RIVAROXABAN (XARELTO®)

Thrombosis Canada
Thrombose Canada

OBJECTIVE:

To provide an overview of the mechanism of action, licensed indications, dosing regimens, and side-effects of rivaroxaban.

BACKGROUND:

Rivaroxaban (Xarelto®) is an oral factor Xa inhibitor. By binding reversibly to the active site of factor Xa, rivaroxaban attenuates thrombin generation and reduces fibrin formation.

INDICATIONS:

Rivaroxaban is currently licensed in Canada for:

- Thromboprophylaxis after elective hip or knee replacement surgery
- Treatment of patients with deep vein thrombosis (DVT) and/or pulmonary embolism (PE), and prevention of recurrent DVT and PE
- Stroke and systemic embolism prevention in patients with non-valvular atrial fibrillation
- Prevention of stroke, myocardial infarction and cardiovascular death, and for the prevention of acute limb ischemia and mortality in patients with coronary artery disease (CAD), with or without peripheral artery disease (PAD), in combination with acetylsalicylic acid (ASA) 75-100 mg daily

DOSING:

1. **Prevention of stroke and systemic embolism in atrial fibrillation:** 20 mg once daily (OD) in patients with CrCl ≥50 mL/min or 15 mg OD for those with CrCl 15 - <50 mL/min. Physicians must use caution when prescribing the 15 mg OD dose for those with CrCl 15 - <30 mL/min. Use is not recommended with CrCl <15 mL/min.
2. **Acute treatment of DVT and PE:** 15 mg twice daily (BID) for 3 weeks and 20 mg OD thereafter. No dosing adjustment is recommended in those with CrCl 15 - <50 mL/min, however, caution is recommended for those with CrCl 15 - <30 mL/min. Use is not recommended with CrCl <15 mL/min.
3. **Continued prevention of recurrent DVT and PE:** For extended therapy beyond 6 months, consideration may be given to reducing the dose to 10 mg OD. No dosing adjustment is recommended in those with CrCl 15 - <50 mL/min, however, caution is recommended for those with CrCl 15 - <30 mL/min. Use is not recommended with CrCl <15 mL/min.
4. **Thromboprophylaxis after arthroplasty:** 10 mg OD starting at least 6-8 h after surgery and continuing for 14 to 35 days after knee or hip replacement surgery, respectively. No dosing adjustment is recommended in those with CrCl 15 - <50 mL/min, however, caution is

recommended for those with CrCl 15 - <30 mL/min. Use is not recommended with CrCl <15 mL/min.

5. **Prevention of stroke, myocardial infarction and cardiovascular death, and for the prevention of acute limb ischemia and mortality in patients with coronary artery disease (CAD) with or without peripheral artery disease (PAD):** 2.5 mg BID in combination with ASA 75-100 mg OD. This regimen is only appropriate for patients without atrial fibrillation. In patients with CAD, PAD, or both, rivaroxaban 2.5 mg BID is not indicated in combination with dual antiplatelet therapy.

MONITORING:

Routine laboratory monitoring is not necessary. Although the prothrombin time/international normalized ratio (PT/INR) and activated partial thromboplastin time (aPTT) do not provide reliable measures of rivaroxaban's anticoagulant activity, the prothrombin time is more responsive to the presence of rivaroxaban. Anti-factor Xa assays using rivaroxaban calibrators, where available, can be used to determine the plasma rivaroxaban concentration. For more details about specific testing, see the **Clinical Guide NOACs/DOACs: Coagulation Tests**.

Although no routine coagulation laboratory monitoring is required for long-term rivaroxaban use, periodic clinical assessment is important to determine and reinforce compliance, review comorbidity and medication changes, including an assessment for possible interacting agents, and provide education. Furthermore, for most patients, at least yearly assessment of creatinine clearance is recommended. The creatinine should be measured more frequently in patients with an abnormal value at baseline or at risk of worsening renal function. [See Clinical Resource: **Direct Oral Anticoagulant (DOAC) Follow-up Checklist for Clinicians**; **Direct Oral Anticoagulant (DOAC) Monitoring Checklist for Pharmacists**].

