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Rapid review

Executive summary

A rapid and systematic review of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists in the medical management of unstable angina

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Background

Unstable angina represents a spectrum of clinical states that fall between stable angina and acute myocardial infarction (MI). It includes angina at rest (typically lasting more than 20 minutes), new-onset angina (within 2 months of onset), increasing angina (increased frequency, longer duration and at lower thresholds), variant angina (ST-segment elevation) and angina occurring more than 24 hours post-MI.

Glycoprotein IIb/IIIa is a receptor on the platelet membrane. This receptor is the final common pathway of platelet aggregation, which is considered to be a major factor in thrombus formation and MI. Therefore, in theory, antagonists of glycoprotein IIb/IIIa could play a very important role in the treatment of unstable angina. Glycoprotein IIb/IIIa antagonists can be used in conjunction with percutaneous coronary intervention (PCI), but this review is limited to their use in patients for whom PCI is not planned. These drugs can be administered intravenously over a few days during the acute episode and orally over several weeks. This review considers both routes of administration.

Epidemiology

Although classification problems complicate reliable estimation, it is likely that between 60,000 and 180,000 new cases of unstable angina occur in the UK each year. Patients with unstable angina have a high risk of MI and death.

Methods

A systematic review of the literature, involving a range of databases, was conducted. Full details are described in the main report.

Results

Number and quality of studies

Evidence from randomised trials was found for six glycoprotein IIb/IIIa antagonists: tirofiban, eptifibatide, lamifiban, sibrafiban, orbofiban and lefradafiban. Focussing on Phase III trials, the literature search found five trials dealing with the intravenous use of tirofiban, eptifibatide or lamifiban, and four trials dealing with the oral use of sibrafiban, orbofiban or lefradafiban. The assessment of the quality of the studies was hindered by a lack of detailed reporting on study methods, most notably on the methods of treatment allocation and the handling of missing values in the data analysis. If inadequate reporting does not reflect inadequate study conduct, the trials generally seem to be of good quality.

Benefits and adverse effects

The results for the three main outcomes at 30 days (MI, death and the composite end-points) from the Phase III trials of the intravenous glycoprotein IIb/IIIa antagonists are summarised in *Table A*.

For the composite end-points measured at 30 days, the trials investigating the intravenous use of the drugs tended to show small to very small benefits and slightly higher rates of side-effects associated with the glycoprotein IIb/IIIa antagonists. For tirofiban alone, the risk was actually slightly increased in one trial (PRISM-PLUS). Because many of the results were not statistically significant, the 95% CIs for many of the NNT values include infinity. Therefore, the NNT data quoted here should be interpreted with **caution**.

All the Phase III trials reported data up to 30 days. The PRISM-PLUS and PURSUIT studies also reported data at 6 months, although only the composite end-point was reported for the PURSUIT study. The risk difference in the composite end-points at 6 months remained very similar to the 30-day results; however, the eptifibatide results at 6 months no longer showed a statistically significant difference, compared with placebo. The tirofiban results for the composite end-point improved slightly, compared with heparin, although the differences remained not statistically significant. The benefits at 6 months with tirofiban were very similar for MI and slightly reduced for death, compared with the 30-day results.

The main adverse effect monitored was bleeding. The incidence of major bleeding was slightly higher in the patients treated with eptifibatide

TABLE A *Intravenous glycoprotein IIb/IIIa antagonists: results for main outcomes at 30 days*

