



Consider ^{Pr} Xarelto[®]

Meet Olivia[†]

- ◆ 80 years old
- ◆ Family history of CKD
- ◆ Diagnosed with CKD
5 years ago (CrCl = 35 mL/min)
- ◆ Recent ECG confirmed AF
- ◆ Declining CrCl observed
at diagnosis

Increasing age is associated with declining renal function. Please consider benefits/risks of anticoagulation therapy before administering Xarelto[®] to patients with moderate renal impairment having a CrCl close to the severe renal impairment category (CrCl <30 mL/min), or to those with a potential to have deterioration of renal function to severe impairment during therapy. Xarelto[®] must be used with caution in patients with severe renal impairment (15 - <30 mL/min) and should not be used in patients with CrCl <15 mL/min.

Xarelto[®] (rivaroxaban) film-coated tablet (10 mg, 15 mg, 20 mg) is indicated for the prevention of stroke and systemic embolism in patients with atrial fibrillation, in whom anticoagulation is appropriate.¹

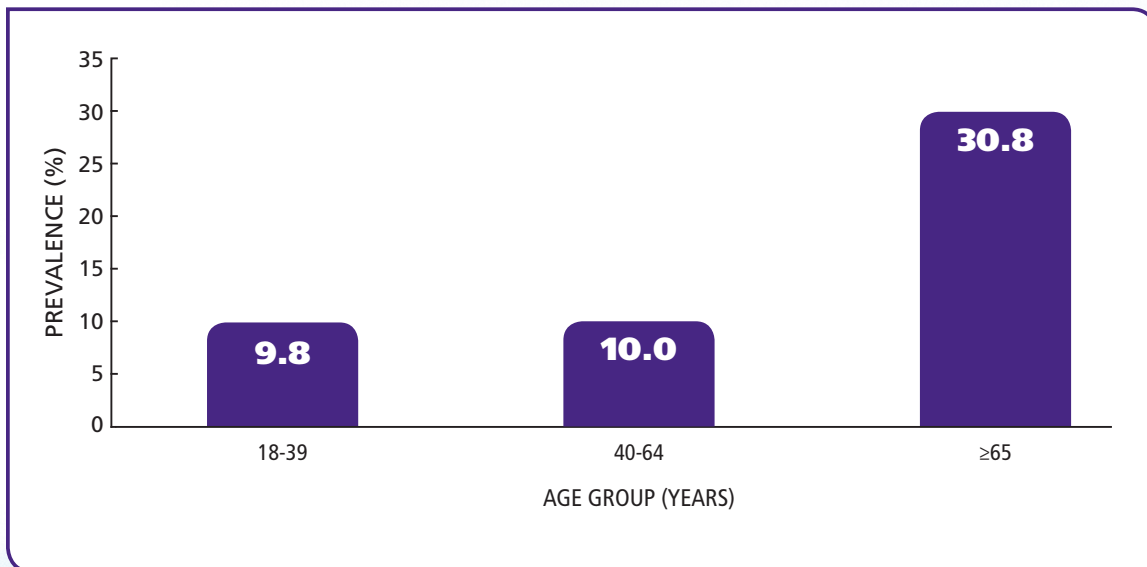


CKD: chronic kidney disease; AF: atrial fibrillation; CrCl: creatinine clearance
[†] Fictitious patient. May not be representative of all patients.

^{Pr} Xarelto[®]

Chronic Kidney Disease Commonly Affects Patients with AF²

The prevalence of renal impairment disease in Canada from 2007-2009^{3†}



Adapted from Arora 2013.³

† Analysis of cycle 1 of the Canadian Health Measures Survey (N=3,689) studying the prevalence of chronic kidney disease in Canadians aged 18 to 79 years conducted between 2007 and 2009. Participants were classified by stage of chronic kidney disease based on the estimated glomerular filtration rate and the presence of albuminuria.³