ADVERSE EFFECTS:

The major adverse effect of rivaroxaban is bleeding; concomitant use of antiplatelet drugs or strong inhibitors of both CYP 3A4 and P-glycoprotein (P-gp) (see below under Special Considerations: Drug Interactions) increases this risk. Rivaroxaban should be avoided in patients with indwelling epidural catheters or with a history of recent spinal puncture, in order to reduce the risk of post-operative epidural hematoma.

A small number of patients may experience dyspepsia. Taking rivaroxaban with food will reduce dyspepsia and improve absorption.

PERI-PROCEDURE MANAGEMENT:

See the **Clinical Guide NOACs/DOACs: Perioperative Management** and the Tool: **Perioperative Anticoagulant Management Algorithm**.

SPECIAL CONSIDERATIONS:

Administration: Rivaroxaban 2.5 mg and 10 mg doses may be taken with or without food. At doses higher than 10 mg OD, rivaroxaban **should be administered with food to maximize absorption.**

Pregnancy and breast feeding: Rivaroxaban crosses the placenta and should not be used in pregnancy. It has been shown that rivaroxaban appears in breast milk; therefore, this drug should also be avoided in nursing mothers.

Renal and hepatic dysfunction: There is limited information on rivaroxaban in patients with CrCl <15 mL/min and in those with moderate or severe hepatic impairment (Child-Pugh class B or C). Rivaroxaban should be avoided in such patients.

Drug interactions: The concomitant use of rivaroxaban and drugs and/or herbal products that inhibit or induce both P-gp and CYP3A4 should be avoided. Patients taking strong inhibitors of P-gp and CYP3A4 (e.g. azole antifungals like ketoconazole, itraconazole, voriconazole, and posaconazole; the HIV protease inhibitor, ritonavir) are at increased risk of bleeding. Although combined P-gp and moderate CYP3A4 inhibitors, such as erythromycin, have no clinically relevant effect on rivaroxaban levels in patients with normal renal function; these drugs should be used with caution in patients receiving rivaroxaban who have mild and moderate renal impairment as co-medication with combined P-gp and moderate CYP3A4 inhibitors increases rivaroxaban levels by approximately 2-fold. Alternately, concomitant use of strong inducers of CYP3A4 (e.g. rifampin, carbamazepine, phenytoin, phenobarbital, St. John's Wort) can reduce rivaroxaban levels and should be avoided.

Bleeding: An antidote for factor Xa inhibitors (andexanet alfa) is in advanced development but is not yet available in Canada, although it has acquired FDA approval in the USA. Approaches to the management of bleeding can be found in the **Clinical Guide NOACs/DOACs: Management of Bleeding** and the Tool **Bleed Management**.

Pediatrics: Limited data are available on the use of rivaroxaban in neonates and children. A single study comparing bodyweight-adjusted 20 mg equivalent dose to standard treatment in neonates and children with acute venous thromboembolism treated with 5-9 days of unfractionated heparin, low-molecular weight heparin or fondaparinux demonstrated a low risk of symptomatic recurrent venous thromboembolism (1% (3/355); hazard ratio [HR] 0.40, 95% CI 0.11-1.41) and major or clinically relevant non major bleeding (3% (10/329), HR 1.58, 95% CI 0.51-6.27). Pediatricians with expertise in thromboembolism should be involved in decisions regarding the management of thromboembolism in pediatric patients and should be consulted prior to using rivaroxaban in this patient population.

Treatment of cancer-associated thrombosis: Rivaroxaban does not currently have a licensed indication in Canada specifically for use in this patient population but a recent small randomized pilot trial comparing rivaroxaban with low molecular weight heparin (LMWH) showed that in this study population, rivaroxaban may be a reasonable alternative to LMWH when the risk of gastrointestinal (GI) bleeding is low and in patients with non-GI solid tumor malignancies, provided that drug-drug interactions and significant thrombocytopenia are not a concern. This study showed fewer episodes of recurrent VTE but a 2- to 3-fold higher risk of major or clinically relevant bleeding (particularly GI bleeding) with rivaroxaban over LMWH. A thorough review of the relative risks and benefits of both anticoagulant options, in addition to potential drug interactions and patient preference and values, is

prudent prior to prescribing anticoagulant therapy in patients with cancer-associated VTE. See the **Clinical Guide Cancer and Thrombosis**.

