1-year mortality in a multivariate model were a history of type 1 diabetes mellitus, hypertension, chronic heart failure, age ≥65 years or a type B2/C lesion.[84]

A pooled analysis comparing the effect of the various percutaneous coronary interventions used in the EPIC, CAPTURE, EPILOG, RAPPORT and EPISTENT trials (n = 8007) demonstrated significant reductions in the incidence of mortality or MI at 30 days and 6 months compared with placebo when either angioplasty, elective or bailout stent or directional coronary atherectomy were used in combination with abciximab therapy (hazard ratios range 0.37–0.64).[85] Combined results from the EPILOG and EPISTENT trials also showed a significant reduction in death or MI at 1 year in patients receiving abciximab in combination with either angioplasty (hazard ratio 0.51; $p < 0.001$) or stent (hazard ratio 0.60; $p = 0.02$) but not placebo plus stent (hazard ratio 1.14; $p = 0.46$) compared to those receiving placebo plus angioplasty.[86]

3.3.1 Comparison with Other Platelet Glycoprotein IIb/IIIa Antagonists

The two meta-analyses reported in this section compared results from prospective, randomised, placebo-controlled studies involving the therapeutic use of abciximab, eptifabatide or tirofiban in patients undergoing percutaneous coronary intervention.[87,88]

The first compared 30-day outcomes in 8876 patients who received either abciximab, tirofiban or eptifibatide in the EPIC, EPILOG, EPISTENT, CAPTURE, RAPPORT, Integrilin to Minimize Platelet Aggregation and Prevent Coronary Thrombosis-1 (IMPACT-1), IMPACT-II and Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis (RESTORE) studies.[87] Briefly, the platelet GP IIb/IIIa antagonist was given shortly before the interventional procedure (except in CAPTURE, where treatment was administered 18–24 hours before percutaneous coronary intervention), and treatment duration following revascularisation ranged from 1–36 hours. All patients also received aspirin and heparin. Overall, no significant reduction in mortality was observed in groups who received abciximab (odds ratio 0.69), eptifibatide or tirofiban (odds ratio for both drugs 0.74) compared with placebo. However, the incidence of acute MI was more than halved with abciximab (odds ratio 0.49; $p = 0.001$), but not with eptifibatide or tirofiban (odds ratio 0.85); all drugs significantly reduced the need for urgent revascularisation (odds ratios 0.42 for abciximab and 0.76 for eptifibatide and tirofiban; $p = 0.001$ and 0.023).[87]

The second analysis pooled results from the randomised and placebo-controlled CAPTURE, Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin (eptifibatide) Therapy (PURSUIT) and Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs (PRISM-PLUS) trials, which administered either abciximab, eptifibatide or tirofiban to patients with ACS (without persistent ST-segment elevation) undergoing percutaneous coronary intervention.[88] A 34% reduction in the risk of death or nonfatal MI was seen in patients who received a platelet GP IIb/IIIa antagonist (n = 6125) compared with placebo (n = 6171; $p < 0.001$). In addition, the event rate during the 48 hours after percutaneous coronary intervention was reduced to a greater extent in patients who received a platelet GP IIb/IIIa antagonist than in those receiving placebo (4.9% vs 8.0%; $p < 0.001$), but did not differ significantly after this time.[88] It is important to note that direct comparative trials give more valid results than meta-analyses, which may not be particularly reliable if patient groups and drug dosages differ.

3.4 In Unstable Angina Pectoris

Results from the CAPTURE study were reported in the previous review in *Drugs*.[8] Briefly, patients

with refractory UAP received either placebo or abciximab (0.25 mg/kg bolus then continuous infusion 10 μg/min) 18–24 hours before undergoing percutaneous coronary revascularisation. All patients also received IV nitroglycerin (glyceryl trinitrate), β-blockers, calcium antagonists and other cardiovascular drugs as necessary. A relative reduction of 29% was seen in the primary 30-day endpoint (death, MI or urgent intervention to treat ischaemia) in patients who received abciximab, largely as a result of a reduced incidence of MI. However, the beneficial effect of abciximab was no longer evident at the 6-month follow-up, where the incidence of ischaemic complications was ≈30% in both groups.[49]

More recent data published from the CAPTURE study focused on angiographic treatment and outcomes,[89] recurrent ischaemia[90] and the relationship between serum troponin T levels and potential clinical benefit with abciximab.[91,92]

Thrombus resolution was greater both before and during angioplasty in 1197 patients with two available angiograms who were treated with abciximab than in those receiving placebo ($p = 0.033$).[89] Repetitive ischaemia and total ischaemic burden were both significantly reduced in a subset of patients who underwent continuous electrocardiographic monitoring and who received abciximab, although the incidence of recurrent ischaemia did not differ between patients treated with abciximab and placebo.[90]

Approximately one-third of patients (excluding those presenting with MI 14 days prior to study entry) for whom serum samples were available ($n = 890$) showed elevated troponin T levels (>0.1 μg/L) at study entry which correlated with an increased risk of death or nonfatal MI at 6 months.[91] The relative risk of death or nonfatal MI associated with abciximab treatment, compared with placebo, in these patients was reduced approximately 70% ($p = 0.002$). This was mainly attributable to a reduction in the rate of MI (odds ratio 0.23; $p < 0.001$). No relationship was observed in patients without elevated serum troponin T levels.

3.5 In Patients Without Early Revascularisation

One large randomised, multicentre study (GUSTO IV-ACS) has investigated whether abciximab would reduce the composite endpoint of death or MI in patients with high risk ACS who were not scheduled to undergo early revascularisation (within 12 hours of end of infusion).[93] Patients received either placebo ($n = 2598$), abciximab bolus and 24-hour infusion ($n = 2590$) or abciximab bolus and 48-hour infusion ($n = 2612$) in addition to aspirin and either unfractionated or low-molecular-weight heparin (dalteparin). Baseline characteristics were well balanced between the groups; 28% of all patients had evolving MI, 59% were positive for serum troponin T or I and 80% showed ST-segment depression. Coronary revascularisation was performed in 30% of patients within 30 days of study entry.

