Coventry & Warwickshire Area Prescribing Committee

Drug Positioning Statement	DPS030
Rivaroxaban (Xarelto®) for Stroke prevention in Atrial Fibrillation	**August 2018**

VERDICT

Rivaroxaban, within its licensed indications and in line with NICE TA256 is recommended as an option for the prevention of stroke in non-valvular AF and should be initiated by a specialist, tailored to the clinical situation of the patient. Follow on prescribers should receive a checklist from the initiating specialist indicating that the patient is suitable for rivaroxaban therapy and has received appropriate guidance form the specialist. If the checklist is not made available, follow on prescribing in primary care should not commence until the specialist has been contacted and a checklist obtained.

For Primary Care Prescribers: The committee recognises the beneficial effect of anticoagulant therapy once a diagnosis of AF has been made in primary care. In this instance, rivaroxaban may be initiated by a primary care prescriber where they have attended a suitable training course and can demonstrate expertise in managing anticoagulant therapy. The committee also advise that the specialist initiated drug checklist is also completed by the primary care prescriber.

Specialist Drugs Status: Specialist Advised (SA)

SUMMARY NOTES

Indication: Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (AF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack. Also licensed for the treatment of Deep Vein Thrombosis, (DVT) and prevention of recurrent DVT and pulmonary embolism (P.E.) following an acute DVT.

Pharmacological action: Rivaroxaban is a selective direct factor Xa inhibitor which interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting thrombin formation and the development of thrombi.

Presentation: Xarelto® 15 mg and 20 mg tablets

Dose: The recommended dose for prevention of AF is 20 mg once daily, which is also the recommended maximum dose. Therapy with rivaroxaban should be continued long term, provided the benefit of prevention of stroke and systemic embolism outweighs the risk of bleeding. If a dose is missed the patient should take rivaroxaban immediately and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

In patients with moderate (calculated creatinine clearance using Cockcroft Gault equation = 30 - 49 ml/min) or severe (calculated creatinine clearance 15 - 29 ml/min) renal impairment, the recommended dose is 15 mg once daily. Use is not recommended in patients with calculated creatinine clearance < 15 ml/min.

Cost comparison: cost per 28 days (eMIMs, Drug Tariff August 2018)

Rivaroxaban 20 mg daily	£50.40
Dabigatran 150 mg or 110 mg bd	£47.60
Apixaban 5 mg bd	£53.20
Edoxaban 30 - 60 mg daily	£49.00
Warfarin 5 mg daily	£0.61 (variable depending on INR; costs including monitoring, range from £220 to £480 per year[8])

DRUG PROFILE

Clinical effectiveness - Rivaroxaban is a selective direct factor Xa inhibitor which interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting thrombin formation and the development of thrombi. The pivotal study for rivaroxaban IS ROCKET-AF. ROCKET-AF was a multicentre, double-blind, double-dummy, randomised controlled trial [2,3,4]. It compared rivaroxaban 20 mg daily (or 15 mg daily where creatinine clearance was 30–49 ml/minute) with warfarin in 14 264 people with AF and either previous systemic embolism, stroke or TIA, or at least two stroke risk factors (mean CHADS2 = 3.5); the primary endpoint was a composite of stroke (ischaemic or haemorrhagic) and systemic embolism.

For the per-protocol population the primary endpoint occurred at a rate of 1.7% per year for rivaroxaban and 2.2% per year for warfarin, with non-inferiority demonstrated (HR 0.79, 95% CI 0.66–0.96; p < 0.001 for non-inferiority). The subsequent safety population analysis indicated that rivaroxaban was superior to warfarin (HR 0.79, 95% CI 0.65–0.95; p < 0.02 for superiority). However, whilst the intention-to-treat analysis continued to demonstrate non-inferiority, it did not confirm superiority (HR 0.88, 95% CI 0.75–1.03; p < 0.001 for non-inferiority, p = 0.12 for superiority). For major and non-major clinically relevant bleeding, the event rate was 14.9% for rivaroxaban and 14.5% for warfarin (HR 1.03, 95% CI 0.96–1.11; p = 0.44). Intracranial haemorrhage occurred less frequently with rivaroxaban (0.5% vs. 0.7% per year, p = 0.02), as did fatal bleeding (0.2% vs. 0.5% per year, p = 0.003). Major GI bleeding was more common for rivaroxaban compared to warfarin (3.2% vs. 2.2%, p ≤ 0.001). A UKMI briefing paper [2] provides a summary of the key issues associated between dabigatran and rivaroxaban.

