CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

Rivaroxaban (XARELTO)

(Bayer Inc.)

Indication: In combination with 75 mg to 100 mg acetylsalicylic acid (ASA), 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).

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

ALI	acute limb ischemia
ASA	acetylsalicylic acid
CAD	coronary artery disease
CDR	CADTH Common Drug Review
CV	cardiovascular
DAPT	dual antiplatelet therapy
DVT	deep vein thrombosis
EQ-5D	EuroQol 5-Dimensions questionnaire
ICER	incremental cost-effectiveness ratio
ICH	intracranial hemorrhage
IS	ischemic stroke
ISTH	International Society on Thrombosis and Haemostasis
MI	myocardial infarction
PAD	peripheral artery disease
QALY	quality-adjusted life-year
VTE	venous thromboembolism

Table 1: Summary of the Manufacturer's Economic Submission

Drug Product	Rivaroxaban (Xarelto)
Study Question	Is rivaroxaban + acetylsalicylic acid (ASA) cost-effective when compared with ASA only in patients with CAD and/or PAD? Is rivaroxaban + ASA cost-effective when compared with ASA only in patients with CAD and PAD?
Type of Economic Evaluation	Cost-utility analysis
Target Population	• Patients with CAD and/or PAD • Patients with CAD and PAD (reimbursement request)
Treatment	Rivaroxaban 2.5 mg + ASA daily
Outcome	Quality-adjusted life-years (QALYs)
Comparators	ASA Secondary comparators: • clopidogrel • clopidogrel + ASA • ticagrelor + ASA
Perspective	Health care system perspective
Time Horizon	20 years (assumed to be lifetime)
Results for Base Case	• For all patients with CAD and/or PAD: the incremental cost per QALY gained for rivaroxaban + ASA versus ASA alone was $29,476 • For all patients with CAD and PAD: the incremental cost per QALY gained for rivaroxaban + ASA versus ASA alone was $15,341
Key Limitations	• The review was initiated pre-NOC, where the anticipated NOC was [redacted], while the final NOC is for patients with CAD, with or without PAD. The manufacturer has provided information only on CAD + PAD (reimbursement request), but not for CAD only. • The manufacturer presented results of their economic evaluation that are not stratified. The three subgroups of interest are: those with CAD alone, PAD alone, or both CAD and PAD. As such, the cost-effectiveness for patients with CAD alone (and PAD alone) is unknown. • As the results of the analysis are based closely on the COMPASS study, the results are most applicable to patients with long-term CAD (approximately 62% of participants in COMPASS had a previous MI with a mean duration of 7 years since the most recent MI). The generalizability of the results to other populations, such as patients with high bleeding risks or who have an indication for DAPT, is unknown, as those patients were excluded from COMPASS. • Major bleeds were included in the economic model, where rivaroxaban + ASA had a higher rate compared with ASA alone. Given the increased chance of major and minor bleeding, bleeding risk needs to be carefully assessed when considering rivaroxaban in patients with CAD and/or PAD. • COMPASS was stopped early at approximately 2 years due to the benefit of rivaroxaban + ASA over ASA alone for the primary outcome. As such, the long-term efficacy and safety of rivaroxaban + ASA are not well established in this chronic disease.
CDR Estimate(s)	• There were no limitations requiring re-estimation. • CDR was unable to provide results for those with CAD alone.

ASA = acetylsalicylic acid; CAD = coronary artery disease; CDR = CADTH Common Drug Review; DAPT = dual antiplatelet therapy; MI = myocardial infarction; NOC = Notice of Compliance; PAD = peripheral artery disease; QALY = quality-adjusted life-year.

Drug	Rivaroxaban (Xarelto)
Indication	In combination with 75 mg to 100 mg acetylsalicylic acid (ASA), 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)
Reimbursement Request	In combination with low-dose ASA, for the prevention of stroke, myocardial infarction, and cardiovascular death in patients with concomitant CAD and PAD
Dosage Form(s)	Film-coated tablet (2.5 mg, 10 mg, 15 mg, and 20 mg)
NOC Date	September 14, 2018
Manufacturer	Bayer Inc.

Executive Summary

Background

Rivaroxaban is a direct-acting oral anticoagulant that has previously been approved for Canada in doses of 10 mg, 15 mg, and 20 mg for the following indications: prevention of venous thromboembolic events (VTE) in patients who have undergone elective total hip replacement or total knee replacement surgery; treatment of VTE (deep vein thrombosis [DVT], pulmonary embolism) and prevention of recurrent DVT and pulmonary embolism; and the prevention of stroke and systemic embolism in patients with atrial fibrillation, for whom anticoagulation is appropriate.[1] The current submission relates to the use of rivaroxaban for patients with coronary artery disease (CAD) with or without peripheral artery disease (PAD).[2] CADTH notes that the anticipated Notice of Compliance (NOC) was for [redacted], as reflected in the manufacturer's economic submission. Following the final NOC, the manufacturer did not provide additional information to address the CAD-alone subgroup; as such, no comment can be provided regarding the cost-effectiveness of rivaroxaban in this population.

The submission centres around the COMPASS clinical trial that compared rivaroxaban 2.5 mg twice daily plus ASA with ASA alone.[3] Rivaroxaban 2.5 mg is priced at $1.44 per tablet.[2] The current request for reimbursement is for a more limited patient population than the COMPASS trial patients with concomitant CAD and PAD. Those patients comprised 17.9% of the total patient population in the COMPASS trial.

