

TA 256: Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation

1	<p>Name of Commissioning Team</p> <p>Long term Conditions Commissioning Team</p>
2	<p>Summary of NICE TA 256: Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation</p> <p>Rivaroxaban (Xarelto®) is recommended as an anticoagulant option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with nonvalvular atrial fibrillation with one or more risk factors such as:</p> <ul style="list-style-type: none"> • congestive heart failure • hypertension • age 75 years or older • diabetes mellitus, • prior stroke or transient ischaemic attack. <p>The decision about whether to start treatment with rivaroxaban should be made after an informed discussion between the clinician and the person about the risks and benefits of rivaroxaban compared with warfarin, and noting the limited direct trial evidence for people with a low risk of stroke (CHADS2 score of less than 2). For people who are taking warfarin, the potential risks and benefits of switching to rivaroxaban should be considered in light of their level of international normalised ratio (INR) control.</p> <p>Overall, it is not clear if people with good INR control with warfarin gain additional clinical benefit by switching to rivaroxaban.</p> <p>It is worth noting that for prevention of stroke and systemic embolism in adults only, the recommended dose is normally 20 mg once daily, which is also the recommended maximum dose. However, in patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment, the recommended dose is 15 mg once daily.</p>
3	<p>Number of people in Northern Ireland expected to take up service/therapy (new cases per year)</p> <p>There were 27,213 adults with atrial fibrillation on GP practice registers in 2011/12. Over 90% (about 24,491) of these are estimated to have non valvular atrial fibrillation. The number of people on atrial fibrillation GP registers increases by c. 1000 patients per year.</p>

Current prescribing of rivaroxaban (Xarelto®) in General Practice in NI

There were approximately 378 prescriptions for Xarelto® 10mg costing £3,769 between April 2011 and March 2012.

(Please note:

- a. these prescriptions may not relate to the patient population in TA256 as 10mg rivaroxaban is only licensed for prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery
- b. the prescription numbers may not take into account adjustments.)

There were also three prescriptions for 20mg rivaroxaban totalling £176.40 from January to March 2012. This would equate to usage by one patient.

4 Outcomes

Rivaroxaban is an option within its license for the prevention of stroke and systemic embolism in adults with non valvular atrial fibrillation. NICE stated that the decision about whether to start treatment with rivaroxaban should be made after an informed discussion between the clinician and the person about the risks and benefits of rivaroxaban compared with warfarin. For people who are taking warfarin, the potential risks and benefits of switching to rivaroxaban should be considered in light of their level of international normalised ratio (INR) control.

NICE concluded that:

1. Rivaroxaban was non-inferior to warfarin in the ROCKET-AF trial. There is suggestion of moderate superiority only in the per-protocol and safety analyses (which may over emphasise effectiveness) and not for the full intention-to-treat population.
2. There is limited direct evidence available on efficacy of rivaroxaban in people with a baseline CHADS2 score of less than 2.

The Committee heard that people with atrial fibrillation treated with warfarin in primary care often have a CHADS2 score of less than 2 and that it is estimated that between 20 and 75% of people with atrial fibrillation and a CHADS2 score of less than 2 are prescribed warfarin in the UK. Only 0.02% of the trial population had a CHADS2 score less than 2.

The clinical specialists agreed that it was likely that although people with a CHADS2 score of 2 or more would benefit similarly to those in the ROCKET-AF trial, this cannot be assumed for people with a CHADS2 score of less than 2. The Committee accepted that, given the broad spectrum of risk covered by the licensed indication for rivaroxaban, there was no plausible reason to expect that the results would not translate to people with a lower CHADS2 score. In spite of the very small number of patients recruited to the ROCKET-AF trial with a baseline CHADS2 score of less than 2, the Committee concluded that the results of the ROCKET-AF trial were generalisable to UK clinical practice.