At 48 hours, higher mortality was evident in patients who received either regimen of abciximab than in placebo recipients (odds ratios 2.3 and 2.9 for 24- and 48-hour abciximab infusions, respectively; $p = 0.048$ and 0.007 vs placebo); the incidence of MI and the combined endpoint of death or MI did not differ significantly between the groups. Similarly, no differences were apparent between the groups in any of the endpoints at either 7 or 30 days (primary endpoint) after treatment. Analysis of various subgroups, including sex, age, weight, presence of diabetes mellitus, geographical region, ST-segment depression and positive troponin T revealed no significant benefit of treatment with abciximab; however, a significantly greater proportion of women treated with the 48-hour abciximab infusion showed adverse outcomes (either death or MI) than those receiving placebo at 30 days (10.1% vs 7.2%, p value not reported).[93]

4. Tolerability

This section provides a brief overview of the incidence and severity of bleeding complications and thrombocytopenia previously reported and includes new data from patients enrolled in the large ADMIRAL,[63] GUSTO IV-ACS[93] and TARGET[51] clinical trials. In addition, new data in patients with acute MI concurrently receiving various fibrinolytic therapies are presented.

4.1 Overview of Haematological Effects

The most commonly occurring adverse events associated with the use of abciximab are bleeding complications and thrombocytopenia, although the risk of major bleeding can be limited through careful selection of patients, use of a low-dose bodyweight-adjusted regimen of heparin, discontinuation of heparin immediately following revascularisation, early removal of the vascular sheath and femoral artery access site care (also see section 6).

4.1.1 Incidence of Bleeding

In recent large, randomised clinical trials (ADMIRAL,[63] GUSTO IV-ACS[93] and TARGET[51]), major bleeding with a standard dose of abciximab (0.6–0.7% of patients) was similar to that seen with placebo (0% and 0.3%)[63,93] and tirofiban (0.9%),[51] although extension of the abciximab infusion to 48 hours significantly increased the incidence of major bleeding complications relative to placebo in one arm of the GUSTO IV-ACS trial (1% vs 0.3%; $p < 0.05$).[93] However, rates of minor bleeding with abciximab were significantly increased (3–12.1%) compared with either placebo (2% and 3.3%)[63,93] or tirofiban (2.8% vs 4.3%) [all $p < 0.05$].[51]

Data from the CADILLAC study suggests that addition of abciximab to either stenting or to coronary angioplasty has no significant effect on the incidence of moderate or severe haemorrhagic complications. Intracranial haemorrhage was also similar between treatment groups.[64] Furthermore, in preliminary results of the multicentre, nonrandomised, nonblind NICE 3 study, patients with ACS were treated with enoxaparin and either abciximab (n = 147), tirofiban (n = 217) or eptifibatide (n = 252). Following treatment with abciximab, non-CABG major bleeding was observed in 0.7% of patients compared with 1.4% and 3.2% of patients who received tirofiban or eptifibatide. In patients who also underwent percutaneous coronary intervention, 0%, 0.9% and 2.4% had major non-CABG bleeding, respectively.[94]

Pooled analysis from the placebo-controlled EPIC, CAPTURE, EPILOG, RAPPORT and EPISTENT trials also suggests that the incidence of minor, but not major, bleeding is significantly increased relative to placebo following either angioplasty or elective stenting; rates of minor bleeding with bailout stenting and directional atherectomy were similar.[85] Rates of major bleeding increased in patients who received abciximab compared with placebo in a meta-analysis of eight placebo-controlled trials involving the use of platelet GP IIb/IIIa antagonists in percutaneous coronary intervention (5.8% vs 3.8%; $p = 0.001$). In contrast, the incidence of major bleeding among patients treated with eptifibatide or tirofiban did not differ significantly from that with placebo (5.0% vs 4.3%).[87] Additionally, subgroup analysis from the EPIC, EPILOG and EPISTENT trials showed an increase in minor bleeding in female patients who received abciximab compared with placebo (4.7% vs 6.7%, $p = 0.017$). Minor bleeding complications were significantly higher in female than in male patients receiving abciximab (6.7% vs 2.2%; $p < 0.001$) and placebo (4.7% vs 2.3%, $p = 0.01$).[82]

A pooled analysis of the EPIC, EPILOG, EPISTENT, RAPPORT and CAPTURE trials in 5721 patients who received abciximab and heparin while undergoing percutaneous coronary intervention showed no excess of intracranial haemorrhage compared with that in placebo and heparin recipients (n

= 3321) [0.14% vs 0.09%].[95] In addition, two preliminary reports reported no significant increase in bleeding or in-hospital complications in patients undergoing revascularisation who were treated with abciximab and were either octogenarians[96] or had chronic renal insufficiency.[97]

The incidence of major and minor bleeding was significantly ($p < 0.001$) higher in prospectively enrolled consecutive patients who underwent percutaneous coronary intervention within 12 hours of acute MI and received abciximab (2.4% and 14.3%; n = 831) than those who did not (0.6% and 5.9%; n = 1728).[98] Patients treated with abciximab were more likely to have been treated within 12 hours of infarction and to have received heparin after the procedure; however, use of abciximab was independently associated with an increase in major and minor bleeding in multivariate analysis.

