New antithrombotic and antiplatelet treatment

K L Neuhaus

Thrombosis is the key pathological process in both unstable angina and acute myocardial infarction (MI). Treatment directed against the thrombus may consist of thrombolysis by plasminogen activators, thrombin inhibition, or platelet inhibition. Data from the TIMI IIIB and IIIB trials have shown conclusively that in contrast to their proven benefits in acute MI, plasminogen activators make the prognosis worse in unstable angina.\textsuperscript{1–3} Thrombolytic treatment is therefore contraindicated in unstable angina, but new types of antithrombotic and antiplatelet agents now offer alternatives to heparin and aspirin.

### Thrombin inhibitors

Specific thrombin inhibitors directly inhibit thrombin without the need for cofactors such as antithrombin III, and unlike heparin they inhibit both free and clot bound thrombin. In theory, this should result in superior efficacy, but clinical trials to date have failed to show that the theoretical advantages provide better results in practice. A major problem with all direct thrombin inhibitors is that they have a narrow therapeutic window, and at present they do not offer an alternative for unfractionated heparin (UFH) as the standard treatment for unstable angina.

The prototype direct thrombin inhibitor is hirudin, a naturally occurring polypeptide with a plasma half life of about one hour. The majority of clinical trials in this area have compared hirudin with UFH, but early trials in acute MI using hirudin (bolus of 0.4–0.6 mg/kg and infusions of 0.15–0.2 mg/kg/h for 48–96 hours) in conjunction with thrombolytics found that the rate of intracranial haemorrhage was unacceptably high.\textsuperscript{4–6} In response to these results, the first trial in unstable angina, GUSTO-IIb, used much lower doses of hirudin (bolus of 0.1 mg/kg followed by infusion of 0.1 mg/kg/h).\textsuperscript{7} However, the results were not very impressive with only a moderate reduction in the rate of death or MI at 30 days.

### Trial acronyms

- **CAPTURE**: C7e3 Fab AntiPlatelet Therapy in Unstable REfractory angina
- **ESSENCE**: Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q wave Coronary Events
- **FRIC**: FRagmin In unstable Coronary artery disease
- **FRISC**: FRagmin during InStability in Coronary artery disease
- **GUSTO**: Global Use of Strategies To Open occluded arteries
- **HIT**: Hirudin for the Improvement of Thrombolysis
- **OASIS**: Organization to Assess Strategies for Ischaemic Syndromes
- **OPUS**: Orbofiban in Patients with Unstable coronary Syndromes
- **ORBIT**: Oral glycoprotein IIb/IIIa Receptor Blockade to Inhibit Thrombosis
- **PARAGON**: Platelet IIb/IIIa Antagonists for Reduction of Acute coronary syndrome events in a Global Organization Network
- **SYMPHONY**: Sibrafiban Versus Aspirin to Yield Maximum Protection from Ischaemic Heart Events Post Acute Coronary Syndromes
- **TIMI**: Thrombolysis In Myocardial Infarction
- **TRIM**: ThRombin Inhibition in Myocardial ischaemia
IIb/IIIa receptor inhibitors in acute coronary syndromes. Reproduced from Topol et al.1

Figure 2 Incidence of death and myocardial infarction in an overview of trials of GP IIb/IIIa receptor inhibitors. Reproduced from Cohen et al.5

Other direct thrombin inhibitors
In addition to hirudin, a number of synthetic thrombin inhibitors have been produced. In general, the synthetic products have been found to be less effective than hirudin.

One such agent, inogatran, was compared to UFH in patients with unstable angina.10 At both seven and 30 days, outcomes were better in the group of patients who had received UFH (bolus of 5000 IU followed by infusion of 1200 IU for 72 hours), and there was no evidence that inogatran (bolus of 1.1–5.5 mg/kg followed by infusion of 2–10 mg/kg/h for 72 hours) had any dose related effect.

Low molecular weight heparins
The principal action of the low molecular weight heparins (LMWHs) is thought to be inhibition of factor Xa early in the coagulation cascade, ultimately inhibiting the generation of thrombin. This indirect thrombin inhibition is dependent on the presence of antithrombin III. Rebound thrombin activation with an increase in the clinical event rate after the cessation of UFH treatment is a recognised problem. Cessation of treatment with LMWHs is less likely to induce rebound since the half life of LMWH is prolonged in comparison to UFH.11