3. There is a possible uncertainty in the trial results related to the relatively low proportion of time in therapeutic range (INR 2.0.-3.0) of 55% in the warfarin arm of the trial. Effectiveness of warfarin could be underestimated if the proportion of time in therapeutic range was low, and the UK context might be better reflected by results where the time in therapeutic range in the warfarin arm more closely matches the usual levels in the UK. The Committee concluded the results were broadly applicable to a UK setting, **but for those already taking warfarin the current level of INR control should be taken into account in any decision to switch to rivaroxaban.**
4. The primary safety end point of all major and non-major clinically significant bleeding events showed no significant differences between rivaroxaban and warfarin. There was a significant reduction in the rate of fatal bleeds and intracranial haemorrhage with rivaroxaban compared with warfarin, but a higher rate of gastrointestinal bleeds. (According to the summary of product characteristics (SPC), approximately 14% of people treated with rivaroxaban in clinical studies experienced adverse reactions. Bleeding occurred in approximately 3.3% of patients and anaemia in approximately 1% of patients. The risk of bleeding may increase in certain patient groups e.g. uncontrolled severe arterial hypertension and/or those taking other treatments that affect haemostasis.)
5. Clinical-effectiveness estimates for rivaroxaban compared with dabigatran etexilate were unreliable. The ROCKET-AF and RE-LY trials had different methodologies with the results reported in different ways such that they cannot be directly compared. The Committee concluded that it would not consider further the clinical effectiveness of rivaroxaban compared with aspirin or dabigatran etexilate.

Please note:

- Long term safety data is limited to the median duration of treatment exposure of 590 days in the ROCKET AF trial.
- There is no specific antidote to rivaroxaban (unlike warfarin) so there could be potentially serious consequences should a patient present with life threatening haemorrhage or require emergency surgery. The SPC suggests use of activated charcoal in overdose and appropriate symptomatic treatment as needed, then administration of a specific procoagulant reversal agent if needed, such as prothrombin complex concentrate, activated prothrombin complex concentrate or recombinant factor VIIa. However, there is very limited clinical experience with the use of these products in patients on rivaroxaban. The recommendation is also based on limited non-clinical data. There is a lack of national consensus on treating haemorrhage. Rivaroxaban should be used with caution in patients with bleeding disorders, concomitant use of drugs that increase risk of bleeding, severe hypertension, active or recent gastro-intestinal ulceration, vascular retinopathy, anaesthesia with postoperative indwelling epidural catheter or recent surgery.
- The stroke rate after the end of the study was higher among patients in the rivaroxaban arm of the trial who had to stop rivaroxaban and transition back to warfarin, possibly due to rivaroxaban's short half life.

