# Do you recognize this CAD patient?

## Susan† has CAD

- 61 years old
- Smoker
- Prior MI
- Her diabetes is being managed (A1C 7.1%)
- Her dyslipidemia is under control

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).

† Fictitious patient. May not be representative of all patients.

PrXarelto®

# In the COMPASS trial

## Coronary artery disease (CAD) was defined as:[2]

- Myocardial infarction within the last 20 years, or
- Multi-vessel coronary disease* with symptoms or with history of stable or unstable angina, or
- Multi-vessel percutaneous coronary intervention (PCI), or
- Multi-vessel coronary artery bypass graft (CABG) surgery

* Refers to stenosis of greater than or equal to 50% in 2 or more coronary arteries, confirmed by invasive coronary angiography, or non-invasive imaging or stress studies (e.g., exercise or pharmacologic) suggestive of significant ischemia in 2 or more coronary territories; or in 1 coronary territory if at least one other territory has been revascularized.

## Peripheral arterial disease (PAD) was defined as:[2]

- Previous aorto-femoral bypass surgery, limb bypass surgery, or percutaneous transluminal angioplasty revascularization of the iliac, or infra-inguinal arteries, or
- Previous limb or foot amputation for arterial vascular disease, or
- History of intermittent claudication and one or more of the following:
  1) An ankle/arm blood pressure (BP) ratio <0.90, or
  2) Significant peripheral artery stenosis (≥50%) documented by angiography, or by duplex ultrasound, or
- Previous carotid revascularization or asymptomatic carotid artery stenosis ≥50% as diagnosed by duplex ultrasound or angiography.

Xarelto® is indicated in patients with CAD with or without PAD, not in patients with PAD alone.

## Eligibility for study entry included the following inclusion and exclusion criteria:

**Inclusion criteria:**

- Established CAD and/or PAD†
- Subjects with CAD must also meet at least one of the following criteria:

☐ Age ≥65

☐ Age <65 plus documented atherosclerosis or revascularization involving at least two vascular beds* or at least two additional risk factors

* Because CAD involves disease in the coronary vasculature, only one additional vascular bed is required: e.g., the aorta, arterial supply to the brain, gastro-intestinal tract, lower limbs, upper limbs, kidneys.

Additional risk factors included:

☐ Current smoker

☐ Diabetes mellitus

☐ Renal dysfunction with estimated glomerular filtration rate <60 mL/min

☐ Heart failure

☐ Non-lacunar ischemic stroke ≥1 month ago

**Select exclusion criteria:**

☐ High risk of bleeding

☐ Need for dual antiplatelet therapy, other non-ASA antiplatelet, or oral anticoagulant therapies

☐ History of ischemic, non-lacunar stroke within 1 month

☐ Any history of hemorrhagic or lacunar stroke

☐ eGFR <15 mL/min

eGFR: estimated glomerular filtration rate

† Xarelto® 2.5 mg in combination with ASA 75-100 mg is not indicated in patients with PAD alone.

