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.

Health Canada Advisory (Dec. 20, 2018):

Increase in all-cause mortality, thromboembolic and bleeding events in patients after transcatheter aortic valve replacement (TAVR) with rivaroxaban have been seen and therefore it is not indicated nor recommended at this time for patients post TAVR procedure.

Indications:

Rivaroxaban (10mg, 15mg, 20mg) is currently licensed in Canada for:

- Thromboprophylaxis after elective hip (THR) or knee (TKR) 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

Rivaroxaban (2.5mg), in combination with acetylsalicylic acid (ASA) 75-100 mg daily, is currently licensed in Canada for:

- 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)
- Prevention of atherothrombotic events in patients with symptomatic PAD at demonstrated high risk of major adverse limb events (MALE) or major adverse cardiovascular and cerebrovascular events (MACCE).

Rivaroxaban granules for oral suspension (1mg/mL)is currently licensed in Canada for:

- Treatment of venous thromboembolic events (VTE) and prevention of VTE recurrence in term neonates, infants and toddlers, children and adolescents aged less than 18 years after at least 5 days of initial parenteral anticoagulation treatment

Dosing:

1. **Prevention of stroke and systemic embolism in atrial fibrillation:** 20 mg once daily (OD) with food in patients with CrCl ≥50 mL/min or 15 mg OD with food for those with CrCl 15 - 49 mL/min. Physicians must use caution when prescribing the 15 mg OD dose for those with CrCl 15 - 49 mL/min. Use is not recommended with CrCl <15 mL/min.
2. **Treatment of DVT and PE:** 15 mg twice daily (BID) with food for 3 weeks followed by 20 mg OD thereafter. No dosing adjustment is recommended in those with CrCl ≥15 mL/min, however, caution is recommended for those with CrCl 15 - 29 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 from 20mg to 10 mg OD, based on an individual risk benefit assessment of the risk of recurrent VTE versus bleed risk. No dosing adjustment is recommended in those with CrCl ≥15 mL/min, however, caution is recommended for those with CrCl 15 - 29 mL/min. Use is not recommended with CrCl <15 mL/min.
4. **Thromboprophylaxis after arthroplasty:** 10 mg OD starting at least 6-10 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 mL/min, however, caution is recommended for those with CrCl 15 - 29 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.
6. **Treatment of DVT and Prevention of VTE recurrence in patients less than 18 years old**: Dosing is based on weight. Please refer to Special Considerations – Pediatrics section below.

Switching from vitamin-k antagonist (VKA) to rivaroxaban:

There are two approaches. After stopping warfarin:

1. It is recommedned that the patient wait until the INR is less than 2.5 before starting rivaroxaban. This is because the onset of action of the DOAC is rapid (peak effect 1-3 hours after ingestion), while the offset of action of warfarin is slower.
2. If INR testing is not readily available, it is reasonable to wait 2-3 days after the last dose of warfarin before starting rivaroxaban.

Note: if the INR is supratherapeutic, it will take longer for the INR to fall to 2.0 or lower.

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** **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 those 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-Procedural Management:

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

Special Considerations:

Administration: Rivaroxaban 15mg tablets, 20mg tablets, and granules for oral suspension must be taken with food (or feeding for the latter) to maximize absorption. Rivaroxaban 2.5mg and 10mg tablets may be taken with or without food.

Rivaroxaban tablets may be crushed and mixed with applesauce and administered immediately after or may be administered via nasogastric (NG) tube. Food, inlcluding NG feeds, should follow right after.

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. Rivaroxaban is contraindicated in combination with strong **inhibitors** of both CYP3A4 and P-glycoprotein (such as ketoconazole, itraconazole, posaconazole, cobicistat and ritonavir) when used concomitantly for systemic therapy as these drugs may increase rivaroxaban plasma concentrations to a clinically relevant degree. Although combined P-gp and moderate CYP3A4 inhibitors, such as erythromycin and fluconazole, 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.

The co-administration of rivaroxaban and nirmatrelvir/ritonavir (Paxlovid) is not recommended due to significant risk of toxicity (Paxlovid may cause accumulation of rivaroxaban). It is advised to hold rivaroxaban for 24 hours prior to starting Paxlovid (hold on day 0, start Paxlovid on day 1) and restarting 2 days after completing treatment (day 7). Alternative anticoagulation should be provided with a lesser risk of toxicity (e.g., LMWH for acute VTE; edoxaban 30 mg daily for atrial fibrillation). See guidance from PHAC for additional details (https://hivclinic.ca/downloads/paxlovid/paxlovid_doac_live.pdf).

Bleeding: Approaches to the management of bleeding can be found in the **Clinical Guide** **DOACs: Management of Bleeding** and the Tool **Bleed Management**.