DRUG PROFILE cont'd

There was no significant difference in the principal safety endpoint of major and non-major clinically relevant bleeding in the ROCKET-AF trial (HR 1.03, 95% CI 0.96 to 1.11, p=0.44). Gastrointestinal bleeding was more common with rivaroxaban than warfarin (3.2% vs. 2.2%, p<0.001), as were decrease in haemoglobin of ≥2g/dl (4.3% vs. 3.6%, p=0.02), need for transfusion (2.6% vs. 2.1%, p=0.04), epistaxis (10.1% vs. 8.6%, p<0.05), and haematuria (4.2% vs. 3.4%, p<0.05) [3, 4].

Intracranial haemorrhage was less common with rivaroxaban than warfarin (0.8% vs. 1.2%, p=0.02), as were critical bleeding (1.3% vs. 1.9%, p=0.007) and fatal bleeding (0.4% vs. 0.8%, p=0.003). There were no significant differences in the incidence of any other adverse event. More rivaroxaban than warfarin treated patients discontinued treatment due to adverse events: 8.3% (594/7,131) versus 7.0% (498/7,133). Liver function test events reported as either alanine aminotransferase >3 times upper limit of normal (ULN) and total bilirubin >2 times ULN on same day occurred with equal frequency in the two groups, 0.47% (33/7,111) of rivaroxaban and 0.50% (35/7,125) of warfarin patients[3,4].

Interactions[1]: Rivaroxaban should be used with caution in patients with renal impairment concomitantly receiving potent inhibitors of CYP3A4, (e.g. clarithromycin, telithromycin), as increased rivaroxaban concentrations may occur in these patients. Rivaroxaban is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree (2.6 fold on average) which may lead to an increased bleeding risk.

Also, care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as non-steroidal anti-inflammatory medicinal products (NSAIDs), acetylsalicylic acid, platelet aggregation inhibitors or other antithrombotic agents.

Given the limited clinical data available with dronedarone, co-administration with rivaroxaban should be avoided. Co-administration of rivaroxaban with the strong CYP3A4 inducer, rifampicin, led to an approximate 50% decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects. The concomitant use of rivaroxaban with other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort) may also lead to reduced rivaroxaban plasma concentrations. Strong CYP3A4 inducers should be co-administered with caution.

CURRENT PLACE IN THERAPY

National Institute for Health and Care Excellence (NICE)[5] Rivaroxaban is recommended as an 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:

- congestive heart failure
- hypertension
- age 75 years or older
- diabetes mellitus
- prior stroke or transient ischaemic attack

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.

Scottish Medicines Consortium (SMC) [6] Accepted for use restricted use in NHS Scotland for the prevention of stroke and systemic embolism in adult patients with non valvular atrial fibrillation with one or more risk factors, such as: congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack. Rivaroxaban is accepted for use in patients who have poor INR control, despite evidence that they are complying with a coumarin anticoagulant and for use in patients who are allergic to or unable to tolerate coumarin anticoagulants. Rivaroxaban was non inferior to standard oral anticoagulation at preventing stroke or systemic embolism in one large, double blind study in patients with atrial fibrillation and moderate to high risk of stroke. This was not associated with a significantly increased risk of major or non major clinically relevant bleeding.

Midlands Therapeutics Review and Advisory Committee (MTRAC)[7] categorised A/Q3 with strong evidence and lower place in therapy
The ROCKET-AF trial showed that rivaroxaban 20mg daily was non-inferior to warfarin for prevention of stroke or systemic embolism, with no differences in the risk of bleeding. The considerable cost impact associated with commissioning this drug and concerns around monitoring adherence to treatment and long term safety gave rivaroxaban a low place in therapy.

The commissioning guidance recommends that warfarin remains a first line option for anticoagulation in patients with atrial fibrillation (AF) at high risk of stroke.

Summary - There is no specific data or guidance indicating how to choose between dabigatran or rivaroxaban in place of warfarin, and it is unlikely such will become available. The ROCKET-AF and RE-LY trials had different methodologies with the results reported in different ways such that they cannot be directly compared [2,4,8].

Despite their relatively short half-lives, a significant concern for both drugs is the lack of an antidote with potentially serious consequences should a patient present with life threatening haemorrhage or require emergency surgery [2,3].

Whilst the lack of the need to monitor therapy has advantages, disadvantages are that the ability to objectively measure anticoagulation and determine adherence is lost and any currently unknown drug interactions will be hard to assess with potentially serious consequences[2].

Rivaroxaban is taken once daily and dabigatran twice daily (although there is no worthwhile or significant difference in levels of compliance between once daily and twice daily regimens). Both dabigatran and rivaroxaban require dose adjustment in renal impairment, and are contra-indicated where there is severe impairment, i.e. calculated creatinine clearance < 15mL/min for rivaroxaban.

References

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