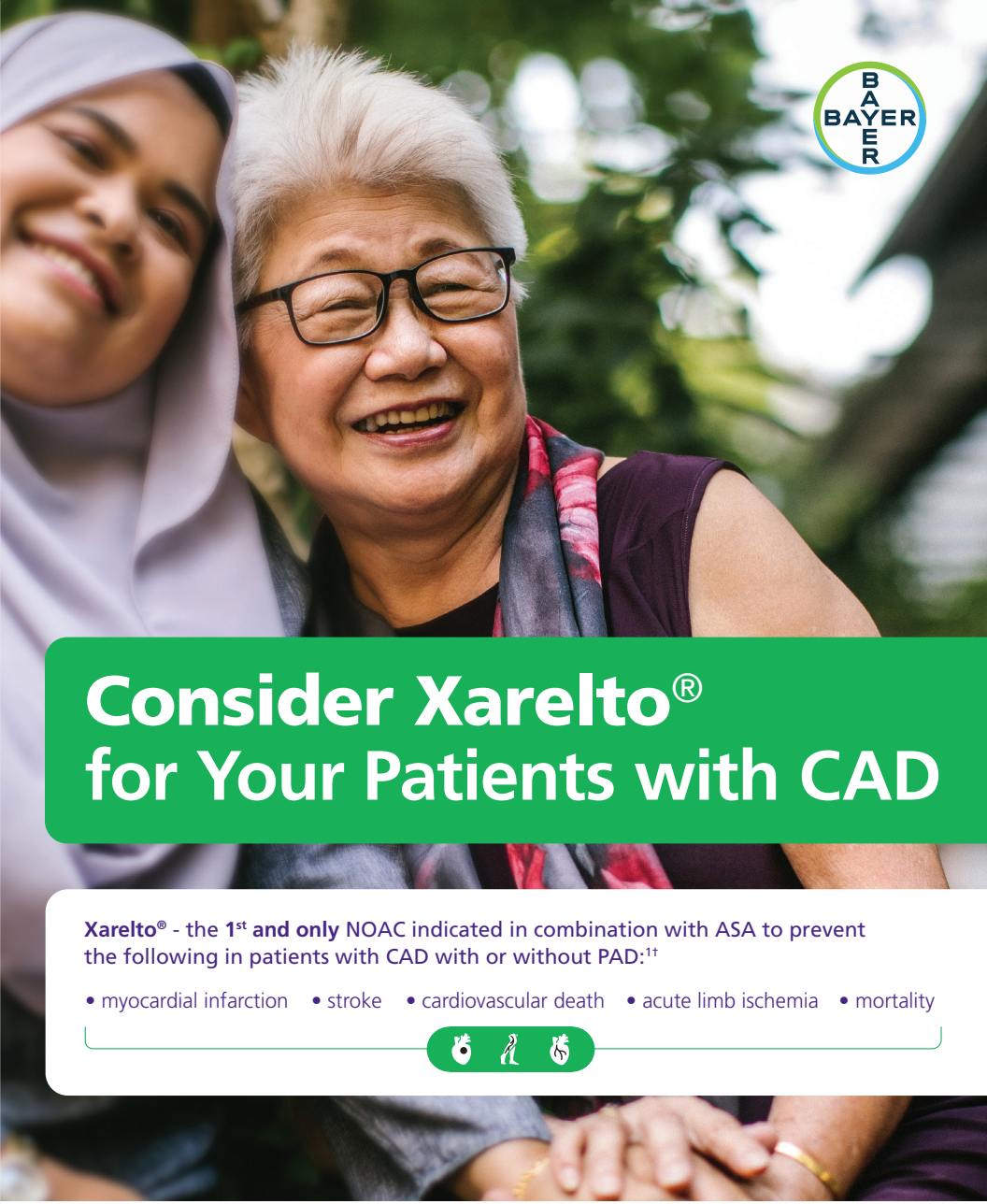


Consider Xarelto®
for Your Patients with CAD

Xarelto® - the **1st and only** NOAC indicated in combination with ASA to prevent the following in patients with CAD with or without PAD:[1†]

- myocardial infarction
- stroke
- cardiovascular death
- acute limb ischemia
- mortality

PrXarelto® (rivaroxaban) film-coated tablet (2.5 mg), in combination with 75 mg-100 mg acetylsalicylic acid (ASA), is indicated for the prevention of stroke, myocardial infarction and cardiovascular 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).

