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

Authors' objectives
To determine the clinical and cost-effectiveness of the glycoprotein IIb/IIIa antagonists (GPAs) in three indications:

(1) for the acute treatment of non-ST-elevation acute coronary syndromes (ACSs);

(2) as an adjunct to percutaneous coronary interventions (PCIs); and

(3) alongside thrombolytic treatment for acute myocardial infarction (MI).

The evidence reviews for the first two indications are updates of two previous reviews (see Other Publications of Related Interest nos.1-2, respectively). (The first reference has also been abstracted for DARE).

Searching
Fifteen databases were searched up until September 2001, including the Cochrane Library, DARE, EMBASE, MEDLINE and HTA; the search terms were provided. The search results were de-duplicated against those of the two previous reviews. Authors of trials identified in the National Research Register and the Cochrane Heart Group were contacted for additional trials, and information that consultees provided to the National Institute for Clinical Excellence (as part of the review process for NICE guidance) was also searched. The bibliographies of the included studies were checked for further studies. Additional searches of four web-based registries, to identify any additional ongoing or late-breaking trials, were conducted in October 2001.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs), subgroup analyses of previously reported trials concerning one or more recognised high-risk groups (the elderly, diabetics, patients with positive troponins, patients with ST-depression on initial electrocardiogram), and full economic evaluations were eligible for inclusion. Pilot studies for other studies were excluded, as was one study that was only available in abstract form and reported only brief details. The duration of follow-up in the included studies ranged from 24 hours to 6 months for indication 1, 36 hours to 7 years for indication 2, and 24 hours to 1 year for indication 3.

Specific interventions included in the review
Studies of GPAs that are licensed in the UK (abciximab, eptifibatide and tirofiban) were eligible for inclusion. Studies that evaluated oral agents, or agents for which no licence applications were expected in the foreseeable future, were excluded. The comparator of interest was placebo. For indication 3, the thrombolytics eligible were alteplase, reteplase, streptokinase and tenecteplase (TNK), and the comparator was thrombolytic therapy alone. The participants would typically be also taking a range of standard medication such as aspirin and unfractionated heparin in unstable angina.

The included studies not only evaluated abciximab, eptifibatide and tirofiban as single agents, but also the following GPA interventions (in both the initial and updated reviews): for indication 1, low- and high-dose eptifibatide, tirofiban with or without heparin, and abciximab given for 24 or 48 hours; and for indication 2, abciximab plus infusion, low- and high-dose eptifibatide, tirofiban plus heparin, abciximab plus standard or high-dose heparin, and abciximab plus stent or balloon. The comparators were aspirin, heparin and placebo for indication 1; and aspirin, heparin, placebo, no abciximab, and other GPAs (one study compared abciximab versus eptifibatide and another abciximab versus tirofiban) for indication 2. The included studies evaluated the following combinations for indication 3: eptifibatide plus TNK, abciximab plus TNK and heparin, 5 or 10 units of abciximab plus reteplase, eptifibatide plus alteplase, abciximab plus half dose reteplase, and three different dosages of bolus eptifibatide plus streptokinase. The
comparators were heparin plus TNK, reteplase plus heparin, reteplase as a single agent, placebo plus alteplase, and placebo plus streptokinase.

Participants included in the review
The inclusion criteria for the review were as follows:

for indication 1, patients presenting with unstable angina or ACS defined as increasing angina, rest angina, new onset angina, variant angina (ST-elevation), non-Q-wave MI and post-MI angina.

for indication 2, patients undergoing acute or elective PCI; and

for indication 3, patients with confirmed acute MI who were undergoing thrombolytic therapy.

The mean age of the participants in the included studies ranged from 63 to 65 years for indication 1, and from 59 to 70 years for indication 2; the age range was not given for studies included for indication 3. Prognostic information collected within each study showed that there was some variation between the studies included for indications 1 and 2, but not 3. For example, there were significant differences with respect to prior medication and co-morbidities for indication 2, but not 1.

Outcomes assessed in the review
Studies reporting the following outcome measures were eligible for inclusion: acute MI or recurrent acute MI, cardiovascular death, overall mortality, composite outcomes, severe recurrent angina, haemorrhagic stroke, fatal bleeding episode, major bleeding episode, minor bleeding episode, revascularisation, other adverse events, quality of life, cost and cost-effectiveness.