Xarelto® Was Prospectively Studied with a Reduced Dose for Patients with Moderate Renal Impairment (CrCl 30-49 mL/min) in a Subgroup Analysis from ROCKET AF^{4‡}

Study population⁴

Comorbidity	C CHF	H Hypertension	A* Age (median)	D Diabetes	S Stroke/TIA/ SE (prior)	CHADS ₂ score (mean)
Patients	66%	92%	79	32%	50%	3.7

* The CHADS₂ score age criteria is ≥75 years. The age indicated corresponds to the median age of the patients from the subgroup. CHADS₂ score is used to estimate stroke risk in patients with non-valvular AF.⁴

ROCKET AF recruited patients with non-valvular AF, as documented on electrocardiography, who were at moderate-to-high risk for stroke. Elevated risk was indicated by a history of stroke, transient ischemic attack, or systemic embolism or at least 2 of the following risk factors: heart failure or a left ventricular ejection fraction of 35% or less, hypertension, an age of 75 years or more, or the presence of diabetes mellitus. According to the protocol, the proportion of patients who had not had a previous ischemic stroke, transient ischemic attack, or systemic embolism and who had no more than 2 risk factors was limited to 10% of the cohort for each region; the remainder of patients were required to have had either previous thromboembolism or 3 or more risk factors.⁵

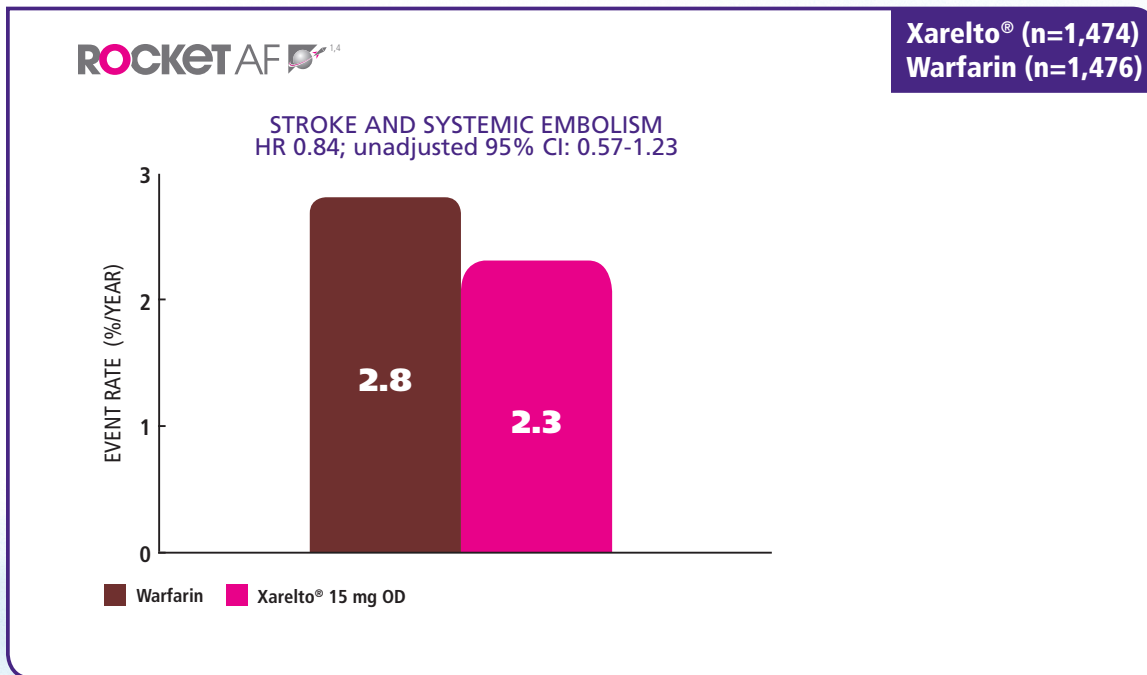
The subgroup of patients with moderate renal impairment (CrCl 30-49 mL/min) was composed of 1,474 patients treated with Xarelto® and 1,476 with warfarin.⁴