4.1.2 Thrombocytopenia

Thrombocytopenia (platelet count $<100 \times 10^9$/L) developed in 2.4–7% of abciximab-treated patients (the higher value was recorded in patients receiving a 48 hour infusion of abciximab in GUSTO IV-ACS) compared with ≈1% of placebo and 0.5% of tirofiban recipients in the ADMIRAL,[63] GUSTO IV-ACS[93] and TARGET[51] clinical trials. Severe thrombocytopenia (platelet count $<50 \times 10^9$/L) was observed in 0.9–2% of patients who received abciximab, 0.04% and 1.3% of placebo recipients and 0.1% of tirofiban recipients. Abciximab-induced thrombocytopenia develops rapidly and usually resolves after discontinuation of therapy.[8]

Mild thrombocytopenia (platelet count 90–100×10^9/L) was more common in patients undergoing coronary intervention enrolled in the EPIC, EPILOG and CAPTURE studies who were treated with abciximab compared with placebo recipients (4.2% vs 2.0%; $p < 0.001$), as was severe thrombocytopenia (platelet count $<50 \times 10^9$/L; 1.0% vs 0.4%; $p = 0.01$). In the CADILLAC study, the incidence of thrombocytopenia was also significantly lower in patients receiving angioplasty only compared to those patients receiving abciximab with either angioplasty or stenting.[64] The incidence of mild or severe thrombocytopenia was not significantly increased in patients who received either eptifibatide or tirofiban in prospective, randomised, placebo-controlled trials.[99] More recently, factors associated with the development of thrombocytopenia in a pooled analysis from the EPIC, EPILOG and EPISTENT trials (n = 178; 2.4% of all patients) were age >65 years, weight <90kg, baseline platelet count <200 x 10^9/L, treatment with abciximab and enrolment in the EPIC trial (all $p < 0.05$).[100] However, patients with thrombocytopenia who also received abciximab prior to coronary intervention had lower rates of bleeding and transfusion than other patients with thrombocytopenia.

Pseudothrombocytopenia (defined as either differing platelet counts with two anticoagulants, platelet clumping on a blood smear from anticoagulated blood, normal platelet count on a blood smear from nonanticoagulated blood or an unexplained reduction in platelet count at 30 minutes to 4 hours after abciximab bolus with recovery to normal) has been reported in an earlier clinical study,[101] although the implications of this for the treatment of patients with abciximab is unknown. 2.1% of patients treated with abciximab were identified as having pseudothrombocytopenia in pooled data from the CAPTURE, EPIC, EPILOG and EPISTENT trials compared with 0.6% of patients who received placebo ($p < 0.001$).[102] Approximately one-third of all patients with thrombocytopenia had pseudothrombocytopenia. Twelve percent of abciximab-treated patients required early cessation of treatment and none in the placebo group; this is in contrast to 34.6% and 44.6% of all patients with thrombocytopenia, respectively. However, the incidence of bleeding, stroke, transfusion or repeat revascularisation was not increased in patients with pseudothrombocytopenia.[102]

Table VII. Incidence of bleeding complications in large, randomised, nonblind, multicentre clinical trials of abciximab (ABC) in combination with a reduced dose of a fibrinolytic drug in patients undergoing percutaneous coronary intervention. All patients received aspirin and bodyweight-adjusted heparin in addition to study treatment

Study	Treatment[a]	Heparin regimen	No. of pts	Bleeding complications (% of pts)		Thrombocytopenia (% of pts)	
				major	minor	platelet count $<100 \times 10^9$/L	platelet count $<50 \times 10^9$/L
ASSENT-3[72]	ABC + Tenecteplase (half dose)	Low dose	2017	4.4*	35.3**	3.2**	1.1**
	Tenecteplase	Enoxaparin	2040	3.0	22.6	1.2	0.3
	Tenecteplase	Std dose	2038	2.2	18.7	1.3	0.3
GUSTO-V[73]	ABC + Reteplase (half dose)	Low dose	8328	1.1**	20.0**	2.9**	1.2**
	Reteplase	Std dose	8260	0.5	11.4	0.7	0.1

a Details of regimens are presented in table VI.

pts = patients; **std** = standard; * p = 0.0005, **p < 0.0001 vs comparators.

4.2 In Combination with Fibrinolytic Therapy

Major bleeding occurs in approximately 20–25% of patients who receive abciximab within 24 hours of full-dose fibrinolytic therapy, although the incidence of intracranial haemorrhage is similar to that seen in all patients treated with a fibrinolytic drug alone.[103] Therefore, the potential for bleeding complications is a particular concern in patients treated with a combination of abciximab and a fibrinolytic drug. This section focuses on studies which have investigated the use of abciximab in combination with either tenecteplase, reteplase or alteplase compared with the fibrinolytic drug alone (refer to section 3.2.2 for study details).

Overall, rates of minor and major bleeding associated with combination abciximab and either reduced-dose reteplase or tenecteplase treatment in the ASSENT-3 and GUSTO-V trials were consistently and significantly higher than those for either reteplase or tenecteplase alone, as were rates for thrombocytopenia (table VII). Bleeding (of any severity) was more frequent in patients who received reteplase and abciximab in the GUSTO-V study than in the group given reteplase alone (24.6% vs 13.7%; p < 0.0001) but bleeding was not increased in patients subsequently undergoing CABG or a cardiac catheterisation procedure.[73] In the ASSENT-3 study, combination therapy with tenecteplase plus abciximab with enoxaparin produced significantly lower rates of the primary efficacy plus safety endpoint than tenecteplase plus unfractionated heparin (14.2% and 13.8% vs 17%; p < 0.05).[72] However, the incidence of major bleeding complications was significantly higher with tenecteplase plus abciximab than with tenecteplase plus unfractionated heparin in patients aged >75 years (4.1% vs 13.3%) or among those with diabetes mellitus (2.2% vs 7.0%).[72]

Major bleeding rates in the SPEED trial were 3.3% for abciximab alone, 5.3% and 9.8% for combination abciximab and reteplase and 3.7% for reteplase alone but differences were not significant. The use of either standard- or low-dose heparin did not affect the incidence of major bleeding (6.3% vs 10.5%).[74]

Transfusion rates were higher with abciximab plus fibrinolytic therapy than with the fibrinolytic alone in GUSTO-V (5.7% vs 4%; p = 0.0001)[73] and ASSENT-3 (4.2% vs 2.3%; p = 0.001),[72] but were similar between groups in the smaller SPEED trial.[74] Rates of intracranial haemorrhage were similar for all groups in all trials (generally <1%).[72-75]

