CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

RIVAROXABAN (XARELTO)

Bayer Inc.

Indication: In combination with 75 mg to 100 mg acetylsalicylic acid, 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 with or without peripheral artery disease.

Service Line:	CADTH Common Drug Review
Version:	Final (with redactions)
Publication Date:	January 2019
Report Length:	103 Pages

CADTH

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.

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

CADTH

Table of Contents

Tables

Figures

Abbreviations

ACS	acute coronary syndrome
AE	adverse event
ALI	acute limb ischemia
ASA	acetylsalicylic acid
CABG	coronary artery bypass graft
CAD	coronary artery disease
CHD	coronary heart disease
CI	confidence interval
CV	cardiovascular
CVD	cardiovascular disease
DAPT	dual antiplatelet therapy
EQ-5D-3L	EuroQol 5-Dimensions 3-Levels questionnaire
HR	hazard ratio
ITT	intention-to-treat population
MALE	major adverse limb event
MI	myocardial infarction
PAD	peripheral arterial disease
PCI	percutaneous coronary intervention
PPI	proton pump inhibitor
RCT	randomized controlled trial
SAE	serious adverse event
VAS	visual analogue scale
WDAE	withdrawal due to adverse event

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

Introduction

People with coronary artery disease (CAD) and/or peripheral artery disease (PAD) are at high risk of cardiovascular (CV) events, while people with PAD are at increased risk of adverse limb events such as amputations. Acetylsalicylic acid (ASA) remains the cornerstone of antithrombotic therapy for both CAD and PAD but, despite its use, the annual risk of CV and adverse limb events remains high. Thus, there is interest in additional antithrombotic therapies to further reduce risk of CV events in CAD and limb events in PAD.

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. For this review, the indication for rivaroxaban is to be used [redacted].

The objective of the review was to perform a systematic review of the beneficial and harmful effects of rivaroxaban 2.5 mg, in combination with ASA 75 mg to 100 mg, for the prevention of stroke, myocardial infarction, and CV death and for the prevention of acute limb ischemia (ALI) and mortality in patients with CAD, with or without PAD.

Note: Rivaroxaban was submitted to the CADTH Common Drug Review (CDR) prior to the issuance of the Health Canada notice of compliance. At the time the review protocol was being prepared and the review report drafted, the indication submitted to CDR was: [redacted]. The review, therefore, includes data in line with the initially proposed indication.

Results and Interpretation

Included Studies

One double-blind, randomized controlled trial (RCT) was included in the review (COMPASS; N = 27,395; mean age 68 years; 78% male), which compared the combination of rivaroxaban 2.5 mg twice daily and ASA 100 mg once daily to ASA 100 mg once daily in patients with stable CAD and/or PAD who predominantly had a history of myocardial infarction (MI), cardiac revascularization, normal renal function, and no history of stroke. The primary outcome of COMPASS was major adverse CV events (composite of stroke, MI, and CV death). Secondary outcomes were: the composite of ALI, MI, ischemic stroke, and coronary heart disease (CHD) death; the composite of ALI, MI, ischemic stroke, and CV death; and all-cause mortality. These three key secondary outcomes were adjusted for multiplicity in the statistical analysis. Health-related quality of life was evaluated using the EuroQol 5-Dimensions 3-Levels (EQ-5D-3L) questionnaire visual analogue scale (VAS) out of 100. The individual components of the primary and secondary composite outcomes were evaluated but were not adjusted for multiplicity. Subgroup analyses for CAD only, PAD only, and concomitant CAD/PAD were conducted, as well as a post-hoc analysis of major adverse limb events (composite of acute or chronic limb ischemia and major amputations) in patients with PAD; none of these analyses were adjusted for multiplicity. The primary safety outcome was the occurrence of major bleeding, which included fatal bleeding, symptomatic bleeding in critical areas and/or organs (e.g., intracranial), and bleeding leading to hospitalization. COMPASS recruited patients from Canada, the US, Western Europe, Eastern Europe, South America, and Asia Pacific. 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. The generalizability of COMPASS results is not clear in those without a history of MI or cardiac revascularization, those with normal renal function, and those with a history of stroke. Patients at high risk of bleeding were excluded from COMPASS; however, no specific criteria for evaluating bleeding risk were applied in the trial.

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 (hazard ratio [HR] 0.76, 95% confidence interval [CI] 0.66 to 0.86). For the secondary composite outcomes, the HRs for the comparison of rivaroxaban/ASA with ASA were: 0.72 (95% CI, 0.63 to 0.83) for the composite of ALI, MI, ischemic stroke, CHD death; 0.74 (95% CI, 0.65 to 0.85) for composite of ALI, MI, ischemic stroke, and CV death; and 0.82 (95% CI, 0.71 to 0.96) for all-cause mortality. The results for all-cause mortality should be interpreted with caution because the statistical comparison of rivaroxaban/ASA versus ASA alone could not be considered statistically significant based on the hierarchical analysis plan used to adjust for multiple comparisons. It is uncertain what the effect of rivaroxaban/ASA is on health-related quality of life and patient function because there are limited or no data for these outcomes.

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. A separate post-hoc analysis of COMPASS participants with PAD (n = 6,391) evaluated the risk of experiencing a composite outcome of major adverse limb events (MALEs) (acute or chronic limb ischemia and major amputations). MALEs were lower in the rivaroxaban/ASA group compared with ASA alone (HR 0.57; 95% CI, 0.37 to 0.88). While subgroup analysis of participants with PAD was specified in the protocol, the definition and analysis of MALEs was not described in the protocol and this outcome data were not found in the Clinical Study Report for COMPASS. In the PAD-only subgroup, there was no difference between the two groups for any outcome. The number of patients in this subgroup was small and event rates were low, which makes it difficult to draw conclusions about the efficacy of the combination of rivaroxaban/ASA in the group of patients with PAD only.

There are no trials comparing rivaroxaban/ASA directly with treatment regimens other than ASA alone in the stable CAD and/or PAD population. [redacted]

Harms

In the overall CAD and/or PAD population of COMPASS, the proportion of participants experiencing adverse events was higher in the rivaroxaban/ASA group (14.7%) compared with ASA alone (13.8%). The proportion of patients experiencing serious adverse events ([redacted] versus [redacted]) and withdrawals due to adverse events (3.4% versus 2.6%) was also higher for rivaroxaban/ASA compared with ASA. Minor bleeding was more common for rivaroxaban/ASA (9.0%) compared with ASA alone (5.3%). Major bleeding was more common for rivaroxaban/ASA-treated patients (3.1%) compared with ASA alone (1.9%). In the rivaroxaban/ASA group, the absolute risk increase for major bleeding was 1.2% compared with ASA alone. In comparison, the absolute risk reduction for the primary outcome for rivaroxaban/ASA compared with ASA alone was 1.3%. The increased risk of major bleeding in the rivaroxaban/ASA arm was due largely to an increased occurrence of GI bleeding, yet it was noted by the clinical expert consulted by CADTH that such bleeding events are often treatable, as compared with the efficacy outcomes, which often cause permanent injury or death. The occurrence of fatal bleeding, non-fatal intracranial bleeding, and non-fatal critical organ bleeding were relatively uncommon and similarly distributed between treatment groups.

[redacted]

Potential Place in Therapy[1]

The clinical expert consulted by CADTH noted that patients with established stable CAD, PAD, or cerebrovascular disease are at substantial risk for atherothrombotic events, despite use of optimal medical therapy. The ischemic consequence of atherothrombosis can result in death, MI, stroke, and/or ALI. The occurrence of these events is a major public health issue.

Monotherapy with low-dose ASA has evolved as the most widely recommended antithrombotic drug used to prevent atherothrombotic events with a relatively low incidence of serious bleeding. However, despite the regular use of low-dose ASA in stable patients with cardiovascular disease (CVD), there is substantial residual atherothrombotic risk.

More efficient antithrombotic strategies involving the addition of a second antiplatelet drug, such as a P2Y12 inhibitor or a thrombin receptor inhibitor, or warfarin added to low-dose ASA, have demonstrated enhanced efficacy, but with unacceptable serious bleeding.

In the COMPASS trial, which was terminated early after a mean follow-up of 23 months, low-dose (2.5 mg twice daily) rivaroxaban combined with low-dose ASA appears to balance efficacy and safety by favourably affecting the residual risk in patients with established, stable CVD on an appropriate background medical regimen. The observed risk reduction in the COMPASS trial occurred through prevention of CV death or permanent damage to the brain (stroke). Therefore, the permanent nature of these events cannot be used to make simple comparisons between the number needed to treat to prevent an event versus the number needed to harm, such as major bleeding events, which are generally treatable conditions. Although more bleeding events were experienced in the COMPASS trial by those assigned to receive the combination therapy of low-dose rivaroxaban and ASA compared with the low-dose ASA-alone group. Reassuringly, the more severe types of bleeds, such as those causing death or bleeding into a critical organ or causing intracranial hemorrhage, were similar in frequency for both treatment groups. The clinical expert observed that the rates of major bleeding events observed in the COMPASS trial appear consistent with prior studies of stable CV disease that have examined the utility of adding a P2Y12 inhibitor (PEGASUS) or antithrombotic therapy (ASPECT-2) to ASA in a stable CV population.

The COMPASS trial may be an important step forward in providing evidence of a treatment strategy for reducing the risk of atherothrombotic events in patients with stable CV disease. However, further data on individual risks and benefits would help personalize treatment beyond the overall results, especially in patients aged 75 years and older and patients with chronic renal failure, where bleeding risk is of concern.

Many patients who might benefit from rivaroxaban plus low-dose ASA are already taking ASA and other medications, and their ability to add (or switch to) another twice-daily medication long term may bear on how readily rivaroxaban plus ASA is adopted in clinical

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

practice. The current recommendation for patients with atherosclerotic CVD is to remain on ASA for life; however, it is unclear whether patients would need to remain on rivaroxaban plus ASA for life, as well.

Conclusions

COMPASS demonstrated that in patients with stable CAD and/or PAD (who predominantly had a history of MI, cardiac revascularization, and normal kidney function, were not at high risk of bleeding, and had no history of a stroke), the combination of rivaroxaban 2.5 mg twice daily and ASA 100 mg once daily significantly reduced the risk of the composite outcome of stroke, MI, and CV death compared with ASA alone over an almost two-year treatment period. This benefit was also seen in the subgroups of patients with stable CAD or concomitant CAD/PAD, although subgroup comparisons were not adjusted for multiple statistical testing. It is uncertain whether rivaroxaban/ASA has any added benefit on health-related quality of life or daily function compared with ASA alone because there was limited or no evidence for these outcomes. Major and minor bleeding were more common with rivaroxaban/ASA compared with ASA alone. Patients with CAD and PAD report being concerned about having future CV events; therefore, the addition of rivaroxaban to ASA may be important to them. However, given the increased chance of major and minor bleeding, bleeding risk is also an important consideration. COMPASS was stopped early at approximately two years due to the pre-specified efficacy criteria of rivaroxaban/ASA over ASA for the primary outcome being met. As such, the long-term efficacy and safety of rivaroxaban/ASA is not well established. Based on this review, rivaroxaban added to ASA reduces the risk of CV events in certain patients with stable CAD and/or PAD compared with ASA alone, but increases the risk of major bleeding.

Table 1: Summary of Results

Outcome	COMPASS	
	Rivaroxaban/ASA	ASA
Composite of MI, Stroke, CV Death[a]		
n/N (%)	379/9,152 (4.1)	496/9,126 (5.4)
HR (95% CI)	0.76 (0.66 to 0.86)	
MI[b]		
n/N (%)	178/9,152 (1.9)	205/9,126 (2.2)
HR (95% CI)	0.86 (0.70 to 1.05)	
Stroke[b]		
n, N (%)	83/9,152 (0.9)	142/9,126 (1.6)
HR (95% CI)	0.58 (0.44 to 0.76)	
CV Death[b]		
n/N (%)	160/9,152 (1.7)	203/9,126 (2.2)
HR (95% CI)	0.78 (0.64 to 0.96)	
Composite of MI, Ischemic Stroke, ALI, CHD Feath[a]		
n/N (%)	329/9,152 (3.6)	450/9,126 (4.9)
HR (95% CI)	0.72 (0.63 to 0.83)	
Composite of MI, Ischemic Stroke, ALI, CV Death[a]		
n/N (%)	389/9,152 (4.3)	516/9,126 (5.7)
HR (95% CI)	0.74 (0.65 to 0.85)	

Outcome	COMPASS	
	Rivaroxaban/ASA	ASA
All-cause Mortality[a]		
n/N (%)	313/9,152 (3.4)	378/9,126 (4.1)
HR (95% CI)	0.82 (0.71 to 0.96)	
Major Bleeding		
n/N (%)	288/9,152 (3.1)	170/9,126 (1.9)
HR (95% CI)	1.70 (1.40 to 2.05)	
Minor Bleeding		
n/N (%)	821/9,134 (9.0)	485/9,107 (5.3)

ALI = acute limb ischemia; CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction.

[a] Adjusted for multiplicity.

[b] Not adjusted for multiplicity.

Introduction

Disease Prevalence and Incidence

Coronary artery disease (CAD) is caused by atherosclerosis of the arteries of the heart, which leads to reduced blood and oxygen supply.[1] People can experience acute manifestations of CAD (e.g., a myocardial infarction [MI]), or they may have stable disease. Symptoms of CAD include shortness of breath and chest pain (angina).[2] Individuals with stable CAD are still at increased risk of acute cardiovascular (CV) events, such as MI or sudden cardiac death.[3] Peripheral artery disease (PAD) is a related condition caused by atherosclerosis and reduced blood supply in the limbs.[4] Individuals with PAD may have pain in their legs with exercise or develop ulcers or gangrene, which can limit function.[4] They are at increased risk of CV events as well as adverse limb events such as limb ischemia and amputations.[4] PAD and CAD can occur concomitantly.

