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Is Rivaroxaban (Xarelto®) an Option for Your Patient?

Indications[1]

- ❑ Non-Valvular Atrial Fibrillation (NVAF)* to prevent stroke & systemic embolism
- ❑ Acute VTE treatment & prevention of recurrent VTE [for deep vein thrombosis (DVT) and pulmonary embolism (PE)]**
- ❑ With ASA for secondary cardiovascular event prevention (including limb ischemia), for patients with CAD, +/- PAD
- ❑ VTE treatment & prevention in Pediatrics (term neonate to 18yrs)***
- ❑ Prevention of venous thromboembolic events (VTE) in elective total hip or knee replacement surgery (THR, TKR)

*CCS definition: AF without mechanical heart valves or without moderate/severe mitral stenosis (rheumatic and non-rheumatic)[2]

**Cancer associated VTE (not an official indication) - limited data suggests similar efficacy to LMWH with more non critical site bleeding[3,4]

*** Pediatric Use Only Requirement: initial therapy of at least 5 days with parenteral anticoagulant. Neonate to < 6 months: see specific recommendations in product monograph

Requirements[1] - NOTE: Rivaroxaban accumulates in hepatic and/or renal dysfunction

- ❑ Stable creatinine clearance (CrCl) greater than 15 mL/min (see dosing recommendations)
- ❑ Stable liver function or Child-Pugh A (i.e. score less than 7) [refer to Contraindications section below]

Contraindications[1,2]

- ❑ Mechanical heart valves
- ❑ Rivaroxaban, like other anticoagulants, is contraindicated in patients at high risk for bleeding
- ❑ Pregnant/Breastfeeding: Safety & dosing has not been studied. Use is NOT recommended
- ❑ Moderate to severe hepatic impairment (including Child-Pugh Class B and C: Score 7 or greater) associated with coagulopathy and clinically relevant bleeding risk. Patients with severe hepatic impairment have not been studied.
- ❑ Drug Interactions: Significant drug interactions involving of both CYP 3A4 and P-glycoprotein - See below

Potential Limitations[1]

- ❑ Not recommended in hemodynamically unstable acute PE or those requiring thrombectomy or thrombolysis
- ❑ Not recommended in antiphospholipid syndrome with a history of thrombosis (especially triple positive)[5]
- ❑ Drug Interactions: AVOID rifampin, select azole antifungals (e.g. ketoconazole, itraconazole but *excluding* fluconazole), select anticonvulsants (e.g. phenytoin, carbamazepine, phenobarbital), HIV protease inhibitors, St. John's Wort & other strong CYP 3A4/P-gp inducers and inhibitors as there is minimal knowledge of clinical outcomes
- ❑ Rapid decline in anticoagulant effect after a missed dose; adherence is critical
- ❑ Limited data supporting the use in extremes of weight (under 50 kg; over 120 kg or BMI > 40)[6]
- ❑ AF Indication Only : Higher GI bleed rate than warfarin, although less critical bleeding events[7]

May offer an advantage over warfarin if:

- ❑ Difficulty stabilizing on warfarin for reasons other than poor medication adherence
- ❑ INR monitoring is problematic (e.g. poor venous access, frequent travel, remote location).
- ❑ AF: lower rate of critical site bleeding including intracranial hemorrhage[7]

Dosing Recommendations[1]*

Indication	CrCl 50 mL/min or greater	CrCl 30–49 mL/min	CrCl 15-30mL/min (use caution)
Stroke Prevention in NVAF	20 mg Once Daily	15 mg Once Daily	
Stroke Prevention in NVAF undergoing PCI with stent **	15 mg Once Daily (while on P2Y12 Inhibitor), then 20 mg Once Daily	10 mg Once Daily (while on P2Y12 Inhibitor), then 15 mg Once Daily	
Acute DVT/PE Treatment	15 mg bid for 3 weeks***, followed by 20 mg Once Daily After at least 6 months of treatment, recommended dose for continued prevention of recurrent DVT/PE is 20 mg or 10mg once daily based on thrombosis and bleeding risk		
Secondary Prevention of CV Events	2.5 mg bid (with ASA 75 to 100mg once daily)		
Hip & Knee Replacement	10 mg Once Daily x 14 days (TKR); x 35 days (THR)		
Pediatrics: VTE Treatment	Refer to Weight Based Dosing Chart in Product Monograph (Oral Suspension)		

* Limited data suggests may crush & suspend in 50 ml water to give orally or via NG; or mix with applesauce[1,8]

**2.5 mg bid with dual antiplatelet therapy may be used with those at high stent thrombosis risk[9]

***During initial 3 weeks: Very important to take 30 mg/day; may mean taking 2 tablets at once (i.e. double dose) if 1 dose is missed[1]

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Monitoring Patients on Rivaroxaban

- CrCl should be determined at baseline and at least annually. Monitor more frequently if older than 75y, with renal dysfunction (CrCl <60 mL/min), or when a decline in renal function suspected
- Monitor for symptoms and signs of bleeding
- No routine coagulation testing required. NOTE: INR is not useful for monitoring. Do not target INR 2 to 3. More specialized testing should only be considered in consultation with an expert in anticoagulation.
- Reassess the rivaroxaban dose when changes to concomitant antiplatelet agents occur

Switching Between Agents[1]

From warfarin *to* rivaroxaban:

- Discontinue warfarin and start rivaroxaban when INR is 2.5 or less.