‡ Moderate renal impaired (CrCl 30-49 mL/min) subgroup analysis of ROCKET AF, a prospective, randomized, double-blind, double-dummy, parallel-group, multicentre, pivotal trial investigating the efficacy and safety profiles of oral Xarelto® (20 mg OD, 15 mg OD for patients with moderate renal impairment [CrCl 30-49 mL/min], N=7,131) vs. warfarin (dose-adjusted to INR 2.5 [range 2.0-3.0], N=7,133) for the prevention of stroke or systemic embolism in patients with AF. Mean treatment duration: 572 days.^{1,4}

Xarelto® Efficacy Results: Combined Stroke and Systemic Embolism in AF Patients with Moderate Renal Impairment

Principal efficacy outcome (stroke and systemic embolism)^{1,4}

Patients with moderate renal impairment (CrCl 30-49 mL/min)



Xarelto® Safety Results: Bleeding Rates in AF Patients with Moderate Renal Impairment



Principal safety outcome (major and clinically relevant non-major bleeding):⁴

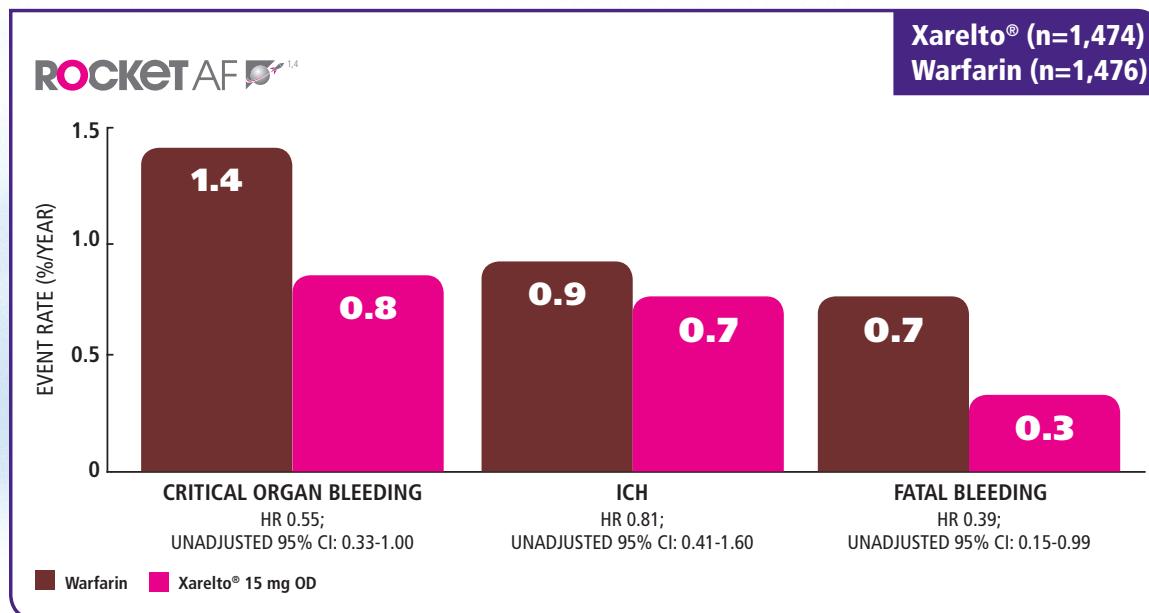
- ◆ 15 mg Xarelto® vs. dose-adjusted warfarin demonstrated no statistically significant difference (17.82%/year vs. 18.28%/year, HR 0.98; unadjusted 95% CI: 0.84-1.14)

Secondary safety outcomes (critical organ bleedings, intracranial hemorrhage and fatal bleedings):⁴



