UNC HEALTH CARE GUIDELINE

Management of Rivaroxaban in Adults

Rivaroxaban (Xarelto®) is an oral anticoagulant that acts as a factor Xa inhibitor. It is approved by the FDA as an alternative to warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and for prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip or knee replacement surgery. Rivaroxaban is **not FDA-approved** for the treatment of DVT or PE at this time.

Key pharmacokinetic data for rivaroxaban include a peak onset of anti-Xa activity within 2-4 hours after oral administration and a half-life of 5-9 hours in patients with normal hepatic and renal function. Approximately 51% of rivaroxaban undergoes hepatic metabolism and 66% is excreted in the urine (36% as unchanged parent drug).

INITIATION OF THERAPY

Patient-specific considerations for initiation of rivaroxaban therapy include the following:

- **Indication for therapy**. (1) For prevention of stroke or systemic embolism in atrial fibrillation: patients must have non-valvular atrial fibrillation and risk factors that warrant therapeutic anticoagulation (i.e., $CHADS_2$ score $\geq$ 1); (2) For prevention of DVT and PE: patients must have undergone knee or hip replacement surgery; rivaroxaban is not indicated for the prevention of DVT and PE in medical or other surgical patients.
- **Renal and hepatic function**. A baseline serum creatinine is required for rivaroxaban use and appropriate dosing (see Table 1). Assessment of hepatic function should also be performed, as rivaroxaban should be avoided in moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or any degree of hepatic impairment associated with coagulopathy.
- **Dosing and administration**. Dosing recommendations are provided in Table 1. When using rivaroxaban for prevention of DVT and PE after knee or hip replacement surgery, the first dose should be given at least 6-10 hours after surgery once hemostasis has been achieved. Rivaroxaban is optimally absorbed in the gastric environment; therefore, if administration via feeding tube is required, the tube should be advanced no further than the stomach. Higher doses of rivaroxaban (15-20 mg) should be given with food to enhance bioavailability (see patient education). For patients with atrial fibrillation taking doses of 15-20 mg, it is recommended that rivaroxaban be given with the evening meal, as this is how the drug was studied in this population. Doses administered at other times of the day have not been studied, so it is unknown whether they would confer the same degree of stroke protection as evening administration.
- **Cost of therapy**. Whether patients can afford rivaroxaban at discharge must also be considered, as costs may exceed $200 per month.

TABLE 1. Initial Rivaroxaban Dosing

Indication	Renal Function[a] (CrCL mL/min)	Recommended Dose[b]
Atrial Fibrillation[c,d] (Stroke Prevention)	$\geq$ 50	20 mg once daily with evening meal
	15 – 49	15 mg once daily with evening meal
	< 15	Do not use
Knee Replacement	$\geq$ 30	10 mg once daily for 12 days
	< 30	Do not use
Hip Replacement	$\geq$ 30	10 mg once daily for 35 days
	< 30	Do not use

[a] For the purpose of rivaroxaban dosing, renal function should be estimated by the Cockcroft-Gault method. It is not appropriate to use the CrCL (MDRD method) automatically reported in the WebCIS lab section.
Cockcroft-Gault equation: CrCL= [(140-age) x weight (kg)] / (SCr x 72) (x 0.85 if female)
[b] Co-administration with p-glycoprotein and strong CYP3A4 inducers (i.e., carbamazepine, phenytoin, rifampin) may warrant a dose increase. Doses > 10 mg should be taken with food.
[c] The median body mass index of patients in ROCKET-AF[1] was approximately 28 ± 3 kg/m^2. No information is available on its safety and efficacy in overweight or obese patients and anti-Xa levels have not been evaluated for guiding drug dosing.
[d] In ROCKET-AF[1], rivaroxaban was not studied in patients with CrCL < 30 mL/min, so recommendations in patients with CrCL 15-30 mL/min are based on the FDA-approved labeling.