CADTH has reviewed rivaroxaban for a number of indications: for the prevention of VTE in patients who have undergone elective total hip or total knee replacement surgery (2008);[4] for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (2012);[5] for the treatment of DVT in patients without symptomatic pulmonary embolism (2012);[6] and for the prevention of recurrent DVT and pulmonary embolism (2014).[7] The CADTH Canadian Drug Expert Committee (CDEC) recommended the reimbursement of rivaroxaban for these indications, with conditions.

The manufacturer has submitted a cost-utility analysis over a 20-year time horizon (the manufacturer suggests this is essentially a lifetime horizon, given that the average age of patients within the COMPASS trial was 68).[8] The analysis was conducted from the perspective of a Canadian public health care payer. An analysis was conducted for both the COMPASS trial population[3] and the subgroup of patients with concomitant CAD and PAD (reimbursement population). The base analysis compared rivaroxaban plus ASA with ASA alone. The manufacturer has also provided an analysis comparing rivaroxaban plus ASA with dual antiplatelet therapy (DAPT). However, the manufacturer provided arguments that rivaroxaban plus ASA represents a different place in therapy than DAPT, and such analyses are not relevant from a reimbursement perspective.

The submission is based on a Markov model, where patients enter the model in an "event-free" state.[8] The model then follows the cohort of patients, allowing them to remain event-free or develop their first acute event (myocardial infarction [MI], ischemic stroke [IS], or intracranial hemorrhage [ICH]), the "first event (acute)" state. Subsequently, patients can move into a post-event state ("first event [post-acute]"), or can develop their second acute event ("second event [acute]") and then enter the second post-acute event state ("second event [post-acute]"). Patients are assumed to have a maximum of two acute events. While in any of these states, patients can also experience other key outcomes that are not modelled as distinct states (major non-fatal extracranial bleed, minor bleed, acute limb ischemia [ALI]; minor amputation, major amputation, and VTE), which have associated costs and disutilities. Patients can also die (enter the death state) during any cycle, with mortality varying by event history. The model uses a cycle length of three months which, it is argued, allows the capture of both the short- and long-term consequences of events.

For a patient population with concomitant CAD and PAD (reimbursement request), rivaroxaban would be both more costly and lead to more quality-adjusted life-years (QALYs), resulting in an incremental cost per QALY gained (incremental cost-effectiveness ratio [ICER]) in the base-case probabilistic analysis of $17,764 per QALY. The manufacturer reported the results of the analysis comparing rivaroxaban plus ASA with clopidogrel plus ASA. That analysis suggests that rivaroxaban plus ASA is dominant over DAPT for the trial population and cost-effective for patients with concomitant CAD and PAD. However, the manufacturer provided arguments that rivaroxaban plus ASA represents a different place in therapy than DAPT, and such analyses are not relevant from a reimbursement perspective. For a patient population with the characteristics of the total COMPASS trial population (CAD and/or PAD), rivaroxaban would be both more costly and lead to greater QALYs, resulting in an ICER in the base-case probabilistic analysis of $31,758.

Summary of Identified Limitations and Key Results

This was a well-designed economic evaluation. In instances where assumptions were required, the manufacturer adopted assumptions which were less favourable to rivaroxaban.

One weakness was noted in the handling of heterogeneity. The analysis was provided for the COMPASS trial population as a whole and for patients with concomitant PAD and CAD as a subgroup. As identified within the recently revised CADTH *Guidelines for Economic Evaluation of Health Technologies: Canada — 4th Edition*,[9] the results for the trial population as a whole are likely biased in instances where results will vary by patient characteristic.[9] A preferred approach would be to conduct a stratified analysis (CAD alone, PAD alone, and CAD with PAD). This would provide more relevant information for decision-makers. By weighting the strata-specific results, it would also facilitate a less biased

estimate for the total population. As the manufacturer is applying for reimbursement solely for those with concomitant CAD and PAD, the failure to provide analyses of CAD alone limits the assessment for the full indication, which may be of interest to decision-makers.

A further limitation of the analysis relates to the reliance 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 and the exclusion of patients with high bleeding risks, the clinical effectiveness (benefit-to-harm ratio) and cost-effectiveness of rivaroxaban in this patient population are unknown. In addition, patients with an indication for DAPT were also excluded from the study. Furthermore, the COMPASS trial was stopped early at approximately two years due to the benefit of rivaroxaban plus ASA over ASA alone for the primary outcome. As such, the long-term efficacy and safety of rivaroxaban plus ASA are not well established in this chronic disease.

Conclusions

The manufacturer provided a well-conducted economic evaluation that provides strong evidence to suggest that rivaroxaban will be cost-effective for a population of patients with concomitant CAD and PAD, assuming a decision-maker would be willing to pay at least $17,764 per QALY gained. For the full COMPASS population (patients with CAD and/or PAD), the incremental cost per QALY was $31,758.

Information on patients with CAD alone was not provided and, as such, the cost-effectiveness of rivaroxaban in this subgroup and the full indication is unknown.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer has submitted a cost-utility analysis with results generated from a Markov model programmed within Microsoft Excel.[8] The analysis used a 20-year time horizon with a three-month cycle length. The analysis was conducted from the perspective of a Canadian public health care payer.

The model structure incorporates the management and consequences of coronary artery disease (CAD) and peripheral arterial disease (PAD) (Figure 1). The cohort of patients enters the model in the "event-free" state. Possible transitions are as follows:

- In subsequent cycles, patients in the event-free state can remain in this state (have no event), can experience an acute event (myocardial infarction [MI], ischemic stroke [IS], or intracranial hemorrhage [ICH]), transition into the "first event (acute)" state, or can die (enter the death state).
- After entering the first event (acute) state, patients can either have no event (move to the "first event [post-acute]" state), can have a subsequent event (transition to the "second event [acute]" state), or can die (enter the death state).
- Similarly, from the first event (post-acute) state, patients can either have no event (remain in the first event [post-acute] state), have a subsequent event (transition to the second event [acute] state), or can die (enter the death state).
- After entering the second event (acute) state, patients can either have no event (move to the "second event [post-acute]" state), or they can die (enter the death state). No subsequent events are allowed.
- Similarly, from the second event (post-acute) state, patients can either have no event (remain in the second event [post-acute] state), or they can die (enter the death state). No subsequent events are allowed.
- Death is an absorbing state; patients remain there once they enter the state.