Cardiovascular disease (CVD) encompasses several disorders, including CAD and PAD, and is the second-leading cause of death annually in Canada.[5] Each year, approximately 4% of patients with CAD and 3% of patients with PAD experience an MI, stroke, or CV death.[6] Patients with PAD have a 2% to 10% yearly risk of experiencing an adverse limb event.[6] In patients with concomitant disease, the yearly risk of an adverse CV event or CV hospitalization is approximately 25%.[6]

Standards of Therapy

Therapy for stable CAD and/or PAD includes medical management and may also include revascularization procedures (coronary for CAD and non-coronary for PAD), depending on the acuity of the disease and the risk of future events.[7] In terms of medical therapy, patients with CAD and/or PAD generally receive a statin, an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker and may also receive a beta blocker, depending on symptoms and CV history.[7,8] Stable patients will also receive antiplatelet monotherapy, most commonly with acetylsalicylic acid (ASA).[7,8] The aim of these treatments is to reduce the risk of future CV and/or adverse limb events.

Despite optimal medical management and revascularization procedures, the rate of CV events remains high in patients with stable CAD and/or PAD.[6] Thus, there is interest in exploring therapies that further reduce risk. Additional antithrombotic medications added to ASA have been evaluated as one option in stable CAD; however, due to an unfavourable balance of benefits and risks (i.e., bleeding) with dual antiplatelet therapy (DAPT) (for example, with a P2Y12 inhibitor such as clopidogrel) and vitamin K antagonists, ASA monotherapy remains the most commonly recommended antithrombotic for stable CAD and PAD.[7,8] However, there remains interest in the potential benefits of antithrombotics in combination with ASA because of the remaining burden of CV morbidity and mortality associated with CAD and PAD.

Drug

Rivaroxaban (Table 2) is a direct-acting oral anticoagulant that selectively inhibits factor Xa and thrombus formation during the blood-clotting cascade. It is already approved in Canada to reduce the risk of stroke and systemic embolism in individuals with atrial fibrillation by reducing the risk of venous thromboembolism after orthopaedic surgery, and for the

treatment and prevention of recurrent thromboembolic events (deep vein thrombosis and pulmonary embolism). Rivaroxaban has been reviewed by the CADTH Common Drug Review (CDR) and the CADTH Canadian Drug Expert Committee (CDEC) has recommended that it be reimbursed for these indications.

Rivaroxaban has a Health Canada indication, at a dose of 2.5 mg twice daily, in combination with 75 mg to 100 mg ASA, for the prevention of stroke, MI, and CV death, and for the prevention of acute limb ischemia (ALI) and mortality in patients with CAD with or without PAD (Table 2). The manufacturer requested that rivaroxaban be reimbursed by CDR-participating drug plans for patients with concomitant CAD and PAD.

Table 2: Key Characteristics of Rivaroxaban and Comparators

	Rivaroxaban	P2Y12 Inhibitors (e.g., Clopidogrel, Ticagrelor, Prasugrel)	Vitamin K Antagonists (e.g., Warfarin)
Mechanism of Action	Inhibits factor Xa.	Specific inhibitor of ADP-induced platelet aggregation.	Inhibits synthesis of vitamin K–dependent clotting factors.
Indication[a]	In combination with 75 mg to 100 mg ASA for the prevention of stroke, MI, and cardiovascular death, and for the prevention of acute limb ischemia and mortality in patients with CAD with or without PAD.	**Clopidogrel:** Secondary prevention of atherothrombotic events (MI, stroke, and vascular death) in patients with atherosclerosis documented by stroke, MI, or established PAD. In combination with ASA for the early and long-term secondary prevention of atherothrombotic events (MI, ischemic stroke, cardiovascular death, and/or refractory ischemia) in patients with acute coronary syndromes — without ST-segment elevation (i.e., unstable angina or non–Q wave MI). For patients with ST-segment elevation acute MI to reduce the rate of an end point of all-cause mortality and the rate of a combined end point of death, re-infarction, or stroke. **Ticagrelor:** With low ASA 75 mg to 150 mg for the secondary prevention of atherothrombotic events in patients with acute coronary syndromes, and patients with a history of MI (at least one year ago) and at high risk of developing an atherothrombotic event. **Prasugrel:** With ASA for the early and long-term secondary prevention of atherothrombotic events in patients with acute coronary syndrome (unstable or non–ST segment elevation MI managed with PCI, or ST-segment elevation MI managed with PCI).	For the prophylaxis and/or treatment of venous thrombosis and its extension, pulmonary embolism, and atrial fibrillation with embolization, and as an adjunct in the prophylaxis of systemic embolism after MI, including stroke and re-infarction.
Route of Administration	Oral	Oral	Oral
Recommended Dose	2.5 mg twice daily	Clopidogrel: 75 mg once daily Ticagrelor: 60 mg twice daily (for treatment > 1 year) Prasugrel: 10 mg once daily	Based on INR
Serious Side Effects /	Contraindicated if clinically significant active bleeding,	Major safety concern is bleeding	Major safety concern is bleeding; numerous

	Rivaroxaban	P2Y12 Inhibitors (e.g., Clopidogrel, Ticagrelor, Prasugrel)	Vitamin K Antagonists (e.g., Warfarin)
Safety Issues	hepatic disease, concomitant systemic treatment with both strong CYP3A4 inhibitors and P-glycoprotein inhibitors, or concomitant treatment with other anticoagulants; major safety concern is bleeding		drug interactions

ADP = adenosine diphosphate; ASA = acetylsalicylic acid; CAD = coronary artery disease; INR = international normalized ratio; MI = myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention.

[a] Health Canada–proposed indication.

Source: Product monographs for rivaroxaban,[9] clopidogrel,[10] ticagrelor,[11] prasugrel,[12] and warfarin.[13]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of rivaroxaban (Xarelto) 2.5 mg, in combination with ASA 75 mg to 100 mg, for the prevention of stroke, MI, and CV death and for the prevention of ALI and mortality in patients with CAD with or without peripheral artery disease (PAD).

Note: Rivaroxaban was submitted to CDR before Health Canada issued the notice of compliance. At the time the review protocol was being prepared and the review report drafted, the indication submitted to CDR was: [redacted].

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the manufacturer's submission to CDR and Health Canada, as well as studies meeting the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient Population	Adult patients with CAD or PAD **Subgroups** Adult patients with concomitant CAD and PAD Adult patients with CAD Adult patients with PAD
Intervention	Rivaroxaban 2.5 mg twice daily in combination with ASA 75 mg to 100 mg once daily
Comparators	ASA 75 mg to 100 mg ASA 75 mg to 100 mg and P2Y12 inhibitor (e.g., clopidogrel, prasugrel, ticagrelor) ASA 75 mg to 100 mg and vitamin K antagonist (e.g., warfarin)
Outcomes	**Efficacy outcomes** CV death[a] Fatal MI[a] Non-fatal MI[a] Fatal stroke[a] Non-fatal stroke[a] All-cause mortality[a] Limb amputations[a] Acute limb ischemia[a] Heart failure[a] Venous thromboembolism[a] Coronary revascularization procedures[a] Non-coronary revascularization procedures[a] CV-related hospitalization[a] Health care resource utilization Patient function (including limitations due to symptoms of underlying disease, such as edema)[a] Health-related quality of life[a]

	Harms outcomes AEs, SAEs, WDAEs, notable harms:[a] any bleeding (including: bleeding from malignancy, procedure-related bleeding, urinary bleeding), fatal bleeding, major bleeding (including site: GI, intracranial), minor bleeding
Study Design	Published and unpublished phase III or IV RCTs

AE = adverse event; ASA = acetylsalicylic acid; CAD = coronary artery disease; CV = cardiovascular; DB = double-blind; GI = gastrointestinal; MI = myocardial infarction; PAD = peripheral artery disease; P2Y12 = receptor involved in platelet aggregation; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Identified as important to patients based on patient input summary.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE ALL (1946–) with in-process records and daily updates through Ovid; Embase (1974–) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Xarelto (rivaroxaban).

No methodological filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on June 21, 2018. Regular alerts were established to update the search until the meeting of CDEC on October 17, 2018. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (www.cadth.ca/grey-matters): Health Technology Assessment Agencies; Health Economics; Clinical Practice Guidelines; Drug and Device Regulatory Approvals; Advisories and Warnings; Drug Class Reviews; Databases; and an Internet search. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

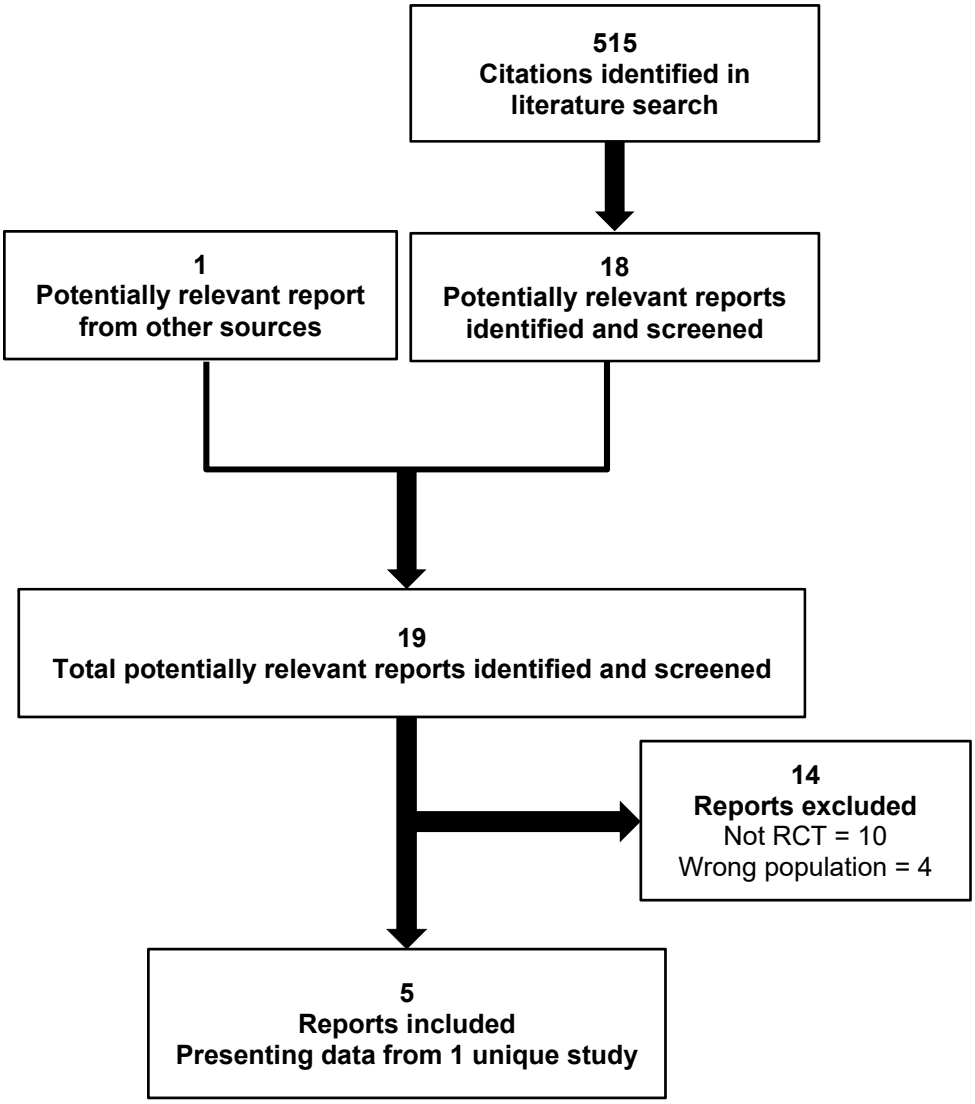
Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in Appendix 3.

Results

Findings From the Literature

A total of five reports[14-18] from one unique study were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies



RCT = randomized controlled trial.

Table 4: Details of Included Studies

		COMPASS
Designs and Populations	**Study Design**	DB RCT
	Locations	Canada, the US, Western Europe, Eastern Europe, South America, Asia Pacific
	Randomized (N)	27,395

	Inclusion Criteria	Criteria for CAD and/or PAD:
		
		Patients with CAD had to have one or more of the following:
		• MI within the last 20 years, or
		• multi-vessel coronary disease[a] with symptoms or history of stable or unstable angina, or
		• multi-vessel PCI, or
		• multi-vessel CABG surgery
		
		and meet at least one of the following criteria:
		• age ≥ 65 years, or
		• age < 65 years and documented atherosclerosis or revascularization involving at least 2 vascular beds (coronary and other vascular beds), or at least 2 additional risk factors (current smoker, diabetes mellitus, eGFR < 60 mL/min, heart failure, non-lacunar ischemic stroke ≥ 1 month ago)
		
		Patients with PAD had to meet the following criteria:
		• previous aorto-femoral bypass surgery, limb bypass surgery, or percutaneous transluminal angioplasty revascularization of the iliac, or infrainguinal arteries, or
		• previous limb or foot amputation for arterial vascular disease (i.e., non-trauma related), or
		• history of intermittent claudication and one or more of the following:
		  ○ an ABI < 0.90, or
		  ○ significant peripheral artery stenosis (≥ 50%) documented by angiography or by duplex ultrasound, or
		• previous carotid revascularization or asymptomatic carotid artery stenosis ≥ 50% as diagnosed by duplex ultrasound or angiography

	Exclusion Criteria	High risk of bleeding, stroke within one month or any history of hemorrhagic or lacunar stroke, severe heart failure (EF < 30% or NYHA class III or IV symptoms), eGFR < 15 mL/min, need for DAPT or oral anticoagulant (e.g., for concomitant atrial fibrillation), non-CVD associated with poor prognosis, systemic treatment with strong inhibitors of both CYP3A4 and P-gp, hepatic disease associated with coagulopathy, pregnant or breastfeeding
Drugs	**Intervention**	Rivaroxaban 2.5 mg twice daily (in combination with ASA 100 mg once daily) Rivaroxaban 5 mg twice daily (alone)
	Comparator(s)	ASA 100 mg once daily
Duration	**Phase**	
	Run-in	28 days
	Double-blind	Mean duration of follow-up was 23 months Trial was event-driven: Trial was designed to continue until at least 2,200 patients experienced the primary efficacy outcome but was terminated early (at 60% of planned events) after a pre-planned interim analysis
	Follow-up	5 years
Outcomes	**Primary End Point**	Composite of MI, stroke, or CV death
	Other End Points	Secondary end points: • composite of CV death, MI, ischemic stroke, or ALI • composite of CHD death, MI, ischemic stroke, or ALI • mortality by any cause Tertiary end points:

		COMPASS
		• hospitalization for CV reasons • revascularization • amputation • EQ-5D-3L (vertical VAS out of 100) • stent thrombosis • unstable angina • worsening angina • heart failure • resuscitated cardiac arrest • new diagnosis of cancer • recurrence of cancer • VTE • individual components of primary and secondary end points
NOTES	**Publications**	Eikelboom 2017,[17] Connolly 2017,[15] Anand 2018,[14] Anand 2017.[16]

ABI = ankle-brachial index; ALI = acute limb ischemia; ASA = acetylsalicylic acid; CABG = coronary artery bypass graft; CAD = coronary artery disease; CHD = coronary heart disease; CVD = cardiovascular disease; DAPT = dual antiplatelet therapy; DB = double-blind; EF = ejection fraction; eGFR = estimated glomerular filtration rate; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; MI = myocardial infarction; NYHA = New York Heart Association; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention; P-gp = P-glycoprotein; RCT = randomized controlled trial; VAS = visual analogue scale; VTE = venous thromboembolism.

