Cardiac Diseases and Therapies
ATRIAL FIBRILLATION
RIVAROXABAN CLINICIAN SUMMARY

Mechanism of Action: Direct Factor Xa inhibitor

BACKGROUND
Rivaroxaban is a direct Factor Xa inhibitor that is administered orally.

Rivaroxaban is currently indicated for:
- prevention of venous thromboembolic events (VTE) in patients who have undergone elective total hip replacement (THR) or total knee replacement (TKR) surgery
- prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation
- treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and for prevention of recurrent DVT and PE.

Place in Therapy
Rivaroxaban is approved at UHN for:
- prevention of stroke and systemic embolism in patients with atrial fibrillation and a $CHADS_2$ score greater or equal to 2.
- treatment of DVT without symptomatic PE

Dosing for ATRIAL FIBRILLATION:
- **Usual dose:** 20 mg orally once daily with food
- **Low dose:** 15 mg orally once daily with food (recommended for patients with moderate renal impairment with an estimated creatinine clearance of 30-49 mL/min)

Dosing for OTHER APPROVED INDICATIONS IN CANADA:
- Prevention of venous thromboembolic events (VTE) in patients who have undergone elective total hip replacement (THR) or total knee replacement (TKR)
  Dose: 10 mg once daily
- Treatment of DVT and/or PE, and prevention of recurrent DVT or PE
  Dose: 15 mg twice daily with food for 3 weeks, followed by 20 mg once daily with food

Administration
- Should be administered with food to maximize bioavailability
- Can be crushed, cut or administered through a feeding tube, if necessary

PHARMACOLOGIC PROFILE
Onset and Peak Effect: 2-4 hours

Bioavailability: ~100% when taken with food (66% in fasting conditions)

Half-Life: 7–11 hours

Elimination: dual route of elimination (renal and hepatic)
- 50% of the active drug is **cleared** unchanged by the kidneys
- 50% of the active drug is **metabolized** to inactive metabolites and excreted by both kidneys and fecally

CONTRAINDICATIONS
- Clinically significant active bleeding (i.e., GI bleeding or spontaneous impairment of hemostasis)

- Lesions at risk of clinically significant bleeding (e.g., hemorrhagic within the last 6 months, active peptic ulcer disease with recent bleeding)
- Concomitant use of strong inhibitors of both CYP3A4 and P-glycoprotein (i.e., ketoconazole, itraconazole, voriconazole, posaconazole, ritonavir)
- Hepatic disease (Child-Pugh Class B and C) associated with coagulopathy and clinically relevant bleeding
- Pregnant and nursing women

PRECAUTIONS

- **Ischemic stroke in the last 6 months**
- **Concomitant use of agents that increase bleeding risk**
  - e.g., Aggrenox, ASA, ibuprofen, naproxen, warfarin, clopidogrel, prasugrel, ticagrelor, etc.
- **Severe renal impairment (CrCl less than 30 mL/min)**
- **Pharmacokinetic drug interactions**
  - Strong CYP3A4 **inhibitors**, such as ketoconazole, voriconazole, protease inhibitors or clarithromycin, would lead to increased concentrations of rivaroxaban
  - Strong CYP3A4 **inducers,** such as carbamazepine, rifampin, phenytoin, phenobarbital and St. John's Wort, can decrease the exposure to rivaroxaban, leading to reduced efficacy

ADVERSE EFFECTS

- bleeding
- significant safety endpoints from ROCKET-AF[7]
  - Rivaroxban demonstrated the following compared to warfarin:
    - Significantly **decreased** rates of intracranial hemorrhage
    - Significantly **increased** rates of major gastrointestinal bleeding, bleeding resulting in reductions in haemoglobin levels of 2g/dL or more, and bleeding requiring transfusions
    - Similar rates of major and non-major bleeding