- ◆ No statistically significant differences were demonstrated in major bleeding between Xarelto® vs. warfarin groups
- ◆ However, there was an increase in hemoglobin drop and transfusions. Xarelto® vs. warfarin: ≥ 2 g/dL fall in hemoglobin (3.76%/year vs. 3.28%/year, HR 1.14; 95% CI: 0.83-1.58); transfusions > 2 units (2.34%/year vs. 2.00%/year, HR 1.17; 95% CI: 0.77-1.76)

Secondary safety outcomes^{1,4}

Patients with moderate renal impairment (CrCl 30-49 mL/min)



Dosing Recommendations[†]

Convenient once-daily dosing ¹					
Renal function/impairment	Normal >80 mL/min	Mild 50-<80 mL/min	Moderate 30-<50 mL/min	Severe* 15-<30 mL/min	<15 mL/min
Recommended dosage and administration for AF patients	20 mg OD 		15 mg OD 		Xarelto [®] is not recommended
To be taken with food. For patients unable to swallow tablets, Xarelto [®] (15 and 20 mg) may be crushed and mixed with applesauce immediately prior to use and administered orally. The crushed tablet should be immediately followed by food.					

Pharmacokinetics of Xarelto^{®1‡}



- ◆ Xarelto[®] should be used with caution in patients with moderate renal impairment (CrCl 30-49 mL/min), especially in those concomitantly receiving other drugs which increase rivaroxaban plasma concentrations.
- ◆ Physicians should consider the benefit/risk of anticoagulant therapy before administering Xarelto[®] to patients with moderate renal impairment having a creatinine clearance close to the severe renal impairment category (CrCl <30 mL/min), or in those with a potential to have deterioration of renal function to severe impairment during therapy.
- ◆ Xarelto[®] must be used with caution in patients with severe renal impairment (CrCl 15-<30 mL/min) and should not be used in patients with CrCl <15 mL/min.
- ◆ Patients who develop acute renal failure while on Xarelto[®] should discontinue such treatment.

OD: once daily

* Must be used with caution.

† Please consult the Product Monograph for complete dosage and administration instructions.

‡ Clinical significance is unknown.

Indications and clinical use not discussed elsewhere in this piece:

Xarelto® (rivaroxaban) film-coated tablet (10 mg, 15 mg, 20 mg) is indicated for the

- treatment of venous thromboembolic events (deep vein thrombosis [DVT], pulmonary embolism [PE]) and prevention of recurrent DVT and PE.
- prevention of venous thromboembolic events (VTE) in patients who have undergone elective total hip replacement (THR) or total knee replacement (TKR) surgery.

Xarelto® film-coated tablet (2.5 mg), in combination with 75 mg-100 mg ASA, is indicated for the:

- prevention of stroke, myocardial infarction (MI) and cardiovascular (CV) death, and for the prevention of acute limb ischemia and mortality in patients with coronary artery disease (CAD) with or without peripheral artery disease (PAD).

For the treatment of VTE, Xarelto® is **not** recommended as an alternative to unfractionated heparin in patients with pulmonary embolus who are haemodynamically unstable, or who may receive thrombolysis or pulmonary embolectomy, since the safety and efficacy of Xarelto® have not been established in these clinical situations.

Xarelto® is not recommended for use in children less than 18 years of age.

Contraindications:

- Clinically significant active bleeding, including gastrointestinal bleeding
- Lesions or conditions at increased risk of clinically significant bleeding, e.g., recent cerebral infarction (hemorrhagic or ischemic), active peptic ulcer disease with recent bleeding, patients with spontaneous or acquired impairment of hemostasis
- Concomitant **systemic** treatment with strong inhibitors of **both** CYP 3A4 and P-glycoprotein (P-gp), such as ketoconazole, itraconazole, posaconazole, or ritonavir
- Concomitant treatment with any other anticoagulant, including:
 - unfractionated heparin (UFH), except at doses used to maintain a patent central venous or arterial catheter,
 - low-molecular-weight heparins (LMWH), such as enoxaparin and dalteparin,
 - heparin derivatives, such as fondaparinux, and
 - oral anticoagulants, such as warfarin, dabigatran, apixaban, except under circumstances of switching therapy to or from Xarelto®.
- Hepatic disease (including Child-Pugh Class B and C) associated with coagulopathy, and having clinically relevant bleeding risk
- Pregnancy
- Nursing women
- Hypersensitivity to Xarelto® (rivaroxaban) or to any ingredient in the formulation