[a] Stenosis of greater than or equal to 50% in two or more coronary arteries, or in one coronary territory if at least one other territory has been revascularized.

Source: Clinical Study Report.[18]

Included Studies

Description of Studies

COMPASS was a phase III, double-blind, double-dummy, placebo-controlled, superiority randomized controlled trial (RCT). The trial used a 3×2 partial factorial design to randomize 27,395 patients with CAD and/or PAD to treatment groups. The trial had two primary objectives:

- to determine whether rivaroxaban 2.5 mg twice daily in combination with ASA 100 mg daily compared with ASA 100 mg daily reduces the risk of a composite outcome of MI, stroke, or CV death in patients with CAD or PAD
- to determine whether rivaroxaban 5 mg twice daily compared with ASA 100 mg daily reduces the risk of a composite outcome of MI, stroke, or CV death in patients with CAD or PAD.

This review only evaluates the rivaroxaban/ASA versus ASA comparison, which is aligned with the Health Canada–recommended treatment regimen. The trial design is shown in Figure 2.

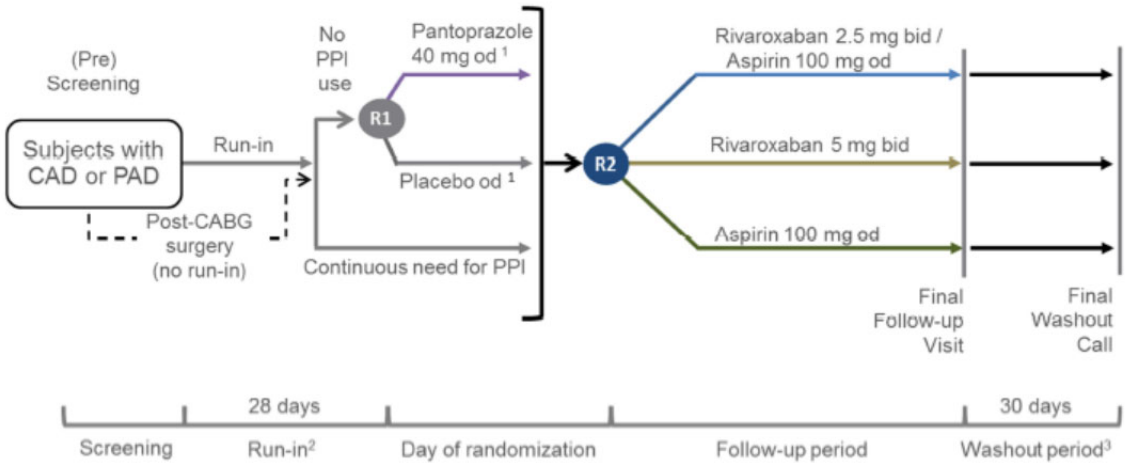
COMPASS was also designed to evaluate the efficacy of pantoprazole compared with placebo for the prevention of upper GI events in patients with CAD or PAD receiving antithrombotic medications (randomization period 1 [R1]); however, the results of this part of the study are not yet available, as this part of the trial is ongoing.

There was a 28-day run-in period before randomized treatment began. The specific aim(s) of the run-in period are not outlined in the protocol or Clinical Study Report. During the run-in, participants discontinued existing antithrombotics and took ASA 100 mg once daily and placebo rivaroxaban twice daily. Following run-in, patients who required proton pump

inhibitor (PPI) therapy could continue their PPI; however, patients with no indication for PPI were randomized 1:1 to receive pantoprazole or placebo (R1 in Figure 2). All patients were then randomized 1:1:1 to receive ASA/rivaroxaban combinations (randomization period 2 [R2] in Figure 2) and stratified according to centre and PPI status (continuous PPI, randomized to PPI, randomized to placebo).

COMPASS also aimed to evaluate whether rivaroxaban 2.5 mg twice daily in combination with ASA or rivaroxaban 5 mg twice daily alone reduces the risk of bypass graft failure, as well as a composite of MI, stroke, or CV death, compared with ASA alone in patients who are four to seven days post–coronary artery bypass graft (CABG). Thus, patients who had undergone CABG surgery could be randomized four to seven days post-surgery if they met the inclusion criteria (Figure 2). These patients underwent the same screening and follow-up as other patients and were included in the main analysis. The planned analysis of graft patency has not yet been completed.

Figure 2: COMPASS Design Schematic



R1 and R2 were performed at same time via the PHRI randomization and drug management system. All study treatments were to be started on the day of randomization or one day thereafter.

1 The pantoprazole/placebo arms of the trial are still ongoing and will be reported at a later stage based on the second database release
2 Aspirin 100 mg od and rivaroxaban placebo as run-in medication
3 Subjects treated according to local standard of care

bid = twice daily; CABG = coronary artery bypass graft; CAD = coronary artery disease; od = once daily; PAD = peripheral artery disease; PHRI = Population Health Research Institute; PPI = proton pump inhibitor; R = randomization.

Source: Clinical Study Report.[18]

Populations

Inclusion and Exclusion Criteria

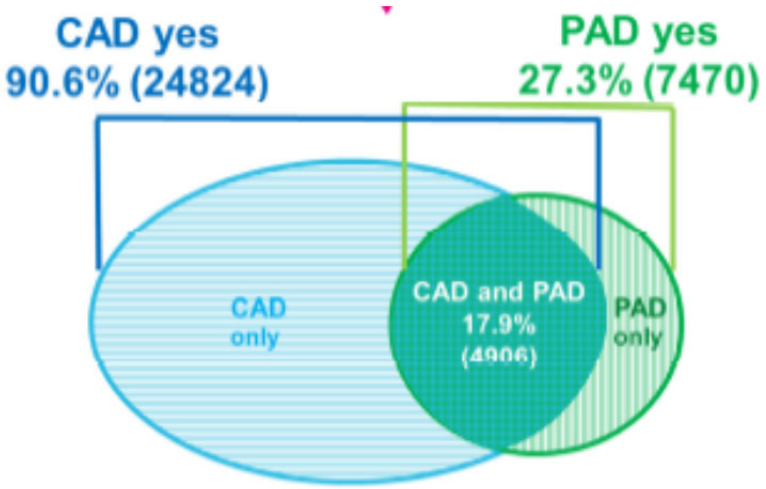
Patients were eligible if they had stable CAD and/or PAD (i.e., they met the definition of CAD and/or PAD outlined in Table 4). Patients could have also entered the trial four to seven days post-CABG surgery if they met the other inclusion criteria. People at high risk of bleeding, based on clinician judgment, were excluded from the trial. Further, people were

excluded if they had an indication for DAPT (e.g., post–acute coronary syndrome [ACS]) or an anticoagulant (e.g., atrial fibrillation).

Baseline Characteristics

The study population was predominantly male (78%) with a mean age of 68 years. There were no notable differences in baseline characteristics between groups. Most participants (91%) had CAD (alone or with PAD), while approximately 27% had PAD, and 18% had both CAD and PAD (Figure 3). Approximately 38% of participants had diabetes. Concomitant medication use was common and included lipid-lowering drugs (90%), ACEIs / angiotensin receptor blockers (71%), beta blockers (70%), and [redacted], which was balanced across groups. Approximately 54% of participants had previously had percutaneous coronary intervention (PCI) and 29% had prior CABG surgery (5% had surgery immediately prior to randomization). In the subgroup populations (CAD only, PAD only, concomitant CAD/PAD), there were no notable differences in baseline characteristics across treatment groups.

Figure 3: Coronary Artery Disease and Peripheral Artery Disease in COMPASS



CAD = coronary artery disease; PAD = peripheral artery disease.

Source: Clinical Study Report.[18]

Table 5: Summary of Baseline Characteristics

	COMPASS	
	Rivaroxaban/ASA (n = 9,152)	ASA (n = 9,126)
Age, mean (SD)	68.3 (7.9)	68.2 (8.0)
Age < 65, n (%)	2,150 (23.5)	2,184 (23.9)
Age 65 to 74, n (%)	5,078 (55.5)	5,045 (55.3)
Age ≥ 75, n (%)	1,924 (21.0)	1,897 (20.8)
Male, n (%)	7,093 (77.5)	7,137 (78.2)
Race, n (%)		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

	COMPASS	
	Rivaroxaban/ASA (n = 9,152)	ASA (n = 9,126)
White	5,673 (62.0)	5,682 (62.3)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Black	76 (0.8)	92 (1.0)
BMI (kg/m^2), mean (SD)	28.3 (4.8)	28.4 (4.7)
Baseline SBP, mean (SD) mm Hg	136 (17)	136 (18)
Baseline DBP, mean (SD) mm Hg	77 (10)	78 (10)
ABI, mean (SD)	1.10 (0.20)	1.10 (0.21)
Tobacco use, n (%)		
Never	2,922 (31.9)	2,903 (31.8)
Former	4,286 (46.8)	4,251 (46.6)
Current	1,944 (21.2)	1,972 (21.6)
Prior coronary PTCA/atherectomy/PCI, n (%)	4,971 (54.3)	4,905 (53.7)
Prior CABG surgery, n (%)		
Study baseline	502 (5.5)	463 (5.1)
Prior history	2,202 (24.1)	2,123 (23.3)
Baseline eGFR (mL/min), mean (SD)	73.9 (17.9)	73.7 (18.1)
eGFR 15 mL/min to 29 mL/min, n (%)	77 (0.8)	86 (0.9)
eGFR 30 mL/min to 59 mL/min, n (%)	1,977 (21.6)	2,028 (22.2)
eGFR ≥ 60 mL/min, n (%)	7,094 (77.5)	7,012 (76.8)
Baseline total cholesterol (mg/dL), mean (SD)	167.2 (177.9)	167.0 (180.4)
CAD, n (%)	8,313 (90.8)	8,261 (90.5)
CAD only, n (%)	6,657 (72.7)	6,620 (72.5)
PAD, n (%)	2,492 (27.2)	2,504 (27.4)
PAD only, n (%)	836 (9.1)	863 (9.5)
CAD and PAD, n (%)	1,656 (18.1)	1,641 (18.0)
MI, n (%)	5,654 (61.8)	5,721 (62.7)
Diabetes, n (%)	3,448 (37.7)	3,474 (38.1)
Hypertension, n (%)	6,907 (75.5)	6,877 (75.4)
Any stroke, n (%)	351 (3.8)	335 (3.7)
Heart failure, n (%)	1,963 (21.4)	1,979 (21.7)
Medication use, n (%)		
ACEI/ARB	6,475 (70.7)	6,462 (70.8)
[redacted]	[redacted]	[redacted]
Diuretic	2,727 (29.8)	2,746 (30.1)
Lipid-lowering drug	8,239 (90.0)	8,158 (89.4)
CCB	2,413 (26.4)	2,482 (27.2)
Beta blocker	6,389 (69.8)	6,394 (70.1)
NSAID	531 (5.8)	473 (5.2)
[redacted]	[redacted]	[redacted]

ABI = ankle-brachial index; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ASA = acetylsalicylic acid; BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; CCB = calcium channel blocker; CV = cardiovascular; DAPT = dual antiplatelet therapy; DB = double-blind; DBP = diastolic blood pressure; EF = ejection fraction; eGFR = estimated glomerular filtration rate; MI = myocardial infarction; NSAID = nonsteroidal anti-inflammatory drug; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention; P-gp = P-glycoprotein; PTCA = percutaneous transluminal coronary angioplasty; RCT = randomized controlled trial; SBP = systolic blood pressure; SD = standard deviation.

Source: Clinical Study Report.[18]

Interventions

COMPASS compared rivaroxaban 2.5 mg twice daily plus ASA 100 mg once daily with ASA 100 mg once daily, and rivaroxaban 5 mg twice daily to ASA 100 mg once daily. Only the former comparison was considered in the CDR systematic review based on the expected Health Canada–recommended regimen. The study used matched placebos to maintain blinding. If participants were not taking pantoprazole at baseline they were also randomized to receive pantoprazole 40 mg once daily or matched placebo. A summary of intervention groups is in Figure 4. Concomitant medication use was allowed if it was not a medication contraindicated with use of rivaroxaban (Table 4). Other anticoagulants and antiplatelets other than ASA were also prohibited.

