Rivaroxaban (Xarelto) for acute coronary syndrome

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The National Horizon Scanning Centre Research Programme is part of the National Institute for Health Research
Rivaroxaban (Xarelto) for acute coronary syndrome

Target group
- Acute coronary syndrome (ACS) – add-on therapy.

Technology description
Rivaroxaban (Xarelto; BAY 59-7939; BAY 597939) is a highly selective direct Factor Xa inhibitor with oral bioavailability and a rapid onset of action. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting thrombin formation (activated Factor II). No effects on platelets have been demonstrated. Rivaroxaban is distributed heterogeneously to tissues and organs, exhibiting only moderate tissue affinity and does not substantially penetrate the blood-brain barrier. Rivaroxaban is an add-on therapy to be administered orally at 2.5mg or 5mg twice daily. The dose is to be confirmed following completion of clinical trials.

Rivaroxaban is licensed for the prevention of venous thromboembolism in patients undergoing elective hip or knee replacement surgery, and is preregistration for the prevention of deep vein thrombosis, embolism, pulmonary embolism and stroke in patients with atrial fibrillation. Recognised adverse effects include abnormal laboratory test results, anaemia, bleeding and nausea.

Innovation and/or advantages
If licensed, rivaroxaban may provide an oral anticoagulant therapy which does not require dose adjustment or routine coagulation monitoring.

Developer
Bayer.

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 (2005).

Relevant guidance
NICE Technology Appraisals
- In development. Rivaroxaban for the treatment of secondary prevention of venous thromboembolism. Expected date of issue to be confirmed.
- In development. Atrial fibrillation (stroke prevention) – rivaroxaban. Expected date of issue to be confirmed.
- Rivaroxaban for the prevention of venous thromboembolism. 2009.

NICE Clinical Guidelines
• Unstable angina and NSTEMI: the early management of unstable angina and non-ST-segment-elevation myocardial infarction. 2010.
• Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. 2010.
• Secondary prevention in primary and secondary care for patients following a myocardial infarction. 2007.

• SIGN. Acute Coronary Syndromes. 2007.
• University of Warwick, Joint Royal Colleges Ambulance Liaison Committee. Acute coronary syndrome. 2006.

Clinical need and burden of disease
ACS encompasses a spectrum of disease from unstable angina to ST elevation myocardial infarction (STEMI), usually caused by coronary atherosclerosis. In a large proportion of cases the episode of coronary instability arises from thrombus formation on atheromatous plaques. Left untreated, prognosis is poor and mortality is high, particularly in people who have had myocardial damage.

In 2009-10, there were 75,088 admissions to hospital for angina pectoris (ICD10 I20) in England, of which 39,368 were specified as unstable angina (ICD10 I20.0). In the same time period, there were 56,784 admissions for acute myocardial infarction (MI) (ICD10 I21) and 27,704 FCEs for subsequent MIs (ICD10 I22). In 2008, 29,330 deaths from acute MI (ICD10 I21) occurred in England and Wales.

Existing comparators and treatments
Current guidelines recommend the use of antiplatelet and antithrombin therapy.
• Antiplatelet therapy: aspirin, clopidogrel, prasugrel (undergoing percutaneous coronary intervention [PCI]), and/or glycoprotein IIb/IIIa inhibitors (GPIs) e.g. abciximab (undergoing PCI), eptifibatide and tirofiban.
• Antithrombin therapy: low molecular weight heparin, fondaparinux, unfractionated heparin, or bivarirudin (undergoing PCI).
• Revascularisation: thrombolysis, PCI angioplasty with stent placement, or coronary artery bypass grafting (CABG).