Primary thrombosis prophylaxis in ambulatory cancer patients: In a randomized trial comparing rivaroxaban 10 mg OD with placebo in ambulatory cancer patients judged to be at high risk for venous thromboembolism according to their Khorana score (≥2), benefit of treatment was not established as rivaroxaban was not associated with significant reduction in the risk of symptomatic or asymptomatic venous thromboembolism or death compared to placebo in the prespecified primary efficacy analysis of up to day 180 (6.0% in the rivaroxaban group versus 8.8% in the placebo group; hazard ratio [HR]: 0.66; 95% CI, 0.40-1.09); although a pre-specified analysis restricted to the period of intervention (first receipt of study drug to last dose plus 2 days), did result in a statistically significant reduction in the risk of venous thromboembolism. There was no increase in major bleeding with rivaroxaban therapy (2.0% of patients receiving rivaroxaban versus 1.0% of those receiving placebo; HR: 1.96; 95% CI, 0.59-6.49). Rivaroxaban is not currently licensed for this indication in Canada. See the **Clinical Guide Cancer and Thrombosis**.

Stable cardiovascular disease: The COMPASS trial compared aspirin 100 mg daily alone, rivaroxaban 5 mg twice daily alone and rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily in patients with stable cardiovascular disease (including PAD) and without atrial fibrillation. Those assigned to the combination of aspirin with rivaroxaban 2.5 mg twice daily had better cardiovascular outcomes and lower mortality but more major bleeding than those assigned to aspirin alone; however, the net clinical benefit favored combination therapy. Rivaroxaban 5 mg twice daily alone did not result in better outcomes than aspirin and was associated with more bleeding events. It is yet to be determined which patients with stable cardiovascular disease will benefit most from the combination of rivaroxaban 2.5 mg twice daily and low-dose aspirin.

Atrial fibrillation patients receiving $P2Y_{12}$ inhibitor for recent acute coronary artery syndrome (ACS) or percutaneous coronary intervention (PCI): The PIONEER AF trial randomized patients to one of three groups: (1) rivaroxaban 15 mg daily (10 mg daily if CrCl 30-50mL/min) with a $P2Y_{12}$ inhibitor; (2) rivaroxaban 2.5 mg twice daily with a $P2Y_{12}$ inhibitor plus ASA; or (3) warfarin (INR 2-3) with a $P2Y_{12}$ inhibitor plus ASA. The most common $P2Y_{12}$ inhibitor used was clopidogrel. The trial found that low dose rivaroxaban (10-15 mg daily) plus a $P2Y_{12}$ inhibitor or very low dose rivaroxaban (2.5 mg twice daily) plus dual antiplatelet therapy resulted in less bleeding and fewer hospitalizations than regimens including dual antiplatelet therapy plus warfarin. There were no observed differences in the incidence of ischemic events between the arms, but the trial was not powered to detect such differences. Pragmatically speaking when rivaroxaban is used in this situation it is typically 15 mg daily (10 mg daily for CrCl 30-50mL/min) with clopidogrel. Rivaroxaban dose should be increased once clopidogrel is discontinued.

OTHER RELEVANT THROMBOSIS CANADA CLINICAL GUIDES, RESOURCES AND TOOLS:

- Anticoagulation in Patients Requiring Antiplatelet Therapy
- Cancer and Thrombosis
- Deep Vein Thrombosis (DVT): Treatment

- NOACs/DOACs: Coagulation Tests
- NOACs/DOACs: Comparison and Frequently Asked Questions
- NOACs/DOACs: Management of Bleeding
- NOACs/DOACs: Perioperative Management
- Peripheral Arterial Disease
- Pulmonary Embolism (PE): Treatment
- Stroke Prevention in Atrial Fibrillation
- Thromboprophylaxis: Orthopedic Surgery
- Clinical Resource: Direct Oral Anticoagulant (DOAC) Follow-up checklist for Clinicians
- Clinical Resource: Direct Oral Anticoagulant (DOAC) Monitoring Checklist for Pharmacists
- Tool: Perioperative Anticoagulant Management Algorithm
- Tool: Bleed Management

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Date of version: 23November2020

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