Figure 4: Interventions in COMPASS

Study Arm	Treatment Assignments	
A	Rivaroxaban 2.5 mg bid + Aspirin 100 mg od + Pantoprazole 40 mg od	Rivaroxaban 2.5 mg bid + Aspirin 100 mg od + Pantoprazole placebo od
B	Rivaroxaban 5 mg bid + Aspirin placebo od + Pantoprazole 40 mg od	Rivaroxaban 5 mg bid + Aspirin placebo od + Pantoprazole placebo od
C	Rivaroxaban placebo + Aspirin 100 mg od + Pantoprazole 40 mg od	Rivaroxaban placebo + Aspirin 100 mg od + Pantoprazole placebo od

bid = twice daily; od = once daily.

Source: Clinical Study Report.[18]

Outcomes

The primary efficacy outcome in COMPASS was the composite of stroke, MI and CV death. The secondary outcomes were the composite of CV death, MI, ischemic stroke or ALI and the composite of coronary heart disease (CHD) death, MI, ischemic stroke or ALI, as well as all-cause mortality. Tertiary outcomes included hospitalization for CV reasons, revascularization (coronary and non-coronary), amputation, and health-related quality of life measured via the EuroQol 5-Dimensions 3-Levels questionnaire (EQ-5D-3L), among others (Table 4). The investigators also reported the individual components of the composite outcomes.

The definition of MI was based on the “third definition of MI” (included non-procedural MI, peri-procedural MI, and probable MI).[19] This is the third version of the criteria proposed for definition of an MI by the Joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation Task Force for the Universal Definition of Myocardial Infarction. Stroke was defined as the presence of acute focal neurological deficit of vascular origin and signs and symptoms lasting 24 hours or longer, or to time of death. Strokes were adjudicated by the study Stroke Expert Group, but no further details on adjudication were provided. Deaths were adjudicated by a national leader or delegate using an algorithm (no further detail provided in the Clinical Study Report). CV deaths were defined as a death where a definite non-CV cause had not been

identified. Uncertain deaths were presumed CV, unless they could be proven otherwise. CHD death was classified as death due to acute MI, sudden cardiac death, or death due to a CV procedure (felt by investigators to be more specific for deaths resulting from underlying CV disease). ALI was limb-threatening ischemia confirmed by limb hemodynamics or imaging that led to a vascular intervention within 30 days of onset of symptoms. Limb ischemia events were adjudicated by the PAD Expert Group. A post-hoc analysis[14] included the outcome of major adverse limb events (MALEs), which was a composite of acute or chronic limb ischemia and major vascular amputations.

The EQ-5D-3L is a generic health-related quality-of-life instrument that has been applied to a wide range of health conditions and treatments. COMPASS only presented analysis for the vertical visual analogue scale (VAS) component of the EQ-5D-3L, which comprises a 20 cm vertical VAS on which a patient provides self-rated health state ranging from "the best imaginable health state," labelled as 100 on the VAS, to "the worst imaginable health status," labelled as 0 on the VAS. Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ-VAS that best represents their health on that day. No information validating the EQ-5D-3L in patients with CAD or PAD has been reported, and the minimal clinically important difference (MCID) specifically in patients with CAD or PAD has not been identified.

The primary safety outcome was major bleeding. This was based on modified International Society on Thrombosis and Haemostasis (ISTH) criteria for major bleeding and was defined as:

- fatal bleeding or
- symptomatic bleeding in a critical area or organ (intracranial, intraocular, intraarticular, intraspinal, liver, pancreas, pericardial, respiratory, adrenal gland or kidney, retroperitoneal or intramuscular with compartment syndrome) or bleeding into a surgical site requiring re-operation or
- bleeding leading to hospitalization (including presentation to an acute care facility without an overnight stay).

An adverse event (AE) was defined as any untoward medical occurrence, while a serious adverse event (SAE) was defined as any untoward medical occurrence that resulted in death, was life-threatening, required inpatient hospitalization, or resulted in persistent disability/incapacity. Bleeding was adjudicated using an algorithm by an events committee (no further details provided).

Statistical Analysis

COMPASS was designed as an event-driven RCT to detect a 20% relative risk reduction between rivaroxaban/ASA and ASA alone with 90% power after 2,200 patients had experienced the primary efficacy outcome. Two interim analyses were planned, when 1,100 (50%) and 1,650 (75%) primary outcome events occurred. The investigators assumed an annual incidence rate of 4% to 5% for the primary outcome in the ASA group and the discontinuation of the study drug at a rate of 6% in the first six months, 4% in the second six months, and 3% thereafter. Unblinding occurred only if essential for patient safety. The investigators noted that interruption of the study drug and knowledge of possible treatments were generally sufficient and, if unblinding occurred, only those who required the information were provided with it. [redacted] A modified Haybittle–Peto rule was

used to account for type I error from interim analyses and to aid in the decision regarding early stopping of the study for futility or efficacy: the log rank Z statistic for the comparison between rivaroxaban/ASA and ASA for the primary efficacy outcome had to be a reduction of four standard deviations at the first interim analysis, or a reduction of three standard deviations at the second interim analysis (no further details were provided on the rationale for standard deviations). If this threshold was crossed at either interim analysis, then data were reanalyzed three to six months later to confirm consistency of the effect. The trial was stopped after the first interim assessment because the efficacy threshold was met.

All analyses were conducted using the intention-to-treat (ITT) principle. Time-to-event occurrence was evaluated using Kaplan–Meier estimates of the cumulative risk. Participants without a documented evaluable event were censored at the earliest cut-off date (i.e., first planned interim analysis) and at the last contact date (as a sensitivity analysis). The main analysis was for events censored at the cut-off date. If no status information was available at the end of the study, the last follow-up contact date where status was known was used as the censoring date (if there were no events up to that point, the participant was deemed event-free). The efficacy of rivaroxaban/ASA was compared with ASA by calculating hazard ratios (HRs) and 95% confidence intervals (CIs). These were estimated from two stratified Cox proportional hazards models (stratified based on PPI use: not randomized to PPI, received pantoprazole, or received placebo), which were not adjusted for any baseline covariates.

Statistical testing had to allow for three sources of multiplicity:

- two interim analyses and one final analysis for the primary efficacy end point to allow for early stopping
- in the final analysis, two treatment comparisons, rivaroxaban 2.5 mg twice daily plus ASA versus ASA alone (the dose and comparison of interest in this report), and rivaroxaban 5.0 mg twice daily versus ASA (mentioned here because of its inclusion in the hierarchy)
- in the final analysis, four end points for each treatment comparison (one primary end point and three secondary end points).

The four outcomes for treatment comparison were as follows:

- primary outcome: Composite of MI, stroke, or CV death
- first secondary outcome: Composite of major thrombotic events (CHD death, MI, ischemic stroke, and ALI)
- second secondary outcome: Composite of major thrombotic events (CV death, MI, ischemic stroke, and ALI)
- third secondary outcome: Mortality.

For the planned final analysis, a Hochberg-based gatekeeping procedure was used. The eight null hypotheses combining two comparisons and four end points were grouped into four families (Figure 5). Within each family, the corresponding end point was tested for both treatment comparisons (two arms).

Testing was planned to proceed sequentially from family 1 through to family 4. Within each arm of the analysis (i.e., rivaroxaban/ASA versus ASA, and rivaroxaban versus ASA), the next family would be tested only if the null hypothesis for the previous step within that arm was rejected. For the first three steps (family 1 through family 3), a truncated Hochberg-

based test was used, which allowed testing in one arm to continue, even if testing in one of the two arms failed to reject the null hypothesis (provided that the significant test met a certain threshold), and more stringent criteria were applied in subsequent steps. In the planned final analysis, as long as both comparisons had rejected the null hypothesis in the previous step, testing was at a level of significance $P < 0.0475$ (derived from alpha = 0.05). If one comparison had failed to reject the null hypothesis with $P < 0.0475$, while the other had rejected with $P < 0.025$, testing would continue in the second arm with P set at 0.0025, either until the null hypothesis was not rejected ($P \geq 0.0025$) or the end of the hierarchy. If $P \geq 0.025$ for the significant arm, testing in both arms would stop.

If one intervention were stopped early for efficacy, testing was expected to proceed as planned using all available data, on the assumption that the P value for the primary efficacy end point for the arm that stopped early would be $P < 0.025$ (criteria for stopping $P < 0.0001267$). There was no prospective planning for testing of secondary end points if multiple arms were stopped early. Since the decision was made, following the first interim analysis, to stop rivaroxaban/ASA, rivaroxaban, and ASA, several post-hoc strategies were developed between the decision itself and the release of the first clinical database:

A. Hierarchical testing per comparison, according to the modified Haybittle–Peto rule applied for the first interim analysis. Hypotheses were tested hierarchically against a two-sided α of 0.0000633 ($P < 0.0000633$ to reject, derived from the alpha used for the interim analysis) within each of the two arms.

B. Hochberg-based gatekeeping, which applied the planned strategy described previously, for two sets of conditions:

   - using the type I error level used for the interim analysis ($\alpha = 0.0001267$) instead of the planned $\alpha = 0.05$ for the calculation of significance thresholds (Haybittle–Peto / Haybittle–Peto)

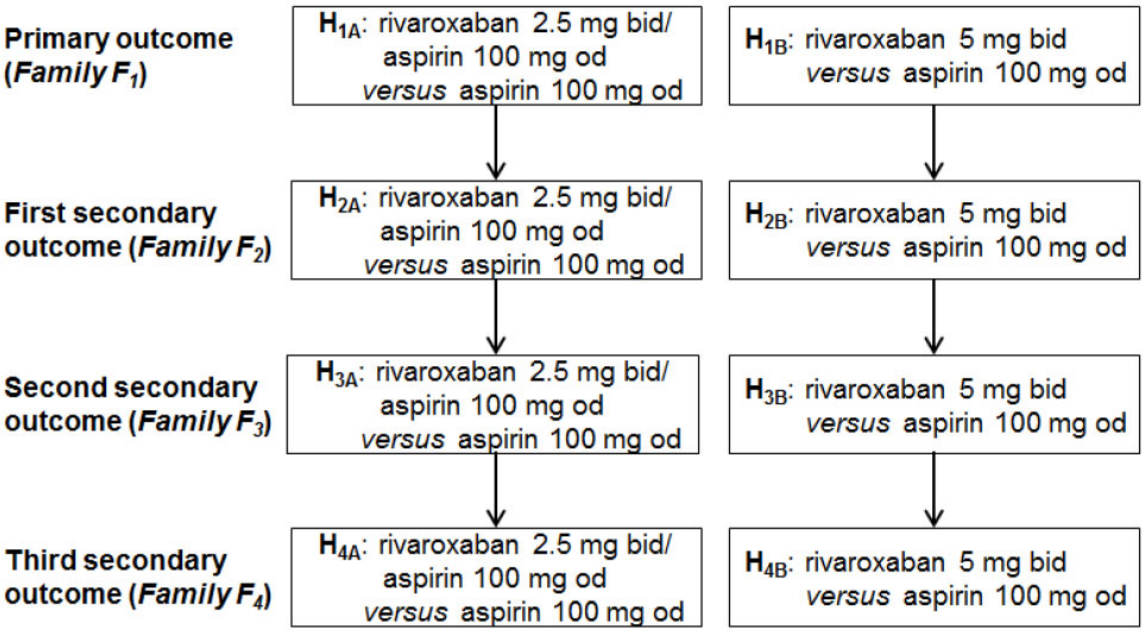
     [redacted].

C. Hochberg-based gatekeeping using $\alpha = 0.05$ as originally planned, disregarding the early discontinuation.

Tertiary outcomes were evaluated in the same way as the primary and secondary outcomes (e.g., calculating HRs using stratified Cox proportional hazards models and Kaplan–Meier estimates); however, tertiary outcomes were not adjusted for multiplicity.

Several subgroup analyses, including by subpopulation (CAD only, PAD only, CAD plus PAD), were pre-specified. Subgroup data were analyzed by adding a subgroup covariate to the stratified Cox proportional hazards model used in the main analysis and including a subgroup interaction term in the model. Subgroup analyses were not adjusted for multiplicity.

Figure 5: Outcome Testing in COMPASS



bid = twice daily; od = once daily.

Source: Clinical Study Report.[18]

Analysis Populations

COMPASS had two analysis sets. The ITT set included all randomized patients. The safety set comprised all unique randomized patients who received at least one dose of study medication.

Patient Disposition

Patient disposition for COMPASS is described in Table 6 and the CONSORT diagram is in Figure 6. The ITT population included all patients randomized in both arms. The discontinuation rate was higher in the rivaroxaban/ASA arm compared with the ASA-alone group, which was driven by AEs (primarily bleeding). A total of 9,797 patients were on continuous PPI therapy [redacted] (Figure 2), while 17,598 were randomized to pantoprazole/placebo at R1. A total of 27,395 were randomized 1:1:1 to rivaroxaban 2.5 mg twice daily plus ASA 100 mg daily, rivaroxaban 5 mg twice daily, or ASA 100 mg daily at R2 (Figure 2). In the rivaroxaban/ASA group 502 patients (5.5%) entered the trial four to seven days post-CABG compared with 463 (5.1%) in the ASA-alone group.

Table 6: Patient Disposition

	COMPASS	
	Rivaroxaban/ASA	**ASA**
[redacted]	[redacted]	
Randomized to rivaroxaban 2.5 mg b.i.d./ASA 100 mg daily, rivaroxaban 5 mg b.i.d., or ASA 100 mg daily; N	27,395	
Randomized, N (%)	9,152 (33.4)	9,126 (33.3)
Discontinued, N (%)		
Both rivaroxaban/placebo and ASA/placebo[a]	1,544 (16.9)	1,452 (15.9)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
ITT, N	9,152 (100)	9,126 (100)
PP, N	NA	NA
Safety, N	9,134 (99.8)	9,107 (99.8)

ASA = acetylsalicylic acid; b.i.d. = twice daily; CABG = coronary artery bypass graft; ITT = intention-to-treat; NA = not applicable; PP = per-protocol; SAE = serious adverse event.