The occurrence of the acute events (MI, IS, and ICH) has effects in terms of costs and disutilities and, in addition, affects the probability of subsequent events and death. Within each state other than death, patients can experience other key outcomes, which were modelled in terms of allowance for their costs and disutilities. Other key outcomes were major non-fatal extracranial bleed, minor bleed, acute limb ischemia (ALI), minor amputation, major amputation, and venous thromboembolism (VTE). Other key outcomes, however, are assumed not to affect the probability of subsequent events and death.

The primary analysis compared rivaroxaban plus ASA with ASA alone. Transition probabilities for ASA for this analysis came mainly from the COMPASS trial.[3] For the first four years of the model, transition probabilities for each of the events were derived from the COMPASS trial, varying by:

- type of event (IS, MI, and ICH)
- population (overall COMPASS population or concomitant CAD and PAD)

- previous events: no previous (transition to first event [acute]); or previous MI, previous IS, or previous ICH (transition to second event [acute])
- time since first event (up to three months, greater than three months); applies to second event only.

In addition, the probability of events after four years was increased by 3% per annum to reflect the effect of age on the risk of an event, as identified by the Reduction of Atherothrombosis for Continued Health (REACH) registry.[10]

The probability of death is a combination of cardiovascular mortality and general population mortality. Cardiovascular mortality is derived from the COMPASS trial, while general population mortality is based on Canadian mortality and adjusted to exclude cardiovascular mortality.[11] In addition, the probability of cardiovascular mortality after four years was increased by 5% per annum to reflect the effect of age on the risk of an event, as identified by the REACH registry.[10]

The impact of rivaroxaban plus ASA on the transition probabilities for events (MI, IS, ICH, and first and second events and cardiovascular death) was incorporated by using hazard ratios from the COMPASS trial that were specific to the patient population considered.[1] Hazard ratios were assumed to remain constant over time.[12]

The probabilities of other key outcomes and the impact of rivaroxaban plus ASA were modelled using the same approach as key events.

Costs included within the analysis were drug costs (rivaroxaban), event-free state costs (incorporating the costs of patient management) and the costs of key events and other key outcomes. Costs were derived from appropriate Canadian sources and were consistent with previous study estimates.[13-21] The costs of ASA were not included, as it was argued that those costs are not borne by public health care plans.

Utility values were primarily obtained from the COMPASS study, which used the EuroQol 5-Dimensions (EQ-5D) questionnaire.[3,22] The EQ-5D baseline data were used for the event-free health state. A multivariate regression analysis of the COMPASS EQ-5D data from COMPASS was conducted to estimate utility values for the key events (MI, IS, and ICH) and disutilities for the other key outcomes (limb and bleeding events). The analysis assumed that utility values were not affected by treatment. For patients experiencing a second event, the patient would have the utility value associated with the lower of the associated utility scores.

A secondary analysis that was provided within an appendix compared rivaroxaban plus ASA with clopidogrel (alone and in combination with ASA) using clinical data from a provided network meta-analysis. However, the manufacturer provided the following justification for not considering these analyses within the submission:

- Clopidogrel without ASA is recommended for patients with CAD who are intolerant to ASA. As rivaroxaban is to be used in combination with ASA, this is not an appropriate comparator.
- Within COMPASS, the requirement for dual antiplatelet therapy (DAPT) was an exclusion factor.[3] Thus, both clopidogrel plus ASA are not direct comparators.

Manufacturer's Base Case

The manufacturer's results found that rivaroxaban plus ASA was estimated to be more costly and produce a greater number of QALYs than ASA alone (Table 2).

In the overall COMPASS population and in a deterministic analysis, rivaroxaban plus ASA was associated with incremental costs of $9,588 with 0.33 incremental QALYs, leading to an incremental cost-effectiveness ratio (ICER) of $29,476. Incremental costs were primarily due to increased drug costs due to a longer time spent in the event-free state, although these were partially offset by reduced costs of ongoing management, cardiovascular events, and other key outcomes. The probabilistic analysis reported similar results, with an ICER of $31,758.

In the population for which reimbursement is requested (concomitant CAD and PAD) and in a deterministic analysis, rivaroxaban plus ASA was associated with incremental costs of $9,909 with 0.65 incremental QALYs, leading to an ICER of $15,341. The incremental costs were due primarily to increased drug costs and ongoing management due to a longer time spent in the event-free state, although these were partially offset by the reduced costs of cardiovascular events and other key outcomes. The probabilistic analysis reported similar results, with an ICER of $17,764.

Within the reimbursement population, the probability that rivaroxaban plus ASA was cost-effective with a threshold of $30,000 per QALY was 87%; for $50,000 per QALY, the probability was 98% (Figure 2). The CDR pharmacoeconomic reviewer reran the probabilistic analysis for the reimbursement population and obtained broadly similar results: an ICER of $17,789.

The manufacturer provided supplemental analyses comparing rivaroxaban plus ASA with clopidogrel and clopidogrel plus ASA (Table 16, Table 17). However, the manufacturer provides arguments that rivaroxaban plus ASA represents a different place in therapy than DAPT, and such analyses are not relevant from a reimbursement perspective.