From non-warfarin anticoagulant (oral or parenteral - e.g. LMWH, apixaban, dabigatran, edoxaban) **to rivaroxaban:**

- Start rivaroxaban 0 - 2 hours *before* the next scheduled dose of the non-warfain anticoagulant was to be administered. NOTE: For prophylactic dosing of parenteral anticoagulants, rivaroxaban can be started 6 or more hours *after* last dose.
- For agents administered by continuous infusion, stop the infusion and start rivaroxaban at the same time

From rivaroxaban *to* warfarin:

- Start warfarin and only discontinue rivaroxaban once INR is 2 or greater. **NOTE:** Rivaroxaban can affect INR; therefore when starting warfarin, INR may initially be unreliable. If possible, checking INR just prior to next rivaroxaban dose may better reflect the anticoagulant effect of warfarin.

From rivaroxaban to non-warfarin anticoagulants (oral or parenteral): (e.g. LMWH, apixaban, dabigatran, edoxaban)

- Discontinue rivaroxaban and give 1st dose of non-warfarin anticoagulant at the time next dose of rivaroxaban is due

Management of Bleeding Episodes with Rivaroxaban

- Vitamin K, protamine, tranexamic acid, plasma and/or idarucizumab will not reverse drug effects
- In the event of major hemorrhagic complications, discontinue rivaroxaban and refer patient for urgent assessment and locally developed management strategies
- Limited evidence demonstrates prothrombin complex concentrates (e.g. Octaplex®/Beriplex®) are able to reverse the anticoagulant effect[10], but the effect of these agents on bleeding outcomes is limited.
- Specific antidotes are not yet available in Canada[11]

Anticoagulation around Invasive Procedures [12] (e.g. surgery, elective day procedures, major dental procedures)

- As with warfarin, very low risk bleed procedures (such as dental extraction) do not require withholding rivaroxaban
- Management plans should be made in consultation with the provider performing the procedure
- Renal and hepatic function significantly impacts clearance of rivaroxaban. If the recommendations below cannot be met, consultation with an expert in anticoagulation management is encouraged.
- Due to the onset/offset time of rivaroxaban, peri-procedural use of LMWH is not required

Pre-Procedure – If required, stop rivaroxaban 10 mg, 15 mg, and 20 mg before procedure as follows*:

Renal function# (CrCl mL/min)	Last intake of drug prior to procedure	
	Low Bleeding Risk	High Bleeding Risk**
30 or more	at least 24 hours	at least 48 hours
15 - 29	at least 36 hours	at least 48 hours

Limited clinical data for CrCL less than 25mL/min, however, if less than 15mL/min, longer duration likely necessary

*For patients on 2.5 mg, rivaroxaban should be stopped at least 12 hours prior to procedure

** Make a careful decision (i.e. hold longer) for patients undergoing major surgery, spinal puncture, or other regional anaesthesia in whom complete hemostasis is required. Consult specialist in these high risk patients/procedures.

For an interactive perioperative management algorithm, see Thrombosis Canada website:
http://thrombosiscanada.ca/?page_id=502&calc=perioperativeAnticoagulantAlgorithm

Post Procedure: Resumption should not be initiated until adequate hemostasis has been achieved and clinical situation allows (usually 1 -3 days). NOTE: Full therapeutic effect occurs approximately 2 hours after ingestion.

References: **1.** Xarelto product monograph. Mississauga, ON: Bayer Inc. January 6, 2021. **2.** Andrade JG et al. Can J Cardiol 2020; 36: 1847-1948. **3.** Young AM et al. J of Clin Oncol 2018; 36(20):2017-2023. **4.** Carrier M et al. Curr Oncol 2018; 25(5):329-337. **5.** Pengo V et al. Blood 2018; 132(13):1365-1371. **6.** Direct oral Anticoagulants in Obese Patients. Thrombosis Canada Website: https://thrombosiscanada.ca/wp-content/uploads/2020/06/DOACS-in-Obesity_24June2020.pdf. Accessed March 15, 2021. **7.** Patel MR et al. N Engl J Med 2011; 365:883-91. **8.** Moore KT et al. Poster presentation 2012 ACCP Annual Meeting, Oct. 21-24, 2012, Hollywood, Florida. **9.** Gibson CM et al, N Engl J Med 2016; 375(25): 2423-2434. **10.** Eerenberg ES, et al. Circulation 2011; 124(14):1573-9. **11.** Connolly S, et al. N Engl J Med 2016; 375:1131-1141. **12.** Steffel J, et al. Eur Heart J 2018; 39(16):1330-1393.