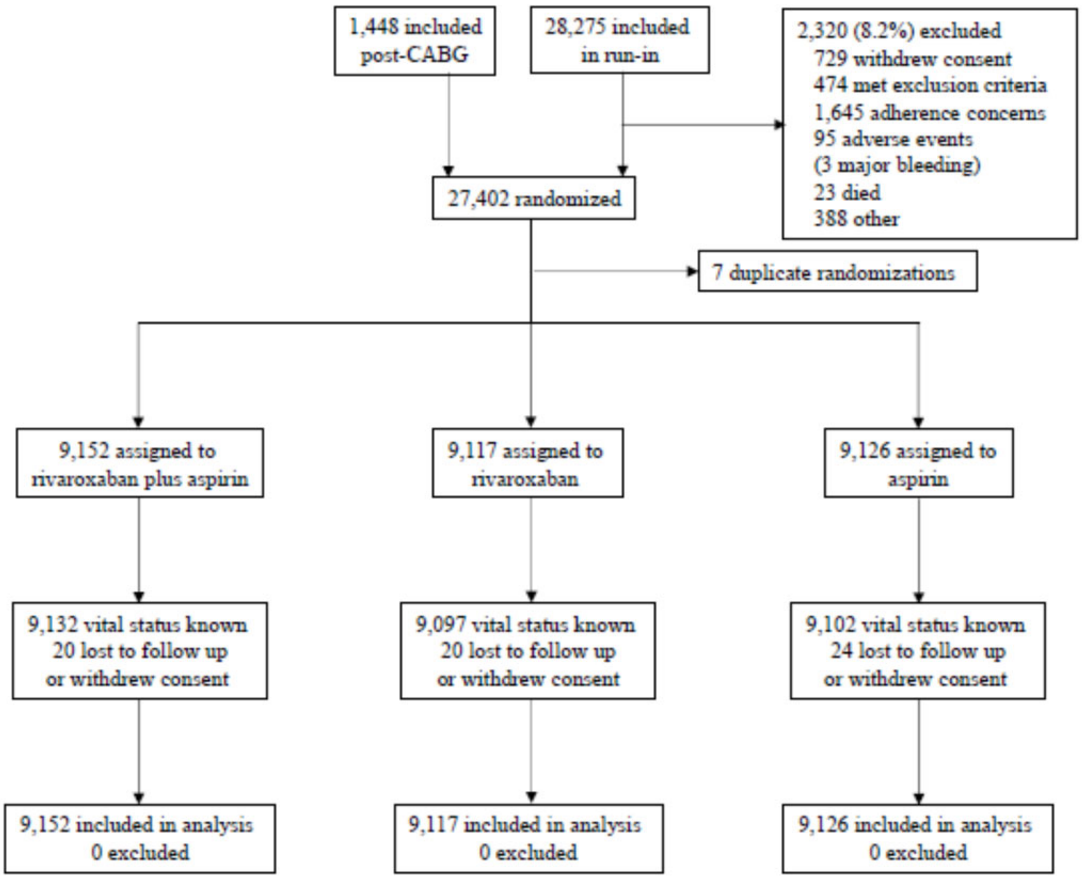
[a] Discontinued both the rivaroxaban/placebo and ASA/placebo treatments.

[b] Discontinued only the rivaroxaban/placebo part of the treatment.

[c] Discontinued only the ASA/placebo part of the treatment.

Source: Clinical Study Report.[18]

Figure 6: CONSORT Diagram for COMPASS



CABG = coronary artery bypass graft.

Source: Eikelboom 2017.[17]

Exposure to Study Treatments

The extent of exposure was calculated based on the date of the last double-blind dose of study treatment subtracted by the randomization date plus one. Adherence was defined as the patient taking at least 80% of the required pills and was assessed by visit and according to randomized treatment. The investigators also evaluated the number of study-drug interruptions and dose reductions.

The median duration of treatment and interquartile range was [redacted] in the rivaroxaban/ASA group and [redacted] in the ASA group. The proportion of participants taking at least [redacted] of pills was approximately [redacted] in both arms at the [redacted]month visit and, at [redacted] years, the proportion was around [redacted] in both arms.

Critical Appraisal

Internal Validity

COMPASS was at low risk of bias for randomization, allocation concealment, and blinding.[20] Randomization and allocation were carried out using a centralized computer system and were conducted by an external agency. Maintenance of blinding (e.g., through use of identical-looking medication tablets, etc.) was not described in the study protocol. There was high risk of bias for selective outcome reporting, since the composite secondary outcome originally outlined in the trial protocol (composite of MI, stroke, CV death, venous thromboembolism, and CV hospitalization) was not reported in the final report. While an amendment noted that new additional secondary outcomes (those outlined in Table 4) would be included, they did not mention removing the original secondary outcome. Similarly, the outcome of MALE (composite of limb ischemia and major amputations) was reported in a separate publication,[14] but this outcome was not defined in the COMPASS protocol. The rate of missing data was low and similar across groups. Baseline characteristics were similar between groups. The detailed risk of bias assessment is in Appendix 4.

The dosing and administration of ASA was appropriate. Although ASA 100 mg is not used in Canada, it is considered therapeutically similar to an 81 mg dose.[21] The dosage of rivaroxaban (2.5 mg twice daily) in COMPASS is not used in Canada, though it was approved by the European Medicines Agency in 2013 to prevent CV events following ACS.[22] However, the efficacy and safety of a 2.5 mg dose in the stable CAD population had not been investigated prior to COMPASS.

The investigators conducted all analyses according to the ITT principle. The interim analysis proceeded as outlined in the protocol and the trial was stopped early due to what the manufacturer described as “consistent benefit” of rivaroxaban/ASA over ASA over three months, per the pre-specified criteria for stopping the trial early for efficacy. The investigators suggested that their stopping rule was conservative, meaning the type I error associated with stopping the trial early was negligible. Though there are concerns with the overestimation of treatment benefit (which has been consistently demonstrated in trials that were stopped early),[23] the total number of events in COMPASS was high (over 1,300) for the primary efficacy composite outcome, which may minimize the risk of inflated treatment effect. Secondary and tertiary outcomes with larger effect estimates and/or fewer events, such as ALI, may be more susceptible to bias due to early termination. It is acknowledged that the criteria used to declare treatment discontinuation for efficacy were conservative and the risk of inflated type I error is likely minimal. Likewise, although the procedures used for testing the three key secondary outcomes at the time of the interim analysis were post hoc, they were also conservative and likely also minimized the risk of type I error. For the interim efficacy and safety analysis, an independent data safety and monitoring board and an independent statistician reviewed unblinded event rates.

The trial was adjusted for multiplicity for the primary and secondary outcomes but not for the tertiary outcomes or subgroup analyses. Thus, there is a concern surrounding type I error with tertiary outcomes and subgroup analyses, and these results should be regarded as descriptive. The subgroup analyses were pre-specified in the protocol according to CAD and PAD status. However, as mentioned previously, the analysis of the composite of MALEs was not described in the protocol.

Deaths with an uncertain cause were coded as CV-related. Overall, few events were coded using this approach, although the occurrence was differential between treatment groups (12 of 160 [7.5%] events in the rivaroxaban/ASA group and 7 of 203 [3.4%] events in the ASA-alone group). Differential misclassification of a component of the primary outcome is a concern; however, as the difference in this instance would potential go in the direction against rivaroxaban/ASA treatment, and the events were infrequent, this likely had minimal impact on the observed efficacy results.

External Validity

The inclusion criteria in COMPASS were fairly broad; however, the majority of the study population had a history of MI (62%), an estimated glomerular filtration rate (eGFR) greater than 60 mL/min (77%), and a history of PCI (54%) and/or CABG (24%). Only 4% of the study population had a history of stroke. Participants generally had long-term CAD. For example, of participants with a previous MI, the mean duration since the last MI was seven years. [redacted]. Thus, the findings are most generalizable to those with a remote history of MI or cardiac revascularization procedure and no history of stroke. The applicability of the findings in those with poor renal function, a history of stroke, or no history of MI or cardiac revascularization is less clear. Further, the results would not apply to patients who are at high bleeding risk or who have an indication for DAPT, as these patients were excluded from COMPASS. One challenge is that high bleeding risk was not defined in the study protocol and was left up to clinician judgment. Therefore, it is unclear how a clinician might explicitly judge appropriateness of therapy (regarding bleeding risk) in clinical practice. According to the clinical expert consulted by CADTH, the study population is likely reasonably representative of the stable CAD population in Canada in terms of concomitant medication use and medical conditions. An external applicability study[24] found that 53% of patients in a large administrative database of CAD patients would meet COMPASS eligibility; common reasons for exclusion were high bleeding risk and anticoagulant usage. However, the patients in this registry had a higher event rate than those in the ASA arm of COMPASS. Thus, COMPASS participants may have been at lower risk of events than those in the general population.

The majority of participants (78%) in COMPASS were male. Approximately 14% of participants were from North America (8.9% from Canada) and 31% from Western Europe; 62% of participants were white and 16% were Asian. Thus, the findings from COMPASS are likely generalizable to the Canadian population. The comparator in COMPASS was ASA, which is the current standard antithrombotic therapy in individuals with CAD and/or PAD,[8] and is therefore a reasonable comparator.

Approximately 8% of patients did not complete the 28-day run-in period, with the most common reason being nonadherence (5.8%). During run-in, all patients received ASA 100 mg once daily; there were three major bleeds and 95 AEs during run-in. Since nonadherent patients were screened out of the trial, there is uncertainty about the real-world effectiveness of rivaroxaban/ASA compared with ASA. The mean duration of follow-up in COMPASS was around two years [redacted], though the trial was stopped early. Given the high annual rate of CV events in the stable CAD population, this was still a meaningful duration of follow-up for a difference between treatment and control to be detected. However, since the trial was stopped early, the longer-term efficacy and safety (e.g., over five years) is unclear, which is a challenge, considering CAD and PAD are chronic diseases with treatment likely persisting for many years.

COMPASS included outcomes that were reported as being important to patients according to the patient group input for this review, particularly future CV events. Patient function was also noted to be important but was not directly measured in COMPASS. Quality of life was measured using the EQ-5D-3L, which is a well validated general measure of health-related quality life. However, the EQ-5D-3L has not been validated specifically in the stable CAD population (Appendix 6).

Efficacy

Only those efficacy outcomes identified in the review protocol are reported in Table 7. Additional data from COMPASS in the PAD subpopulation with respect to the composite MALEs outcome can be found in Appendix 5.

Efficacy Outcomes

Fewer patients treated with rivaroxaban/ASA experienced the primary composite outcome than those treated with ASA alone (4.1% versus 5.4%). The risk of the primary outcome occurring was lower in the rivaroxaban/ASA arm compared with ASA alone (HR 0.76; 95% CI, 0.66 to 0.86). For the components of the primary outcome, the HRs comparing rivaroxaban/ASA with ASA alone were: MI (HR 0.86; 95% CI, 0.70 to 1.05), stroke (HR 0.58; 95% CI, to 0.44 to 0.76) and CV death (HR 0.78; 95% CI, 0.64 to 0.96), though these were tested outside of the statistical hierarchy. Strokes were primarily ischemic (64 out of 83 [77%] in the rivaroxaban/ASA group and 125 out of 142 [88%] in the ASA group). The proportion of patients with hemorrhagic stroke in the rivaroxaban/ASA group was 15 out of 83 (18%) compared with 10 out of 142 (7%) in the ASA group.

The risk of the secondary composite outcome of MI, ischemic stroke, ALI, and CHD 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 MI, ischemic stroke, ALI, and CV death (HR 0.74; 95% CI, 0.65 to 0.85). These composite outcomes were adjusted for multiplicity (see Table 7 and the Statistical Analysis section). All-cause mortality was lower in the rivaroxaban/ASA group compared with ASA alone (HR 0.82; 95% CI, 0.71 to 0.96); however, the between-group difference should be interpreted with caution because the *P* value was greater than the pre-specified threshold (i.e., $P > 0.0025$) for the hierarchical statistical analysis plan for COMPASS. Fewer patients experienced ALI in the rivaroxaban/ASA group compared with ASA alone (HR 0.55; 95% CI, 0.32 to 0.92). There was no difference between the two groups for heart failure (HR 1.02; 95% CI, 0.84 to 1.24) and [redacted].

The risk of CV hospitalizations was lower in the rivaroxaban/ASA group compared with ASA (HR 0.92; 95% CI, 0.85 to 0.99), though this was outside of the statistical hierarchy. There was no difference between groups for amputations (HR 0.64; 95% CI, 0.40 to 1.00) and venous thromboembolism (HR 0.61, 95% 0.37 to 1.00).

As there was no pre-planned strategy for testing secondary end points should the decision be made to discontinue multiple interventions, four potential strategies were applied in a post-hoc analysis (Table 8). For the hierarchy that tested both arms (comparisons) separately (A), each against a two-sided $\alpha = 0.0000633$, the null hypothesis was rejected for the first two secondary end points but not for the third. In the analysis that used Hochberg-based gatekeeping based on significance levels reserved for the first interim analysis (B), the null hypothesis was not rejected for any of the secondary efficacy

end points. Those in the rivaroxaban/ASA group versus ASA were tested against the extremely small α defined for a single-arm hierarchy. In the hierarchy that used Hochberg-based gatekeeping at $\alpha = 0.05$, which was planned for the final analysis, the null hypothesis of no difference between rivaroxaban/ASA and ASA was rejected for the first secondary end point (CHD death, MI, ischemic stroke, and ALI) and the second secondary end point (CHD death, MI, ischemic stroke, and ALI), but not for the third (all-cause mortality).