How were decisions on the relevance of primary studies made?
Two reviewers independently screened the results of the literature searches (titles and abstracts) for relevant studies, and assessed the retrieved papers for inclusion. A third reviewer was consulted to resolve any disagreements.

Assessment of study quality
The included efficacy studies were assessed in a standardised fashion using a list of criteria that examined components of internal validity relating to study population, randomisation, blinding and statistical analysis. Two reviewers independently assessed each unmasked study with any differences being resolved by consensus, or through a third party if necessary.

Data extraction
One independent reviewer extracted the data, which were checked by a second reviewer. A third reviewer was consulted to resolve any disagreements.

Methods of synthesis
How were the studies combined?
Due to the variation between eligible studies, statistical pooling was not considered. The studies were therefore pooled in a narrative summary (along with structured tables of the data extraction and quality assessment). Summary results, i.e. relative risks and 95% confidence intervals, of the individual studies were also presented as forest plots.

How were differences between studies investigated?
The heterogeneity of the studies was assessed by clinical judgements of differences in the patients enrolled, interventions, outcome phenomena and study quality.

Results of the review
Twenty-two studies relating to efficacy were identified in the updated review. For indication 1, there was one RCT and two papers reporting a subgroup analysis of previously reported trials (4 further RCTs that were included in the
previous review met the inclusion criteria for the update); for indication 2, there were 5 RCTs (12 further RCTs had been included in the previous review); and for indication 3, there were 5 RCTs. The total number of participants (for RCTs included in all reviews) was 22,635 for indication 1, 28,749 for indication 2, and 23,211 for indication 3.

The use of GPAs in the medical treatment of ACSs (indication 1).

The included studies were generally of good methodological quality but tended to have problems in their reporting. Overall, the effect sizes observed in the trials were small compared with other interventions for ACS. All the studies showed a small but mainly non-statistically significant reduction in the composite end point (measured at various time-points). The studies also reported an increase in major and minor bleeding, thrombocytopenia and blood transfusion, but in most cases the absolute effects were small.

The use of GPAs alongside PCIs (indication 2). Most of the studies (10 of which were placebo-controlled) evaluated abciximab, which was shown to have a clear benefit particularly in terms of nonfatal MI. Two studies that were identified in the updated review, which compared abciximab with eptifibatide or tirofiban, failed to show any clear benefit of abciximab.

The use of thrombolytics alongside GPAs (indication 3).

Overall, the effect sizes were small and not always in favour of the glycoproteins (most patients were randomised to abciximab).

Cost information
For indication 1, 7 full economic evaluations were identified in the original review with no additional studies being identified in the update. For indication 2, 18 economic evaluations were identified in the original review with a further 6 studies being identified in the update. No relevant economic evaluations were identified for indication 3.

When considering studies with findings that are the most relevant to UK practice, the cost per life-year gained ranged from £8,179 to £11,079 (depending on the discount rate used for future survival) for indication 1, and from £3,554 to £13,191 for indication 2.

Authors' conclusions
Indication 1: although all trials reported an increase in major and minor bleeding, thrombocytopenia and blood transfusions, in most cases the absolute effects were small.

Indication 2: newer trials identified in the update did not alter the conclusion of the initial review, i.e. that abciximab has shown a clear benefit, particularly for nonfatal MI, across a wide range of patients and settings.

Indication 3: the evidence to date does not demonstrate convincingly that the benefits outweigh the harms.

CRD commentary
This was a well-conducted review that was based on clearly reported inclusion and exclusion criteria. A comprehensive search of the literature, which included a review of unpublished data, was undertaken. Two reviewers independently assessed the relevance of the studies and assessed the included studies for quality, while the data extraction was conducted by one reviewer and checked by a second. This would have helped minimise any errors or potential bias in the process. Sufficient details of the included studies were reported and, in view of the differences between the studies, a narrative summary was appropriate.

Implications of the review for practice and research
Practice: The authors did not report any implications for practice.

Research: The authors reported that further research is required. This should:
assess the benefits, if any, of GPAs in non-ST-elevation ACS (in particular, subgroups such as women and those not scheduled for PCI) and in similar troponin-negative patient subgroups;

assess the benefits of GPAs as an adjunctive to PCI in urgent and elective patients already receiving clopidogrel or starting clopidogrel at the time of randomisation, and the optimal timing in conjunction with urgent PCI; and

assess the cost-effectiveness of GPAs used with thrombolytics in selected patients with acute MI, preferably in a revised formulation that reduces unwanted bleeding.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.