

# Rivaroxaban in Atrial Fibrillation

Rivaroxaban (Xarelto®), a direct Factor Xa inhibitor, is a new oral anticoagulant indicated for the prevention of stroke and systemic embolism in at-risk patients with non-valvular atrial fibrillation (AF). This drug is currently listed as Limited Coverage benefit under PharmaCare. Please visit the PharmaCare website for the [eligibility criteria](#).

Similar to dabigatran, **rivaroxaban should not be prescribed for patients with prosthetic heart valves or other significant valvular heart diseases** due to a lack of evidence for efficacy and safety in this patient population.<sup>1</sup> There is currently no known antidote to treat rivaroxaban-induced bleeding.

**Warfarin has been used for over 60 years and is safe and effective especially when supported with a structured care plan** (e.g., education, INR testing and interpretation, dose adjustments, and side effect monitoring).<sup>2</sup> The Canadian Agency for Drugs and Technologies in Health (CADTH) has recently published reports and practice tool to support optimal warfarin use.<sup>2</sup> When a structured approach is used, **most patients can be adequately managed on warfarin therapy**. Point-of-care testing and mobile laboratory services may further optimize warfarin therapy for some patients.

Some options for patients who cannot access a laboratory for INR blood tests:

- **Pharmacy on-site testing:** Trained pharmacists in some community pharmacies provide point-of-care INR testing.
- **Point-of-care INR monitor:** Trained patients conduct self-testing with results phoned to your office for drug dosing.
- **Mobile laboratory service:** Free, mobile laboratory services are available to qualified people in many communities. Physician referral is required. For details, please contact:
  - BC Biomedical Laboratories: [www.bcbio.com/services/mobile-lab-service](http://www.bcbio.com/services/mobile-lab-service)
  - LifeLabs: [www.lifelabs.com/Lifelabs\\_BC/Contact.asp](http://www.lifelabs.com/Lifelabs_BC/Contact.asp)

## ROCKET AF: Rivaroxaban's pivotal clinical trial

ROCKET AF\* is the only published randomized controlled trial that evaluated the efficacy and safety of rivaroxaban for prevention of stroke and systemic embolism in patients with non-valvular AF and other risk factors.<sup>3</sup> In this trial, 14,264 patients at moderate-to-high risk for stroke were randomized to receive fixed-dose rivaroxaban (20 mg daily, or 15 mg daily if CrCl was 30 to 49 mL/min) or adjusted-dose warfarin. Follow-up time was approximately 24 months.

## Efficacy

For the primary composite efficacy endpoint (stroke and systemic embolism), rivaroxaban was non-inferior but also not superior to warfarin (Hazard ratio 0.88; 95%CI: 0.74-1.03; p=0.12 for superiority).<sup>3</sup>

Note that there is currently no validated clinical test to monitor rivaroxaban's efficacy in any particular patient.

## Safety

During the short duration of the trial, there was no significant difference in the risk of major bleeding between rivaroxaban and warfarin.<sup>3</sup>

Although intracranial and fatal bleeding was less common in the rivaroxaban group, the following are more common in the rivaroxaban group: gastrointestinal bleeding, bleeding that led to a drop in the hemoglobin level and bleeding that required a transfusion.<sup>3</sup>

\* Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation

At present, there is no established effective antidote for rivaroxaban. Uncontrolled bleeding may occur and can be difficult to treat. Therefore, **rivaroxaban should only be prescribed for patients who have ready access to appropriate medical services to manage a major bleeding event.**

Post-marketing information also suggests that rivaroxaban may be associated with significant risks. As of March 31, 2012, a total of 267 serious adverse reaction reports have been received by Health Canada.<sup>4</sup>

Elderly and patients with renal impairment have increased bleeding risk. Therefore, renal function should be assessed regularly (baseline, at least yearly, and when clinically appropriate). Rivaroxaban is contraindicated in patients with severe renal impairment (CrCl or eGFR <30 mL/min).<sup>1</sup>

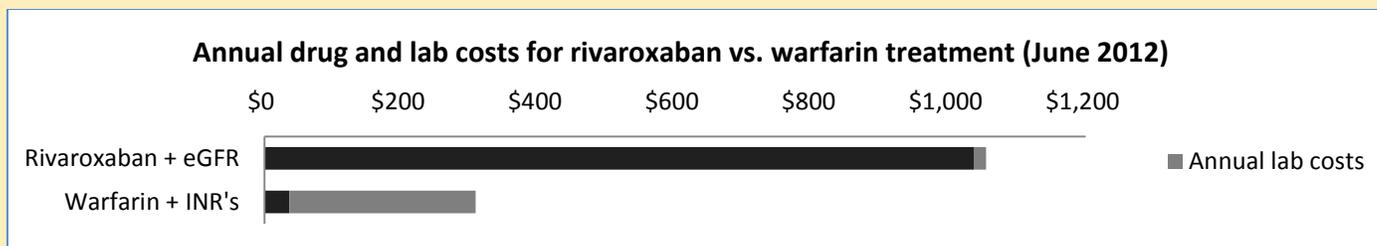
## Dosage for prevention of stroke and systemic embolism in non-valvular atrial fibrillation

Creatinine clearance (CrCl), mL/min	Dosage <sup>1</sup>
≥50	20 mg once daily with food
30-49	15 mg once daily with food
<30	Not recommended

Rivaroxaban is known to interact with inducers and inhibitors of both CYP3A4 and p-glycoprotein systems (e.g., ketoconazole, some antibiotics).<sup>1</sup> Concurrent use of drugs that affect hemostasis also increases risk of bleeding (e.g., ASA, NSAIDs, anti-platelet drugs, or other antithrombotic agents). Consult the latest product monograph for potential drug interactions.

## Costs

Rivaroxaban is significantly more expensive than warfarin, even when laboratory costs are considered (i.e., one eGFR or 16 INR tests per year, respectively, for the average patient in B.C.). Note that monitoring should be individualized and more frequent monitoring may be required.



Until longer-term data becomes available and an effective antidote has been identified for these newer anticoagulants, **well-managed warfarin is a safe and cost-effective agent for most patients.**

## Switching from rivaroxaban to warfarin<sup>1</sup>

To ensure adequate anticoagulation when transitioning from rivaroxaban to warfarin, rivaroxaban should overlap with warfarin until INR is ≥2.0.

- First two days of conversion: While on rivaroxaban, initiate warfarin at usual starting doses. INR testing not needed.
- After two days and thereafter: While on concurrent therapy, test INR just before next dose of rivaroxaban.
- Once INR >2.0: Discontinue rivaroxaban. INR may be done at least 24 hours after last dose of rivaroxaban.

## References

1. Xarelto®[product monograph on the Internet]. Toronto (ON):Bayer Inc.;2012 [cited 2012 July 8]; Available from [www.bayer.ca/files/XARELTO-PM-ENG-13FEB2012-145763.pdf?#](http://www.bayer.ca/files/XARELTO-PM-ENG-13FEB2012-145763.pdf?#).
2. Canadian Agency for Drugs and Technologies in Health (CADTH). Optimal warfarin management for the prevention of thromboembolic events in patients with atrial fibrillation [Internet]. [cited 2012 Jul 9]; Available from [cadth.ca/en/products/optimal-use/warfarin-management](http://cadth.ca/en/products/optimal-use/warfarin-management).
3. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-91.
4. Health Canada. MedEffect Canada - Canada Vigilance Adverse Reaction Online Database - Health Canada [Internet]. 2009 Sept 24 [cited 2012 Jul 9]; Available from [www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/index-eng.php](http://www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/index-eng.php).