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

Indications

- 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.
- Prevention of venous thromboembolic events (VTE) in elective total hip or knee replacement surgery (THR, TKR)
- *CCS definition: AF without mechanical heart valves, rheumatic mitral stenosis, or moderate/severe non-rheumatic mitral stenosis
- **Cancer associated VTE (not an official indication) - limited data suggests similar efficacy to LMWH with more non critical site bleeding

Requirements - 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

- 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

- 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)
- Drug Interactions: AVOID rifampin, selectazole 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)
- Less than 18 years of age: Safety & dosing has not been established.
- AF Indication Only: Higher GI bleed rate than warfarin, although less critical bleeding events

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). NOTE: Use of warfarin with point-of-care (POC) INR testing (e.g. Coaguchek XS™) may be an alternative solution
- AF: lower rate of critical site bleeding including intracranial hemorrhage

Dosing Recommendations

<table>
<thead>
<tr>
<th>Indication</th>
<th>CrCl 50 mL/min or greater</th>
<th>CrCl 30–49 mL/min</th>
<th>CrCl 15-30mL/min (use caution)</th>
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<tbody>
<tr>
<td>Stroke Prevention in NVAF</td>
<td>20 mg Once Daily</td>
<td>15 mg Once Daily</td>
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<tr>
<td>Stroke Prevention in NVAF undergoing PCI with stent **</td>
<td>15 mg Once Daily (while on P2Y12 Inhibitor), then 20 mg Once Daily</td>
<td>10 mg Once Daily (while on P2Y12 Inhibitor), then 15 mg Once Daily</td>
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<tr>
<td>Acute DVT/PE Treatment</td>
<td>15 mg bid for 3 weeks***, followed by 20 mg Once Daily</td>
<td>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</td>
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<tr>
<td>Secondary Prevention of CV Events</td>
<td>2.5 mg bid (with ASA 75 to 100mg once daily)</td>
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<tr>
<td>Hip &amp; Knee Replacement</td>
<td>10 mg Once Daily x 14 days (TKR); x 35 days (THR)</td>
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* Limited data suggests may crush & suspend in 50 mL water to give orally or via NG; or mix with applesauce
** 2.5 mg bid with dual antiplatelet therapy may be used with those at high stent thrombosis risk
*** 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

Inform Your Patient:

- Carry information indicating they are on an anticoagulant and inform their healthcare providers, including dentists
- Venous Thromboembolism: Ensure clarity of dose change after initial 3 weeks
- 15 and 20 mg dose must be taken with food; adherence is essential to avoid treatment failure
- Report symptoms/signs of bleeding (including abnormal uterine bleeding), stroke, or DVT/PE
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
- 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-warfarin 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, 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\(^\text{11}\), but the effect of these agents on bleeding outcomes is limited.
- Specific antidotes are not yet available in Canada\(^\text{12}\)

Anticoagulation around Invasive Procedures\(^\text{10}\) (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*:

<table>
<thead>
<tr>
<th>Renal function(^\text{8}) (CrCl mL/min)</th>
<th>Last intake of drug prior to procedure</th>
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<tbody>
<tr>
<td>Low Bleeding Risk</td>
<td>High Bleeding Risk**</td>
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<tr>
<td>30 or more</td>
<td>at least 24 hours</td>
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<tr>
<td>15 - 29</td>
<td>at least 36 hours</td>
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# 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.

References: