Consider Xarelto®

in patients with nonvalvular AF who undergo PCI with stent placement

Data on efficacy in this population are limited

PrXarelto® (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]

MEET JOHN†

- 71 years old
- Married for 38 years and grandfather of 2
- Retired accountant
- Diagnosed with AF 5 years ago
- Recently started experiencing angina and was diagnosed with stable CAD
- No history of kidney disease
- Will have to undergo PCI with stent placement

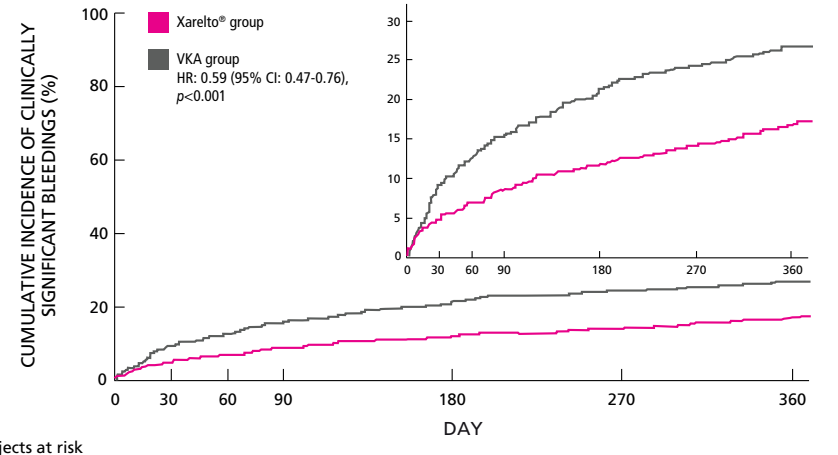
Increasing age is associated with declining renal function. Use caution in elderly patients. Data on efficacy in patients with nonvalvular AF who undergo PCI with stent placement are limited. The safety profile of Xarelto® in patients with AF who undergo PCI with stent placement was assessed based on clinical data available from an open-label interventional study.[1]

AF: atrial fibrillation; PCI: percutaneous coronary intervention; CAD: coronary artery disease
† Fictitious patient. May not be representative of all patients.

Xarelto® rivaroxaban tablet

PIONEER AF-PCI (open-label study design): Xarelto®-based regimen demonstrated a safety profile in patients with nonvalvular AF who underwent PCI with stent placement[1,2†]

Significantly lower risk of clinically significant bleeding events vs. VKA-based regimen (primary endpoint)[1,2‡]



No. subjects at risk							
Xarelto® group	696	628	606	585	543	510	383
VKA group	697	593	555	521	461	426	329

Adapted from Xarelto® Product Monograph[1]

Clinically significant bleeding events occurred in 109 patients (15.7%) on the Xarelto®-based regimen and in 167 patients (24.0%) on the VKA regimen (HR 0.59; 95% CI: 0.47-0.76; $p<0.001$).[1]

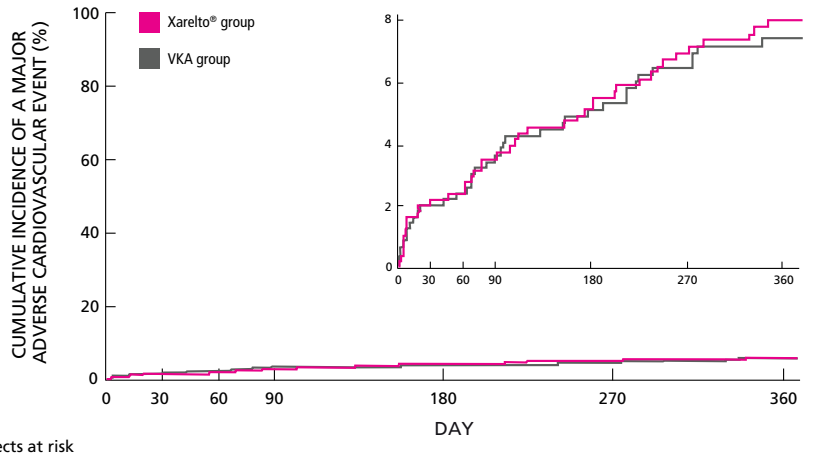
VKA: vitamin K antagonist; HR: hazard ratio; CI: confidence interval; TIMI: thrombolysis in myocardial infarction; BRMA: bleeding requiring medical attention

† A randomized, open-label, multicenter study comparing the 12-month safety of two antithrombotic regimens (Xarelto® 15 mg OD (10 mg OD for patients with CrCl 30-49 mL/min) plus a $P2Y_{12}$ inhibitor (e.g., clopidogrel) (n=696); dose-adjusted VKA plus DAPT (n=697)) in patients with AF who underwent PCI with stent placement for primary atherosclerotic disease. Patients with a history of stroke or TIA were excluded from the trial.[1]

‡ Clinically significant bleeding events are a composite of TIMI major bleeding, TIMI minor bleeding and BRMA.[1]

PIONEER AF-PCI (open-label study design): Xarelto®-based regimen demonstrated a safety profile in patients with nonvalvular AF who underwent PCI with stent placement[1,2†]

Incidence of major adverse cardiovascular events in nonvalvular AF patients undergoing PCI with stent (secondary endpoint)[1,2‡]



No. subjects at risk							
Xarelto® group	694	648	633	621	590	562	430
VKA group	695	635	607	579	543	514	408

Adapted from Xarelto® Product Monograph[1]

Major adverse cardiovascular events, a composite of CV death, MI, or stroke, occurred in 41 patients (5.9%) on Xarelto®-based regimen and in 36 patients (5.2%) on the VKA regimen.[1]

Stent thrombosis occurred in 5 patients on Xarelto®-based regimen and in 4 patients on the VKA regimen.[1]

CV: cardiovascular; MI: myocardial infarction

† A randomized, open-label, multicenter study comparing the 12-month safety of two antithrombotic regimens (Xarelto® 15 mg OD (10 mg OD for patients with CrCl 30-49 mL/min) plus a $P2Y_{12}$ inhibitor (e.g., clopidogrel) (n=696); dose-adjusted VKA plus DAPT (n=697)) in patients with AF who underwent PCI with stent placement for primary atherosclerotic disease. Patients with a history of stroke or TIA were excluded from the trial.[1]

PIONEER study was not designed to compare efficacy between treatment arms

Recommended dose for nonvalvular AF patients who undergo PCI with stent placement[1†]

Reduce Xarelto® dose
Add a $P2Y_{12}$ inhibitor
Maximum of 12 months

Increase Xarelto® dose
Remove antiplatelet
Revert back to standard dose after completion of the antiplatelet therapy

After PCI

Xarelto® 15 mg OD‡ + $P2Y_{12}$ inhibitor

Xarelto® 20 mg OD

† Please consult the Product Monograph for complete dosage and administration instructions.
‡ In PCI patients with moderate renal impairment (CrCl 30-49 mL/min), the Xarelto® reduced dose should be 10 mg OD during concomitant treatment with $P2Y_{12}$ inhibitor and 15 mg OD after completion of antiplatelet therapy.
§ Comparative clinical significance is unknown.

Xarelto® - the **1st** and **only** NOAC with dosing instructions and precautions for nonvalvular AF patients undergoing PCI with stent in its Product Monograph[3§]

Dosing considerations

In patients with moderate renal impairment (CrCl 30-49 mL/min), the Xarelto® reduced dose should be 10 mg OD during concomitant treatment with $P2Y_{12}$ inhibitor and 15 mg OD after completion of antiplatelet therapy.[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.[1]
- 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.[1]
- Xarelto® 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/min.[1]
- Patients who develop acute renal failure while on Xarelto® should discontinue such treatment.[1]
- Xarelto® should always be taken with food.[1]
- For patients unable to swallow tablets, Xarelto® (10, 15 and 20 mg) may be crushed and mixed with applesauce immediately prior to use and administered orally. After the administration of a crushed Xarelto® 15 and 20 mg tablet, the dose should be immediately followed by food.[1]

Indications and clinical use not discussed elsewhere in this piece:

Xarelto® 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 and ASA in patients with CAD with or without PAD, in combination 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 other valve procedures or those with hemodynamically significant rheumatic heart disease, especially mitral stenosis. Not indicated for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement.
- Patients diagnosed with antiphospholipid syndrome and with a history of thrombosis
- 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.

Xarelto®-based regimen for AF patients undergoing PCI with stent placement

- Demonstrated significantly lower risk of clinically significant bleeding in nonvalvular AF patients undergoing PCI with stent placement vs. a VKA-based regimen[1]
- Once-daily 15 mg dosing with $P2Y_{12}$ inhibitor† for nonvalvular AF patients undergoing PCI with stent placement[1]

Consider Xarelto® 15 mg for patients like John‡

† For a maximum of 12 months and followed by a reversion to standard dose after completion of the antiplatelet therapy.[1]
‡ Fictitious patient. May not be representative of all patients.

References: 1. Xarelto® (rivaroxaban tablet) Product Monograph. September 20, 2019.
2. Gibson MC *et al. NEJM* 2016;375(25):2423-34. **3.** Data on file. Bayer Inc.

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