Pediatrics: Rivaroxaban is an oral Factor Xa inhibitor, approved for treatment of VTE and pevention of VTE recurrence in the pediatric population in Canada in January 2021. Evidence for use is based on the EINSTEIN Jr trials which were randomized, multi-centred trials assessing the pharmacokinetics, efficacy, and safety of rivaroxaban in children. The EINSTEIN Jr phase III trial specifically used weight adjusted regimens for rivaroxaban dosing and showed non-inferiority to standard anticoagulants (low molecular weight heparin or vitamin K antagonist) and a similar safety profile. The study treatment period was 3 months with the exception of catheter-related VTE in children younger than 2 years, for whom it was 1 month. Children received at least 5 days of initial heparinization before starting rivaroxaban treatment. Body weight adjusted 20 mg equivalent dosing was based on phase 1 and 2 data. In total, 335 children were allocated to rivaroxaban. Symptomatic recurrent VTE occurred in 2 children (0.6%) during treatment. No major bleeds occurred on treatment. *All children <18 years of age requiring rivaroxaban should be managed in consultation with a Pediatric Hematologist. Please view Canadian Pediatric Thrombosis & Hemostasis Network (CPTHN) document on rivaroxaban use in pediatric patients (September 2021) for further details and information on dosing.*

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 patients with cancer: 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). However, 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.

Patients with atrial fibrillation 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.

Anticoagulation for patients with a Fontan circulation for single-ventricle physiology: The UNIVERSE trial (2022) studied 112 pediatric patients, who were randomized to rivaroxaban at an adult dose of 10 mg or equvalent or ASA starting within 4 months of Fontan procedure. At 12 months there was 1 thromboembolic event with rivaroxaban versus 3 with ASA, with a comparable safety profile. However, more studies are needed to confirm these findings prior to widespread use of DOACs (including rivaroxaban) versus LMWHs or VKAs in this population. Similarly, DOACs (including rivaroxaban) are currently not indicated for use in adult fontan patients.

Other Relevant Thrombosis Canada Clinical Guides, Resources and Tools

- Anticoagulation in Patients Requiring Antiplatelet Therapy
- Cancer and Thrombosis
- Deep Vein Thrombosis (DVT): Treatment
- DOACs: Coagulation Tests
- DOACs: Comparison and Frequently Asked Questions
- DOACs: Management of Bleeding
- 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:

- https://recalls-rappels.canada.ca/en/alert-recall/xarelto-rivaroxaban-increase-all-cause-mortality-thromboembolic-and-bleeding-events
- https://www.onlinecjc.ca/article/S0828-282X(22)00078-2/fulltext
- https://covid19-sciencetable.ca/sciencebrief/nirmatrelvir-ritonavir-paxlovid-what-prescribers-and-pharmacists-need-to-know-3-0/
- https://covid19-sciencetable.ca/sciencebrief/paxlovid-for-a-patient-on-a-doac-2-0/
- https://clinicaltrials.gov/ct2/show/NCT02234843
- https://health-products.canada.ca/dpd-bdpp/info.do?lang=en&code=99437

Eikelboom JW et al. Rivaroxaban with or without ASA in stable cardiovascular disease. N Engl J Med 2017;377(14):1319-1330.

EINSTEIN Investigators, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363(26):2499-2510.

EINSTEIN-PE Investigators, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012;366(14):1287-1297.

Eriksson BI, et al. Oral rivaroxaban for the prevention of symptomatic venous thromboembolism after elective hip and knee replacement. J Bone Joint Surg Br 2009;91(8):636-644.

Gibson CM, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. N Engl J Med 2016; 375:2423-2434.

Gibson CM, et al. Recurrent hospitalizations among patients with atrial fibrillation undergoing intracoronary stenting treated with 2 treatment strategies of rivaroxaban or a dose-adjusted oral vitamin K antagonist treatment strategy. Circulation 2017;135:323-33.

Grindrod K, et al. Paxlovid for a patient on a DOAC who is also at high risk of hospitalization from COVID-19. Online resource: https://hivclinic.ca/downloads/paxlovid/paxlovid_doac_live.pdf. Accessed on Feb 26, 2024.

Khorana AA, et al. Rivaroxaban for thromboprophylaxis in high-risk ambulatory patients with cancer. N Engl J Med. 2019;380:720-728.

Male C et al. Rivaroxaban compared with Standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomized, controlled, phase 3 trial. Lancet Haematol 2020;7(1):e18-e27.

Patel MR, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365(10):883-891.

Schulman S, Crowther MA. How I treat with anticoagulants in 2012: new and old anticoagulants, and when and how to switch. Blood 2012;119(13):3016-3023.

Turpie AG, et al. Management consensus guidance for the use of rivaroxaban – an oral, direct factor Xa inhibitor. Thromb Haemost 2012;108(5):876-888.

Weitz JI, et al. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. N Engl J Med 2017;376:1211-1222.

Wiesen HJ et al. The direct factor Xa inhibitor rivaroxaban passes into human breast milk. Chest 2016;150(1):e1-e4.

Xarelto (rivaroxaban) Product Monograph. Bayer Inc. Mississauga, Ontario. September 20, 2019.

Young AM et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). J Clinic Oncol 2018 Jul 10;36(20):2017-2023.

Date of version: 28February2024

Please note that the information contained herein is not to be interpreted as an alternative to medical advice from your doctor or other professional healthcare provider. If you have any specific questions about any medical matter, you should consult your doctor or other professional healthcare providers, and as such you should never delay seeking medical advice, disregard medical advice or discontinue medical treatment because of the information contained herein.