	<ul style="list-style-type: none"> As no anticoagulation monitoring is needed it will be more difficult to assess compliance. 										
4.1	<p>Additional life expectancy gain / progress improvement</p> <p>The current standard treatment for the prevention of stroke and systemic embolism in people with atrial fibrillation is warfarin. Aspirin is used only in people for whom warfarin is unsuitable as it is less effective. Warfarin is associated with a number of problems such as patient fear of having a stroke, anxiety about keeping the INR within the therapeutic range, the need for regular monitoring and dose adjustments, occasionally involving complicated regimens such as different doses on alternate days which can cause difficulties with adherence to treatment. In addition, people might find regular GP and hospital visits disruptive and inconvenient. A substantial proportion of people taking warfarin have poorly controlled INR and are often not within the target therapeutic range at any one time. Older people with atrial fibrillation are more likely to have poorly controlled INR because of co-morbidities.</p> <p>Rivaroxaban is an oral therapy which unlike warfarin does not require frequent drug monitoring or dose titration. NICE recognised the potential benefits of alternatives such as rivaroxaban for people with atrial fibrillation, including the positive effect on quality of life of removing the restrictions and difficulties associated with taking warfarin.</p>										
4.2	<p>Reduction in morbidity</p> <p>The London New Drugs Group put the numbers needed to treat with rivaroxaban 20 mg at 200.</p>										
4.3	<p>Cost per patient per annum</p> <p>The price of rivaroxaban is £58.80 for a pack of 28 15-mg / 20mg tablets (NI Pricing Book May 2012).</p> <table border="1" data-bbox="225 1413 1402 2007"> <thead> <tr> <th data-bbox="225 1413 437 1525">Drug</th> <th data-bbox="437 1413 611 1525">Dose</th> <th data-bbox="611 1413 742 1525">Cost per month</th> <th data-bbox="742 1413 887 1525">Annual cost</th> <th data-bbox="887 1413 1402 1525">Additional costs</th> </tr> </thead> <tbody> <tr> <td data-bbox="225 1525 437 2007">rivaroxaban</td> <td data-bbox="437 1525 611 2007">20mg o.d. or 15mg o.d.</td> <td data-bbox="611 1525 742 2007">£63 (30 days)</td> <td data-bbox="742 1525 887 2007">£766.50</td> <td data-bbox="887 1525 1402 2007"> Mucosal bleeds are more frequent with rivaroxaban compared with VKAs so the manufacturer recommends <ul style="list-style-type: none"> lab testing haemoglobin/haematocrit to detect occult bleeding, as appropriate. Monitoring sub-groups at increased risk of bleeding for signs/ symptoms of bleeding complications and anaemia after initiation of treatment </td> </tr> </tbody> </table>	Drug	Dose	Cost per month	Annual cost	Additional costs	rivaroxaban	20mg o.d. or 15mg o.d.	£63 (30 days)	£766.50	Mucosal bleeds are more frequent with rivaroxaban compared with VKAs so the manufacturer recommends <ul style="list-style-type: none"> lab testing haemoglobin/haematocrit to detect occult bleeding, as appropriate. Monitoring sub-groups at increased risk of bleeding for signs/ symptoms of bleeding complications and anaemia after initiation of treatment
Drug	Dose	Cost per month	Annual cost	Additional costs							
rivaroxaban	20mg o.d. or 15mg o.d.	£63 (30 days)	£766.50	Mucosal bleeds are more frequent with rivaroxaban compared with VKAs so the manufacturer recommends <ul style="list-style-type: none"> lab testing haemoglobin/haematocrit to detect occult bleeding, as appropriate. Monitoring sub-groups at increased risk of bleeding for signs/ symptoms of bleeding complications and anaemia after initiation of treatment 							

				<ul style="list-style-type: none"> Searching for a bleeding site if there is any unexplained fall in haemoglobin or blood pressure. <p>There is no need for monitoring of coagulation parameters during treatment with rivaroxaban but rivaroxaban levels can be measured by calibrated quantitative anti-Factor Xa tests if required.</p> <p>The SPC does not note a need to do U&Es but it may be useful to monitor renal function as dose needs adjusted if renal function declines*.</p>
dabigatran	150mg b.d	£65.90	£801.80	Renal function as per MHRA guidance.
warfarin	As per INR	£0.93- £1.98	£23.76	Drug monitoring costs = >£2.03 m / annum in primary care
aspirin	75 - 300mg	£0.83	£9.96	

* The London New Drugs Group (LNDG) recommends checking renal function prior to initiation. The BNF advises using rivaroxaban with caution if eGFR 15–29 mL/minute/1.73 m² or if eGFR 30–49 mL/minute/1.73 m² and concomitant use of drugs that increase plasma-rivaroxaban concentration. Avoid if eGFR is less than 15 mL/minute/1.73 m. MHRA advised caution in moderate hepatic impairment.

Rivaroxaban is also contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, and is not recommended in those also taking strong inhibitors of cytochrome P 3A4 enzyme or P-glycoprotein. Therefore some monitoring may be required.

The additional drug cost of rivaroxaban compared to warfarin is £742.74 year/patient (£766.50 minus £23.76).

The maximum potential additional costs are therefore £18.19m (estimated 24,491 patients with non valvular AF x £742.74).

4.4 In year cost per patient per annum

£766.50/patient/year for rivaroxaban;

£23.76/yr for warfarin;

Additional cost = £742.74/year/pt;

These costs exclude INR and other monitoring.