Table 2: Summary of Results of the Manufacturer's Base Case

	Total Costs ($)	Incremental Cost of Rivaroxaban + ASA ($)	Total QALYs	Incremental QALYs for Rivaroxaban + ASA	Incremental Cost per QALY
DETERMINISTIC ANALYSES					
Overall COMPASS Population (CAD and/or PAD)					
ASA	26,319		9.86		
Rivaroxaban + ASA	35,908	9,588	10.19	0.33	29,476
Concomitant CAD + PAD					
ASA	36,130		8.68		
Rivaroxaban + ASA	46,039	9,909	9.32	0.65	15,341
PROBABILISTIC ANALYSES (Manufacturer's Submission)					
Overall COMPASS Population					
ASA	NR		NR		
Rivaroxaban + ASA	NR	10,010	NR	0.315	31,758
Concomitant CAD + PAD					
ASA	NR		NR		
Rivaroxaban + ASA	NR	10,897	NR	0.613	17,764
PROBABILISTIC ANALYSES (CDR Reanalysis)					
Overall COMPASS Population					
ASA	26,317		9.87		
Rivaroxaban + ASA	36,253	9,936	10.18	0.318	31,238
Concomitant CAD + PAD					
ASA	36,096		8.68		
Rivaroxaban + ASA	46,963	10,867	9.29	0.611	17,789

ASA = acetylsalicylic acid; CAD = coronary artery disease; CDR = CADTH Common Drug Review; NR = not reported; PAD = peripheral arterial disease; QALY = quality-adjusted life-year.

Source: Manufacturer's submission, tables 30, 32, 35, and 37.[8]

Summary of Manufacturer's Sensitivity Analyses

For both populations considered (the overall COMPASS population and the reimbursement population), detailed scenario analyses were conducted. These included varying key parameters (hazard ratios, baseline transitions, and baseline utility values) by upper and lower values (specified by 95% confidence interval or by alternative values from the literature), and a series of scenario analyses relating to the time horizon, discount rate, treatment discontinuations, utilities, and costs for second events and utility values.

Within the overall COMPASS population, the only scenario under which the ICER rose to greater than $50,000 per QALY gained was the adoption of a 10-year time horizon (ICER of $57,487). For the concomitant CAD and PAD population, there were no scenarios under which the ICER was greater than $50,000 per QALY, with the highest ICER recorded for the upper value of the hazard ratio for ICH: an ICER of $31,372.

Limitations of Manufacturer's Submission

The manufacturer adopted an appropriate approach to conducting the submitted evaluation. The model structure is appropriate and where assumptions were necessary the manufacturer has made a number of assumptions that were not likely to favour their product in terms of cost-effectiveness.

One assumption that resulted in results that were more favourable to the manufacturer's product was the assumption of increasing the risk of events by age, which was modelled to occur after the fourth year within the model. However, excluding this had little effect on the results, increasing the ICER in the deterministic analysis from $15,341 to $17.303 per QALY for the concomitant CAD and PAD population.

Another favourable assumption was that the hazard ratios for rivaroxaban plus ASA would stay constant beyond the time horizon of the model. The justification for this assumption was weak given the lack of long-term data specific to rivaroxaban. It was not possible to incorporate any waning of treatment effect within the model. However, the CDR pharmacoeconomic reviewer conducted a simple sensitivity analysis that adopted an extreme scenario to assess the impact of this, whereby the increased/decreased risk of an event associated with rivaroxaban plus ASA was halved. Under this scenario, the incremental cost per QALY gained was still less than $35,000, suggesting that treatment waning was unlikely to impact the results of the analysis.

A further limitation with the submitted analyses and model is that results based on a stratified analysis, as suggested by the recent Canadian economic guidelines, were not provided or possible using the economic model, i.e., an analysis for those with CAD alone and those with PAD alone was not possible.[9] Given that this review is being undertaken prior to the Notice of Compliance from Health Canada, this level of stratification would have been helpful.

CADTH Common Drug Review Reanalyses

Given the quality of the submitted model and the consistent approach adopted when assumptions were required, there were no limitations requiring reanalysis.

Given that analysis identified that the incremental cost per QALY gained for rivaroxaban plus ASA versus ASA alone was significantly lower than previously considered thresholds and the certainty around the result was high, no reanalysis based on price reduction scenarios was necessary.

Issues for Consideration

- One issue for consideration is that analysis for the population with either CAD alone or PAD alone was not possible. Thus, the recommendation regarding reimbursement has to be restricted to the population with concomitant CAD and PAD. The potential for adoption to a wider patient population, therefore, has to be considered.
- A further issue relates to concern over the possible rate of bleeds and the risk/benefit trade-off in this population. Thus, consideration of the evolving literature in this area is warranted.

Patient Input

Patient input was received from the Cardiac Health Foundation of Canada. Overall, patients indicated their conditions were well managed with current medications; however, poor management of disease may lead to heart attacks or death; thus, patients tend to be diligent about taking their medications. A common concern shared by all respondents was the constant fear of having another serious cardiovascular event. Mental stress resulting from such fear persists long after patients are physically healed, and limits their participation in daily activities and physical exercise. Events have been captured directly in the manufacturer's economic evaluation, which captures the outcomes of greatest interest to patients.

Conclusions

The manufacturer provided a well-conducted economic evaluation that provides strong evidence to suggest that rivaroxaban will be cost-effective for a population of patients with concomitant CAD and PAD assuming a decision-maker would be willing to pay at least $17,764 per QALY gained. For the full COMPASS population (patients with CAD and/or PAD), the incremental cost per QALY was $31,758.

Information on patients with CAD alone was not provided; thus, the cost-effectiveness of rivaroxaban in this subgroup and the full indication is unknown.

