CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

RIVAROXABAN (XARELTO — BAYER INC.)
Indication: Coronary artery disease with or without peripheral artery disease

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that rivaroxaban should be reimbursed in combination with acetylsalicylic acid (75 mg to 100 mg) for the prevention of stroke, myocardial infarction, and cardiovascular death, and for the prevention of acute limb ischemia and mortality in patients with concomitant coronary artery disease and peripheral artery disease if the following condition is met:

Condition
- For patients with concomitant coronary artery disease and peripheral artery disease, as defined in the Implementation Considerations.

Service Line:	CADTH Drug Reimbursement Recommendation
Version:	Final
Publication Date:	November 2018
Report Length:	7 Pages

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Indication: Coronary artery disease with or without peripheral artery disease.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that rivaroxaban be reimbursed in combination with acetylsalicylic acid (ASA; 75 mg to 100 mg) for the prevention of stroke, myocardial infarction, and cardiovascular death, and for the prevention of acute limb ischemia and mortality in patients with concomitant coronary artery disease (CAD) and peripheral artery disease (PAD) if the following condition is met:

Condition

- For patients with concomitant CAD and PAD as defined in the Implementation Considerations.

Reasons for the Recommendation

1. One double-blind, randomized controlled trial (RCT) (COMPASS; N = 27,395) in patients with stable CAD and/or PAD who predominantly had a history of CAD with normal renal function and no history of stroke, and who were not at high risk of bleeding, demonstrated that the combination of rivaroxaban 2.5 mg twice daily and ASA 100 mg once daily statistically significantly reduced the risk of the composite outcome of stroke, myocardial infarction, and cardiovascular death as compared with ASA alone (hazard ratio [HR]: 0.76; 95% confidence interval [CI], 0.66 to 0.86; $P < 0.001$]) over 23 months. Furthermore, the pre-specified subgroup analysis of patients with concomitant CAD and PAD found that the combination of rivaroxaban 2.5 mg twice daily and ASA had a numerically greater benefit over ASA alone for the same composite end point (HR: 0.67; 95% CI, 0.52 to 0.87).
2. The manufacturer-provided price for rivaroxaban 2.5 mg is $1.44 per tablet. The submitted cost-utility analysis suggested that the combination of rivaroxaban 2.5 mg twice daily and low dose ASA, compared with ASA alone, is most cost-effective in patients with concomitant CAD and PAD, with an incremental cost-effectiveness ratio (ICER) of $17,764 per quality-adjusted life-year (QALY) gained. Although rivaroxaban has a Health Canada indication for use in combination with 75 mg to 100 mg ASA for the prevention of stroke, myocardial infarction, and cardiovascular death, and for the prevention of acute limb ischemia and mortality in patients with CAD with or without PAD, a cost-effectiveness analysis specific to patients with CAD alone was not provided; hence, it is unknown if rivaroxaban in combination with ASA would be considered cost-effective for patients with CAD alone.

Implementation Considerations

- Patients with CAD are defined as having one or more of the following:
  - myocardial infarction within the last 20 years
  - multi-vessel coronary disease (i.e., stenosis of ≥ 50% in two or more coronary arteries, or in one coronary territory if at least one other territory has been revascularlized) with symptoms or history of stable or unstable angina
  - multi-vessel percutaneous coronary intervention
  - multi-vessel coronary artery bypass graft surgery
  - **and** meet at least one of the following criteria:
    - aged 65 years or older, or
    - aged younger than 65 years with documented atherosclerosis or revascularization involving at least two vascular beds (coronary and other vascular) or at least two additional risk factors (current smoker, diabetes mellitus, estimated glomerular filtration rate < 60 mL/min, heart failure, non-lacunar ischemic stroke 1 month or more ago).

- Patients with PAD are defined as having one or more of the following:
  - previous aorto-femoral bypass surgery, limb bypass surgery, or percutaneous transluminal angioplasty revascularization of the iliac or infrainguinal arteries
  - previous limb or foot amputation for arterial vascular disease

  - history of intermittent claudication and one or more of the following: 1) an anklebrachial index less than 0.90, or 2) significant peripheral artery stenosis (≥ 50%) documented by angiography or by duplex ultrasound
  - previous carotid revascularization or asymptomatic carotid artery stenosis greater than or equal to 50%, as diagnosed by duplex ultrasound or angiography.