Main outcome	Risk difference between treatment and control groups (95% CI)	NNT (95% CI)
Death		
Eptifibatide	–0.2% (–1.0% to 0.6%)	504 (105 to infinity)
Tirofiban*	–1.3% (–2.5% to –0.1%)‡	77 (40 to 729)
Tirofiban†	1.6% (–1.1% to 4.9%)	–64 (negative infinity to –91)§
Tirofiban + heparin†	–0.9% (–2.9% to 1.1%)	112 (34 to infinity)
MI		
Eptifibatide	–0.9% (–2.3% to 0.5%)	111 (44 to infinity)
Tirofiban*	–0.2% (–1.7% to 1.2%)	404 (61 to infinity)
Tirofiban†	–3.1% (–6.1% to 0.4%)	33 (16 to infinity)
Tirofiban + heparin†	–2.6% (–5.3% to 0.1%)	39 (19 to infinity)
Composite end-points		
Eptifibatide	–1.5% (–2.9% to –0.1%)‡	67 (35 to 1919)
Tirofiban*	–1.2% (–3.7% to 1.4%)	85 (27 to infinity)
Tirofiban†	1.1% (–4.0% to 6.6%)	–87 (negative infinity to –15)§
Tirofiban + heparin†	–3.8% (–7.8% to 0.2%)	27 (13 to infinity)
Lamifiban	–1.0% (–2.8% to 0.8%)	102 (37 to infinity)

CI, confidence interval; NNT, number needed to treat

* *PRISM trial*

† *PRISM-PLUS trial*

‡ *Statistically significant difference, compared with control*

§ *Number needed to harm*

compared to placebo (10.6% vs 9.1%) and in those treated with tirofiban compared to tirofiban plus heparin (4.0% vs 3.0%, in PRISM-PLUS trial). The incidence of major bleeding was equal (0.4%) in the two groups (tirofiban vs heparin) in the PRISM study. Although the data were not reported for lamifiban, the abstract of the PARAGON B trial results states that major bleeding was not higher in the lamifiban group.

The results for the trials investigating the oral administration of these drugs were consistently negative: no benefits and possibly more bleeding.

Cost-effectiveness

An unpublished economic analysis of tirofiban in the UK reported cost-effectiveness ratios of £8760 at 7 days and £9955 at 6 months per composite end-point prevented. In a further cost-offset analysis, 22% of the costs of tirofiban could be offset by the reduction of events (MI and recurrent ischaemia).

An unpublished economic analysis of eptifibatide in the UK reported that this drug was dominant to placebo in costs per life-years saved at 30 days. The cost-effectiveness analysis at 30 days resulted in an estimated saving of £213 per death or MI avoided by using eptifibatide.

It is concerning that a US-based analysis found a cost per life-year gained of over US$16,000, while the UK-based analysis found that eptifibatide is dominant (i.e. is more effective and costs less). This discrepancy is particularly a concern because the efficacy rate for the composite end-point assumed in the US-based study was 3.5% and in the UK-based study only 1%, making it even more unlikely to find eptifibatide dominant. While the PCI rate is lower in the UK than in the US, there was no difference in the rate of PCI between the treatment and placebo groups in the PURSUIT study. However, in the UK patient data, the number of percutaneous transluminal coronary angioplasty or stent procedures performed in the placebo arm was 1.8 times that of the eptifibatide group. The sample sizes for UK resource use data were small relative to the whole trial. If this difference in PCI rates is real, then eptifibatide may indeed be dominant to placebo. However, the smaller sample size and the fact that the PURSUIT study did not find a difference in

PCI rates suggest that this result should be interpreted with caution.

No cost-effectiveness analyses of lamifiban were identified.

Conclusions

Generalisability

While patients with acute coronary syndrome are very high risk in general, the generalisability of this review's findings is limited by the characteristics of the patients enrolled. For example, the mean ages of the patients enrolled in these trials (range, 59–67 years) were notably lower than the ages of patients generally seen in clinical practice. Furthermore, there may be subgroups of clinically homogeneous patients in whom these drugs are more or less effective. The results for the overall group may then underestimate or overestimate the effect for these subgroups. The trials also restricted the use of coronary interventions during the period of drug infusion, except for patients requiring emergency procedures. Because this restriction would not be in place in clinical practice, the results may not be generalisable.

Recommendations for research

Further research into the clinical effectiveness and cost-effectiveness of these drugs, including testing the troponins T and I as markers of patients who will benefit, is recommended.

Two additional trials, TACTICS TIMI-18 and GUSTO IV ACS, are reported to have completed enrolment. TACTICS TIMI-18 is a trial of tirofiban, and GUSTO IV ACS is a trial of abciximab. When data from these trials are available, this review will need to be updated.

Publication

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