Rivaroxaban (XARELTO) LOW-DOSE (2.5 mg twice daily)
Criteria for Use in
Chronic Coronary Artery Disease (CAD) or Peripheral Arterial Disease (PAD)
February 2019
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.

The Product Information should be consulted for detailed prescribing information. See the VA National PBM-MAP-VPE Monograph Addendum on this drug at the PBM INTERnet or PBM INTrAnet site for further information.

NOTE: This document provides clinical guidance for the use of LOW-DOSE (2.5 mg twice daily) rivaroxaban plus aspirin ONLY in the setting of CHRONIC, STABLE CAD and/or PAD.

- Additional PBM guidance is available for the use of rivaroxaban for its other indications (see https://vaww.cmopnational.va.gov/cmop/PBM/default.aspx):
  - Direct Oral Anticoagulants (DOAC) CFU and Algorithm for Nonvalvular Atrial Fibrillation
  - DOAC CFU and Algorithm for VTE Treatment
  - DOAC CFU for VTE prophylaxis in Orthopedic Surgery

Exclusion Criteria

If the answer to ANY item below is met, then the patient should NOT receive LOW-DOSE (2.5 mg twice daily) rivaroxaban.

- Indication for non-aspirin antiplatelet therapy including dual antiplatelet therapy (e.g., aspirin plus clopidogrel, ticagrelor, or prasugrel)
- Indication for therapeutic dose of an oral anticoagulant (e.g., atrial fibrillation, venous thromboembolism treatment, etc.) (See Issues for Consideration)
- Recent stroke (within 1 month) or any history of hemorrhagic stroke
- Heart failure (ejection fraction [EF] less than 40% or NYHA class III or IV symptoms)
- Estimated glomerular filtration rate (eGFR) less than 15 ml/min
- Known hepatic disease associated with coagulopathy
- History of hypersensitivity to rivaroxaban or aspirin
- Concurrent use of drugs that are strong dual inducers (e.g., rifampin, carbamazepine, phenytoin) or strong dual inhibitors (e.g., ketoconazole, itraconazole, rifonavir and ritonavir combinations, cobicistat) of P-glycoprotein and CYP3A4
- Pregnancy (i.e., known pregnancy or positive pregnancy test)
- Breastfeeding
- High risk of bleeding (not further defined in COMPASS trial; clinician discretion to be used)

Note: There was a significantly higher risk of major bleeding with rivaroxaban plus aspirin vs. aspirin alone in a population not at a high risk of bleeding. The most common sites for excess major bleeding were the gastrointestinal tract and skin/injection site. See Issues for Consideration, Summary from COMPASS.

Inclusion Criteria

1. STABLE CORONARY ARTERY DISEASE (CAD)
   a. The answers to one of the following must be fulfilled in order to meet criteria
      - Documented myocardial infarction in the past 20 years
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☐ Multivessel coronary disease* with symptoms or with history of angina (stable or unstable)
☐ Multivessel percutaneous coronary intervention
☐ Multivessel coronary artery bypass graft (CABG) surgery

*Multivessel coronary disease was defined in the COMPASS trial as stenosis of 50% or more in 2 or more coronary arteries or in 1 coronary territory if at least 1 other territory has been revascularized

b. **AND, patients with CAD must have additional risk factor(s):**

☐ Age 65 years or older (See Issues for Consideration, Age, for potential concerns for use in patients 75 years and older)

Or, if younger than 65 years, patients must have:
☐ Documented atherosclerosis or revascularization in two vascular beds (coronary vascular bed plus one additional vascular bed - e.g., aorta, brain, gastrointestinal tract, limbs, kidneys)

**OR 2 or more of the following:**
☐ Current smoker (within the past year)
☐ Diabetes
☐ Renal impairment (estimated GFR less than 60 ml/min)
☐ Atherosclerotic ischemic stroke at least one month ago

2. **STABLE PERIPHERAL ARTERIAL DISEASE (PAD)** (see Issues for Consideration, Age, for potential concerns for use in patients 75 years and older)

*The answers to one of the following must be fulfilled in order to meet criteria*

☐ Prior revascularization for the treatment of PAD
☐ History of limb or foot amputation due to PAD
☐ Symptomatic PAD, including history of intermittent claudication or critical limb threatening ischemia with objective clinical confirmation (i.e., ankle-brachial index [ABI] ratio measures, peripheral angiography)*

*For patients with carotid artery disease ONLY, or PAD without CAD, see Issues for Consideration, Summary from COMPASS

**Dosage and Administration** (see Prescribing Information for additional details)

- The recommended dose of rivaroxaban is 2.5 mg twice daily, taken with or without food, in combination with aspirin 75 - 100 mg daily.
- Dose adjustment based on renal function is not necessary (avoid use if eGFR is less than 15 ml/min).

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Monitoring

- Patients should be monitored for signs and symptoms of bleeding.