SWITCHING FROM OTHER AGENTS *to* RIVAROXABAN

- **Switching from *intermittent* parenteral anticoagulants (e.g., low molecular weight heparins) to rivaroxaban**
  - Patients on *intermittent* parenteral anticoagulants who are switching to rivaroxaban can do so 0-2 hours before the NEXT dose of parenteral anticoagulant is due
- **Switching from *continuous* parenteral anticoagulants (e.g., heparin infusions) to rivaroxaban**
  - If switching to rivaroxaban from *continuous infusions* (e.g., heparin infusion), administer the first dose of rivaroxaban at the time of discontinuation
- **Switching from warfarin *to* rivaroxaban**
  - Stop warfarin and determine the INR. If INR is less than or equal to 2.5, start rivaroxaban at usual dose. If INR is greater 2.5, delay start of rivaroxaban until INR is less than or equal to 2.5
- **Switching from dabigatran *to* rivaroxaban[8]**

Creatinine Clearance	Rivaroxaban dose	Time to Initiate Rivaroxaban After Last Dose of Dabigatran
Greater or equal to 50 mL/min	20 mg daily	12–24 hours
30–50 mL/min	15 mg daily	24–48 hours

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SWITCHING FROM RIVAROXABAN *to* OTHER AGENTS

- **Switching *to intermittent* parenteral anticoagulants (e.g., low molecular weight heparins) OR *to continuous* parenteral anticoagulants (e.g., heparin infusions)**
  - Patients on rivaroxaban who are switching to parenteral anticoagulants (e.g., low molecular weight heparins or continuous heparin infusion), for the indication of **continued anticoagulation for the prevention of stroke,** should wait 24 hours before switching
- **Switching to warfarin**
  - Switching from rivaroxaban to warfarin is complex.
  - The monograph suggests that rivaroxaban can be continued concurrently with warfarin until the INR is greater than 2.0, then to discontinue rivaroxaban.[9]
  - However, the INR readings can be falsely elevated by rivaroxaban and may not be indicative of warfarin's effects.
  - The most ideal time to test the INR would be 24 hours after the previous dose of rivaroxaban, since at this time, the remaining rivaroxaban concentration in the circulation is too low to have a clinically important effect on the INR.
- **Switching to dabigatran or apixaban**
  - Start dabigatran or apixaban at the time that the next dose of rivaroxaban would be due (ie. 24 hours after the last dose of rivaroxaban)

NEURAXIAL ANESTHESIA AND RIVAROXABAN

There is limited experience with the use of factor Xa inhibitors with neuraxial anesthesia.

When neuraxial (epidural/spinal) anesthesia or spinal puncture is performed, patients treated with antithrombotics are at risk for developing an epidural or spinal hematoma that may result in long-term neurological injury or permanent paralysis. The American Society of Regional Anesthesia and Pain Management (ASRA) guidelines for 2010 state: "Although there have been no reported spinal hematomas, the lack of information regarding the specifics of block performance and prolonged half-life warrants a cautious approach".

Based on previous recommendations in the Dabigatran Clinician Summary, we recommend to **discontinue rivaroxaban 5 days prior to neuraxial intervention.** This will ensure adequate time for cessation of the medication in the majority of patients.

You may consider bridging for select patients with a high risk of stroke; see table below.

The **first dose** of rivaroxaban may be administered ***not earlier than* 6 hours** following spinal anesthesia, lumbar plexus block or epidural catheter removal.

Rivaroxaban should not be administered to patients with an indwelling epidural catheter; and should not be administered until 6 hours after the removal of an epidural catheter.

In cases of urgent or emergency surgery, a benefit/risk analysis should be performed when a neuraxial technique is strongly indicated over alternative anaesthesia. Haematology Service advice may be warranted in such instances to attempt reversal with prothrombin complex concentrate (PCC).

Patients who have undergone epidural puncture and who are receiving rivaroxaban should be frequently monitored for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, bowel or bladder dysfunction).

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PERIPROCEDURAL/PERIOPERATIVE MANAGEMENT

Consider both the risk of bleeding in the patient and the surgical bleeding risk.