- Rivaroxaban should not be reimbursed for patients who have CAD or PAD alone or in patients with any one of the following characteristics:
  - at high risk of bleeding
  - a history of stroke within one month of treatment initiation or any history of hemorrhagic or lacunar stroke
  - severe heart failure with a known ejection fraction less than 30% or New York Heart Association class III or IV symptoms
  - an estimated glomerular filtration rate less than 15 mL/min
  - require dual antiplatelet therapy, other non-ASA antiplatelet therapy, or oral anticoagulant therapy.

- It is estimated that a substantial number (~295,000) of Canadians have concomitant CAD and PAD. Therefore, even though rivaroxaban is cost-effective in patients with concomitant CAD and PAD at the submitted price, the budget impact for CADTH-participating drug plans is likely to be considerable. Consequently, a lower price would further increase the cost-effectiveness of rivaroxaban in patients with concomitant CAD and PAD and increase affordability of this treatment.

Discussion Points

- Although the COMPASS trial included patients with CAD and/or PAD, the Health Canada—approved indication for rivaroxaban 2.5 mg twice daily is for use in patients with CAD with or without PAD; PAD alone is currently not an approved indication.
- Generalizability of the COMPASS trial results to patients with CAD and PAD who do not meet that trial's eligibility criteria is uncertain. For example, there is insufficient evidence to determine how the COMPASS trial results apply to patients without a history of myocardial infarction or cardiac revascularization, those with abnormal renal function, and those with a history of stroke.
- Major and minor bleeding events were more common with rivaroxaban/ASA compared with ASA alone in COMPASS. CDEC discussed that the rates of fatal bleeding, fatal and non-fatal intracranial bleeding, and non-fatal critical organ bleeding in the trial were relatively low and similarly distributed between treatment groups. The benefit to risk of treatment with rivaroxaban/ASA, as compared with ASA alone, in patients with concomitant CAD and PAD should be considered on an individual patient basis.
- The COMPASS trial was stopped prematurely because it met the pre-specified criteria for early discontinuation based on efficacy. Patients in COMPASS received a median duration of treatment of approximately two years. Given the chronic nature of stable CAD and PAD, the long-term efficacy and safety of rivaroxaban/ASA is not well-established. As well, the optimal duration of therapy with rivaroxaban/ASA is unknown.
- It is uncertain whether rivaroxaban/ASA has any added benefit on health-related quality of life (HRQoL) or daily function for patients with concomitant CAD and PAD as compared with ASA alone because of limited or no evidence for these outcomes in the COMPASS trial.
- There is uncertainty with respect to the comparative efficacy and safety of rivaroxaban/ASA versus dual antiplatelet therapies used for the treatment of concomitant CAD and PAD, based on a manufacturer-provided network meta-analysis (NMA).

Background

Rivaroxaban is a direct acting oral anticoagulant that inhibits factor Xa, which plays a key role in the cascade of blood coagulation. Rivaroxaban is indicated for the prevention or treatment of thrombus formation in various indications. The current indication considered was for the use of rivaroxaban in combination with 75 mg to 100 mg ASA for the prevention of stroke, myocardial infarction, and cardiovascular death, and for the prevention of acute limb ischemia and mortality in patients with CAD with or without PAD.