Appendix 1: Cost Comparison

The comparators presented in the following table have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice, versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing Product Listing Agreements are not reflected in the table and, as such, may not represent the actual costs to public drug plans.

Table 3: CDR Cost Comparison Table for the Prevention of Stroke, Myocardial Infarction, and Cardiovascular Death in Coronary Artery Disease and Peripheral Arterial Disease

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dosage	Average Cost per Month ($)[a]	Average Cost per Year ($)[a]
Rivaroxaban (Xarelto)	**2.5 mg**	**Film-coated tablet**	**1.4350[b,c]**	**2.5 mg twice daily in combination with low-dose ASA (75 mg to 100 mg) once daily[d]**	**87**	**1,048**
ASA (generic)	81 mg	Tablet	0.0530[e]	75 mg to 162 mg[f]	2 to 3	19 to 39
Clopidogrel (Plavix, generics)	75 mg	Tablet	0.2631	75 mg once daily with or without ASA (80 mg to 325 mg)	8	96
Ticagrelor (Brilinta)	60 mg 90 mg	Tablet	1.4800[g] 1.5470	60 mg twice daily	90	1,080

ASA = acetylsalicylic acid; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; CDR = CADTH Common Drug Review; PAD = peripheral arterial disease.

Source: Ontario Drug Benefit / Comparative Drug Index (effective from June 8, 2018). Unless otherwise noted, annual period assumes 52 weeks, 365 days.[23]

[a] Daily costs exclude any concomitant use of ASA.

[b] Based on manufacturer's submission.[2]

[c] List price of rivaroxaban is $1.4200 in British Columbia, Manitoba, Nova Scotia, Prince Edward Island, New Brunswick, and Newfoundland and Labrador.

[d] From product monograph for rivaroxaban.[1]

[e] Price obtained from British Columbia Drug Benefit Formulary (June 8, 2018).[24]

[f] Based on CCS guidelines on the management of chronic CAD and/or PAD.[25]

[g] IQVIA (accessed August 15, 2018).[26]

Appendix 2: Summary of Key Outcomes

Table 4: When Considering Only Costs, Outcomes and Quality of Life, How Attractive is Rivaroxaban Plus ASA Relative to ASA Alone?

Rivaroxaban + ASA Versus ASA	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	N/A
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes	X					
Quality of life	X					
Incremental CE ratio or net benefit calculation	$17,764 per QALY for patients with CAD and PAD $31,759 per QALY for patients with CAD and/or PAD					

ASA = acetylsalicylic acid; CAD = coronary artery disease; CE = cost-effectiveness; N/A = not applicable; PAD = peripheral arterial disease; QALY = quality-adjusted life-year.

Note: Results are based on a Canadian health care payer perspective and are based on the manufacturer's probabilistic analysis.

Appendix 3: Additional Information

Table 5: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?	X		
Comments Reviewer to provide comments if checking “no”	None		
Was the material included (content) sufficient?	X		
Comments Reviewer to provide comments if checking “poor”	None		
Was the submission well organized and was information easy to locate?	X		
Comments Reviewer to provide comments if checking “poor”	None		

Table 6: Authors Information

Authors of the Pharmacoeconomic Evaluation Submitted to CDR

☒ Adaptation of global model/Canadian model done by the manufacturer

☐ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer

☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the manufacturer

☐ Other (please specify)

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document		X	
Authors had independent control over the methods and right to publish analysis		X	

CDR = CADTH Common Drug Review.

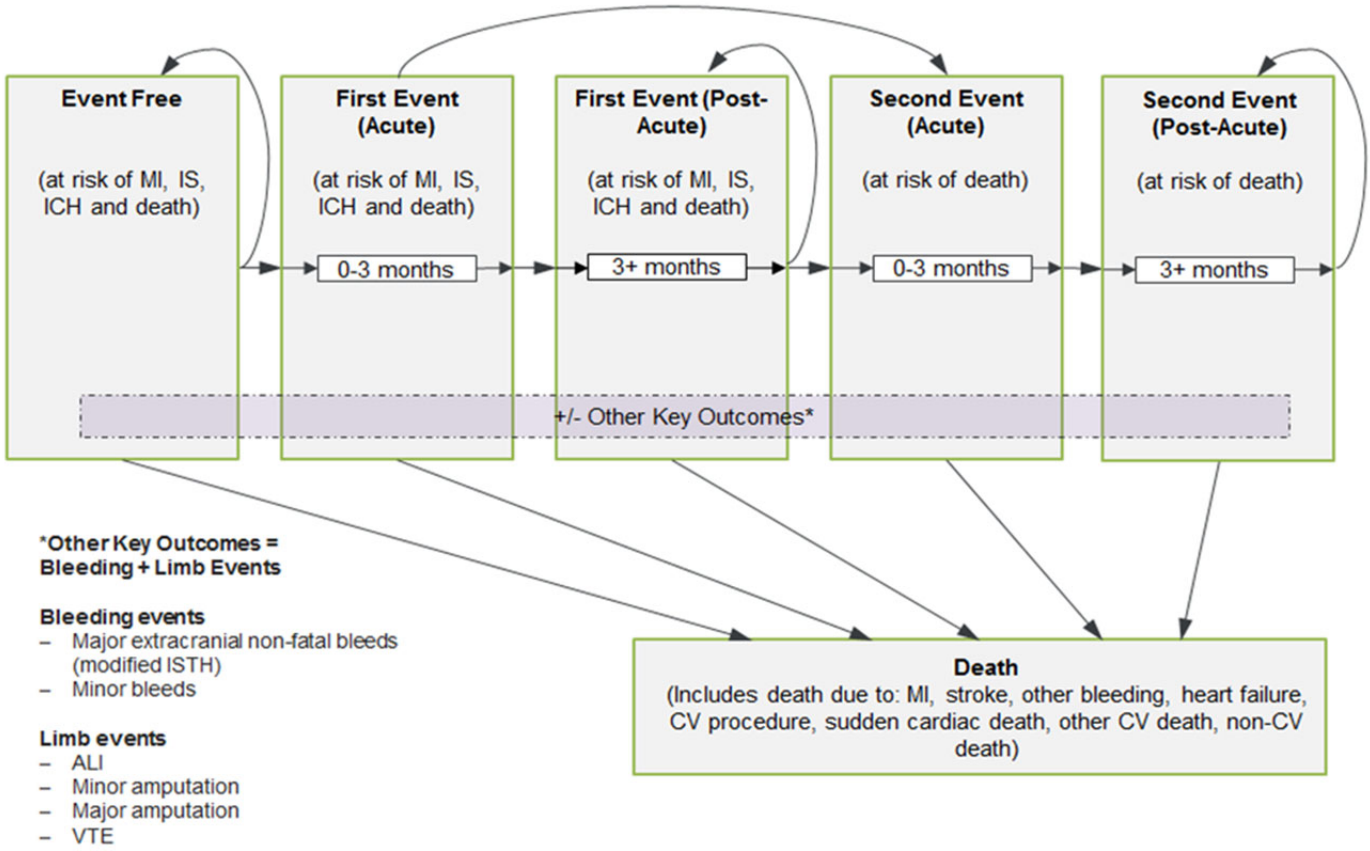
Appendix 4: Summary of Other HTA Reviews of Drug

