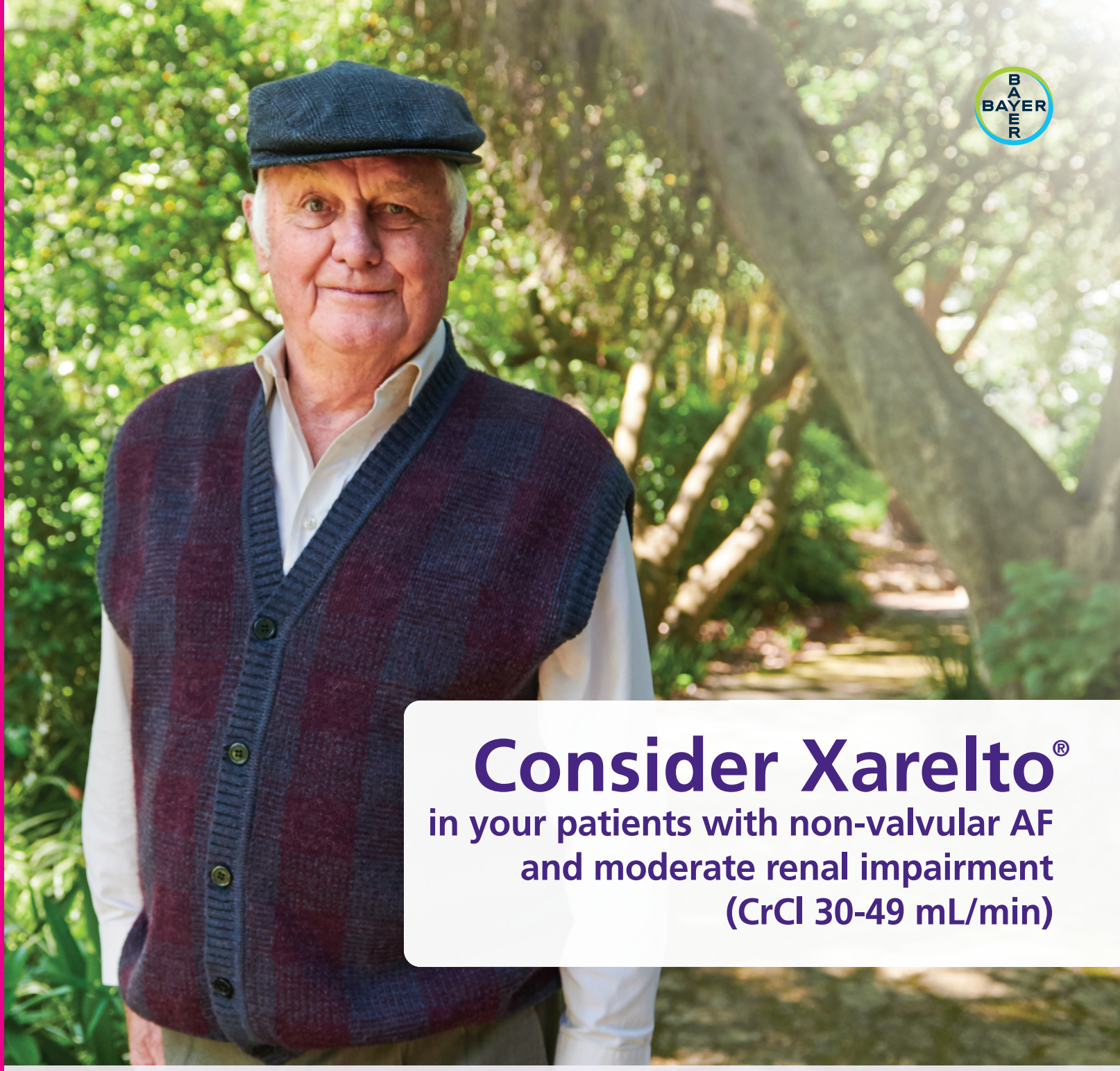


Consider Xarelto®

in your patients with non-valvular AF and moderate renal impairment (CrCl 30-49 mL/min)