[redacted]

Table 7: Efficacy Outcomes

	COMPASS	
	Rivaroxaban/ASA (n = 9,152)	**ASA (n = 9,126)**
COMPOSITE OF MI, STROKE, OR CV DEATH[a]		
N (%)	379 (4.1)	496 (5.4)
HR (95% CI)	0.76 (0.66 to 0.86)	
P value	0.00004	
MI[b]		
N (%)	178 (1.9)	205 (2.2)
HR (CI)	0.86 (0.70 to 1.05)	
P value	0.14	
STROKE[b]		
N (%)	83 (0.9)	142 (1.6)
HR (95% CI)	0.58 (0.44 to 0.76)	
P value	0.00006	
CV DEATH[b]		
N (%)	160 (1.7)	203 (2.2)
HR (95% CI)	0.78 (0.64 to 0.96)	
P value	0.021	
COMPOSITE OF MI, ISCHEMIC STROKE, ALI, CHD DEATH[a]		
N (%)	329 (3.6)	450 (4.9)
HR (95% CI)	0.72 (0.63 to 0.83)	
P value	0.00001	
ALI[b]		
N (%)	22 (0.2)	40 (0.4)
HR (95% CI)	0.55 (0.32 to 0.92)	
P value	0.021	
COMPOSITE OF MI, ISCHEMIC STROKE, ALI, CV DEATH[a]		
N (%)	389 (4.3)	516 (5.7)
HR (95% CI)	0.74 (0.65 to 0.85)	
P value	0.00001	
ALL-CAUSE MORTALITY[a]		
N (%)	313 (3.4)	378 (4.1)
HR (95% CI)	0.82 (0.71 to 0.96)	
P value	0.011	
HEART FAILURE[b]		
N (%)	197 (2.2)	192 (2.1)
HR (95% CI)	1.02 (0.84 to 1.24)	

	COMPASS	
	Rivaroxaban/ASA (n = 9,152)	ASA (n = 9,126)
P value	0.84	
VTE[b]		
N (%)	25 (0.3)	41 (0.4)
HR (95% CI)	0.61 (0.37 to 1.00)	
P value	0.046	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
AMPUTATION[b]		
N (%)	30 (0.3)	47 (0.5)
HR (95% CI)	0.64 (0.40 to 1.00)	
P value	0.050	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

ALI = acute limb ischemia; ASA = acetylsalicylic acid; CAD = coronary artery disease; CCB = calcium channel blocker; CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; PPI = proton pump inhibitor; VTE = venous thromboembolism.

[a] Adjusted for multiplicity; HRs and 95% CIs calculated from Cox proportional hazards model stratified by PPI use.

[b] Not adjusted for multiplicity; HRs and 95% CIs calculated from Cox proportional hazards model stratified by PPI use.

[c] Not adjusted for multiplicity.

Source: Clinical Study Report.[18]

Table 8: Testing Decisions for Primary and Secondary Efficacy Analyses According to Potential Testing Strategies

Outcome	Comparison	Nominal *P* Value	A. Hierarchical by Comparison (α = 0.0000633, Two-Sided)	B1. Hochberg-Based, Haybittle–Peto/Haybittle–Peto (α = 0.0001267)	B2. Hochberg-Based, Haybittle–Peto/Pocock (α = 0.0001267)	C. Hochberg-Based Gatekeeping (α = 0.05)
Primary efficacy outcome	RIV/ASA versus ASA	0.000369	Yes	Yes	Yes	Yes
	RIV versus ASA	0.1148992	No	No	No	No
First secondary outcome	RIV/ASA versus ASA	0.0000068	Yes	No	No	Yes
Second secondary outcome	RIV/ASA versus ASA	0.0000107	Yes	No testing under hierarchy	No testing under hierarchy	Yes
Third secondary outcome	RIV/ASA versus ASA	0.0106195	No	No testing under hierarchy	No testing under hierarchy	No

ASA = acetylsalicylic acid; RIV = rivaroxaban.

Note: No = did not reject null hypothesis; yes = rejected null hypothesis.

Subgroups

Subgroup analyses were conducted in participants with CAD only, PAD only, and concomitant CAD and PAD. None of the analyses were adjusted for multiplicity. The risk of the primary outcome was lower in the rivaroxaban/ASA group compared with ASA alone for the CAD-only subgroup (HR 0.77; 95% CI, 0.66 to 0.91) and the concomitant CAD/PAD subgroup (HR 0.67; 95% CI, 0.52 to 0.87), but there was no difference in the PAD-only group (HR 0.89; 95% CI, 0.55 to 1.44). The risk of the composite outcome of MI, ischemic stroke, ALI, and CHD death was lower in the rivaroxaban/ASA group for the CAD-only population (HR 0.75; 95% CI, 0.63 to 0.90) [redacted], but there was no difference in the PAD-only population. Fewer patients treated with rivaroxaban/ASA experienced the composite outcome of MI, ischemic stroke, ALI, and CV death compared with ASA alone in the CAD-only population (HR 0.77; 95% CI, 0.65 to 0.90) [redacted], but not the PAD-only population (HR 0.88; 95% CI, 0.57 to 1.34). The risk of all-cause mortality was lower in the CAD-only population (HR 0.77; 95% CI, 0.64 to 0.94) but not the PAD population (HR 1.33; 95% CI, 0.87 to 2.01) [redacted]. Results for the comparisons for the components of the composite outcomes in the subgroups are in Table 9. Data on the rate of MALEs from the subgroup of patients with PAD are presented in Appendix 5. There were no subgroup analyses for tertiary outcomes.

Table 9: Subgroups

	COMPASS					
	CAD Only		PAD Only		Concomitant CAD and PAD	
	Rivaroxaban/ ASA (n = 6,657)	ASA (n = 6,620)	Rivaroxaban/ ASA (n = 836)	ASA (n = 863)	Rivaroxaban/ ASA (n = 1,656)	ASA (n = 1,641)
COMPOSITE OF MI, STROKE, OR CV DEATH[a]						
N (%)	253 (3.8)	322 (4.9)	32 (3.8)	36 (4.2)	94 (5.7)	138 (8.4)
HR (95% CI)	0.77 (0.66 to 0.91)		0.89 (0.55 to 1.44)		0.67 (0.52 to 0.87)	
P value	0.0023		0.64		0.0026	
MI[a]						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]		[redacted]	
P value	[redacted]		[redacted]		[redacted]	
STROKE[a]						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]		[redacted]	
P value	[redacted]		[redacted]		[redacted]	
CV DEATH[a]						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]		[redacted]	
P value	[redacted]		[redacted]		[redacted]	
COMPOSITE OF MI, ISCHEMIC STROKE, ALI, CHD DEATH[a]						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	0.75 (0.63 to 0.90)		0.78 (0.48 to 1.25)		[redacted]	
P value	0.0015		0.30		[redacted]	
ALI[a]						
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	NR		0.71 (0.30 to 1.67)		[redacted]	
P value	NR		0.42		[redacted]	
COMPOSITE OF MI, ISCHEMIC STROKE, ALI, CV DEATH[a]						
N (%)	247 (3.7)	318 (4.8)	40 (4.8)	46 (5.3)	[redacted]	[redacted]
HR (95% CI)	0.77 (0.65 to 0.90)		0.88 (0.57 to 1.34)		[redacted]	
P value	0.0016		0.54		[redacted]	
ALL-CAUSE MORTALITY [a]						
N (%)	184 (2.8)	236 (3.6)	51 (6.1)	39 (4.5)	[redacted]	[redacted]
HR (95% CI)	0.77 (0.64 to 0.94)		1.33 (0.87 to 2.01)		[redacted]	
P value	0.0084		0.18		[redacted]	

ALI = acute limb ischemia; ASA = acetylsalicylic acid; CAD = coronary artery disease; CCB = calcium channel blocker; CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; NNT = number needed to treat; PAD = peripheral arterial disease; PPI = proton pump inhibitor; VTE = venous thromboembolism.

[a] Not adjusted for multiplicity; HRs and 95% CIs calculated from Cox proportional hazards model stratified by PPI use and using subgroup variable as a covariate in the model.

Source: Clinical Study Report.[18]

Harms

Only those harms identified in the review protocol are reported in Table 10. Only those AEs occurring in more than 1% of participants are listed, except for notable harms.

Adverse Events

The proportion of participants in COMPASS experiencing AEs was higher in the rivaroxaban/ASA group (14.7%) compared with ASA alone (13.8%).

Serious Adverse Events

The proportion of participants with SAEs was higher in the rivaroxaban/ASA group ([redacted]) versus ASA ([redacted]). The results were reported separately in Japanese (n = 1,553) and non-Japanese participants (n = 25,798) due to differences in reporting protocols in Japanese regions (e.g., in Japan, participants had more frequent visits and more frequent laboratory tests). No SAEs occurred at a rate above 1% in the non-Japanese participants. [redacted]

Withdrawals Due to Adverse Events

There were more WDAEs in the rivaroxaban/ASA group (3.4%) compared with ASA (2.6%), but no specific reason occurred in more than 1% of participants [redacted].

Mortality

[redacted].

Notable Harms

Major bleeding (see Outcomes section for definition) occurred in 3.1% of the rivaroxaban/ASA group and 1.9% of the ASA-alone group. In the rivaroxaban/ASA arm, 1.5% of participants experienced a major GI bleed compared with 0.7% in the ASA arm. Intracranial major bleeding was rare, occurring in 0.3% of rivaroxaban/ASA participants and 0.3% of ASA participants. Minor bleeding was more common in the rivaroxaban/ASA group (9.0%) compared with the ASA group (5.3%), and was consistently more common for minor GI bleeds, urinary tract bleeds, and skin and injection-site bleeds. The ITT data set was used for most of the AE reporting; however, some of the data were reported with the safety analysis set (data for 99.8% of ITT population).

Table 10: Harms

	COMPASS	
	Rivaroxaban/ASA (n = 9,152)	ASA (n = 9,126)
AEs		
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
SAEs		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
WDAEs		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Notable Harms		
Major bleeding overall[c]	288 (3.1)	170 (1.9)
Rate of major bleeding overall (n/100 patient-years [95% CI])	[redacted]	[redacted]
HR (95% CI)	1.70 (1.40 to 2.05)	
Major bleeding — gastrointestinal	140 (1.5)	65 (0.7)
Major bleeding — intracranial	28 (0.3)	24 (0.3)
Fatal bleeding	15 (0.2)	10 (0.1)
Rate of fatal bleeding (n/100 patient-years [95% CI])	[redacted]	[redacted]
HR (95% CI)	1.49 (0.67 to 3.33)	
Fatal — gastrointestinal	[redacted]	[redacted]
Fatal – intracranial	[redacted]	[redacted]
Critical organ bleeding (non-fatal)	63 (< 1)	49 (< 1)
Rate of critical organ bleeding (non-fatal) (n/100 patient-years [95% CI])	[redacted]	[redacted]
HR (95% CI)	[redacted]	

	COMPASS	
	Rivaroxaban/ASA (n = 9,152)	**ASA (n = 9,126)**
Critical organ — intracranial	21 (0.2)	19 (0.2)
Bleeding into surgical site requiring re-operation	10 (0.1)	8 (< 0.1)
Rate of bleeding requiring re-operation (n/100 patient-years [95% CI])	[redacted]	[redacted]
HR (95% CI)	1.24 (0.49 to 3.14)	
Surgical site — gastrointestinal	6 (< 0.1)	2 (< 0.1)
Bleeding leading to hospitalization (non-fatal, non-critical organ, not leading to re-operation)	208 (2.3)	109 (1.2)
Rate of bleeding requiring hospitalization (n/100 patient-years [95% CI])	[redacted]	[redacted]
HR (95% CI)	1.91 (1.51 to 2.41)	
	Rivaroxaban/ASA (n = 9,134)[d]	**ASA (n = 9,107)[d]**
Minor bleeding — overall	821 (9.0)	485 (5.3)
Minor bleeding — gastrointestinal	243 (2.7)	131 (1.4)
Minor bleeding — urinary tract	144 (1.6)	75 (0.8)
Minor bleeding — skin or injection site	251 (2.7)	161 (1.8)

AE = adverse event; ASA = acetylsalicylic acid; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; ITT = intention-to-treat; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Frequency > 1%.

[b] Data separated by Japanese and non-Japanese populations due to differences in reporting; frequency did not exceed 1% in non-Japanese participants.

[c] Primary safety outcome; HRs and 95% CI calculated from Cox proportional hazards model.

[d] Data available only for safety analysis set (comprising 99.8% of the ITT population).

Source: Clinical Study Report.[18]

Discussion

Summary of Available Evidence

This review is based on one double-blind RCT (COMPASS; N = 27,395), that investigated the efficacy and safety of rivaroxaban 2.5 mg twice daily administered with ASA 100 mg once daily versus ASA 100 mg daily alone in persons with stable CAD and/or PAD. The primary outcome was a composite of stroke, MI, and CV death.

Interpretation of Results

Efficacy

COMPASS demonstrated that the combination of rivaroxaban and ASA reduced the risk of major adverse CV events compared with ASA alone in patients with stable CAD and/or PAD over a two-year treatment duration. This appeared to be driven by a reduction in the risk of stroke and CV death, whereas there was no significant difference in the risk of MI between the two groups. Rivaroxaban/ASA also reduced the risk of secondary composite outcomes (MI, ischemic stroke, ALI, or CVD death; MI, ischemic stroke, ALI, or CHD death) compared with ASA alone in the full population.

There was no difference between the two groups for the occurrence of heart failure, ALI, revascularization procedures, venous thromboembolism, and amputations. However, no concrete conclusions could be made with respect to the potential effects of rivaroxaban/ASA versus ASA alone for these outcomes, outside of the pre-specified hierarchical statistical analysis plan.

Health-related quality of life was assessed using the EQ-5D-3L. The manufacturer only reported analysis for the VAS out of 100, as opposed to the more comprehensive global scale, and no between-group comparisons were reported. Therefore, there is limited evidence indicating the effects of rivaroxaban/ASA versus ASA alone on health-related quality of life.