# Xarelto® Efficacy Results: COMPASS subgroup analysis – CAD patients with or without PAD†

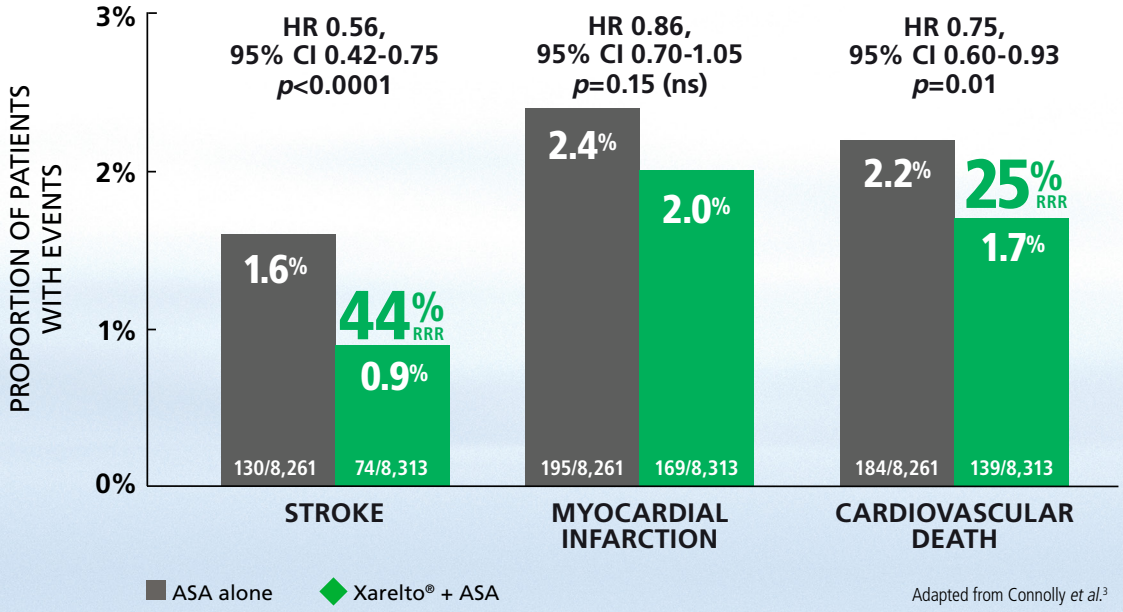
- Xarelto® + ASA demonstrated a superior reduction in the primary composite outcome of stroke, myocardial infarction, or cardiovascular death vs. ASA alone (4.2% vs. 5.6%, HR 0.74, 95% CI 0.65-0.86)[1,3]

## Results for the individual components of the primary composite outcome

### Primary endpoint components[3]

N=16,574

CAD WITH OR WITHOUT PAD POPULATION

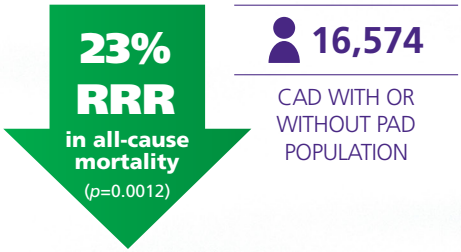



Adapted from Connolly *et al.*[3]