Issues for Consideration

- Summary from COMPASS:
  - **Overview:** FDA approval of low dose rivaroxaban in combination with aspirin to reduce major cardiovascular events was based on results from the COMPASS trial that evaluated over 27,000 patients with stable atherosclerotic CAD or PAD over about 2 years. PBM exclusion and inclusion criteria are based largely on the COMPASS population in effort to identify candidates where a proven favorable risk/benefit profile was shown. Much of the COMPASS study population was also receiving additional secondary prevention therapies (e.g., lipid lowering agents, anti-hypertensives).
  - **Efficacy:** The combination of low dose rivaroxaban plus aspirin was shown to reduce the primary composite outcome of cardiovascular death, stroke, and myocardial infarction compared to aspirin alone: 4.1% vs. 5.4%; hazard ratio (HR) (95% confidence interval [CI]) 0.76 (0.66-0.86); number needed to treat to prevent one event over 23 months = 77.
  - **Bleeding:** There was an increased risk of major bleeding with combination rivaroxaban plus aspirin vs. aspirin alone: 3.1% vs. 1.9%; HR 1.70 (1.40-2.05); number needed to harm to cause one event over 23 months = 83. The sites related to most of the excess bleeding events were the gastrointestinal tract and skin or injection site. Of note, the majority of the COMPASS population was receiving proton pump inhibitor (PPI) therapy either at baseline or as part of a separate analysis (ongoing). There was an excess number of fatal bleeds and symptomatic bleeds into a critical organ with combination treatment vs. aspirin alone, but the differences did not reach statistical significance.
  - **Age:** Though no significant interactions were noted, subgroup analysis of patients by age showed that patients 75 years of age and older appeared to have less benefit and a higher risk of major bleeding with rivaroxaban plus aspirin vs. aspirin alone. Patients less than 75 years of age maintained a significant benefit with combination therapy offset by increased major bleeding. Patients less than 65 years of age seemed to derive the most benefit with the combination for the efficacy and bleeding endpoints.
  - **PAD cohort:** The majority of patients in the PAD cohort also had co-existing CAD (66% of patients). The efficacy advantage of rivaroxaban plus aspirin over aspirin in PAD patients appeared to be driven by patients with PAD and co-existing CAD. The benefit of rivaroxaban plus aspirin in patients with PAD only (no co-existing CAD) is less clear. Patients with asymptomatic PAD were identified from the CAD cohort and included in the PAD analyses. All patients with asymptomatic PAD had co-existing CAD.
  - **Carotid artery disease:** Though the design was to evaluate PAD, approximately 26% of the population in the PAD cohort appeared to have carotid artery disease (defined as prior carotid endarterectomy or stent or asymptomatic carotid artery stenosis of at least 50%) as their only qualifying condition. A definitive benefit for the rivaroxaban plus aspirin strategy in this subpopulation cannot be concluded from the available data.
  - **Risk vs. benefit:** In COMPASS, there was a 1.2% increase in the risk of major bleeding and a 1.3% reduction in primary efficacy endpoint events. Balance potential harms and benefits when considering low dose rivaroxaban plus aspirin vs. aspirin alone (i.e., patients with a high thrombotic/ischemic and low bleeding risk).

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- **Antithrombotic therapy in PAD:** The 2016 American Heart Association/American College of Cardiology (AHA/ACC) Guidelines were published prior to the publication of the COMPASS trial and do not include recommendations for rivaroxaban. AHA/ACC recommend single antiplatelet therapy (aspirin or clopidogrel) to reduce the risk of MI, stroke and vascular death in patients with symptomatic PAD.

- **Antithrombotic therapy in stable CAD:** Daily aspirin is recommended indefinitely in nearly all patients with CAD. Dual antiplatelet therapy (DAPT, with aspirin plus a P2Y12 inhibitor) may be indicated in selected patients with chronic, stable cardiovascular disease. DAPT strategies have been shown to reduce cardiovascular events but increase bleeding (e.g., PEGASUS-TIMI 54, DAPT, CHARISMA). A careful risk-benefit should be performed. Patients with an indication for dual antiplatelet therapy (DAPT) with aspirin plus a P2Y12 inhibitor should not receive low dose rivaroxaban 2.5 mg for CAD/PAD risk reduction. It is unknown how outcomes using strategies containing a P2Y12 inhibitor compare to the approved rivaroxaban plus aspirin combination, as P2Y12 inhibitors (e.g., clopidogrel, ticagrelor, or prasugrel) were not evaluated in the COMPASS trial.

- **Indication for therapeutic doses of anticoagulant:** Patients with indications for therapeutic doses of anticoagulants (e.g., stroke prevention in atrial fibrillation, venous thromboembolism treatment, etc.) should NOT be prescribed low dose rivaroxaban 2.5 mg twice daily for cardiovascular risk reduction. Higher doses of rivaroxaban were used in the studies to establish efficacy in patients requiring therapeutic anticoagulation.

- **Patients with heart failure:** In COMPASS, patients could have qualified for the CAD cohort with heart failure as a risk factor, though patients with an EF of less than 30% were excluded from the trial. PBM CFU were modified such that: 1) heart failure is not included as a qualifying risk factor for CAD patients; and 2) patients with an EF less than 40% are excluded from therapy. The modifications were based on results from the COMMANDER HF study that showed no benefit of the same low dose of rivaroxaban in patients with heart failure in patients with an ejection fraction less than 40% (N Engl J Med. 2018;379:1332-42).

- Based on results from COMPASS, patients who may benefit from intensifying antithrombotic therapy (adding rivaroxaban to aspirin) may be those with high cardiovascular risk, low bleeding risk, age less than 75 years, and PAD patients who have co-existing CAD.

### Renewal Considerations

- Periodically re-evaluate bleeding risk: patient ischemic/thrombotic benefit ratio with continued combination therapy.

### References:


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