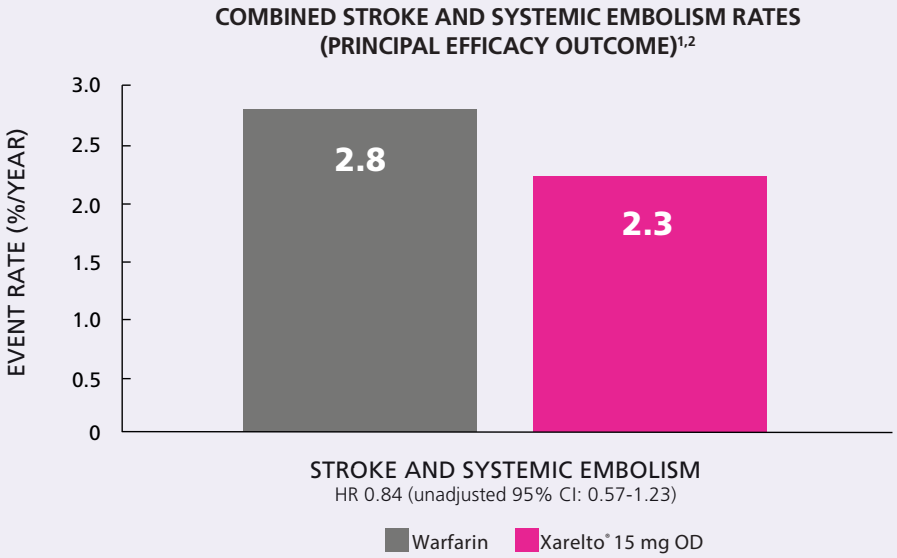
Increasing age is associated with declining renal function. Please consider the benefits and risks of anticoagulation therapy before administering Xarelto® to patients with moderate renal impairment having a CrCl close to the severe renal impairment category (CrCl <30 mL/min), or to those with a potential to have deterioration of renal function to severe impairment during therapy.[1]

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

AF: atrial fibrillation; CrCl: creatinine clearance

Xarelto® rivaroxaban tablet

Xarelto® was prospectively studied with a reduced dose in patients with moderate renal impairment (CrCl 30-49 mL/min) in a subgroup analysis from ROCKET AF[1,2†]



ROCKET AF [1,2]

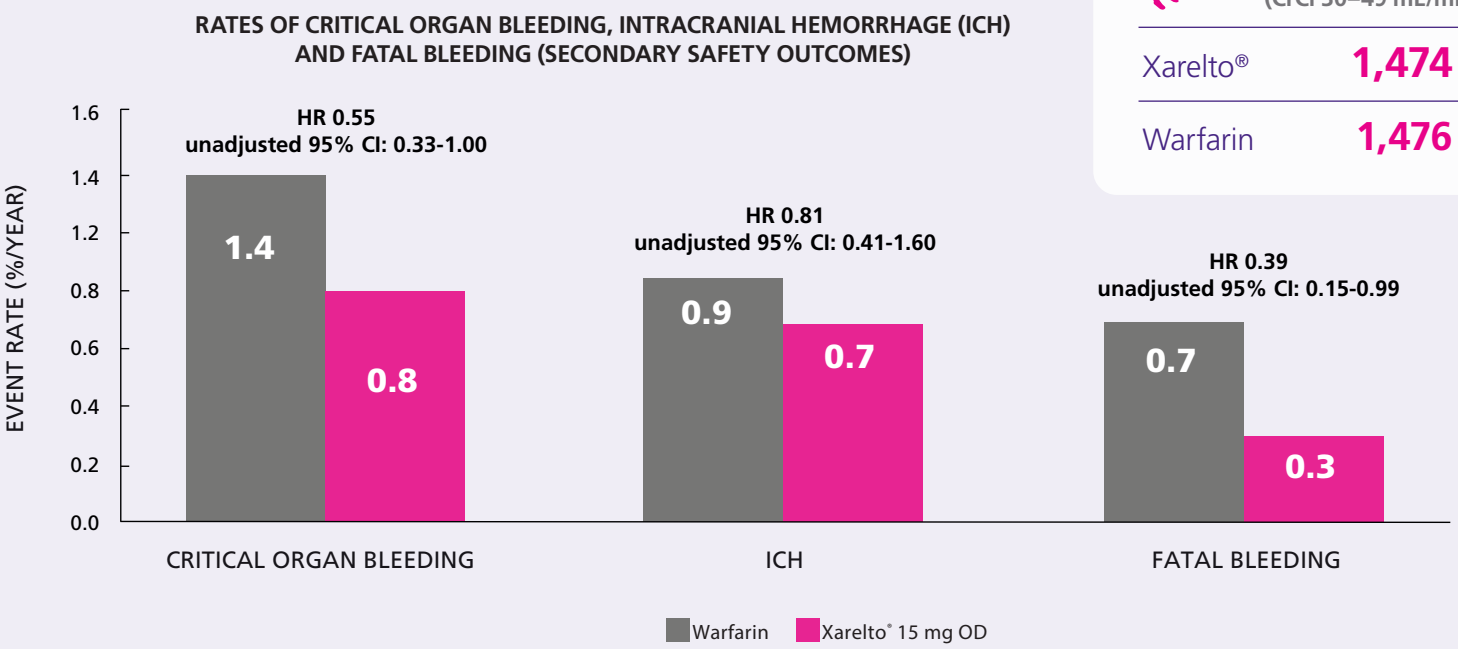
Patients with moderate renal impairment (CrCl 30–49 mL/min)