4.3 Readministration

At the time of the previous review, evidence suggested that abciximab could be safely readministered to patients, although a greater incidence, severity and duration of thrombocytopenia had been reported.[8] In addition, the human-murine composition of the monoclonal chimaeric Fab fragment comprising abciximab is potentially antigenic and has led to concern over the potential for anaphylaxis and attenuated efficacy.[104]

Human antichimaeric antibodies (HACA) were documented in 6.5% of patients in the EPIC trial.[47] However, no cases of anaphylactic, allergic or other hypersensitivity reactions have been reported in 500 patients enrolled in the ReoPro Readministration Registry, of whom 4.8% were HACA-positive before readministration of abciximab. Major bleeding was reported in 1.6% of patients, all of whom required red blood cell transfusions. Thrombocytopenia was seen in 4.6% of these patients (severe in 3.2%) and was unrelated to baseline HACA status. Clinical success (defined as angiographically successful procedure without any major adverse cardiac events) was similar between patients who received abciximab for the first and second time (94.7% vs 90.9%).[105]

A retrospective analysis of 164 consecutive patients undergoing percutaneous coronary intervention indicated that 4% experienced severe thrombocytopenia (platelet count $<50 \times 10^9$/L) following readministration of abciximab. Moreover, the rate of severe thrombocytopenia increased when abciximab was readministered within 2 weeks of the first dose (12% vs 2%; $p = 0.046$) as was the requirement for a blood transfusion (20% vs 6%; $p < 0.05$).[106]

5. Pharmacoeconomic Considerations

The pharmacoeconomics of abciximab for use in percutaneous coronary revascularisation were recently reviewed in *PharmacoEconomics*.[9] This section provides an overview of previous analyses from major trials and focuses on newly available information pertaining to the pharmacoeconomics of abciximab from the EPISTENT and EPILOG clinical trials and in comparison with other platelet GP IIb/IIIa antagonists.

Economic analyses attached to the EPILOG and EPISTENT trials were prospectively designed; however, the majority of other analyses were retrospective. There have also been several retrospective pharmacoeconomic analyses from the practice setting and these are reported in section 5.2. A notable exception to this was the prospectively designed PRICE trial (see section 5.3).

5.1 Cost Analyses Based on Major Clinical Trials

A previously reported prospective economic substudy (in which hospital costs, inpatient physician fees and drug acquisition costs were considered) carried out in conjunction with the EPIC study in high-risk patients showed use of abciximab resulted in an incremental cost compared with standard care of $US293 per patient over 6 months (1991/1992 values). Abciximab was cost saving in patients with UAP in a subgroup analysis. This section focuses on more recent pharmacoeconomic data associated with the EPISTENT and EPILOG studies.

5.1.1 Analyses Based on EPISTENT

A cost analysis is available from a prospectively defined subset of patients in the US who participated in the EPISTENT study (n = 1438).[57] Total baseline hospital costs were higher in the stent plus abciximab than in the stent plus placebo or angioplasty plus abciximab groups ($US13 228 vs 11 923 vs 11 357; 1997 values; $p < 0.0001$). At 1 year, follow-up costs (including hospital and physician costs) were similar between groups ($US5096, $US4723 and $US6013 for the three groups, respectively); cumulative costs at 1 year were higher in both the stent plus abciximab (by $US932) and

Table VIII. Resource use and average costs per patient in the EPILOG study.[108] Data were collected for patients at both low and high risk of ischaemic complications after percutaneous coronary revascularisation. Year of currency not specified. Study design and dosage details are presented in section 3.1.2. All patients received aspirin and heparin

	Placebo + std heparin (n = 939)	Abciximab + low-dose heparin (n = 935)	Abciximab + std heparin (n = 918)
Resource use (% of patients)			
Urgent repeat revascularisation during initial hospitalisation	4.0	2.0*	1.9*
Follow-up hospitalisations	47.2	51.1	49.2
Follow-up PCI	12.0	15.8	14.3
Costs per patient ($US)			
Initial hospitalisation[a]	9632	10 215**	10 546**
During 6-month follow-up[b]	3568	4221	3923
Cumulative 6-month medical cost[c]	13 200	14 436*	14 468*

a Including cost of abciximab.

b Included hospital cost and physician fees.

c Cost of hospitalisation at baseline and follow-up costs (including abciximab).

PCI = percutaneous coronary intervention; **std** = standard; * $p < 0.05$, ** $p < 0.001$ vs placebo.

angioplasty plus abciximab ($US581) groups than in the stent plus placebo group ($p = 0.0008$).[57]

In addition, one cost analysis extrapolated the results of the EPISTENT trial to a European setting based on an economic evaluation from the BElgian NEtherlands Stent (BENESTENT)-II study.[107] The analysis was from a societal perspective and included only direct medical costs. The estimated mean costs per patient after 6 months' treatment with either stent plus placebo, stent plus abciximab or angioplasty plus abciximab were EUR8207, EUR8971 ($p < 0.01$ vs both groups) and EUR8085, respectively (1998 values).

5.1.2 Analyses Based on EPILOG

A prospectively designed economic substudy of EPILOG gathered information on medical costs and medical resource use in both high- and low-risk patients undergoing percutaneous coronary revascularisation (table VIII).[108] Cost savings in baseline hospital costs associated with efficacy and bleeding events with abciximab were for the most part attributed to a reduced requirement for repeat revascularisation and bailout stenting and shorter hospital stays. At baseline, hospitalisation costs associated with abciximab were significantly higher than for the placebo group. Over a 6-month follow-up period, hospitalisation costs remained higher in the abciximab groups because of an increase in the number of patients undergoing nonurgent revascularisation. This resulted in significantly greater cumulative 6-month costs in the abciximab groups than with placebo.[108]

5.1.3 Analyses Based on Other Studies

An abstract has reported on the cost of abciximab and stenting from the CADILLAC trial (see section 3.2.1 for study details).[109] These preliminary results suggest that the mean (or median) hospital costs associated with either angioplasty or stenting in combination with abciximab are not significantly different from those seen with angioplasty alone. Moreover, the average hospital stay was also similar between groups (range 3.8–4.4 days).