CONVERSION TO RIVAROXABAN

TABLE 2. Converting to Rivaroxaban

Agent	Conversion Instructions
Heparin	Discontinue the heparin infusion when the first evening dose of rivaroxaban is administered.
Enoxaparin	Start rivaroxaban at the time the next evening dose of enoxaparin was to be administered (may overlap by up to 2 hours). If enoxaparin was adjusted for renal function, rivaroxaban may also require dose adjustment or be avoided altogether, depending on its indication for use (see Table 1).
Dabigatran	Start rivaroxaban 12 hours after the last morning dose of dabigatran.
Fondaparinux	Discontinue fondaparinux. Start rivaroxaban in the evening on the following day.
Warfarin	Discontinue warfarin and start rivaroxaban in the evening when the INR is < 3.0.

CONVERSION FROM RIVAROXABAN

In a clinical trial of patients with non-valvular atrial fibrillation[1], discontinuation of rivaroxaban was associated with an increased risk of thrombotic events (primarily driven by an increased risk of stroke). If rivaroxaban must be discontinued for reasons other than bleeding, administration of an alternative anticoagulant should be strongly considered. If it is deemed that ongoing anticoagulation is appropriate, patients should be bridged to the new anticoagulant (i.e., warfarin or dabigatran) using the recommendations outlined on the following page.

Strategies for converting patients to or from rivaroxaban have not been evaluated in clinical trials. The approved labeling for rivaroxaban recommends the initiation of an alternative anticoagulant at the time the next dose of rivaroxaban was to be administered. However, based on the pharmacokinetics of the drug, initiating an alternative anticoagulant as early as 12 hours after the last dose of rivaroxaban may be considered in patients who are at increased risk of thrombosis (e.g., recent cardioversion or ablation procedure, higher $CHADS_2$ scores, conditions that may increase baseline risks of thromboembolism).

TABLE 3. Converting Rivaroxaban to Warfarin

Taking into consideration the risk of stroke and embolism in each individual patient (i.e., $CHADS_2$ score, recent cardioversion), it may be reasonable to continue rivaroxaban until the INR is 2–3.[a,b]

Strategy	Renal Function (CrCL mL/min)	Conversion Instructions
Strategy 1 (Parenteral)	≥ 50	Start parenteral anticoagulant 12-24 hours after the last rivaroxaban dose (consider 12 hours in patients at greater risk of stroke). Start warfarin at the next standard administration time.
	< 50	Start parenteral anticoagulant 24 hours after the last rivaroxaban dose. Start warfarin at the next standard administration time.
Strategy 2 (Oral)	≥ 50	Start warfarin and overlap with rivaroxaban for at least 5 days. Discontinue rivaroxaban on day 5 or when INR is 2–3.
	15 – 49	Start warfarin and overlap for at least 3 days with rivaroxaban. Discontinue rivaroxaban on day 3 or when INR is 2–3.
	< 15	Same as for patients with CrCL 15-30 mL/min; however, this patient should not resume rivaroxaban.[b]

[a] Examples of increased stroke risk include recent cardioversion or ablation, higher $CHADS_2$ score, and conditions that may increase baseline risks of thromboembolism (e.g., medically ill).
[b] Rivaroxaban may contribute to an elevated INR for up to 2 days after discontinuation.
[c] Limited data exist in patients with CrCL < 30 mL/min or in patients on hemodialysis. Recommendations are extrapolated from pharmacokinetic data and comparison of relative risks and benefits.

TABLE 4. Converting Rivaroxaban to Parenteral Anticoagulants (Heparin, Enoxaparin, or Fondaparinux)

Renal Function (CrCL mL/min)	Conversion Instructions[a]
≥ 50	Start parenteral anticoagulant 12-24 hours after the last rivaroxaban dose (consider 12 hours in patients at greater risk of stroke).
< 50	Start parenteral anticoagulant 24 hours after last rivaroxaban dose.

[a] Methods for converting rivaroxaban to parenteral anticoagulants have not been studied and are based on the approved product labeling and pharmacokinetics of the drug. Clinical decisions should be made based on patient-specific risk of bleeding vs. thromboembolism.

