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), both acute and extended treatment
- Stroke 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 OD in patients with CrCl ≥50 mL/min or 15 mg OD for those with CrCl 30 - <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 once daily (OD) starting at least 6-8 h after surgery and continuing for 14 to 30 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 twice daily (BID) in combination with ASA 75-100 mg OD. This regimen is only appropriate for patients without atrial fibrillation. In patients with CAD with or without PAD, 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 laboratory monitoring is required for long-term rivaroxaban use, periodic clinical assessment is important to determine and reinforce compliance, review comorbidity and medication changes, 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:**

SPECIAL CONSIDERATIONS:

Administration: Rivaroxaban 2.5 mg and 10 mg 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 that inhibit or induce both P-glycoprotein (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, such as erythromycin, 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®) is in advanced development but is not yet available in Canada. Approaches to the management of bleeding can be found in the Clinical Guide “NOACs/DOACs: Management of Bleeding” and the Tool “Bleed Management”.

Pediatrics: Rivaroxaban is not recommended for use in children until ongoing studies establish the pharmacokinetics, pharmacodynamics, safety, and efficacy of rivaroxaban in neonates and children.

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 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.

Primary thrombosis prophylaxis in ambulatory cancer patients: In a randomized trial comparing rivaroxaban 10 mg once daily 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 recent 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.

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

REFERENCES:


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