<p>4.5</p>	<p>Any cost savings and how these will be secured</p> <p>From section 4.3: additional drug cost of rivaroxaban compared to warfarin is £742.74 year/patient (£766.50 annual drug cost of rivaroxaban minus £23.76 annual drug cost of warfarin). The additional costs would be borne by the primary care prescribing budget.</p> <p>The anti-coagulation monitoring payments made to GP practices, and fixed costs associated with secondary care monitoring may reduce with time, but are likely to be modest as it is likely that a large proportion of patients will remain on warfarin; this will need to be kept under review.</p> <p>With an NNT of 200 (from LNDG), and an annual cost per stroke of £3,660, rivaroxaban may prevent 122 strokes in a maximum population of 24,491, giving a maximum potential saving of £446.5k. The savings are notional in secondary care in that they would not be realised in cash terms.</p> <p><u>There is a maximum annual cost of £4.136m as per NICE costing template based upon 25% eligible patients choosing rivaroxaban.</u> The net cost based upon the NICE costing template was £340K. These costs are based upon NICE estimates on unit costs.</p> <p>In the United States, the PINNACLE-AF Registry reported in August 2012 that of the patients in the registry who received oral anticoagulation, 87.4% were treated with warfarin in 2011 while 12.6% were prescribed dabigatran or rivaroxaban (please note: this registry is sponsored by pharmaceutical companies).</p>
<p>4.6</p>	<p>Recurrent overall cost</p> <p>See section 4.5 for details.</p> <p>The additional drug cost would be £4.136m per year (using the NICE costing template base assumptions) The net cost based upon the NICE costing template was £340K which is the difference between current practice and future practice.</p> <p>These costs are based upon NICE estimates on unit costs.</p>
<p>4.7</p>	<p>Cost per QALY</p> <p>NICE stated that the ICER for rivaroxaban compared with warfarin would be between £2,870 and £29,500 per QALY gained.</p>
<p>4.8</p>	<p>Other treatments available for this condition</p> <p>Warfarin (and aspirin) Newer agents e.g. dabigatran, apixaban, edoxaban, betrixaban</p>
<p>4.9</p>	<p>Readiness to implement</p> <p>There will be a managed process to communicate the risks and benefits of rivaroxaban to GPs and secondary care primarily, through:</p>

	<ul style="list-style-type: none"> • ICP Clinical Leads • Practice-level reports providing comparisons of prescribing rates with peers, and trends • Medicines Management advisers routine visits to practices & encouraging practices to use the NICE TA audit where appropriate. • GP educational events <p>Secondary care clinicians often initiate treatment and maintenance treatment is overseen by primary care, common protocols need to be developed between primary and secondary care at Trust level.</p>
5	<p>DHSSPS Legislative / Policy Caveats</p> <p>This advice does not override or replace the individual responsibility of health professionals to make appropriate decisions in the circumstances of their individual patients, in consultation with the patient and/or guardian or carer. This would, for example, include situations where individual patients have other conditions or complications that need to be taken into account in determining whether the NICE guidance is fully appropriate in their case.</p>
6	<p>What will Commissioning Team do to secure funding for the implementation of this TA including any proposals for disinvestment</p> <p>Any cost pressure will appear in the primary care prescribing budget. There is no contingency for this.</p> <p>Potential savings to Trusts should be calculated where appropriate pro rata according to the degree of use of rivaroxaban and offset against other Trust cost pressures. However with increasing numbers of older patients and stroke being more common in older age groups any reduction in numbers of strokes as a result of effective management of AF would probably be offset by the increase in numbers of strokes as a result of an aging population.</p>
7	<p>Commissioning arrangements</p> <p>As outlined in this statement.</p>
8	<p>Monitoring arrangements</p> <p>The prescribing trends for this drug will be monitored by medicines management advisers where appropriate.</p> <p>The Medicines Management Commissioning team will track trends in the use of this drug. The introduction of this drug should be monitored carefully in view of the limited longterm (ie >2 years) safety data available.</p>