At the time of this review, no reviews for rivaroxaban for patients with coronary artery disease and/or peripheral arterial disease have been conducted by health technology assessment organizations.

Appendix 5: Reviewer Worksheets

Manufacturer's Model Structure

Figure 1: Manufacturer's Detailed Model Schematic



ALI = acute limb ischemia; CV = cardiovascular; ICH = intracranial hemorrhage; IS = ischemic stroke; ISTH = International Society on Thrombosis and Haemostasis; MI = myocardial infarction; VTE = venous thromboembolism.

Source: Manufacturer's economic submission (page 43).[8]

Table 7: Data Sources for Primary Analysis

Data Input	Description of Data Source	Comment[a]
Baseline characteristics	COMPASS clinical trial[3]	Appropriate given the analysis presented for the CAD and PAD population is generalizable to this specific population as per the reimbursement request
Efficacy	COMPASS clinical trial[3]	Appropriate
Natural history	COMPASS clinical trial[3] REACH Registry[10]	Appropriate
Utilities	COMPASS clinical trial[3] EQ-5D[22]	Appropriate
Adverse events	COMPASS clinical trial[3]	Appropriate
Mortality	COMPASS clinical trial[3] Canadian specific mortality data[11]	Appropriate
Resource use and costs	Various[13-21]	Appropriate

CAD = coronary artery disease; EQ-5D = EuroQol 5-Dimensions questionnaire; PAD = peripheral arterial disease; REACH = Reduction of Atherothrombosis for Continued Health.

Table 8: Manufacturer's Key Assumptions

Manufacturer's Assumption	CDR Pharmacoeconomic Reviewer's Comment
COMPASS patient population is representative of the Canadian population.	May not be appropriate. Results for the overall COMPASS population may not be generalizable to the total population covered by the indication. However, analysis for the concomitant CAD and PAD group is more likely to be generalizable.
Baseline risks and hazard ratios for years 1 to 4 in the model were calculated directly from COMPASS data.	Reasonable.
Patients may experience up to one CV event within a three-month cycle.	Appropriate simplification.
Patients cannot experience more than two CV events (MI, IS, or ICH) in the model.	Appropriate simplification. Likely biases result against rivaroxaban if there is continued long-term effects after CV events.
Treatment interruption or treatment discontinuation is not modelled, as it is incorporated into the COMPASS ITT data that is used to inform the transition probabilities.	Reasonable and biased against rivaroxaban.
The same HRs were applied for rivaroxaban 2.5 mg + ASA transition probabilities for the first and second event health states.	Probably appropriate.
The baseline risk of CV events and death was adjusted annually to account for increased CV risk with age, based on REACH data, and extrapolated to a lifetime horizon.	Reasonable. CDR reanalysis confirmed that this had little effect on the conclusion from the analysis.
HRs used to calculate the rivaroxaban 2.5 mg + ASA transition probabilities were constant over time.	Reasonable. CDR reanalysis confirmed this had little effect on the conclusion from the analysis.
Other key outcomes were implemented via a constant probability per cycle, independent of the health state.	Appropriate.
The costs and disutilities for minor and major amputations were considered for one cycle (0 to 3 months).	Appropriate simplification.
The costs and disutilities for major extracranial non-fatal and minor bleeding events were considered for one cycle (0 to 3 months).	Appropriate simplification.

Manufacturer's Assumption	CDR Pharmacoeconomic Reviewer's Comment
For patients with more than one event in their history, only the disutility from the worse state is included.	Reasonable and biased against rivaroxaban.

ASA = acetylsalicylic acid; CAD = coronary artery disease; CDR = CADTH Common Drug Review; CV = cardiovascular; HR = hazard ratio; ICH = intracranial hemorrhage; IS = ischemic stroke; ITT = intention-to-treat; MI = myocardial infarction; PAD = peripheral arterial disease; REACH = Reduction of Atherothrombosis for Continued Health.