5.2 Cost Analyses In the Practice Setting

Three nonrandomised studies have compared clinical outcomes and costs of consecutive patients who received abciximab and underwent percutaneous coronary interventions in a single medical practice (year of currency not specified).[110-112]

In a US-based study, 3758 patients underwent elective revascularisation over a 2.5-year period; 908 received abciximab and 633 received abciximab plus a stent. Overall, the incidence of major cardiac events was significantly lower in patients who received abciximab with stenting or angioplasty than angioplasty alone (all $p < 0.002$) because of a decreased need for revascularisation. Total in-hospital costs were lower in patients who received angioplasty alone than for the other patients ($p < 0.001$). Independent predictors of increased costs in multivariate regression analysis were death ($US16 098), urgent revascularisation ($US13 678), use of multiple stents ($US1423/device) and use of abciximab ($US1269).[111]

A Dutch observational study also showed a decreased incidence of major cardiac events in patients who received abciximab in addition to stenting compared with those who did not receive a stent (6.9% vs 16.9%; $p = 0.04$); however, total costs at 6 months were similar between the two groups (EUR7844 vs EUR7904).[112] In-hospital mortality was not significantly different between patients who did and did not receive abciximab in addition to coronary intervention ($n = 986$ and 486, respectively), but was lower at 6 months in patients who were treated with abciximab (4.98% vs 1.55%; $p = 0.003$).[110]

5.3 Cost Analyses in Comparison with Other Platelet Glycoprotein IIb/IIIa Antagonists

Among lower risk patients undergoing elective percutaneous coronary revascularisation, the use of abciximab therapy has been associated with higher total in-hospital and 6-month medical costs compared with eptifibatide therapy.[113] In a prospective study (PRICE) in the US, consecutive patients undergoing elective coronary revascularisation (excluding those with acute MI within 48 hours, or UAP with ST-segment elevation) were randomised to receive either abciximab ($n = 163$) or eptifibatide ($n = 157$). Subsequently, total median in-hospital costs were higher in those who received abciximab than eptifibatide ($US8268 vs $US7207; $p = 0.009$; 1998 values), primarily because of the higher acquisition cost of abciximab ($p < 0.0001$ vs eptifibatide); this was evident up to 30 days after treatment ($US8336 vs $US7207).[113] As this study excluded patients with acute MI, the data are not generalisable to other patient populations and the small staudy sample size means that it was insufficiently powered to detect clinical differences betwen treatments.[113]

The economic implications of the use of glycoprotein IIb/IIIa inhibitors have been examined in patients with acute coronary syndromes and undergoing percutaneous coronary intervention using data from up to 14 clinical studies.[114] For patients undergoing percutaneous coronary intervention, procurement costs ranged from $US400–$US1500 (1999 costs); for abciximab, mean procurement costs were estimated at $US1407 per patient treated. These costs were, at least partially offset by subsequent savings in other direct medical costs, and when the clinical outcomes of using abciximab in this setting (including coronary stenting) were accounted for, procurement costs of $US10 500–$US37 000 per death or MI prevented were estimated. Cost effectiveness ratios for abciximab were $US2875–$US14 765 per life-year or QALY saved.[114]

5.3.1 Effect of Abciximab on Length of Hospital Stay

Two retrospective analyses have compared the effect of treatment with abciximab and either eptifibatide or tirofiban on length of hospital stay in patients undergoing percutaneous coronary intervention.[115,116] Data were captured from the HCIA Clinical Pathways Database which included information from 72 hospitals in the US performing percutaneous coronary revascularisations between 1 July 1998 and 30 June 1999. Patients treated with abciximab spent fewer days in hospital than patients

who received tirofiban (3.34 vs 4.32 days; p < 0.001) even when the analysis was restricted to patients with acute MI (4.28 vs 5.09 days; p < 0.001).[116] Similarly, hospital stays for patients treated with abciximab were 0.83 days shorter than for those who received eptifibatide (p < 0.001).[115] In both analyses patients treated with tirofiban or eptifibatide were significantly older and a higher proportion received a stent or angioplasty compared with those in the abciximab groups.[115,116]

5.4 Cost-Effectiveness Analyses

5.4.1 Based on Major Clinical Trials

Costs included in a prospectively defined subset of patients who took part in the EPISTENT study in the US (n = 1438) were hospital costs, physician fees and drug acquisition costs ($US450/vial of abciximab). Lifetime cost effectiveness was evaluated based on US cost data and overall 1-year survival data.[57] Analyses were performed from a societal perspective but did not include productivity, nonmedical or outpatient costs; incremental costs beyond 1 year were discounted at 3%.

After taking incremental life expectancy into consideration, the stent plus abciximab group showed an incremental cost of $US932, or cost-effectiveness ratio of $US6213 per added life-year compared with the stent and placebo group. Compared with patients in the abciximab and angioplasty group, patients who received abciximab plus stent had an incremental cost of $US581 and a cost-effectiveness ratio of $US5291 per added life-year.[57]

The incremental cost-effectiveness ratios for the addition of abciximab to treatment in MI-free and major cardiac event-free patients when the results of the EPISTENT study were extrapolated to a European setting are presented in figure 5. Costs included the initial stenting procedure, cost of abciximab and the need for bailout stenting or repeated procedures. Follow-up costs included further use of abciximab, the requirement for repeat revascularisation and re-