Efficacy and safety

<table>
<thead>
<tr>
<th>Trial</th>
<th>ATLAS ACS TIMI 51 Trial, NCT00809965, CR014710, RIVAROXACS3001; adults; rivaroxaban vs placebo; phase III.</th>
<th>ATLAS ACS TIMI 46 Trial, NCT00402597, CR013417, 39039039ACS2001; adults; rivaroxaban vs placebo; phase II.</th>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Johnson &amp; Johnson Pharmaceutical Research &amp; Development, LLC.</td>
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<td>Status</td>
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<tr>
<td>Source of information</td>
<td>Trial registry\textsuperscript{22}, manufacturer.</td>
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<td>Location</td>
<td>EU (inc UK), USA, Canada and other countries.</td>
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<td>Design</td>
<td>Randomised, placebo-controlled.</td>
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<td>Participants and schedule</td>
<td>n=15,529 (planned); adults; patients who have been hospitalised for symptoms suggestive of ACS lasting at least 10 minutes at rest and occurred 48 hours or less before attending hospital; receiving aspirin therapy alone or in combination with thienopyridine. Randomised to rivaroxaban 2.5mg or 5mg, twice daily for up to 6 months, or placebo twice daily for up to 6 months. n=3,491; adults; symptoms of ACS lasting at least 10 minutes at rest occurring within 7 days of randomisation; diagnosis of ST-elevation MI or non-ST elevation MI/unstable angina. Randomised to: Stratum 1, patients on low dose aspirin, plus: Arm 1: rivaroxaban 5mg, 10mg, or 20mg, given as two divided doses. Arm 2: rivaroxaban 5mg, 10mg or 20mg, once daily plus placebo once daily. Arm 3: Placebo twice daily. Stratum 2, patients on low dose aspirin and thienopyridine, plus: Arm 1: rivaroxaban 5mg, 10mg, 15mg, or 20mg, given as two divided doses. Arm 2: rivaroxaban 5mg, 10mg, 15mg or 20mg, once daily plus placebo once daily. Arm 3: placebo twice daily.</td>
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<td>Follow-up</td>
<td>Active treatment period up to 6 months. Active treatment period 6 months, 1 month follow-up.</td>
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<td>Primary outcomes</td>
<td>Reduction in risk of cardiovascular death, MI or stroke. Clinically significant bleeding.</td>
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<td>Secondary outcomes</td>
<td>Severe recurrent ischaemia and net clinical outcome, all cause death, MI, or stroke. Primary efficacy endpoint: death, MI, stroke, or severe recurrent ischaemia requiring revascularisation; major or minor bleeding to assess net clinical benefit.</td>
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<td>Key results</td>
<td>Clinically significant bleeding, rivaroxaban 5mg, 10mg, 15mg, 20mg and placebo respectively, %, 6.1, 10.9, 12.7, 15.3, 3.3 (all p&lt;0.0001), hazard ratio vs placebo (HR), 2.21 (95% CI 1.25-3.91), 3.35 (2.31-4.87), 3.60 (2.32-5.58), 5.06 (3.45-7.42) (p&lt;0.0001); clinically significant bleeding, rivaroxaban vs placebo, HR, stratum 1, 3.96 (1.40-11.23), stratum 2, 3.66 (2.54-5.27). For ribaroxaban and placebo respectively: primary efficacy endpoint, %, 5.6, 7.0 (HR 0.79, 95% CI 0.60–1.05, p=0.10); HR, stratum 1, 0.53 (CI 0.33–0.84), stratum 2, 0.99 (CI 0.69–1.42); death, %, 1.3, 1.4 (HR 0.91, 95% CI 0.49–1.67); MI, %, 3.0, 4.0 (HR 0.75, 95% CI 0.52–1.10); stroke, %, 0.3, 0.5 (HR 0.50, 95% CI 0.16–1.54); severe recurrent ischaemia requiring revascularisation, %, 2.0, 1.6 (HR 1.22, 95% CI 0.71 – 2.12).</td>
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Secondary efficacy endpoint (death, MI or stroke), rivaroxaban and placebo respectively, %, 3.9, 5.5 (HR 0.69, 95% CI 0.50–0.96); stratum 1, HR 0.54 (CI 0.32 – 0.89), stratum 2, HR 0.83 (CI 0.54 – 1.28).

Net clinical outcome (clinically significant bleeding and primary efficacy endpoint), rivaroxaban vs placebo, HR, entire cohort, 0.99 (95% CI 0.76–1.29), stratum 1, 0.56 (0.35–0.88), stratum 2, 1.29 (0.93–1.81).

Estimated cost and cost impact

The company estimate the cost of rivaroxaban will be between £100 and £1,000 per annum for ACS. The cost of rivaroxaban for currently licensed indications is £44.15 for 10 x 10mg. The annual costs of clopidogrel (Plavix) 75mg once daily, and aspirin 75mg once daily are £463.32\(^a\) and £14.04 respectively.\(^{25} \)

Claimed or potential impact – speculative

Patients
- Reduced mortality or increased length of survival
- Reduction in associated morbidity or 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 organisation
- Staff requirements
- Decreased use
- Other: None identified

Costs
- Increased unit cost compared to alternative
- New costs: additional add on treatment option
- Increased costs: more patients coming for treatment
- Increased costs: capital investment needed
- Savings: anticipated reduced events
- Other: None identified

Other issues
- Clinical uncertainty or other research question identified: None identified

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\(^a\) In the UK, generic clopidogrel is not marketed for use in ACS.
References

19 University of Warwick, Joint Royal Colleges Ambulance Liaison Committee. Acute coronary syndrome. Care guideline. JRCALC; October 2006.
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