Summary of Evidence Considered by CDEC

The committee considered the following information prepared by the CADTH Common Drug Review (CDR): a systematic review of RCTs of rivaroxaban in combination with ASA, a manufacturer-provided indirect comparison (NMA), and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience in treating patients with CAD and PAD, and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

The Cardiac Health Foundation of Canada provided input for this submission. Patient perspectives were obtained from telephone interviews. The following is a summary of key input from the perspective of the patient group(s):

- Patients expressed that they have ongoing concerns and stress around their future risk for cardiovascular events, including heart attack and/or death. They were also concerned about disease complications and limitations in function (e.g., inability to walk due to cramps in leg).
- Patients indicated that their conditions were well-managed with current medications; however, they stated that poor management of disease may lead to heart attacks or even death, requiring patients to be diligent about taking their medications. Patients noted they would like to manage their condition and symptoms with fewer pills, ideally one pill per day.
- The patient group was not able to consult with any patients on rivaroxaban or rivaroxaban/ASA specifically, therefore no information was provided on expectations for combination rivaroxaban/ASA.

Clinical Trials

The CDR systematic review included one double-blind RCT (COMPASS) that included patients with CAD and/or PAD. COMPASS (N = 27,395; mean age, 68 years; 78% male) compared the combination of rivaroxaban 2.5 mg twice daily and ASA 100 mg once daily with ASA 100 mg once daily in patients with stable CAD and/or PAD who predominantly had a history of myocardial infarction, cardiac revascularization, normal renal function, and who had no history of stroke.

The trial was stopped early (at the first of two planned interim analysis time points) when the mean duration of treatment was approximately two years, when the pre-specified stopping criteria were met. As the trial was stopped early, the long-term efficacy and safety of this combination is not clear. Patients at high risk of bleeding were excluded from COMPASS; however, no specific criteria for evaluating bleeding risk were applied in the trial.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the committee discussed the following:

- cardiovascular death
- stroke
- myocardial infarction
- all-cause mortality
- limb amputations
- patient function
- HRQoL
- adverse events (AEs), including major and minor bleeding events, among others.

The primary outcome in COMPASS was major adverse cardiovascular events (composite of stroke, myocardial infarction, and cardiovascular death). The primary analysis population was in the full COMPASS population (i.e., patients with CAD and/or PAD). Subgroup analyses were conducted in patients with CAD only, PAD only, and concomitant CAD and PAD.

Efficacy

- Fewer patients in the rivaroxaban/ASA group experienced the primary outcome compared with those in the ASA group (4.1% versus 5.4%). Rivaroxaban/ASA reduced the risk of the primary outcome compared with ASA alone (HR: 0.76; 95% CI, 0.66 to 0.86).
- It is uncertain what the effect of rivaroxaban/ASA is on HRQoL and patient function is because of limited or no data for these outcomes.
- The risk of the secondary composite outcome of myocardial infarction, ischemic stroke, acute limb ischemia, and coronary heart disease death was lower in the rivaroxaban/ASA group compared with ASA alone (HR: 0.72, 95% CI, 0.63 to 0.83), and the risk was also lower for the composite of myocardial infarction, ischemic stroke, acute limb ischemia, cardiovascular death (HR: 0.74, 95% CI, 0.65 to 0.85). These composite outcomes were adjusted for multiplicity.
- For the outcome of all-cause mortality, the HR for the comparison of rivaroxaban/ASA to ASA was 0.82 (95% CI, 0.71 to 0.96). The results for all-cause mortality should be interpreted with caution because the statistical comparison between rivaroxaban/ASA versus ASA alone could not be considered statistically significant based on the hierarchical analysis plan used to adjust for multiple comparisons.
- The HRs for the primary outcome in the rivaroxaban/ASA group compared with the ASA group for the subgroups were: CAD only (HR: 0.77; 95% CI, 0.66 to 0.91), PAD only (HR: 0.89; 95% CI, 0.55 to 1.44), and concomitant CAD and PAD (HR: 0.67; 95% CI, 0.52 to 0.87). Subgroup analyses were not adjusted for multiplicity (conducted outside the planned statistical hierarchy) and should be interpreted with this in mind.