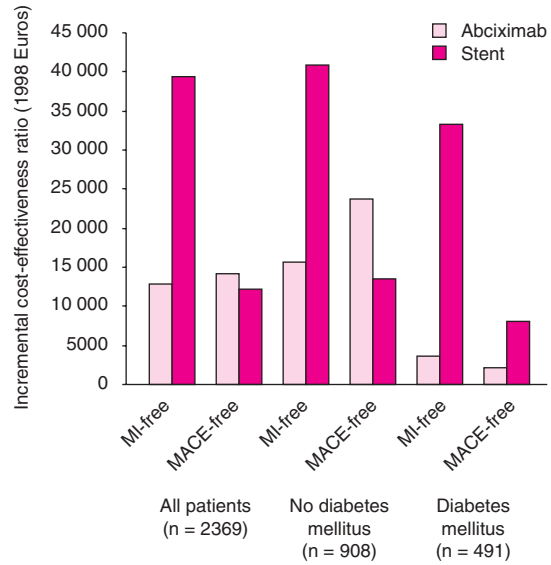

Fig. 5. Incremental cost-effectiveness ratios (cost per event avoided) at 6 months for the addition of either abciximab or stenting to treatment for patients enrolled in the randomised, placebo-controlled, multicentre EPISTENT study.[107] Estimates of unit costs were based on results from the economic study attached to BENESTENT II. All values are 1998 Euros. **MACE** = major adverse cardiac event; **MI** = myocardial infarction.

source use associated with MI. Initial hospitalisation costs included diagnostic procedures (hospital visits, tests and angiography), where subsequent visits did not.[107]

These values compare broadly with accepted benchmarks for cost-effectiveness in other medical arenas.[117] Accepted cost-effectiveness benchmarks for coronary bypass surgery compared with medical therapy, medical therapy compared with no medical therapy for severe hypertension and haemodialysis compared with no dialysis for chronic renal failure are US$32 678, US$7000 and US$35 000 per year of life saved (1993 costs).[117]

5.4.2 Based on Other Studies

One Italian-based analysis has evaluated the cost effectiveness of abciximab based on 6-month results from the EPILOG, EPIC (not including patients who received only abciximab bolus) and CAPTURE studies.[118] The cost of abciximab was calculated

assuming that patients were between 51 and 91kg and required three 10mg vials of the drug; event-associated costs were based on diagnosis-related groups. Costs are expressed in millions of lire (year of currency not specified). Total treatment costs associated with abciximab and placebo for 100 patients scheduled to undergo angioplasty were L1244 and L1079, respectively; increased costs in the abciximab group were primarily because of drug acquisition costs. The corresponding numbers of patients needed to treat to prevent one death, reinfarction, CABG, angioplasty or composite endpoint were 227, 24, 75, 37 and 21, respectively. Moreover, the cost-effectiveness ratios for patients in the abciximab and placebo groups were L16.6 and L15.4 per event-free patient (approximately $US7543 and $US6998; 2002 values), resulting in an incremental cost-effectiveness ratio of L34.3 ($US15 587) per event avoided at 6 months after intervention. The cost per year of life saved at this time point was L32.3 ($US14 678).[118]

5.4.3 In the Practice Setting

Incremental cost-effectiveness ratios (adjusted for nonrandomisation and expressed as euros per life-year gained) in a Dutch observational study, were EUR1243 for all patients and EUR1933 for those also receiving a stent; for patients with and without diabetes mellitus these were EUR617 and EUR1066, respectively.[112] Costs were based on values derived from the Netherlands in an economic substudy attached to BENESTENT-II.

In patients with acute MI undergoing percutaneous coronary intervention, those receiving abciximab had significantly lower risk-adjusted mortality than those not treated with glycoprotein IIb/IIIa inhibitors (odds ratio = 0.74, p = 0.007).[119] There was no significant difference between patients receiving eptifibatide or tirofiban and those not treated with this class of agent. Treatment with abciximab also resulted in a significantly shorter hospital stay of 0.21 days compared to those not receiving glycoprotein IIb/IIIa inhibitors. ($p < 0.0013$) [119]

6. Dosage and Administration

Abciximab is approved for use as an adjunct to heparin and aspirin for the prevention of ischaemic cardiac complications in patients undergoing percutaneous coronary intervention and for the short-term treatment of patients with UAP who have been scheduled for percutaneous coronary intervention within 24 hours after not responding to conventional therapy.[28] It has not been approved for use in combination with fibrinolytic drugs.

The recommended dosage of abciximab is a 0.25 mg/kg IV bolus administered 10–60 minutes before the start of percutaneous coronary intervention, followed by a continuous IV infusion of 0.125 μg/kg/min (up to a maximum of 10 μg/min) for 12 hours. Patients with UAP may be treated with abciximab 0.25 mg/kg IV bolus followed by an 18- to 24-hour IV infusion of 10 μg/min which finishes 1 hour (US recommendation) or 12 hours (UK recommendation) after percutaneous coronary intervention. Abciximab and heparin should be discontinued in the event of serious bleeding which is unable to be managed by compression alone.[28]

Because the risk of bleeding may be increased with abciximab therapy, the drug is recommended to be given in addition to a low-dose, weight-adjusted heparin regimen.[28] Abciximab is contraindicated where patients are at an increased risk for bleeding complications, such as those with active internal bleeding, recent gastrointestinal or genitourinary bleeding, history of stroke, bleeding diathesis, previous treatment with oral anticoagulants (within 7 days), thrombocytopenia, major surgery or trauma within the last 6 weeks, severe and uncontrolled hypertension, history of vasculitis or use of IV dextran prior to percutaneous coronary intervention. Caution is also required in patients receiving other drugs that affect haemostasis, including fibri-

nolytics, oral anticoagulants, NSAIDs, dipyridamole and ticlopidine or clopidogrel.