Converting Rivaroxaban to Dabigatran

The approved labeling for rivaroxaban recommends giving the first dabigatran dose at the time the next evening dose of rivaroxaban was to be administered. For patients who are transitioning from rivaroxaban in the community setting, starting dabigatran the following evening may be acceptable. However, for patients with normal renal function (CrCL ≥ 50 mL/min) who are at greater risk of stroke (e.g., recent cardioversion or ablation procedure, higher $CHADS_2$ scores, other conditions that may increase baseline risks of thromboembolism), starting dabigatran 12 hours after the last dose of rivaroxaban may be considered. For patients with impaired renal function (CrCL < 50 mL/min), dabigatran may be started 24 hours after the last dabigatran dose.

PERIOPERATIVE MANAGEMENT

TABLE 5. Discontinuation Prior to Inpatient or Outpatient Procedures[2, 3]

Renal Function (CrCL mL/min)	**Half-life** (hours)	**Timing of Discontinuation Prior to Procedure[a] (Minimum)**	
		Standard Risk of Bleeding[b]	**High Risk of Bleeding[c]**
≥ 50	5 – 9	18 – 24 hours	1 – 2 days
< 50	> 9	24 – 48 hours	> 2 days
Hepatic Function (Child-Pugh Score)	**Half-life** (hours)	**Standard Risk of Bleeding[b]**	**High Risk of Bleeding[c]**
Mild Impairment (Child-Pugh A)	8	24 hours	1 – 2 days
Moderate Impairment (Child-Pugh B)	12 – 16	≥ 48 hours	≥ 4 days
Severe Impairment (Child-Pugh C)	Unknown	72 – 120 hours	≥ 1 week

[a] No published data exist on optimal perioperative management of rivaroxaban, so the recommendations here have been extrapolated from the pharmacokinetics and pharmacodynamics of the drug.
[b] Examples: electrophysiology procedures, cardiac catheterizations, no additional patient-specific risk factors.
[c] Examples: surgery involving major organs, procedures requiring complete hemostasis (e.g., spinal anesthesia), or when additional patient-specific risk factors are present.

Bridging to Procedures with Parenteral Anticoagulants
For patients at high risk of thromboembolic events in whom inpatient procedures are planned, some clinicians may wish to bridge with parenteral anticoagulants (e.g., unfractionated heparin, enoxaparin). The necessity for this depends on a patient's risk for thromboembolism while off anticoagulation, and for bleeding if on anticoagulants. This may be performed by (1) converting rivaroxaban to the desired parenteral anticoagulant as described in Table 4, and (2) continuing to hold rivaroxaban for the minimum amount of time recommended in Table 5, based on an individual patient's renal function and risk of bleeding. Parenteral anticoagulation may then be discontinued prior to the planned procedure according to usual standards of care.

Dental Procedures
Many dental procedures can be safely performed on full-dose anticoagulation, and this is also likely true with rivaroxaban. Consider risk of bleeding versus risk of thromboembolism when deciding to hold doses of rivaroxaban for a dental procedure.

ADVERSE EFFECTS

Rivaroxaban is associated with similar rates of overall bleeding events compared to warfarin and enoxaparin. Rates of intracranial hemorrhage and fatal bleeding events are lower with rivaroxaban, whereas gastrointestinal (GI) bleeding is more common. The most common non-hemorrhagic adverse effects are GI-related disturbances (e.g., nausea, vomiting, and constipation), epistaxis, peripheral edema, dizziness, and nasopharyngitis.[1,4,5]

The following section outlines strategies for the management of rivaroxaban-related bleeding events.

