MTRAC
Midlands Therapeutics Review and Advisory Committee

Implementation support

Rivaroxaban 2.5 mg twice daily (Xarelto®▼)

For the secondary prevention of atherosclerotic events in adults with CAD or symptomatic PAD

Commissioning guidance:

Commissioners may wish to bear the following in mind when considering the implementation of the NICE guidance on the use of Rivaroxaban for preventing atherothrombotic events in people with coronary or peripheral artery disease (TA607)[2]:

- Most patients will have been discharged from secondary care for at least a year following an athero--sclerotic event (*ca*. 62% had suffered a myocardial infarction [MI] in the COMPASS trial) and subsequent dual anti-platelet treatment, so this will be an issue for primary care.
- The NICE guidance describes the use of rivaroxaban plus aspirin as an option for preventing atherothrombotic events in adults with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) who are at high risk of ischaemic events.
  - Assess the person's risk of bleeding before considering rivaroxaban, and only start treatment after an informed discussion of the risks of atherothrombotic events weighed against the risk of bleeding.
  - The risks and benefits of continuing treatment with rivaroxaban should be reviewed regularly.
  - NICE CG172 (secondary prevention of MI)[3] advises use of a proton pump inhibitor in patients with aspirin-induced ulcer bleeding, and in people with dyspepsia. The Oxford Vascular Study[7] suggested that all patients over 75 receiving antiplatelet treatment following an ischaemic vascular event should have a PPI co-prescribed with aspirin.
- Consider local care pathways if implementing the use of rivaroxaban:
  - The committee considered that there would be significant resource/capacity issues associated with screening patients for eligibility for rivaroxaban treatment. Options for patient selection include: initiation in new patients only, an option for discussion at the patients' annual review, or via case finding; with assessment of the associated resource/capacity needs.
  - Potential for development of a local CCG or STP-wide implementation plan, and liaison with vascular centres (both CABG/PAD).
  - An option for discussion with local Primary Care Networks, case-finding or reviews potentially a job for PCN pharmacists
  - Other local arrangement with Secondary care e.g. use of Blueteq to facilitate secondary care initiation of treatment
- Localities need to decide how to assess/record bleeding risk – to ensure an informed discussion of risks and benefits with patients. The HAS-BLED score is a potential tool, with the *caveat* that it has only been validated for use in people with atrial fibrillation.
- Appropriate monitoring arrangements need to be in place to assess continued benefit/risk balance. At least an annual review and more frequently in people with comorbidities.
- NICE estimates a low impact of the guidance and uptake similar to the use of ticagrelor. This may be due to the need to discuss the risk of a bleed. In the West Midlands, this cost is estimated to be between £0.5 to 1.5 million per year, based on an uptake of between 2.9% and 5.8% in atherosclerosis patients.
- Consider an audit of GI bleeds in patients receiving rivaroxaban and aspirin, given the significantly greater incidence compared with aspirin alone (see Adverse events section).

MTRAC considered the implementation of the NICE guidance at the request of local Commissioners

Description of technology

Rivaroxaban is an oral direct factor Xa inhibitor that acts by inhibiting thrombin formation and thus formation of thrombi (blood clots)[1]. This guidance is for the vascular dose for rivaroxaban 2.5 mg twice daily, in addition to ASA (75 to 100 mg daily), for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events.

The Summary of Product Characteristics (SPC) advises that duration of treatment should be determined for each individual patient based on regular evaluations and should consider the risk for thrombotic events *versus* the bleeding risks. For full details of administration and contraindications, see the SPC[1].

Background

The use of rivaroxaban plus aspirin for this indication was considered in a NICE technology appraisal in 2019[2], advising that:

Rivaroxaban plus aspirin is recommended within its marketing authorisation, as an option for preventing atherothrombotic events in adults with CAD or symptomatic PAD) who are at high risk of ischaemic events, defined as:

- aged 65 or over, or

● atherosclerosis in at least two vascular territories such as coronary, cerebrovascular, or peripheral arteries, or

● two or more of the following risk factors: current smoking, diabetes, heart failure, previous non-lacunar ischaemic stroke, kidney dysfunction (eGFR < 60 ml/min; *n.b. rivaroxaban contraindicated if eGFR <15 ml/min; use with caution if CrCl 15-29ml/min and in patients with CrCl 30-49ml/min receiving medicines which increase rivaroxaban plasma concentration*).

Clinical evidence for efficacy and safety

A single RCT (COMPASS trial; n = 27,395)[4-6] evaluated the vascular dose of rivaroxaban 2.5 mg twice daily plus aspirin 100 mg daily (n = 9125), *versus* aspirin alone (n = 9126), or rivaroxaban 5 mg twice daily alone (n = 9117 *[n.b. not a licensed dose]*) in people with a history of stable atherosclerotic vascular disease (CAD, PAD, or both). A comparison of pantoprazole *vs*. placebo, also in the trial, will not be further described[8,9]. Patients with CAD younger than 65 years of age also had to have documented atherosclerosis involving at least two vascular beds, or at least two additional risk factors (current smoking, diabetes mellitus, eGFR <60 ml per minute, heart failure, or non-lacunar ischaemic stroke ≥1 month earlier). Patients with severe heart failure (ejection fraction <30%, NYHA III or IV) and previous non-lacunar ischaemic stroke within 1 month were excluded.