NOAC: non-vitamin K oral anticoagulants
† Comparative clinical significance unknown.

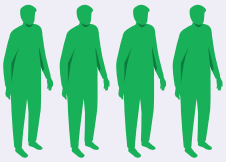
Xarelto® rivaroxaban tablet

Xarelto® + ASA demonstrated a superior reduction in the primary composite outcome

vs. ASA alone in a subgroup of CAD patients with or without PAD[2,3†]

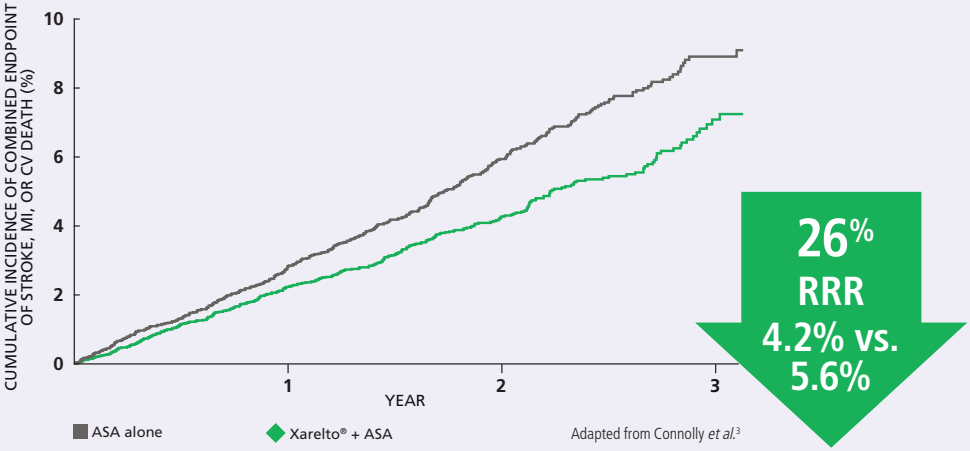
Composite outcome of stroke, myocardial infarction, or cardiovascular death (primary efficacy outcome)

- **4.2%** for Xarelto® + ASA (n=8,313) vs. **5.6%** for ASA alone (n=8,261) (HR 0.74, 95% CI 0.65-0.86, *p*=0.00003)[2]



CAD with or without PAD population **16,574**

COMPASS – CAD with or without PAD population



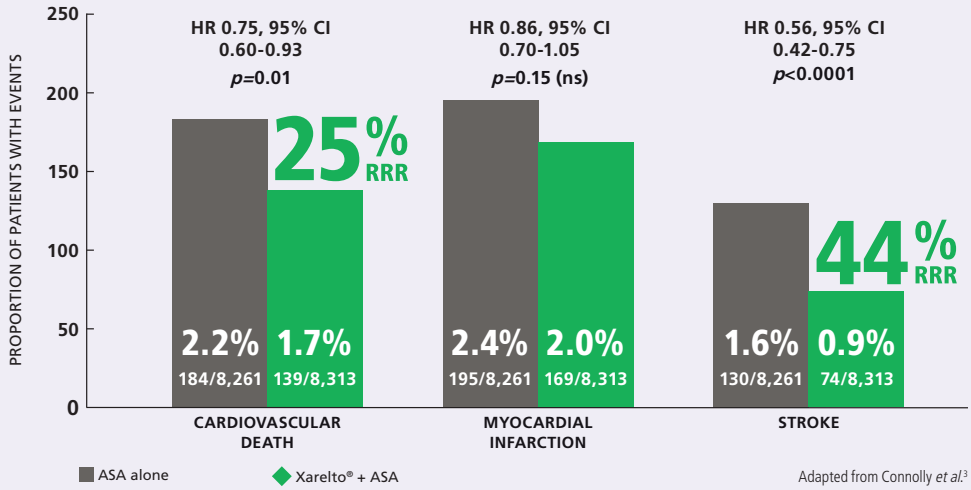
MI: myocardial infarction; CV: cardiovascular; RRR: relative risk reduction; BID: twice daily; OD: once daily; eGFR: estimated glomerular filtration rate