The risk of bleeding may be minimised through adherence to anticoagulation guidelines, careful vascular access site management, discontinuation of heparin following the procedure (within 6 hours if aPTT ≤50 seconds or ACT ≤175 seconds) and early femoral artery sheath removal.[28]

Platelet counts should be monitored before and during treatment (at approximately 2–4 following the bolus dose and at 24 hours prior to discharge). If thrombocytopenia (<100 × 10^9/L and a ≥25% decrease from the pretreatment value) is confirmed, abciximab (and possibly heparin) should be discontinued and appropriate treatment initiated. Platelet transfusions can be used to restore platelet function to reverse profound thrombocytopenia (<20 × 10^9/L), if patients require emergency surgery, or in the event of serious uncontrolled bleeding.[28]

Administration of abciximab may result in human anti-chimeric antibody formation (as indicated by approximately 5.8% of abciximab-treated patients in clinical trials).[28] Results from a small group of patients indicate that the incidence of the antibody formation may be increased upon abciximab readministration (further details available in section 4.3).[28]

7. Place of Abciximab in the Management of Ischaemic Heart Disease

Conventional therapy for patients with ACS has involved early initiation of medical management followed by noninvasive risk stratification to identify patients who require urgent catheterisation, and possibly revascularisation, rather than pharmacotherapy alone. Antiplatelet therapy with aspirin and antithrombotic therapy with heparin have been the cornerstone of treatment for patients with ACS. However, consistently observed benefits with GP IIb/IIIa antagonists as an adjunct to aspirin and heparin in large randomised clinical trials have also led to their therapeutic use in patients undergoing percutaneous coronary intervention. Furthermore, interventional management may consist of either early invasive or conservative strategies. No clear difference has been observed between the two,[120] although an invasive strategy is likely to be more beneficial in high-risk patients.[121]

Abciximab, eptifibatide and tirofiban are the three IV GP IIb/IIIa platelet antagonists currently approved by the US Food and Drug Administration for therapeutic use in ACS and/or as adjunctive therapy to percutaneous coronary intervention. In addition, American College of Cardiology/American Heart Association guidelines for management of percutaneous coronary intervention,[122] and European Society of Cardiology recommendations[123] for ACS both indicate the use of IV GP IIb/IIIa receptor antagonists in patients undergoing angioplasty, especially high-risk patients. Each of the GP IIb/IIIa antagonists has been approved for use in slightly different indications based on the results of major clinical trials. Abciximab is approved for use as an adjunct to percutaneous coronary intervention for the prevention of cardiac ischaemic complications in patients undergoing percutaneous coronary intervention or in patients with UAP not responding to conventional medical therapy when percutaneous coronary intervention is planned within 24 hours. In comparison, tirofiban is indicated for patients with unstable angina or non-Q-wave MI who are to be managed medically and those undergoing PTCA or atherectomy, and eptifibatide for patients undergoing percutaneous coronary intervention, including those undergoing intracoronary stenting, and patients with unstable angina/non-Q-wave MI, including those who are to be managed medically and those undergoing percutaneous coronary intervention.[124] Several orally administered GP IIb/IIIa platelet antagonists have also been developed; however, these have shown poor results in four large

clinical trials and none have been approved for clinical use.[125-127]

Abciximab has a stronger affinity for the GP IIb/IIIa receptor than do either tirofiban or eptifibatide; it also binds to vitronectin and Mac-1 receptors where the other platelet GP IIb/IIIa antagonists do not. While these other receptors modulate smooth muscle cell adhesion and proliferation[46] and are thought to be important for platelet-leucocyte interactions, the clinical significance of this is not yet apparent. Other important differences exist between these drugs. Tirofiban and eptifibatide have relatively short durations of action while the duration of action of abciximab may be longer (see section 2.1.1). In addition, the three drugs are structurally distinct: eptifibatide is a synthetic cyclic heptapeptide[33] and tirofiban a synthetic nonpeptide,[128] whereas abciximab is a monoclonal antibody.[8]

The TARGET study investigated the relative efficacies of abciximab and tirofiban as adjunctive therapy to percutaneous coronary intervention. Abciximab demonstrated a significantly greater reduction than tirofiban in the composite endpoint of death, nonfatal MI or urgent target-vessel revascularisation at 30 days. This difference in primary endpoint at 30 days was largely due to a significant reduction in the incidence of MI in patients treated with abciximab compared to those treated with tirofiban and this was maintained at 6 months (section 3.1.1). Interestingly, abciximab plus enoxaparin provided effective anticoagulation during percutaneous coronary intervention in this study. The low-molecular-weight heparins have been recommended for use as antithrombotic therapy in ACS;[121] whether the combination of low-molecular-weight heparins with abciximab is better than unfractionated heparin remains to be demonstrated in clinical trials.

The beneficial effect of abciximab in high-risk patients reported in the EPIC study is also confirmed in patients with differing risk levels, as shown by the findings of the EPISTENT and EPILOG studies (at 30 days and 1 year). A significantly reduced incidence of MI, target-vessel revascularisation and composite of death, MI and target-vessel revascularisation was observed in patients treated with abciximab compared with placebo, although not on death alone. This effect was consistent across a range of subgroups including age, sex, bodyweight or indication for revascularisation (section 3.1.2).

Patients with diabetes mellitus are at higher risk for ischaemic heart disease than patients without diabetes mellitus, potentially because of alterations in platelet aggregation and thrombus formation. In addition, outcomes both during and following revascularisation or CABG are worse in patients with diabetes mellitus than in those without.[129] The composite endpoint of death, MI or target-vessel revascularisation was reduced relative to placebo in a prospectively defined subset of patients with diabetes mellitus in EPISTENT who received abciximab in addition to stenting. There was also a 65% reduction in the 6-month mortality rate which was maintained at 1 year in patients receiving stent plus abciximab relative to those who received stent plus placebo; these differences in mortality rates between treatments were not statistically significant (section 3.1.2).