CAD only, PAD only, and CAD plus PAD subpopulations were pre-specified as relevant subgroups for this review. As well, the manufacturer's reimbursement request focused on the effects of rivaroxaban/ASA in the combined CAD/PAD subpopulation. However, subgroup analyses were outside of the pre-specified hierarchical statistical analysis plan and not adjusted for multiplicity. The subgroup analyses showed benefit of rivaroxaban/ASA over ASA alone for CV outcomes in patients with CAD or concomitant CAD and PAD, but not in patients with PAD only. The risk of the secondary composite outcomes was reduced in both the CAD-only group and in the concomitant CAD/PAD group. The outcomes of ALI and amputations are particularly important to the group with concomitant CAD and PAD. In this group, however, the effects of rivaroxaban/ASA on ALI were unclear, both because of the relatively smaller sample size and infrequent events, and because this outcome was not adjusted for multiplicity. There were no data on amputations for subgroups in the COMPASS Clinical Study Report. However, a separate post-hoc analysis of COMPASS participants with PAD (n = 6,391) evaluated the risk of experiencing a composite outcome of MALEs: acute or chronic limb ischemia and major amputations). MALEs were reduced within the rivaroxaban/ASA group compared with ASA alone (HR 0.57; 95% CI, 0.37 to 0.88) (Appendix 5). While subgroup analysis of participants with PAD was specified in the protocol, the definition and analysis of MALEs was not described in the protocol and this

outcome data was not found in the Clinical Study Report. Further, the components of MALE were not adjusted for multiplicity. Thus, these results should be interpreted with caution. In the PAD-only subgroup, there was no difference between the two groups for any outcome. The number of patients in this subgroup was small and event rates were low, which makes it difficult to draw conclusions about the efficacy of combination rivaroxaban/ASA in the group of patients with PAD only.

The patient input summary suggested that patients are concerned about having another CV event, daily function, and ability to exercise. Patients were also concerned about the number of pills they were taking and would prefer to manage their disease with fewer pills. The reduction in the risk of CV events for the combination of rivaroxaban/ASA compared with ASA alone will likely be important to patients. However, as mentioned, the effects of rivaroxaban/ASA on quality of life are uncertain, and its effect on daily function was not specifically measured in COMPASS. Although patients reported wanting to take fewer pills, it is unclear whether the twice-daily administration of rivaroxaban would be considered burdensome because patient satisfaction with treatment was not directly evaluated in COMPASS.

The current standard of long-term antithrombotic therapy in stable CAD (and PAD) has been low-dose ASA monotherapy (or clopidogrel monotherapy if ASA is contraindicated).[7,25,26] Vitamin K antagonists (e.g., warfarin), in addition to ASA, have been evaluated in individuals with stable CAD, but the risk of bleeding outweighed the CV benefits.[27] While DAPT has demonstrated advantages over ASA monotherapy in reducing the risk of CV events in patients with stable CAD, it also increases the risk of bleeding.[22,26] Therefore, DAPT has generally not been recommended beyond the indicated duration following ACS/PCI (e.g., 6 to 12 months). The 2018 Canadian Cardiovascular Society guidelines do suggest that DAPT can be used for up to three years following ACS/PCI if a patient is at low risk of bleeding, but not if a patient is at high risk of bleeding.[26] Beyond three years, the recommendation would be that the patient receive ASA monotherapy. Participants in COMPASS would generally be in this category (for example, the mean duration since MI in COMPASS was seven years). In summary, many patients with long-term stable CAD will be on low-dose ASA monotherapy. Despite ASA monotherapy and other medical management, the rate of CV events in individuals with CAD remains high.[6] The results from COMPASS suggest that the combination of rivaroxaban 2.5 mg twice daily and low-dose ASA is superior to ASA alone in reducing the risk of major adverse CV outcomes in patients with CAD and/or PAD, particularly for patients with CAD only or with CAD and concomitant PAD.

Individuals with PAD may also be concerned about adverse limb events (e.g., amputations and limb ischemia). In patients with PAD only, rivaroxaban did not appear to be beneficial when taken together with ASA. In the main analysis (CAD and/or PAD), the risk of ALI was numerically lower in the rivaroxaban/ASA group, but this outcome was outside of the pre-specified hierarchical analysis plan. [redacted] As mentioned, a separate analysis[14] (Appendix 5) reported benefit for rivaroxaban plus ASA for a composite outcome of major adverse limb events. This analysis was not well described in the COMPASS protocol and there was no adjustment for multiplicity. Thus, there may be a benefit in adverse limb events with rivaroxaban/ASA over ASA alone, but there were important limitations in this analysis.

One of the challenges with interpreting the results from COMPASS is that it was stopped early at approximately two years. Although rivaroxaban/ASA demonstrated CV benefit after less than two years, in general, there is a risk of overestimating the benefit when trials are stopped early; although the pre-specified trial-stopping criteria were conservative and the possibility of overestimating the effects of the treatment on the primary outcome is somewhat mitigated by these criteria. Nevertheless, the long-term efficacy of rivaroxaban in addition to ASA is unclear. Many patients with stable CAD will be medically treated long term; COMPASS does not provide an understanding of whether the benefits of rivaroxaban are likely to be sustained over several years. COMPASS participants generally had long-term and stable CAD (e.g., mean seven years since last MI, [redacted] but had no history of stroke. Thus, the results are likely most applicable in the population with long-term CAD but with no history of stroke.

There are no trials comparing rivaroxaban and ASA directly with DAPT in the stable CAD and/or PAD population; however, the manufacturer provided an indirect comparison based on network meta-analyses (NMA). A summary can be found in Appendix 7. [redacted] There was a high degree of heterogeneity across eligible studies, including differences in populations, duration of follow-up, and outcome definitions. The rivaroxaban/ASA node was informed only by a single trial (COMPASS), which was not well connected in all outcome networks, meaning there is uncertainty regarding the robustness of the analysis. [redacted].

Harms

Any potential benefit of rivaroxaban/ASA over ASA alone must be weighed against potential harms. The risk of major and minor bleeding was increased with rivaroxaban/ASA compared with ASA alone. There were more major GI bleeds with rivaroxaban/ASA therapy compared with ASA alone, although the rate of major intracranial bleeds was similar. Fatal bleeding, bleeding leading to hospitalization, and critical organ bleeding were more common in the rivaroxaban/ASA group than in the ASA-alone group. Surgical- site bleeding rates were similar. The rate of minor bleeding was higher at all sites (GI, urinary tract, skin). There were no other notable differences between groups for other AEs.

Bleeding is the primary safety concern in patients receiving antithrombotic medications. Patients with high bleeding risk were excluded from COMPASS; thus, individuals with stable CAD who are at high bleeding risk would not be suitable candidates for the addition of rivaroxaban to ASA. One challenge with interpreting the results from COMPASS is that there was no definition provided or criteria for high bleeding risk, which may make it challenging for clinicians to weigh harms against benefits in clinical practice. Further, because the trial was stopped early, the long-term safety of using rivaroxaban in stable CAD is not well established in COMPASS.

The absolute risk reduction for the primary outcome for rivaroxaban/ASA versus ASA alone was 1.3%, compared with an absolute increase of 1.2% in the risk of major bleeding. The main contributor to major bleeding in COMPASS was GI bleeds requiring hospitalization,

whereas the occurrence of fatal bleeding and (major) intracranial bleeding events were relatively less common and occurred in similar proportions of patients between treatment arms. The clinical expert consulted by CADTH noted that GI bleeding, while important, is often treatable, whereas the primary efficacy outcomes could cause permanent injury and also included CV death.

The primary efficacy analysis seems valid, based on the conservative analysis approach. The trial was powered based on the primary efficacy outcome and did not include assumptions about the safety outcomes and, therefore, the impact of this on the safety analysis is unclear. Given the trial was stopped early (based on the pre-specified criteria), it is possible the risk of harms, especially less frequently occurring serious events, may be underestimated.

Results from the manufacturer-provided NMA also suggested that rivaroxaban/ASA may increase the risk of bleeding events, especially major bleeding, compared with ASA alone. Harms comparisons versus other analyzed treatment regimens were generally either not significant or there were no data. Therefore, the comparative harms between rivaroxaban/ASA and other treatments administered with ASA are uncertain. However, the results must be interpreted with caution due to the limitations of the NMA (as outlined earlier and in Appendix 7).

Potential Place in Therapy[2]

The clinical expert consulted by CADTH noted that patients with established stable CAD, PAD, or cerebrovascular disease are at substantial risk for atherothrombotic events despite use of optimal medical therapy. The ischemic consequence of atherothrombosis can result in death, MI, stroke, and/or ALI.[28] The occurrence of these events is a major public health issue.[29]

Monotherapy with low-dose ASA has evolved as the most widely recommended antithrombotic drug to prevent atherothrombotic events and has a relatively low incidence of serious bleeding.[7] However, despite the regular use of low-dose ASA in stable patients with CVD, there is substantial residual atherothrombotic risk.

More efficient antithrombotic strategies that include the addition of a second antiplatelet drug, such as a P2Y12 inhibitor or a thrombin receptor inhibitor, or warfarin added to low-dose ASA, have demonstrated enhanced efficacy but with unacceptable serious bleeding.

In the COMPASS trial, which was terminated early after a mean follow-up of 23 months, low-dose (2.5 mg twice daily) rivaroxaban combined with low-dose ASA appears to balance efficacy and safety by favourably affecting the residual risk in patients with established, stable CVD who are on an appropriate background medical regimen. The observed risk reduction in the COMPASS trial occurred through the prevention of CV death or permanent damage to the brain (stroke). The permanent nature of these events cannot therefore be used to make simple comparisons of the number needed to treat to prevent an event versus number needed to harm, such as those for major bleeding, which are generally treatable conditions. More bleeding events were experienced in the COMPASS trial by those assigned to receive the combination therapy of low-dose rivaroxaban and ASA compared with the low-dose ASA-alone group. Reassuringly, the more severe types of bleeds, such as those causing death or bleeding into a critical organ, or causing intracranial

[2] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

hemorrhage, were similar in frequency for both treatment groups. The clinical expert observed that the rates of major bleeding events observed in the COMPASS trial appear consistent with prior studies of stable CV disease that have examined the utility of adding a P2Y12 inhibitor (PEGASUS) or antithrombotic therapy (ASPECT-2) to ASA in a stable CV population.

The COMPASS trial may be an important step forward in providing evidence of a treatment strategy for reducing the risk of atherothrombotic events in patients with stable CV disease. However, further data on individual risks and benefits will help personalize treatment beyond the overall results, especially in patients aged 75 years and older and patients with chronic renal failure, where bleeding risk is of concern.

Many patients who might benefit from rivaroxaban plus low-dose ASA are already taking ASA and other medications, and their ability to add (or switch to) another twice-daily medication long term may bear on how readily rivaroxaban plus ASA is adopted in clinical practice. The current recommendation for patients with atherosclerotic CVD is to remain on ASA for life; however, it is unclear whether patients would need to remain on rivaroxaban plus ASA for life, as well.

Conclusions

COMPASS demonstrated that in patients with stable CAD and/or PAD (who predominantly had a history of MI and cardiac revascularization and who had normal kidney function, were not at high risk of bleeding, and had no history of a stroke), the combination of rivaroxaban 2.5 mg twice daily and ASA 100 mg once daily significantly reduced the risk of the composite outcome of stroke, myocardial infarction, and CV death compared with ASA alone over an almost two-year treatment period. This benefit was also seen in the subgroups of patients with stable CAD only and concomitant CAD/PAD, although subgroup comparisons were not adjusted for multiple statistical testing. It is uncertain whether rivaroxaban/ASA has any added benefit on health-related quality of life or daily function compared with ASA alone, because of limited or no evidence for these outcomes. Major and minor bleeding were more common with rivaroxaban/ASA compared with ASA alone. Patients with CAD and PAD report being concerned about having future CV events and, therefore, the addition of rivaroxaban to ASA may be important to them. However, given the increased chance of major and minor bleeding, bleeding risk is also an important consideration. COMPASS was stopped early at approximately two years due to the pre-specified efficacy criteria of rivaroxaban/ASA over ASA for the primary outcome being met. As such, the long-term efficacy and safety of rivaroxaban/ASA is not well established. Based on this review, rivaroxaban added to ASA reduces the risk of CV events in certain patients with stable CAD and/or PAD compared with ASA alone, but increases the risk of major bleeding.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

One patient group, the Cardiac Health Foundation of Canada, provided input for this CDR review. This foundation runs a number of support programs for prevention, education, and cardiovascular rehabilitation. The Cardiac Health Foundation of Canada partnered with Hill+Knowlton Strategies, a national strategic communications consultancy to conduct interviews and draft the submission for this review. Three pharmaceutical companies provided financial support to the Cardiac Health Foundation of Canada in the past two years: Amgen, Boehringer Ingelheim, and Lilly Diabetes Alliance provided amounts ranging between $10,001 and $50,000, and AstraZeneca provided less than $5,000.

2. Condition-Related Information

The information for the submission was gathered via telephone interviews. Participants were recruited through social media platforms and fundraising events. In total, six respondents (four males, two females) with varying degrees of coronary heart disease were recruited through the outreach initiatives. Patient experiences varied in terms of the extent, severity, and duration of the condition. Some had been living with their condition for almost 25 years while others had been managing their disease for a short period of time. The impact of the disease ranged from difficulty walking for long periods of time and cramps due to leg blockage, which is manageable through regular exercise and monitoring, to more serious symptoms requiring various lifestyle changes and medication regimens resulting in "slowing down" in everyday activities. Patients also indicated that the thought that inadequately managed heart disease could lead to future heart attacks or death is a constant source of concern, which can be stressful. Sometimes, other comorbidities, such as illnesses affecting the thyroid, can negatively impact underlying cardiovascular disease by increasing body weight. Other notable patient experiences included mistaking chest pains for heart attacks and the swelling of the feet and abdomen due to underlying cardiovascular disease.