Most serious warnings and precautions:

PREMATURE DISCONTINUATION OF ANY ORAL ANTICOAGULANT, INCLUDING XARELTO®, INCREASES THE RISK OF THROMBOTIC EVENTS. To reduce this risk, consider coverage with another anticoagulant if Xarelto® is discontinued for a reason other than pathological bleeding or completion of a course of therapy.

Bleeding: Xarelto®, like other anticoagulants, should be used with caution in patients with an increased bleeding risk. Any unexplained fall in hemoglobin or blood pressure should lead to a search for a bleeding site. Patients at high risk of bleeding should not be prescribed Xarelto®. **Should severe bleeding occur, treatment with Xarelto® must be discontinued and the source of bleeding investigated promptly.** See Other relevant warnings and precautions for concomitant use of drugs affecting hemostasis.

Peri-operative spinal/epidural anesthesia, lumbar puncture: The risk of developing an epidural or spinal hematoma that may result in long-term neurological injury or permanent paralysis is increased by the use of indwelling epidural catheters or the concomitant use of drugs affecting hemostasis. Accordingly, the use of Xarelto®, at doses greater than 10 mg, is not recommended in patients undergoing anesthesia with post-operative indwelling epidural catheters. The risk may also be increased by traumatic or repeated epidural or spinal puncture. **If traumatic puncture occurs, the administration of Xarelto® should be delayed for 24 hours.** Patients who have undergone epidural puncture and who are receiving Xarelto® 10 mg should be frequently monitored for signs and symptoms of neurological impairment. If neurological deficits are noted, urgent diagnosis and treatment is necessary. The physician should consider the potential

benefit versus the risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis and use Xarelto® 10 mg only when the benefits clearly outweigh the possible risks. An epidural catheter should not be withdrawn earlier than 18 hours after the last administration of Xarelto®. Xarelto® should be administered not earlier than 6 hours after the removal of the catheter. No clinical experience with the use of Xarelto® 15 mg and 20 mg, or Xarelto® 2.5 mg in combination with ASA in these situations.

Renal impairment: Xarelto® must be used with caution in patients with severe renal impairment (CrCl 15-30 mL/min). Xarelto® should be used with caution in patients with moderate renal impairment (CrCl 30-49 mL/min), especially in those concomitantly receiving other drugs which increase rivaroxaban plasma concentrations. Xarelto® is not recommended in patients with CrCl <15 mL/min. Determine estimated creatinine clearance (eCrCl) in all patients before instituting Xarelto®.

Monitoring and laboratory tests: Although Xarelto® therapy will lead to an elevated INR, depending on the timing of the measurement, the INR is not a valid measure to assess the anticoagulant activity of Xarelto®. The INR is only calibrated and validated for vitamin K antagonists (VKA) and should not be used for any other anticoagulant, including Xarelto®.

Other relevant warnings and precautions:

- Fall in hemoglobin or blood pressure
- Concomitant use of drugs affecting hemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid (ASA), platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs)
- Chronic concomitant treatment with NSAIDs if receiving Xarelto® 2.5 mg with ASA
- Atrial fibrillation and having a condition that warrants single or dual antiplatelet therapy
- Use of Xarelto® 2.5 mg with ASA in patients with CAD with or without PAD, with or as a replacement for dual antiplatelet therapy (DAPT). Not indicated in patients with unstable atherosclerotic disease when DAPT is indicated.
- Use of antiplatelet agents, prasugrel and ticagrelor
- Use of thrombolytics during acute myocardial infarction (AMI) or acute stroke due to expected increased risk of major bleeding
- Patients with prosthetic heart valves or those with hemodynamically significant rheumatic heart disease, especially mitral stenosis
- Patients with atrial fibrillation who undergo PCI with stent placement
- CAD/PAD patients with history of previous haemorrhagic or lacunar stroke
- CAD/PAD patients in the first month after an ischemic, non-lacunar stroke
- Interaction with strong inhibitors of both CYP 3A4 and P-gp, such as ketoconazole, itraconazole, posaconazole, or ritonavir. These drugs may increase Xarelto® plasma concentrations which increases bleeding risk.
- Patients with mild and moderate renal impairment concomitantly treated with combined P-gp and moderate CYP 3A4 inhibitors such as erythromycin increased exposure to rivaroxaban. Caution is required.
- Interaction with strong CYP 3A4 inducers, such as rifampicin, and the anticonvulsants, phenytoin, carbamazepine, phenobarbital
- Patients with hepatic impairment
- Patients who undergo surgery or invasive procedures including fracture-related surgery of the lower limbs (limited clinical data), pre-operative phase (associated with risk of bleeding) and peri-operative phase when neuraxial (epidural/spinal) anesthesia or spinal puncture is performed (associated with risk of epidural or spinal hematoma that may result in long-term neurological injury or permanent paralysis) and post-procedural period (to avoid unnecessary increased risk of thrombosis)
- Patients with lactose sensitivity
- Use of Xarelto® 2.5 mg BID + ASA in patients with chronic CAD with or without PAD ≥75 years of age

For more information:

Please consult the Xarelto® Product Monograph at www.bayer.ca/omr/online/xarelto-pm-en.pdf for important information relating to adverse reactions, drug interactions, and dosing information which have not been discussed in this piece.

The Product Monograph is also available by calling 1-800-265-7382.

Demonstrated efficacy and safety profile in AF patients with moderate renal impairment¹

Xarelto® 15 mg OD[†]

- ◆ Prospectively studied in patients with moderate renal impairment²
- ◆ Must be used with caution in patients with severe renal impairment (CrCl 15-<30 mL/min) and is not recommended in patients with CrCl <15 mL/min¹

Extensive Global Experience

- ◆ **55 million patients treated** in clinical practice worldwide across all indications^{6*}
- ◆ **145** ongoing clinical trials worldwide⁷
- ◆ **>1.5 million patients** projected to be enrolled in these clinical trials⁷

* Xarelto® is indicated for the treatment of venous thromboembolic events (deep vein thrombosis [DVT], pulmonary embolism [PE]) and prevention of recurrent DVT and PE; the prevention of stroke and systemic embolism in patients with atrial fibrillation, in whom anticoagulation is appropriate; and the prevention of venous thromboembolic events (VTE) in patients who have undergone elective total hip replacement (THR) or total knee replacement (TKR) surgery.¹

† Please consult the Product Monograph for complete dosage and administration instructions.

References:

1. Xarelto® (rivaroxaban) Product Monograph. September 18, 2018.
2. Skanes AC, *et al.* Society Guidelines. Focused 2012 Update of the Canadian Cardiovascular Society Atrial Fibrillation Guidelines: Recommendations for Stroke Prevention and Rate/Rhythm Control. *Can J Cardiol* 2012;28:125-36.
3. Arora P, *et al.* Prevalence estimates of chronic kidney disease in Canada: results of a nationally representative survey. *CMAJ* 2013;185(9):417-23.
4. Fox K.A., Piccini J.P., Wojdyla D., *et al.* Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-vascular atrial fibrillation and moderate renal impairment. *Eur Heart J*. 2011;32(19):2387-94.
5. Patel MR, Mahaffey KW, Garg J, *et al.* Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. *New Engl J Med* 2011;365:883-91.
6. IMS Health MIDAS, Database: Quaterly sales Q1 2019.
7. ClinicalTrials.gov. Last accessed July 25, 2018.



© TM see www.bayer.ca/tm-mc
© 2019, Bayer Inc.



XO463-0819E
PP-XAR-CA-0357-1

Xarelto®