The diagnostic value of the serum troponins for identifying patients who may benefit from treatment with GP IIb/IIIa receptor antagonists has been shown in several studies. In troponin-positive patients with UAP, the relative risk of death or nonfatal MI associated with abciximab treatment, compared with placebo, in these patients was reduced approximately 70% and was mainly attributable to a reduction in the rate of MI. However, no relationship was observed in patients without elevated serum troponin T levels (section 3.4). In addition, several analyses have demonstrated the efficacy of GP IIb/IIIa antagonists in those undergoing early angiography and revascularisation.[48,49,130] Paradox-

ically, this was not replicated in a large prospective trial, GUSTO IV-ACS, of patients with UAP or non-Q-wave MI (58–60% of whom were serum troponin positive) treated with abciximab who were not scheduled to undergo early revascularisation and were given the drug as primary medical therapy (section 3.5). This was an unexpected result given the benefits demonstrated with other GP IIb/IIIa antagonists as primary medical therapy.[131-133] A number of factors may have contributed to the findings of this study. The event rate in the placebo group was ≈3% lower than expected and nearly 40% of patients were female. In addition, the low incidence of ST-segment depression may have also allowed patients without active coronary artery disease to be enrolled.[93] Whether this is an isolated finding, given the body of current evidence which suggests otherwise, requires further investigation.

The primary aim of therapy for acute MI is achievement of complete and timely coronary blood flow restoration, as restoration of normal antegrade flow is directly related to reductions in mortality.[4,134] Currently, this is achieved with either primary angioplasty or fibrinolytic therapy, which achieve TIMI grade 3 blood flows in approximately 80% and 40% of patients, respectively.[134] The use of stenting as an adjunct to angioplasty has been increasing over the past 5 years in the UK and was used in approximately half of all angioplasty procedures in 1996;[3] intracoronary stenting during primary percutaneous coronary intervention results in a wider arterial lumen and less infarct-related artery reocclusion.[4]

Long term, the addition of abciximab to stenting has shown reductions in mortality, repeated target-vessel revascularisation and angiographic restenosis. However, results from the ADMIRAL and CADILLAC studies appear in opposition to one another. Where the addition of abciximab to stenting was beneficial in patients with acute MI in the double-blind ADMIRAL study (reducing the primary composite endpoint approximately 60% compared with placebo at 30 days), combination of the two provided no additional benefit over either abciximab or stenting alone in the nonblind CADILLAC trial (see section 3.2.1). This may have been because of the early use of abciximab prior to revascularisation in more than 25% of patients in the ADMIRAL trial. In addition, baseline TIMI 3 flow rates were significantly higher in the combination group in this study than those randomised to receive stenting alone at baseline, whereas these groups were evenly balanced in the CADILLAC study. However, the lack of benefit demonstrated with combined abciximab and stenting in the CADILLAC trial may also have been a result of the relatively low-risk population, reflected in the overall low mortality rate compared with other primary trials involving percutaneous coronary intervention.

Additionally, adjunctive use of a platelet GP IIb/IIIa antagonist with a fibrinolytic drug is used to achieve patency and reperfusion of revascularisation procedures (facilitated percutaneous coronary intervention). The earlier SPEED and TIMI-14 studies showed that combination of a reduced-dose plasminogen activator (alteplase or reteplase) with abciximab provided myocardial reperfusion greater than or equivalent to the use of alteplase or reteplase alone. The combination of abciximab with reduced doses of a fibrinolytic agent in the recent GUSTO-V and ASSENT-3 studies has resulted in similar or improved mortality rates to that seen with standard fibrinolytic therapy, without a concomitant increase in intracranial haemorrhage or nonfatal disabling stroke (sections 3.2.2 and 4.2), although the incidence of bleeding was increased.[134] In particular, the incidence of bleeding in patients aged >75 years who received a abciximab-containing fibrinolytic regimen was three-times that observed in patients treated with a heparin-containing regimen. The currently ongoing Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FI-

NESSE) trial has been designed to compare therapy with abciximab either alone or with reteplase in patients undergoing primary stenting.[135]

Overall, it appears that the risk of minor, but not major, bleeding is increased with abciximab treatment in patients undergoing percutaneous coronary intervention. Although the risk of major bleeding was increased relative to placebo in some pooled analyses, this is probably due to the inclusion of the EPIC study which showed an excess risk of bleeding in abciximab-treated patients.[47] Subsequent large studies (ADMIRAL, GUSTO IV-ACS and TARGET) have shown a similar risk of bleeding to that with placebo with an improved protocol for administration of the drug. However, the risk of bleeding (both minor and major) is approximately twice that observed with fibrinolytic therapy alone when abciximab is combined with a reduced dose of a fibrinolytic drug. Importantly, bleeding events are costly, second only to CABG surgery; therefore, any increase in bleeding complications is likely to offset any potential cost savings achieved by a reduction in ischaemic endpoints.[136,137]

Treatment with abciximab is generally associated with higher costs than other treatments, such as eptifibatide, tirofiban and revascularisation alone, primarily because of increased drug acquisition costs. Overall, abciximab has been shown to be cost effective in patients receiving the drug in conjunction with stenting and in certain groups of patients at high risk of ischaemic complications. However, this may not extend to elective procedures, as suggested by the PRICE cost analysis, where the acquisition cost of the drug did not appear to be offset by other costs associated with treatment (see section 5.3). Prospective economic comparisons of abciximab, tirofiban and eptifibatide would help establish the relative cost effectiveness of the drugs.

In conclusion, an additional body of data has confirmed that the GP IIb/IIIa receptor antagonist abciximab reduces the short- and long-term risk of ischaemic complications in patients with ACS undergoing percutaneous revascularisation when used against a background of aspirin and heparin. High-risk patients (including those with diabetes mellitus) derive particular benefits from abciximab treatment. Clinical trials have also shown that adequate reperfusion is achieved in patients with acute MI when abciximab is given together with a reduced-dose fibrinolytic drug, although with increased rates of bleeding and thrombocytopenia compared with the fibrinolytic drug alone. Abciximab remains an important therapeutic option for the prevention of complications in patients with ischaemic heart disease undergoing revascularisation procedures.

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