†A pivotal phase III double-blind study investigating the efficacy and safety of Xarelto® 2.5 mg BID + ASA (100 mg OD) (n=9,152) and ASA alone (n=9,126) for the prevention of the composite of stroke, myocardial infarction, or cardiovascular death in patients with stable atherosclerotic vascular disease. Patients with established CAD, PAD or a combination of CAD and PAD were eligible. Xarelto® 2.5 mg in combination with ASA 75-100 mg is not indicated in patients with PAD alone. Coronary artery disease patients <65 years old were required to have documentation of atherosclerosis involving at least two vascular beds or to have at least two additional cardiovascular risk factors (current smoker, diabetes mellitus, an eGFR <60 mL per minute, heart failure, or non-lacunar ischemic stroke ≥1 month earlier). Patients in need of dual antiplatelet, other non-ASA antiplatelet, or oral anticoagulant therapies as well as patients with a history of ischemic, non-lacunar stroke within 1 month, any history of hemorrhagic or lacunar stroke, or patients with eGFR <15 mL/min were excluded from the study. Mean duration of follow-up was 23 months.[2]

Results for the individual components of the primary composite outcome[3]

CAD with or without PAD population **16,574**

Primary endpoint components



Adapted from Connolly *et al.*[3]

ns: not significant

Xarelto® + ASA demonstrated superiority for all-cause mortality

vs. ASA alone (secondary endpoint)[3]

CAD with or without PAD population **16,574**

- **3.0%** for Xarelto® + ASA vs. **4.0%** for ASA alone (HR 0.77, 95% CI 0.65-0.90, *p*=0.0012)

23%
RRR
in all-cause mortality
3.0% vs. 4.0%

Adapted from Connolly *et al.*[3]

Bleeding safety profile in the overall population†‡

- **3.1%** of patients treated with Xarelto® + ASA vs. **1.9%** of patients treated with ASA alone experienced modified ISTH major bleeding events§ (HR 1.70, 95% CI 1.40-2.05, *p*<0.00001, primary safety outcome)[2]

mISTH: modified International Society on Thrombosis and Haemostasis
† Intention-to-treat analysis set, primary analyses.
‡ The overall population consisted of patients with established CAD, PAD or a combination of CAD and PAD - Xarelto® 2.5 mg in combination with ASA 75-100 mg is not indicated in patients with PAD alone.
§ mISTH major bleeding is defined as fatal bleeding, symptomatic bleeding into critical area or organ, bleeding into surgical site requiring reoperation or bleeding leading to hospitalization.[2]

COMPASS subgroup analysis – CAD patients with or without PAD

Demonstrated superior reduction in the composite of stroke, MI, or CV death vs. ASA alone

4.2% for Xarelto® + ASA (n=8,313) vs. **5.6%** for ASA alone (n=8,261) (HR 0.74, 95% CI 0.65-0.86, *p*=0.00003; 26% RRR)[2,3]

Demonstrated superiority for all-cause mortality vs. ASA alone

3.0% for Xarelto® + ASA vs. **4.0%** for ASA alone (HR 0.77, 95% CI 0.65-0.90, *p*=0.0012; 23% RRR)[3]

A well-studied bleeding profile[2]

Consider the Xarelto® vascular protection regimen for your CAD patients with or without PAD†

Prevention of stroke, myocardial infarction, cardiovascular death, acute limb ischemia and mortality

Xarelto® 2.5 mg BID in combination with 75-100 mg ASA OD‡

Xarelto®
2.5 mg BID

ASA
75-100 mg OD

Xarelto® 2.5 mg BID is not indicated in combination with DAPT.

Speak to your Bayer representative to find out more about Xarelto® 2.5 mg for use in combination with ASA.

DAPT: dual antiplatelet therapy
† Clinical significance is unknown.
‡ Please consult the Product Monograph for complete dosage and administration information.

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:

- prevention of stroke and systemic embolism in patients with atrial fibrillation (AF), in whom anticoagulation is appropriate.
- 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.

For the treatment of VTE, Xarelto® is **not** recommended as an alternative to unfractionated heparin in patients with pulmonary embolus who are hemodynamically 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, edoxaban, 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 other valve procedures or those with hemodynamically significant rheumatic heart disease, especially mitral stenosis. Not indicated 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 hemorrhagic 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.

References: 1. Data on file. Bayer Canada Inc. **2.** Xarelto® (rivaroxaban tablet) Product Monograph. Bayer Inc. September 20, 2019.
3. Connolly SJ *et al. Lancet* 2017; 391(10117):205-218.

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Xarelto® rivaroxaban tablet