Harms (Safety)

- The proportion of participants experiencing AEs was higher in the rivaroxaban/ASA group (14.7%) compared with ASA alone (13.8%) in the overall CAD and/or PAD population of COMPASS.
- The proportion of patients experiencing serious AEs ([redacted] versus [redacted]) and withdrawals due to AEs (3.4% versus 2.6%) was also higher for rivaroxaban/ASA compared with ASA.
- Major bleeding was more common for rivaroxaban/ASA-treated patients (3.1%) compared with patients treated with ASA alone (1.9%) (HR: 1.70; 95% CI, 1.40 to 2.05). Minor bleeding was also more common in the rivaroxaban/ASA group (9.0%) compared with the ASA group (5.3%).
- The increased risk of major bleeding in the rivaroxaban/ASA group was contributed to largely by an increased occurrence of gastrointestinal bleeding. Occurrences of fatal bleeding, fatal and non-fatal intracranial bleeding, and non-fatal critical organ bleeding were relatively uncommon and similarly distributed between treatment groups.

Indirect Treatment Comparisons

- A manufacturer-provided indirect comparison based on NMA compared rivaroxaban/ASA [redacted] with ASA alone as the central comparator. There was a high degree of heterogeneity across studies in the NMA, including differences in populations, duration of follow-up, and outcome definitions. There is uncertainty in the robustness of the analysis. In the full population of persons with CAD and/or PAD, the results of the NMA suggested that rivaroxaban/ASA was more efficacious than ASA alone [redacted]
- Results from the manufacturer-provided NMA also suggested that rivaroxaban/ASA may increase the risk of bleeding events, especially major bleeding, as compared with ASA alone. Harms comparisons versus other analyzed treatment regimens were [redacted]

Cost and Cost-Effectiveness

Rivaroxaban 2.5 mg is administered twice daily. It is priced at $1.44 per tablet.

The manufacturer did not provide information to address the CAD alone subgroup, as such no comment regarding the cost-effectiveness of rivaroxaban in this population can be made. The manufacturer's request for reimbursement was in a more limited patient population than the population of the COMPASS trial, specifically patients with concomitant CAD and PAD, which comprised 17.9% of the total patient population in the COMPASS trial.

The manufacturer submitted a cost-utility analysis over a 20-year time horizon (the manufacturer suggested that this is essentially a lifetime horizon given that the average age of patients within the COMPASS trial was 68 years). The analysis was conducted from the perspective of a Canadian public health care payer. The analysis was conducted for both the COMPASS trial population and the subgroup of patients with concomitant CAD and PAD (the requested reimbursement population). The base analysis compared rivaroxaban/ASA with ASA alone.

For a patient population with concomitant CAD and PAD, rivaroxaban would be more costly and would lead to greater QALYs, resulting in an ICER in the base-case probabilistic analysis of $17,764 per QALY. The probability that rivaroxaban/ASA was cost-effective at a threshold of $50,000 per QALY was 98%. For a patient population with the characteristics of the total COMPASS trial population (CAD and/or PAD), rivaroxaban would be more costly and would lead to greater QALYs, resulting in an ICER in the base-case probabilistic analysis of $31,758.

CADTH identified the following key limitations with the manufacturer's submitted economic model:

- The analysis is provided for the COMPASS trial population as a whole and for patients with concomitant PAD and CAD as a subgroup. A preferred approach would be to conduct stratified analysis (CAD alone, PAD alone, and CAD with PAD). The failure to provide analyses for CAD alone limits the assessment for the full indication.
- The economic evaluation is reliant on data from the COMPASS trial. This impacts generalizability in terms of the appropriateness of extrapolation to a wider patient population; i.e., beyond those with long-term CAD. In addition, given the higher rates of major and minor bleeds, the exclusion of patients with high bleeding risks, the clinical effectiveness (benefit-to-harm ratio), and cost-effectiveness of rivaroxaban in this patient population is unknown. In addition, patients with an indication for dual antiplatelet therapy were also excluded from the study. Furthermore, the COMPASS trial was stopped early at approximately two years due to benefit of rivaroxaban/ASA over ASA for the primary outcome. As such, the long-term efficacy and safety of rivaroxaban/ASA is not well-established in this chronic disease.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Ms. Heather Neville, Mr. Allen Lefebvre, Dr. Rakesh Patel, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

October 17, 2018 Meeting

Regrets

One CDEC member did not attend.

Conflicts of Interest

None