Bivalirudin (Angiox) for acute myocardial infarction with persistent ST-segment elevation treated by primary percutaneous coronary intervention

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The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Bivalirudin (Angiox) for acute myocardial infarction with persistent ST-segment elevation treated by primary percutaneous coronary intervention

Target group
- Acute myocardial infarction (MI) with persistent ST segment elevation treated by primary percutaneous coronary intervention (PPCI).

Technology description
Bivalirudin (Angiox) is a direct thrombin inhibitor and is intended for anticoagulation during PPCI as a substitute for heparin and a glycoprotein IIb/IIIa antagonist (e.g. abciximab). Bivalirudin is administered as an intravenous (IV) bolus of 0.75mg/kg followed by an IV infusion of 1.75mg/kg per hour for the duration of the PCI procedure. Bivalirudin will be administered in combination with aspirin and clopidogrel.

Bivalirudin is approved in the EU (in combination with aspirin and clopidogrel) as an anticoagulant during PCI and for patients with acute coronary syndromes (ACS) - unstable angina/non-ST-elevation myocardial infarction (UA/NSTEMI) planned for urgent or early intervention.

Innovation and/or advantages
Unlike glycoprotein IIb/IIIa antagonists, infusion of bivalirudin may be discontinued at the end of the PCI procedure.

Developer
The Medicines Company.

Availability, launch or marketing dates, and licensing plans:
In phase III clinical trials.

NHS or Government priority area
This topic is relevant to The National Service Framework for Coronary Heart Disease (2000).

Relevant guidance
NICE Technology Appraisals
- Guidance on the use of coronary artery stents. 20032.
- The clinical effectiveness and cost effectiveness of drugs for early thrombolysis in the treatment of acute myocardial infarction. 20023.
- Glycoprotein IIb/IIIa inhibitors in the treatment of acute coronary syndromes. 20024.

NICE Clinical Guidelines.
- Acute coronary syndromes: the management of unstable angina and non-ST segment elevation myocardial infarction. Expected February 20105.

Other Guidance.
- Scottish Medicines Consortium. Bivalirudin, 250mg powder for concentrate for solution for injection or infusion (Angiox). 20086.
• SIGN. Acute coronary syndromes. 2007.
• SIGN. Antithrombotic therapy. 1999.
• The Department of Health. Treatment of heart attack national guidance - final report of the national infarct angioplasty project. 2008.

Clinical need and burden of disease
Approximately 110,000 people in England have a MI each year and in 2007, in England and Wales, there were 31,283 registered deaths from acute MI. The rate of MI increases with age for both sexes and is higher in men than in women. It is also higher in less affluent people at all ages. In England and Wales in 2007/08, 4,525 patients underwent primary angioplasty for acute MI. The figure for 2008/09 will be higher and will continue to increase significantly. The mortality at 30 days for patients undergoing PPCI is an estimated 5.6%.

Existing comparators and treatments
Initial management
• Antiplatelets – aspirin and clopidogrel.
• Oxygen, nitrates, morphine, anti-emetics (as indicated).

Revascularisation
• Plasminogen activators (thrombolysis) – streptokinase, alteplase, reteplase, tenecteplase.
• PPCI with a heparin and a glycoprotein IIb/IIIa inhibitor to reduce the risk of immediate vascular occlusion.

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>HORIZONS-AMI, NCT00433966: bivalirudin vs. heparin plus glycoprotein IIb/IIIa inhibitor; phase III.</th>
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</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>The Medicines Company; Boston Scientific; The Cardiovascular Research Foundation.</td>
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<tr>
<td>Status</td>
<td>Published, oral presentation.</td>
</tr>
<tr>
<td>Location</td>
<td>USA, EU (inc. UK), Argentina and Israel.</td>
</tr>
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<td>Design</td>
<td>Randomised, controlled, single-blind, open-label.</td>
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<td>Participants and schedule</td>
<td>n=3,602; adults; STEMI undergoing primary PCI; &gt;20 mins and &lt;12 hrs from symptom onset. Randomised to: bivalirudin 0.75mg/kg then 1.75mg/kg/hr or unfractionated heparin (UFH) 60IU/kg with a glycoprotein IIb/IIIa inhibitor (GPI), either abciximab or eptifibatide. All patients received aspirin and clopidogrel or ticlopidine. After patency was restored, eligible patients were randomised to receive a paclitaxel eluting (TAXUS Express; Boston Scientific) or bare metal stent (Express; Boston Scientific).</td>
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<tr>
<td>Follow-up</td>
<td>30 days, 1 year.</td>
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</table>
Primary outcomes | Composite (net adverse clinical events) of major adverse clinical events (MACE: death, reinfarction, stroke or ischaemic target vessel revascularisation) and major bleeding.
---|---
Secondary outcomes | Major adverse clinical events (MACE: death, reinfarction, stroke or ischaemic target vessel revascularisation) and major bleeding.
Key results | At 30 days bivalirudin vs. UFH + GPI respectively:
Net adverse clinical events 9.2% vs. 12.1% (relative risk 0.76; 95% CI 0.63-0.92; p=0.005); owing to a reduced rate of major bleeding 4.9% vs. 8.3% (relative risk 0.60; 95% CI 0.46-0.77; p<0.001). There was no difference in MACE at 30 days.
Death rate from cardiac causes 1.8% vs. 2.9% (relative risk, 0.62; 95% CI, 0.40 to 0.95; p= 0.03) and death from all causes 2.1% vs. 3.1% (relative risk, 0.66; 95% CI, 0.44 to 1.00; p= 0.047).
Between 30 days and 1 year bivalirudin vs. UFH + GPI respectively:
Net adverse clinical events 7.3% vs. 7.8% (p=0.52). Death 1.4% vs. 1.8% (p=0.31); death or re-infarction 3.0% vs. 4.4% (p=0.02); ischemic target vessel revascularisation 4.7% vs. 4.3% (p=0.57); stroke 0.4% vs. 0.5% (p=0.77); major adverse cardiovascular events 6.8% vs. 7.3% (p=0.52); and major bleeding (non-CABG) 0.8% vs. 0.7% (p=0.71).
At one year bivalirudin vs. UFH + GPI respectively:
Net adverse clinical events 15.7% vs. 18.3% (Hazard ratio 0.84; 95%CI 0.71 to 0.98; p=0.03); and major bleeding (5.8% vs. 9.2%; p<0.0001). There was no difference in MACE at 1 year.

Estimated cost and cost impact
The cost of bivalirudin is £310 per patient per procedure (based on one vial per patient). Cost of existing treatment is£19:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Per procedure*</th>
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<tr>
<td>Abciximab</td>
<td>250 micrograms/kg by IV injection then 125 nanograms/kg/ for 12 hrs.</td>
<td>£781</td>
</tr>
</tbody>
</table>

Potential or intended impact – speculative
Whether PCI is used as the first-line treatment for an individual patient is dependent on time to admission and resources and expertise at the admitting hospital.

Patients
☑ Reduced morbidity ☑ Reduced mortality or increased length of survival ☑ Improved quality of life for patients and/or carers
☐ Quicker, earlier or more accurate diagnosis or identification of disease ☐ Other:
☐ None identified

Services
☐ Increased use ☐ Service reorganisation required ☐ Staff or training required
☐ Decreased use ☐ Other:
☐ None identified

Costs
☐ Increased unit cost compared to alternative ☐ Increased costs: more patients coming for treatment ☐ Increased costs: capital investment needed

*Costings based on average weight 67.5kg (men and women) and assuming wastage.
5 New costs: ☑ Savings: decreased cost per procedure.

References