Table 9: Hazard Ratios for Rivaroxaban Plus ASA Versus ASA Alone

Event	Value	
	Concomitant CAD and PAD	CAD and/or PAD
MI	[redacted]	0.86
IS	[redacted]	0.51
ICH	[redacted]	1.16
Acute limb ischemia	[redacted]	0.55
Minor amputation	[redacted]	[redacted]
Major amputation	[redacted]	[redacted]
Major non-fatal extracranial bleed (modified ISTH criteria)	[redacted]	[redacted]
VTE	[redacted]	0.61
Minor bleed	[redacted]	1.70
CV mortality	[redacted]	0.78
Fatal bleeding	[redacted]	1.49

ASA = acetylsalicylic acid; CAD = coronary artery disease; CV = cardiovascular; ICH = intracranial hemorrhage; IS = ischemic stroke; ISTH = International Society on Thrombosis and Haemostasis; MI = myocardial infarction; PAD = peripheral arterial disease; VTE = venous thromboembolism.

Source: Manufacturer's economic submission.[8]

Table 10: Cost Estimates

Resource/Event	Cost ($)
Daily cost of rivaroxaban	2.87
Event-free per cycle	77.85
MI — first cycle (acute event)	17,126.45
IS — first cycle (acute event)	47,452.28
ICH — first cycle (acute event)	31,856.85
MI — subsequent cycle (post-acute)	402.62
IS — subsequent cycle (post-acute)	1,554.95
ICH — subsequent cycle (post-acute)	11,977.97
Acute limb ischemia	13,685.89
Minor amputation	13,188.05
Major amputation	38,788.37
Major non-fatal extracranial bleed (modified ISTH criteria)	5,417.69
VTE	6,656.79
Minor bleed	77.20
CV mortality	10,408.59
Fatal bleeding	7,927.08

CV = cardiovascular; ICH = intracranial hemorrhage; IS = ischemic stroke; ISTH = International Society on Thrombosis and Haemostasis; MI = myocardial infarction; VTE = venous thromboembolism.

Source: Manufacturer's economic submission.[8]

Table 11: Utility Values for Concomitant Coronary Artery Disease and Peripheral Arterial Disease

Event	Value
Event-free	[redacted]
Utility Weight for Cardiovascular Events	
MI — first cycle (acute event)	[redacted]
IS — first cycle (acute event)	[redacted]
ICH — first cycle (acute event)	[redacted]
MI — subsequent cycle (post-acute)	[redacted]
IS — subsequent cycle (post-acute)	[redacted]
ICH — subsequent cycle (post-acute)	[redacted]
Utility Decrement for Other Key Outcomes	
Acute limb ischemia	[redacted]
Minor amputation	[redacted]
Major amputation	[redacted]
Major non-fatal extracranial bleed (modified ISTH criteria)	[redacted]
VTE	[redacted]
Minor bleed	[redacted]

ICH = intracranial hemorrhage; IS = ischemic stroke; ISTH = International Society on Thrombosis and Haemostasis; MI = myocardial infarction; VTE = venous thromboembolism.

Source: Manufacturer's economic submission.[8]

Manufacturer's Results

Table 12: Results Summary: Estimated Costs for the Population With Concomitant Coronary Artery Disease and Peripheral Arterial Disease

Cost Category	Rivaroxaban + ASA	ASA	Difference
Drug costs	$12,819	$0	$12,819
Ongoing medical care	$19,653	$17,425	$2,228
Non-fatal acute CV events	$7,943	$11,053	−$3,110
Mortality	$2,568	$3,701	−$1,133
Other key outcomes	$3,057	$3,951	−$894
Total costs	$46,039	$36,130	$9,909

ASA = acetylsalicylic acid; CV = cardiovascular.

Source: Manufacturer's economic submission.[8]

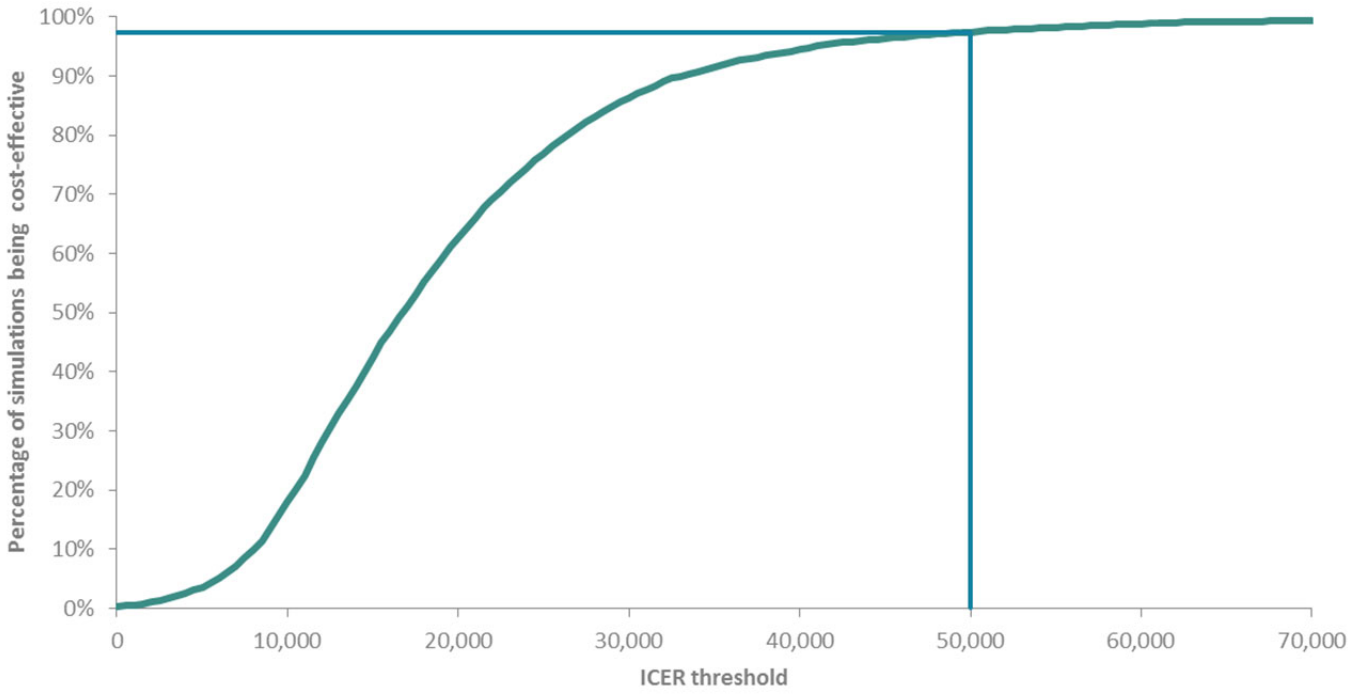
Table 13: Results Summary: Estimated Costs for the Complete COMPASS Population