Please refer to the UHN Periprocedural Hemostasis Policy & Procedures:
http://documents.uhn.ca/sites/uhn/Policies/Clinical/Blood_Transfusion/3.130.009.pdf

Hold rivaroxaban as per patient's creatinine clearance:

Calculated Creatinine Clearance	Last dose pre-procedure	
	Procedures with low risk of bleeding	Procedures with moderate to significant risk of bleeding
Greater or equal to 50 mL/min	24 hours	2 days
Less than 50 mL/min	At least 2 days	At least 4 days

** see list of procedures and bleed risk under UHN Periprocedural Hemostasis Policy*
Note: Cardiac catheterizations may be considered a procedure with a low or high risk of bleeding. Please check with the interventionalist or cardiac triage.

When Is Bridging Required?

As per UHN Periprocedural Hemostasis Policies, consult hematology for discussion of bridging anticoagulation in patients with:

- mechanical heart valves
- Atrial fibrillation with prior neurologic event
- Recent (less than 3 months ago) venous thromboembolism
- Intracardiac thrombus
- Antiphospholipid syndrome

When to Resume Rivaroxaban Post-procedure

Time to resume rivaroxaban depends on the postoperative risk of bleeding.

When rivaroxaban has been withdrawn for an invasive procedure, therapy can be restarted 1 day after hemostasis is established post-procedure. (usually 48 hours for a procedure with a low risk of bleeding and 72 hours for a procedure with an intermediate or high risk of bleeding).[10]

For procedures such as major abdominal surgery or urologic surgery with incomplete hemostasis, rivaroxaban should only be resumed when there is no drainage or other evidence of active bleeding.

ACUTE MANAGEMENT OF ACUTE CORONARY SYNDROMES (ACS)

For patients who arrive in the Emergency Department on rivaroxaban and who need treatment for acute coronary syndrome:

- Should be treated according to usual clinical practice
- Consideration should be given to temporarily suspend rivaroxaban in the setting of ACS, due to need for invasive procedures, such as PCI or CABG, or if thrombolytic therapies are to be initiated

- Timing, choice and dose of parenteral anticoagulation should be balanced against last intake of rivaroxaban and the risk of bleeding, noting that rivaroxaban has a short half-life of 7-11 hours in normal renal function. Recent intake (i.e., within the last 7 hours) will increase the risk of bleeding when initiating parenteral full-dose anticoagulation

ASPIRIN THERAPY

Always re-assess indication for ASA when starting rivaroxaban. If it was previously prescribed for the sole indication of stroke prevention in atrial fibrillation, ensure ASA is discontinued when rivaroxaban is initiated.

MANAGEMENT OF BLEEDING COMPLICATIONS OR REVERSAL OF RIVAROXABAN

- Contact poison control for most up-to-date guidelines
- There is currently no antidote available. Phase III trials underway for antidote: andexanet alfa
- Expert opinion suggests the following:
  - Discontinue rivaroxaban: With its short half-life (7-11 hours), withholding further doses and supportive care are likely to be sufficient for most patients
    - For patients with normal kidney function, the anticoagulant effect of rivaroxaban should dissipate in 1-2 days
  - For overdoses: within 1-2 hours, activated charcoal and gastric lavage can be given to prevent further drug absorption
  - Identify and definitively treat the bleeding source
  - Supportive measures:
    - maintain diuresis
    - fluid resuscitation
    - hemodialysis is **not** a useful option for rivaroxaban, since the drug is highly protein bound (92-95%)
    - transfusion of blood products:
      Haematology Service should be consulted in cases of life-threatening bleeding to assist in the administration of blood products and reversal agents, such as:
      - Prothrombin complex concentrate (PCC), e.g., FEIBA or OCTAPLEX
        - PCC consists of 4 clotting factor concentrates (II, VII, IX and X)
        - Studied in a randomized control trial involving 12 healthy volunteers: administration on nonactivated 4-factor PCC normalized the prothrombin time (PT) after administration of rivaroxaban
        - Unknown how it reverses bleeding tendency in patients on rivaroxaban

      or

      - recombinant activated factor VII (rVIIa), e.g., NovoSeven
        - rVIIa was shown to decrease bleeding time in rats given rivaroxaban, however it does not reverse anticoagulant effects measured through laboratory tests, and there are no human studies and clinical experience to date.

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