# Xarelto® Efficacy Results: COMPASS subgroup analysis – CAD patients with or without PAD†

## Xarelto® + ASA demonstrated superiority for all-cause mortality vs. ASA alone (secondary endpoint)[3]

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



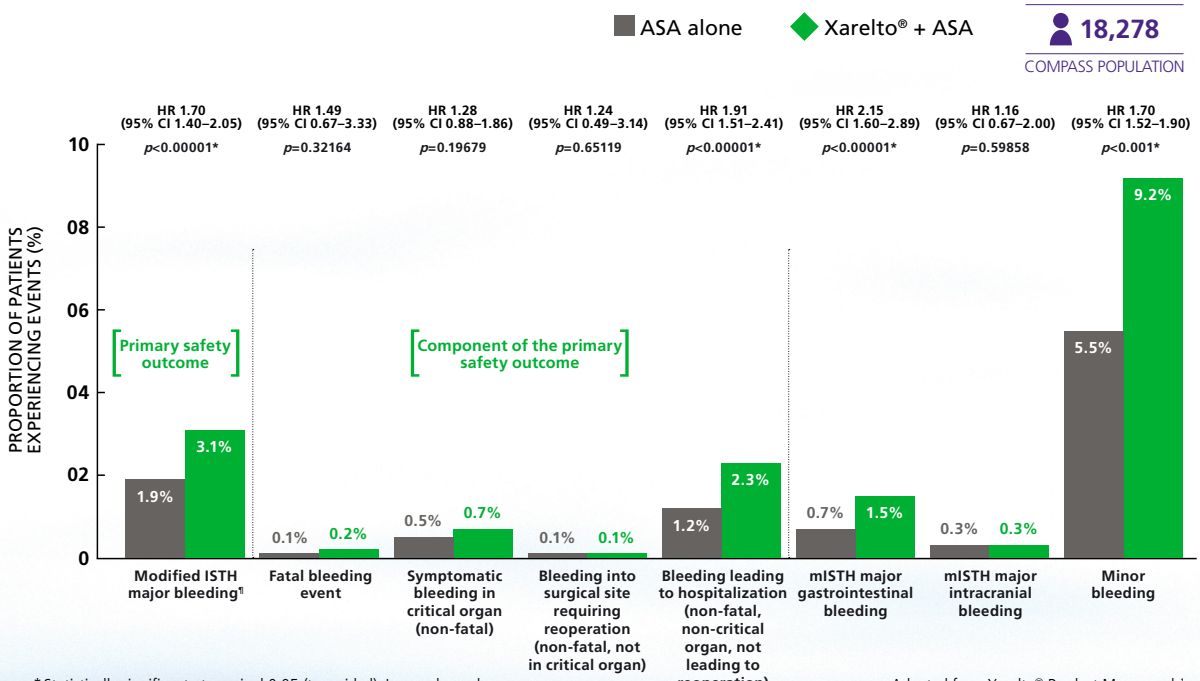

Adapted from Connolly *et al.*[3]

RRR: relative risk reduction; BID: twice daily; OD: once daily

† 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.[1]

# Bleeding safety profile in the overall population

## Bleeding events of the overall population (time to first event)[1†‡§]




* Statistically significant at nominal 0.05 (two-sided). Log-rank *p*-value.

Adapted from Xarelto® Product Monograph[1]

Of the bleeding events leading to hospitalization:

- Hospitalization where admission data < discharge date:
  1.9% vs. 1.0% for events in patients treated with Xarelto® + ASA vs. ASA alone
  (HR 1.91, 95% CI 1.48-2.46, *p*<0.00001*)
- Hospitalization where admission date = discharge date:††
  0.4% vs. 0.2% for events in patients treated with Xarelto® + ASA vs. ASA alone
  (HR 1.70, 95% CI 0.99-2.92, *p*=0.04983)

mISTH: modified International Society on Thrombosis and Haemostasis

† For each outcome, the first event experienced per subject is considered; therefore, subsequent events of the same type are not shown. Each event is counted in the most severe hierarchical category (fatal; critical organ bleeding; bleeding into surgical site requiring re-operation; bleeding leading to hospitalization) only. The bar graph includes events that are classified as major bleedings during the adjudication process.

‡ 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.[1]

†† Refers to hospitalization or presentation to an acute care facility with discharge the same day.

**Indications and clinical use not discussed elsewhere in this piece:**

Xarelto® 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 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, 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® 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 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.

# Introducing the new Xarelto® vascular protection regimen for your CAD patients with or without PAD†

## For the 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.

- Xarelto® may be taken with or without food.
- Treatment should be continued long term provided the benefit outweighs the risk.
- Xarelto® should be used with caution in patients with CrCl 15-<30 mL/min.§ Xarelto® is not recommended in patients with CrCl <15 mL/min.

DAPT: dual antiplatelet therapy

† Clinical significance is unknown.
‡ Please consult the Product Monograph for complete dosage and administration information.
§ Xarelto® should be used with caution in patients 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 with a creatinine clearance close to the severe renal impairment category (CrCl <30 mL/min) or with a potential to have deterioration of renal function during therapy. Renal function should be followed carefully in these patients. Patients who develop acute renal failure while on Xarelto® should discontinue such treatment.

**References: 1.** Xarelto® (rivaroxaban tablet) Product Monograph. Bayer Inc. September 18, 2018. **2.** Eikelboom JW *et al. NEJM* 2017;377(14):1319–30. Supplemental Appendix. **3.** Connolly SJ *et al. Lancet* 2017; doi: 10.1016/S0140–6736(17)32458–3.



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