Xarelto®	1,474
Warfarin	1,476

Xarelto® bleeding profile in AF patients with moderate renal impairment (CrCl 30-49 mL/min)[1,2]

Principal safety endpoint:

- The rates of total major and clinically relevant nonmajor bleeding events were not statistically significantly different between Xarelto® vs. warfarin (17.82%/year vs. 18.28%/year [HR 0.98, unadjusted 95% CI: 0.84-1.14])



ROCKET AF [1,2]

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

Xarelto®	1,474
Warfarin	1,476

CrCl: creatinine clearance; OD: once daily; HR: hazard ratio; CI: confidence interval

† 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.[1,2]

Which Xarelto® dose is appropriate for your AF patient?

Patient diagnosed with atrial fibrillation (AF) and anticoagulation is appropriate as per CCS guidelines*

Does any of the following apply to your patient?

- ☐ Patient has clinically significant active bleeding (including in the GI tract)
- ☐ Patient has 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, spontaneous or acquired impairment of hemostasis)
- ☐ Patient is receiving concomitant systemic treatment with strong inhibitors of both CYP 3A4 and P-glycoprotein (such as ketoconazole, itraconazole, posaconazole, or ritonavir)
- ☐ Patient is receiving concomitant treatment with an anticoagulant, including:
  - UFH (except at doses used to maintain a patent central venous or arterial catheter)
  - LMWHs (such as enoxaparin and dalteparin)
  - Heparin derivatives (such as fondaparinux)
  - Oral anticoagulants (such as warfarin, dabigatran, apixaban, edoxaban)†
- ☐ Patient has a hepatic disease (including Child-Pugh Class B and C) associated with coagulopathy and clinically relevant bleeding risk
- ☐ Patient is pregnant or nursing

* The CCS guidelines for the management of AF recommend oral anticoagulation for most patients aged ≥65 years, and for younger patients with a CHADS score ≥1.[2]

No

Yes

Do not prescribe Xarelto®

Has your patient undergone (or is currently on antiplatelet therapy following) a recent PCI with stent placement?

No

What is your patient's renal function?

Normal renal function (CrCl >80 mL/min)	Mild renal impairment (CrCl 50-80 mL/min)	Moderate renal impairment (CrCl 30-49 mL/min)	Severe renal impairment (CrCl 15-<30 mL/min)	CrCl <15 mL/min
Xarelto® 20 mg OD	Xarelto® 20 mg OD	Xarelto® 15 mg OD	Xarelto® 15 mg OD* * Use with caution	Xarelto® is not recommended

Yes

What is your patient's renal function?

Normal renal function (CrCl >80 mL/min)	Moderate renal impairment (CrCl 30-49 mL/min)
Xarelto® 15 mg OD + $P2Y_{12}$ inhibitor for maximum 12 months after PCI with stent placement, followed by the standard dose of 20 mg OD Xarelto®	Xarelto® 10 mg OD + $P2Y_{12}$ inhibitor for maximum 12 months after PCI with stent placement, followed by the standard dose of 15 mg OD Xarelto®

Please see the back of this form for relevant warnings and precautions for use in patients with moderate renal impairment and patients undergoing PCI with stent placement. For the complete dosing information please consult the Product Monograph.

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

CCS: Canadian Cardiovascular Society; GI: gastrointestinal; UFH: unfractionated heparin; LMWH: low-molecular-weight heparin; CrCl: creatinine clearance; OD: once daily; PCI: percutaneous coronary intervention

† Patient on an oral anticoagulant (such as warfarin, dabigatran, apixaban, edoxaban) can receive Xarelto® except under circumstances of switching therapy to or from Xarelto®.[1]

Xarelto® rivaroxaban tablet

Important dosing considerations for your AF patient[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 is not recommended in patients with CrCl <15 mL/min.
- Patients who develop acute renal failure while on Xarelto® should discontinue such treatment.
- Xarelto® 15 mg and 20 mg tablets should be taken with food.

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]

Indications and clinical:

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 (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.

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, 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 and ASA in patients with CAD without 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.

AF: atrial fibrillation; CrCl: creatinine clearance; OD: once daily

References: 1. Xarelto® (rivaroxaban tablet) Product Monograph. Bayer Inc. September 20, 2019.
2. CCS guidelines for the management of atrial fibrillation. *CJC* 2018;34:1371-1392.

Xarelto® rivaroxaban tablet

- 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]

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.

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).

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® 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®.

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- 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 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
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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. Xarelto® (rivaroxaban tablet) Product Monograph. Bayer Inc. September 20, 2019. **2.** Fox K.A. *et al. Eur Heart J* 2011;32(19):2387-94.

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Xarelto® rivaroxaban tablet