A further advantage of LMWHs is that they are much easier to use than UFH or direct thrombin inhibitors, since they can be given by subcutaneous injection once or twice daily and do not require routine laboratory monitoring.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Agent</th>
<th>Number</th>
<th>Placebo (%)</th>
<th>GP IIb/IIIa (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percutaneous coronary intervention trials</td>
<td>Abciximab</td>
<td>2099</td>
<td>10.2</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>Epic</td>
<td>Eptifibatide</td>
<td>4010</td>
<td>8.4</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>Impact-II</td>
<td>Abciximab</td>
<td>2792</td>
<td>9.1</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Capture</td>
<td>Abciximab</td>
<td>1265</td>
<td>9.0</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td>Restore</td>
<td>Tirofiban</td>
<td>2139</td>
<td>6.3</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>Epistent</td>
<td>Abciximab</td>
<td>2399</td>
<td>10.2</td>
<td>5.2</td>
<td></td>
</tr>
<tr>
<td>Unstable angina/non-Q wave MI trials</td>
<td>Tirofiban</td>
<td>3231</td>
<td>7.0</td>
<td>5.7</td>
<td></td>
</tr>
<tr>
<td>Prisim</td>
<td>Tirofiban</td>
<td>1570</td>
<td>11.9</td>
<td>8.7</td>
<td></td>
</tr>
<tr>
<td>Prisim plus</td>
<td>Tirofiban</td>
<td>2282</td>
<td>11.7</td>
<td>11.3</td>
<td></td>
</tr>
<tr>
<td>Pursuit</td>
<td>Eptifibatide</td>
<td>10948</td>
<td>15.7</td>
<td>14.2</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>32735</td>
<td>11.1</td>
<td>9.0</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2 Incidence of death and myocardial infarction in an overview of trials of GP IIb/IIIa receptor inhibitors in acute coronary syndromes. Reproduced from Topol et al.12 with permission of the Lancet.
odds ratio from trials in over 30 000 patients was 0.79 in favour of GP IIb/IIIa inhibitors. The figure shows a class specific effect that there is a benefit of GP IIb/IIIa inhibitors over placebo. Trials of parenterally administered abciximab show a much greater qualitative reduction in adverse events than trials of other parenterally administered agents such as lamifiban and tirofiban. These four trials have all been done in patients undergoing percutaneous coronary intervention and show a drug specific effect; there was a more pronounced reduction in the end point of death or non-fatal MI at 30 days than that seen with other agents in this setting.

ROLE OF REVASCULARISATION
Most trials of GP IIb/IIIa receptor inhibitors have been undertaken in patients undergoing percutaneous transluminal coronary angioplasty (PTCA). However, PTCA is itself followed by a cluster of events, and the main benefits of GP IIb/IIIa receptor inhibitor treatment have been seen after revascularisation. One interpretation of these findings is that GP IIb/IIIa receptor inhibition only reduced the additional risks presented by undergoing a revascularisation procedure. A full assessment of the effects of GP IIb/IIIa receptor inhibitors in unstable angina therefore requires data from trials in which patients were treated conservatively. Currently, there are few data of this type available. The CAPTURE trial included a preintervention phase, but most of the improvement was seen after PTCA, and it is not possible to say whether the benefits were caused by abciximab or the revascularisation. PARAGON, one of the few trials to date to address this issue directly, compared two doses of the GP IIb/IIIa receptor inhibitor lamifiban with heparin. At 30 days, there was no difference between lamifiban (either dose) plus heparin or heparin alone, although at six months there was a significant benefit from low dose, but not high dose, lamifiban treatment. These findings require further investigation before any conclusions can be drawn, but it appears that overall, non-antibody GP IIb/IIIa receptor inhibitors may be less effective than abciximab.

ORAL AGENTS
Prolonged GP IIb/IIIa receptor inhibition beyond the acute phase will require agents that can be given orally. Several such agents have been evaluated in phase II trials and some are now entering phase III. The pilot ORBIT trial included a preintervention phase, but most of the improvement was seen after PTCA, and it is not possible to say whether the benefits were caused by abciximab or the revascularisation. PARAGON, one of the few trials to date to address this issue directly, compared two doses of the GP IIb/IIIa receptor inhibitor lamifiban with heparin. At 30 days, there was no difference between lamifiban (either dose) plus heparin or heparin alone, although at six months there was a significant benefit from low dose, but not high dose, lamifiban treatment. These findings require further investigation before any conclusions can be drawn, but it appears that overall, non-antibody GP IIb/IIIa receptor inhibitors may be less effective than abciximab.1

Conclusions
Despite the central role of thrombosis in both unstable angina and acute MI, they are different conditions and require different management. Clinical trial programmes have shown that there are distinct variations between different agents in the same class, and experimental data relating to one agent cannot be used to draw any conclusions about another agent in the same class.

Direct thrombin inhibitors were expected to offer a new approach to antithrombin treatment in acute coronary syndromes, but finding the right combination of safety and efficacy has proved difficult. Hirudin appears to be the most promising of these agents but the data currently available still do not justify a recommendation for routine use. LWMHs offer a good alternative to UFH. Their use is supported by the results of clinical trials showing that they are at least as effective, and in some cases—for example, enoxaparin—more effective than UFH. LMWHs have a similar safety profile, but are much easier to use and reduce the overall medical cost of treatment.

GP IIb/IIIa receptor inhibitors have been extensively studied in conjunction with PTCA and are now established as a significant advance over aspirin for patients undergoing invasive procedures. However, more data are still required to establish whether they also offer significant benefits to unstable angina patients treated conservatively. The optimum duration of treatment with both GP IIb/IIIa receptor inhibitors and antithrombin agents is not clear, and trials to investigate whether prolonged treatment offers additional benefits are ongoing. If it is established that continuing treatment beyond the acute phase improves the outcome, then the availability of agents that can be self administered by the patient at home will be the key to longer regimes becoming part of routine clinical practice.

References

*Enrolment for the OPUS TIMI 16 trial was prematurely halted in November 1998 because of an increase in mortality in one of the treatment arms of orbofiban compared with placebo at 30 days. No significant benefit in the combined triple end point of death, MI, and urgent revascularisation was demonstrated for orbofiban over placebo. Full trial results have not yet been published (source: 48th annual scientific session of the American College of Cardiology, New Orleans, USA, March 7–10, 1999: late breaking clinical trials III abstract).


