

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

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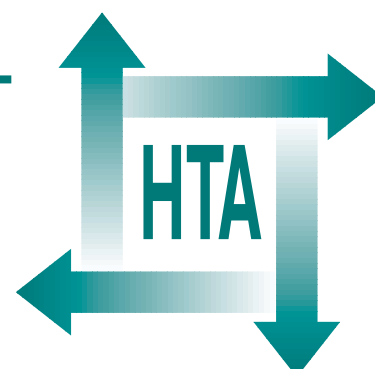
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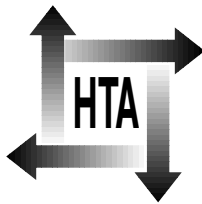


## *Executive summary*

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## Executive summary

### Background

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

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

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

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

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eptifibatide or lamifiban, four trials concerned with oral GPAs, and seven economic studies – two of which were unpublished company submissions.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

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- cost-effectiveness was uncertain, but one unpublished analysis suggested that eptifibatide was dominant to placebo in costs per life-years gained (LYG) at 30 days.

The second review considered 12 trials on the intravenous use of abciximab, tirofiban or

eptifibatide, and one trial of an oral agent. A total of 17 published economics studies and one company submission were also included. The main findings were:

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

### Specification for update/objectives

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

### Methods

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

### Results

#### Indication 1

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



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

### Indication 2

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

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

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

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

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

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

TACTICS, in which all patients received tirofiban, has also been included in the review because it is frequently referred to in the relevant company

submission (and was also identified in the update searches). A lower 30-day rate of death/MI was observed than in previous trials, suggesting that early GPA treatment might offer particular benefit when PCI was planned.

### Indication 3

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

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

### Cost-effectiveness

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

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

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

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

## Conclusions

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

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

The following conclusions may be drawn from the update:

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

## Recommendations for further research

Further research is desirable to:

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

## Publication

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