The primary efficacy outcome was a composite of cardiovascular (CV) death, stroke, or MI. The main safety outcome was the incidence of major bleeding (composite of: fatal bleeding, symptomatic bleeding into a critical organ, surgical site requiring reoperation, or requiring hospitalisation).

Results: participants receiving rivaroxaban 2.5 mg twice daily plus aspirin had a significantly lower incidence of the primary outcome than with aspirin treatment alone (4.1% *vs*. 5.4%; p < 0.001; number needed to treat to benefit [NNTB] = 77). There was no significant difference in this outcome for participants receiving rivaroxaban 5mg twice daily *versus* aspirin treatment alone. This result was also reported for the subgroups of participants with CAD (91% of participants; of which 19.8% also had PAD) and PAD (27.3% of participants).

Secondary composite outcomes of ischaemic stroke, MI, acute limb ischaemia and either death from coronary heart disease (CHD) or CV causes were also significantly lower in the rivaroxaban plus aspirin group *vs.* aspirin alone (nominal p value < 0.001). There were significantly fewer major limb amputations (HR 0.30, 95%CI 0.11 to 0.80)[6] and fewer incidences of a composite of all major adverse limb events plus all major amputations of a vascular cause (HR 0.54, 95%CI 0.35 to 0.82).[6]

Adverse events

The incidence of major bleeding events was significantly greater with rivaroxaban plus aspirin treatment that with aspirin alone (288 patients [3.1%] *vs.* 170 patients [1.9%]; hazard ratio, 1.70; 95% CI 1.40 to 2.05; p <0.001; number needed to treat to harm [NNTH] = 84). The most common site of major bleeding was the gastrointestinal (GI) tract (140/9152 [1.5%] for rivaroxaban plus aspirin *vs*. 65/9126 [0.7%] for aspirin alone; HR: 2.15; 95% CI: 1.60 to 2.89; p < 0.0001)[10]. Major bleeding events also occurred in more patients in the rivaroxaban-alone (5 mg twice daily) group than in the aspirin-alone group (255 patients [2.8%] *vs.* 170 patients [1.9%]; hazard ratio, 1.51; 95% CI, 1.25 to 1.84; p < 0.001)[5].

Considerations for cost impact

Using 2017/18 data from the quality and outcomes framework, the estimated numbers of patients involved from the West Midlands is 200,885 (3.2%) and 36,996 (0.6%), with CAD and PAD, respectively.

At current prices, the yearly costs of rivaroxaban plus aspirin are shown below; the total cost of the combination is £674.99. Some patients may also need a PPI (more detail in guidance box).

- Aspirin (generic) 75mg tablets £17.99
- Rivaroxaban (Xarelto®▼) 2.5mg tablets twice daily £657.00

Use of rivaroxaban for this indication will result in an increased drug acquisition cost per patient per year. Implementing TA607 may reduce the number of people who have an ischaemic event, and a reduction in the number of people who have ischaemic events would result in a reduction in costs from unplanned admissions and interventions.[11]

References

1. Bayer plc. Xarelto 2.5 mg film-coated tablets 2020.
2. NICE. Rivaroxaban for preventing atherothrombotic events in people with coronary or peripheral artery disease (TA607) 2019.
3. NICE. Myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular events (CG172) 2013.
4. Eikelboom JW et al. Rivaroxaban with or without Aspirin in Stable CV Disease. *NEJM* 2017;377(14):1319-30.
5. Anand SS et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2018;391(10117):219-29.
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7. Li L et al. Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study. *The Lancet* 2017;390(10093):490-99.
8. Moayyedi P et al. Pantoprazole to Prevent Gastroduodenal Events in Patients Receiving Rivaroxaban and/or Aspirin in a Randomized, Double-Blind, Placebo-Controlled Trial. *Gastroenterology* 2019;157(2):403-12.e5.
9. Moayyedi P et al. Safety of Proton Pump Inhibitors Based on a Large, Multi-Year, Randomized Trial of Patients Receiving Rivaroxaban or Aspirin. *Gastroenterol.* 2019;157(3):682-91.e2.
10. Eikelboom JW et al. Major Bleeding in Patients With Coronary or Peripheral Artery Disease Treated With Rivaroxaban Plus Aspirin. *JACC* 2019;74(12):1519-28.
11. NICE. Resource impact report: Rivaroxaban for preventing atherothrombotic events in people with coronary or peripheral artery disease (TA607) 2019.