Cost Category	Rivaroxaban + ASA	ASA	Difference
Drug costs	$13,325	$0	$13,325
Ongoing medical care	$12,385	$12,605	−$220
Non-fatal acute CV events	$6,162	$9,024	−$2,862
Mortality	$1,955	$2,482	−$527
Other key outcomes	$2,081	$2,208	−$128
Total costs	$35,908	$26,319	$9.588

ASA = acetylsalicylic acid; CV = cardiovascular.

Source: Manufacturer's economic submission.[8]

Figure 2: Manufacturer's Cost-Effectiveness Acceptability Curve for Concomitant Coronary Artery Disease and Peripheral Arterial Disease



ICER = incremental cost-effectiveness ratio.
Source: Manufacturer's economic submission.[8]

Table 14: Scenario Analysis: Incremental Cost-Effectiveness Ratios for Rivaroxaban Plus ASA Versus ASA Alone in Concomitant CAD and PAD

Scenario		Incremental Costs ($)	Incremental QALYs	ICER ($/QALYs)
Base case		9,909	0.65	15,341
Time horizon	10 years	5,242	0.23	23,034
Discount rate	0%	11,372	0.77	14,813
	3%	8,716	0.55	15,915
Treatment discontinuation	Patients move to CLO + ASA in all cases	9,684	0.65	14,992
	Patients move to TIC + ASA in all cases	9,637	0.65	14,920
Second events	Costs: Most recent event	10,856	0.65	16,808
	Costs: Additive	9,542	0.65	14,773
	Utilities: Most recent event	9,909	0.65	15,341
	Utilities: Multiplicative	9,909	0.67	14,756
Utilities	Targeted literature review	9,909	0.67	14,760

ASA = acetylsalicylic acid; CAD = coronary artery disease; CLO = clopidogrel; ICER = incremental cost-effectiveness ratio; PAD = peripheral arterial disease; QALY = quality-adjusted life-year; TIC = ticagrelor.

Source: Manufacturer's economic submission.[8]

Table 15: Scenario Analysis: Incremental Cost-Effectiveness Ratios for Rivaroxaban Plus ASA Versus ASA Alone in Complete COMPASS Population

Scenario		Incremental Costs ($)	Incremental QALYs	ICER ($/QALYs)
Base case		9,588	0.33	29,476
Time horizon	10 years	6,322	0.11	57,487
Discount rate	0%	10,729	0.39	27,678
	3%	8,641	0.28	31,412
Treatment discontinuation	Patients move to CLO + ASA in all cases	9,407	.33	28,917
	Patients move to TIC + ASA in all cases	9,390	.33	28,868
Second events	Costs: Most recent event	10,049	0.33	30,892
	Costs: Additive	8,953	0.33	27,523
	Utilities: Most recent event	9,588	0.32	29,556
	Utilities: Multiplicative	9,588	0.36	26,964
Utilities	Targeted literature review	9,588	0.35	27,651

ASA = acetylsalicylic acid; CLO = clopidogrel; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; TIC = ticagrelor.

Source: Manufacturer's economic submission.[8]

Table 16: Results Summary: Compared With Clopidogrel

	Total Costs ($)	Incremental Cost of Rivaroxaban + ASA ($)	Total QALYs	Incremental QALYs of Rivaroxaban + ASA	Incremental Cost per QALY
Overall COMPASS Population (CAD and/or PAD)					
Clopidogrel	24,907		9.98		
Rivaroxaban + ASA	35,908	11,001	10.19	0.20	53,844
Concomitant CAD + PAD					
Clopidogrel	32,936		8.83		
Rivaroxaban + ASA	46,039	13,103	9.32	0.49	26,659

ASA = acetylsalicylic acid; CAD = coronary artery disease; PAD = peripheral arterial disease; QALY = quality-adjusted life-year.

Source: Manufacturer's economic submission.[8]

Table 17: Results Summary: Compared With Clopidogrel Plus ASA

	Total Costs ($)	Incremental Cost of Rivaroxaban + ASA ($)	Total QALYs	Incremental QALYs of Rivaroxaban + ASA	Incremental Cost per QALY
Overall COMPASS Population (CAD and/or PAD)					
Clopidogrel	25,769		9.87		
Rivaroxaban + ASA	35,908	10,138	10.19	0.32	31,794
Concomitant CAD + PAD					
Clopidogrel	36,542		8.72		
Rivaroxaban + ASA	46,039	9,497	9.32	0.61	15,596

ASA = acetylsalicylic acid; CAD = coronary artery disease; PAD = peripheral arterial disease; QALY = quality-adjusted life-year.

Source: Manufacturer's economic submission.[8]

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