MANAGEMENT OF BLEEDING EVENTS

Currently, no available evidence exists to guide clinicians in the management of rivaroxaban-associated bleeding events. While *in vitro* data and studies in animals and healthy human volunteers indicate some pharmacologic agents (e.g., factor products) may have an impact on the anticoagulant effects of rivaroxaban, these have not been evaluated for the management of bleeding events in patients and should not be used for clinical decision-making.[6]

An outline for supportive management of rivaroxaban-related bleeding events based on bleeding severity is provided in Table 6. **If patients require pharmacologic therapy to manage hemorrhagic complications, a Hematology/Coagulation consult is also required.**

TABLE 6. Management of Rivaroxaban-Related Bleeding Events

Bleeding Severity	Management Recommendations
Mild	Delay next dose or discontinue rivaroxaban.
Moderate	*Consider any of the following based on bleeding severity:* • Symptomatic treatment • Mechanical compression • Surgical intervention • Fluid replacement and hemodynamic support • Blood product transfusion • Oral activated charcoal (if previous dose ingested within 2 hours) Dose: Liquid charcoal with sorbitol 50 g PO x 1 dose *If hemostasis is not achieved with the strategies outlined above, proceed to the steps below and obtain a Hematology/Coagulation consult for further recommendations.*
Severe or Life-threatening	*Consider any of the strategies outlined above based on bleeding severity. No agent currently available in the US has been shown to successfully reverse the anticoagulant effects of rivaroxaban or treat rivaroxaban-related bleeding events. Therefore, the pharmacologic interventions below may be considered* ***but are not required*** *in the management of rivaroxaban-related bleeding.* *A Hematology/Coagulation consult must be obtained prior to the following*: 1. Prothrombin Complex Concentrate (PCC) a. Low risk for thrombotic complications: Consider activated prothrombin complex concentrate (aPCC) (FEIBA®) 50 units/kg x 1.[a] b. High-risk for thrombotic complications: Consider non-activated prothrombin complex concentrate (PCC) (Profilnine®) 50 units/kg x 1. 2. If (b) is chosen above and adequate hemostasis is not achieved, consider also giving recombinant factor VIIa (NovoSeven®) 45-90 mcg/kg IV x 1.[b] After several hours, consider using aPCC (FEIBA®) 50 units/kg (with Hematology/Coagulation guidance) based on bleeding severity and degree of hemostasis achieved. To investigate potential causes of the bleeding event, obtain the following: serum creatinine, aPTT, PT/INR, CBC (platelets), anti-Xa level (send-out lab; write "patient on rivaroxaban").

[a] Both activated PCC (FEIBA®) and recombinant factor VIIa (NovoSeven®) are associated with thrombotic complications, so the risk of bleeding versus thrombosis must be considered.
[b] A starting dose of 45-90 mcg/kg was chosen based review of clinical trials and case series as well as a dose-related risk of thromboembolic complications.[7,8]

PATIENT EDUCATION

Rivaroxaban Discontinuation
Patients who are taking rivaroxaban for the prevention of stroke and systemic embolism in the setting of atrial fibrillation should be advised that discontinuation of therapy may place them at an increased risk of thrombotic events (primarily stroke). Patients who experience adverse effects (including rivaroxaban-related bleeding events) should contact their provider immediately, but should not discontinue therapy until instructed to do so. An alternative means of anticoagulation may be required.

Dosing & Oral Administration
The absolute bioavailability of rivaroxaban is dose-dependent. For patients taking rivaroxaban 10 mg for the prevention of DVT and PE after hip or knee replacement surgery, the drug may be taken once daily with or without food (bioavailability about 80-100%). However, for patients taking 15-20 mg of rivaroxaban for the prevention of stroke or systemic embolism in atrial fibrillation, doses should be taken once daily with the evening meal (fasting bioavailability about 66%; mean AUC and C_{max} is increased by 39% and 76%, respectively, with food).

Management of Missed Doses
If a dose of rivaroxaban is not taken at the scheduled time, the dose should be taken as soon as possible, unless it is within 12 hours of the next dose. The dose of rivaroxaban should not be doubled to make up for a missed dose.

Management of a Doubled Dose
No specific strategy has been recommended by the manufacturer for patients who take a doubled dose of rivaroxaban. However, based on the pharmacokinetics of the drug, patients with normal hepatic and renal function should be able to resume their usual dose at the next scheduled time without skipping a dose (i.e., 24 hours later after the doubled dose).

Additional Information
For additional information on blood clots and anticoagulation therapy, patients (and health care providers) may visit the University of North Carolina *Clot Connect* website at http://www.clotconnect.org.

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