3. Current Therapy–Related Information

Overall, patients indicated their conditions were well managed with current medications; however, poor management of disease may lead to heart attacks or even death, requiring patients to be diligent about taking their medications. Treatments received by the patients surveyed varied widely, depending on disease severity, and involved different combinations of medications, exercise, and diet. Medications taken by the respondents included low-dose ASA as well as a variety of other cardiovascular risk–reducing medications such as statins, beta blockers, and angiotensin receptor blockers. In addition to exercise and diet modifications, reducing alcohol consumption, minimizing stress, and smoking cessation were noted by a few patients. The cost of treatments was generally not of concern for most respondents because their medications were covered by drug plans or private insurance; however, one patient indicated having out-of-pocket costs for a certain medication, but that this was not a burden. A common concern shared by all respondents was the constant fear of having another serious cardiovascular event. Mental stress resulting from such fear was reported to persist after patients were physically healed, and caused them to limit participation in daily activities and physical activity. Some patients indicated feeling a loss of confidence and "worthlessness" that is difficult to manage, even with considerable mental-health support and rehabilitation, services that are not accessible to all patients. Other

notable areas for improvement from current treatments included management of symptoms with fewer pills, ideally, one pill per day.

4. Expectations About the Drug Being Reviewed

The patient group was not able to consult with any patients on rivaroxaban or rivaroxaban/ASA; therefore, no information was provided.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE ALL 1946 to present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	June 21, 2018
Alerts:	Bi-weekly search updates until October 17, 2018
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded
SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.dq	Candidate term word (Embase)
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.nm	Name of substance word
.pt	Publication type
.rn	Case Registry/EC number/Name of substance
medall	Ovid database code; MEDLINE ALL (1946–)
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
Line#	**Search String**
1	(rivaroxaban* or xarelto* or bay 59-7939 or bay59-7939 or bay597939 or bay 597939 or 9NDF7JZ4M3).ti,ot,ab,rn,hw,rn,nm,kf.
2	(aspirin* or acetylsalicylic acid or asa or R16CO5Y76E).ti,ab,ot,rn,hw,rn,nm,kf.
3	1 and 2
4	3 use medall
5	*acetylsalicylic acid/
6	(Aspirin* or acetylsalicylic acid or ASA or R16CO5Y76E).ti,ab,kw.
7	*rivaroxaban/
8	(rivaroxaban* or xarelto* or bay 59-7939 or bay59-7939 or bay597939 or bay 597939 or 9NDF7JZ4M3).ti,ab,kw.
9	5 or 6
10	7 or 8
11	9 and 10
12	11 use oemezd

MULTI-DATABASE STRATEGY	
Line#	**Search String**
13	4 or 12
14	compass.ti,ab,kw,kf.
15	1 and 14
16	13 or 15
17	conference abstract.pt.
18	16 not 17
19	remove duplicates from 18

OTHER DATABASES		
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.	

Grey Literature

Dates for Search:	June 2018
Keywords:	Xarelto, rivaroxaban
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet search

Appendix 3: Excluded Studies

Table 11: Excluded Studies

Reference	Reason for Exclusion
Borzak 2017[30]	Not RCT
Bosch 2017[31]	Not RCT
Capell 2018[32]	Not RCT
Darmon 2018[24]	Not RCT
Fanaroff 2017[33]	Not RCT
Kohlman-Trigoboff 2017[34]	Not RCT
Kruger 2018[35]	Not RCT
Olinic 2018[36]	Not RCT
Gibson 2013[37]	Wrong population
Gibson 2011[38]	Wrong population
Mant 2018[39]	Not RCT
Mega 2013[40]	Wrong population
Ohman 2017[41]	Wrong population
Shah 2016[42]	Not RCT

RCT = randomized controlled trial.

Appendix 4: Risk of Bias Assessment

Table 12: Detailed Risk of Bias Assessment for COMPASS

Domain	Rating
Randomization	Low. Randomization conducted via PHRI (external agency) and drug management system "computer programmers who worked on randomization" suggests randomization via computer.
Allocation concealment	Low. Assignment done via PHRI (external agency) drug management system and assigned to patient — "subjects, site personnel, persons performing assessments, analysts blind to identity of treatment from randomization."
Blinding of participants	Low. "Subjects, site personnel, persons performing assessments, analysts blind to identity of treatment from randomization until database unlock." How blinding maintained (i.e., identical tablets, etc.) not described. Unblinding was rare and occurred in 43 in the rivaroxaban/ASA group and 46 in the ASA-alone group.
Blinding of outcome assessment	Low. "Subjects, site personnel, persons performing assessments, analysts blind to identity of treatment from randomization until database unlock." How blinding was maintained (e.g., through the use of identical tablets, etc.) was not described. Appears outcome assessors were blind to treatment allocation.
Incomplete outcome data	Low. Very low rate of missing data and balanced across groups (20 patients in rivaroxaban/ASA and 24 patients in ASA alone).
Selective reporting	High. Most outcomes reported in results were outlined in protocol. Protocol notes planned a secondary outcome of composite of MI, stroke, CV death, venous thromboembolism, and CV hospitalization. This was not reported in the results. Modifications to secondary outcomes were noted in amendments but there was no mention of dropping this outcome. The composite outcomes of CHD death, MI, ischemic stroke, ALI, and CV death; and MI, ischemic stroke, and ALI were not originally in the protocol but were added in an amendment.
Other bias	Low.

ALI = acute limb ischemia; ASA = acetylsalicylic acid; CHD = coronary heart disease; CV = cardiovascular; MI = myocardial infarction; PHRI = Population Health Research Institute.

Appendix 5: Additional Data

Background

This data comes from a separate publication of subgroup data from COMPASS.[14] This paper reported major adverse limb events (MALEs) in COMPASS participants with peripheral arterial disease (PAD) (n = 6,391). These participants could also have coronary artery disease (CAD). The data could not be located in the Clinical Study Report and were only available in the publication.

MALEs were a composite of acute or chronic limb ischemia and major vascular amputations. While the subgroup analysis of participants with PAD was specified in the protocol, the definition of MALEs and the analysis methodology were not found in the protocol. The analysis was not included in the adjustment for multiple comparisons and, therefore, the results should be interpreted with this in mind.

Results

Table 13: Major Adverse Limb Events in Participants With PAD

	COMPASS	
Major Adverse Limb Events	**Rivaroxaban/ASA (n = 2139)**	**ASA (n = 2123)**
N (%)	32 (1.5)	56 (2.6)
HR (95% CI)	0.57 (0.37 to 0.88)	
P value	0.01	

ASA = acetylsalicylic acid; CI = confidence interval; HR = hazard ratio.

Source: Anand 2018.[14]

Appendix 6: Validity of Outcome Measures

Aim

To summarize the evidence assessing the validity and reliability of the EuroQol 5-Dimensions (EQ-5D) 3-Levels questionnaire (EQ-5D-3L).

Findings

The EQ-5D-3L is a generic preference-based health-related quality-of-life instrument that has been applied to a wide range of health conditions and treatments, including peripheral arterial disease (PAD).[43,44] The first of two parts of the EQ-5D-3L is a descriptive system that classifies respondents (aged ≥ 12 years) into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three possible levels (1, 2, or 3) representing "no problems," "some problems," and "extreme problems," respectively. Respondents are asked to choose one level that reflects their own health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D-3L index score) to self-reported health states from a set of population-based preference weights.[43,44] The second part is a vertical, calibrated 20 cm visual analogue scale (EQ-VAS) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state," respectively. Respondents are asked to rate their own health by drawing a line from an anchor box to the point on the EQ-VAS that best represents their own health on that day. Hence, the EQ-5D-3L produces three types of data for each respondent:

- a profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 33211, etc.
- a population preference-weighted health index score based on the descriptive system
- a self-reported current health status based on the EQ-VAS that is used to assess the overall health of the respondent rather than selected dimensions of the individual's health.

The EQ-5D-3L index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., in the US or UK). The lowest possible overall score (corresponding to severe problems on all five attributes) varies, depending on the utility function that is applied to the descriptive system (e.g., −0.59 for the UK algorithm and −0.109 for the US algorithm). Scores below 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively.

The EQ-5D has been validated extensively across countries around the world and in various conditions; however, no information on the validity of the EQ-5D-3L was found for the specific populations under review.

Minimal Clinically Important Difference

Information regarding a minimal clinically important difference (MCID) for the EQ-5D-3L VAS among the specific populations under review (CAD and/or PAD) was not found.

Appendix 7: Summary of Network Meta-Analysis

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

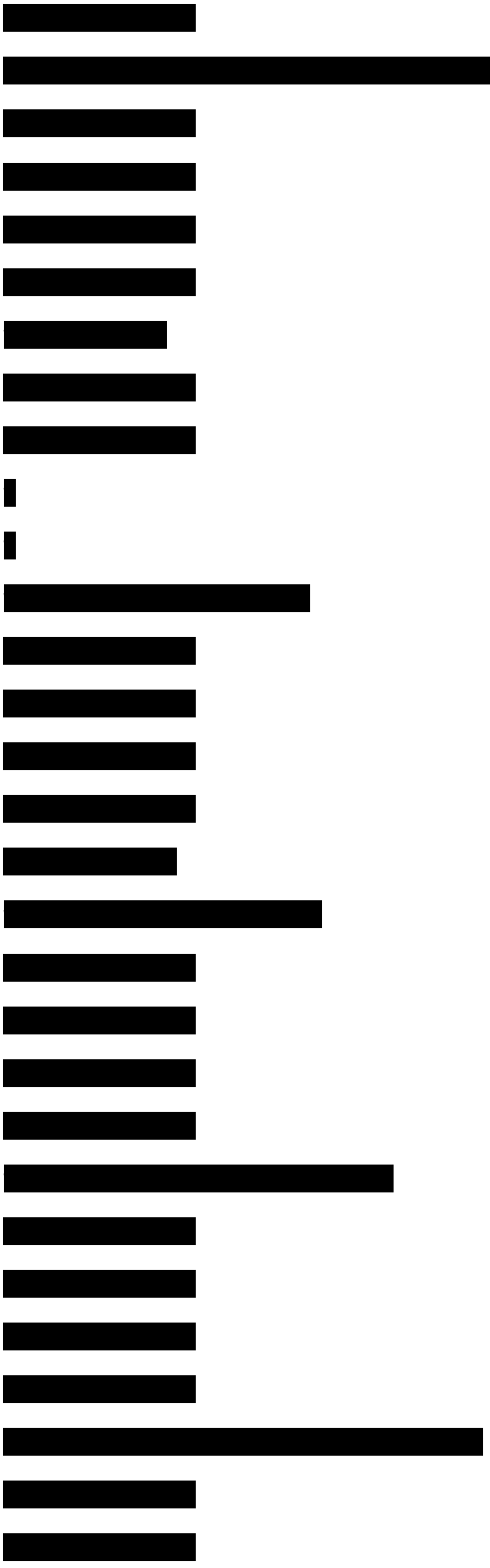
[redacted]

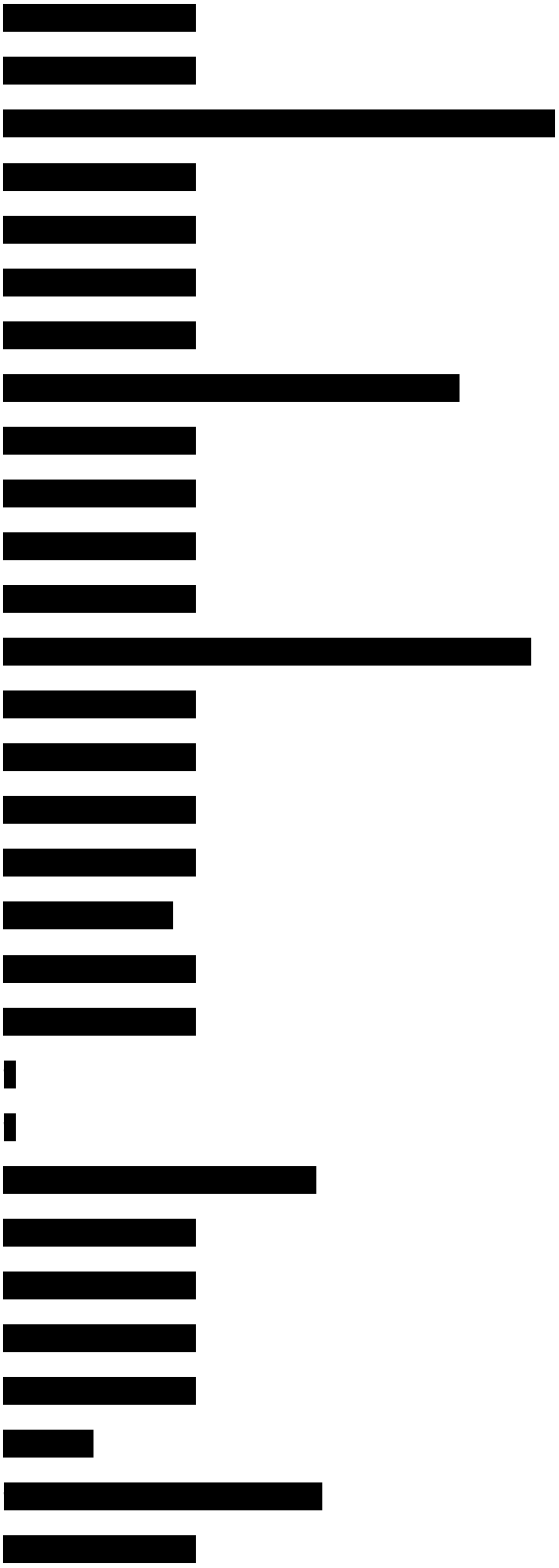
[redacted]

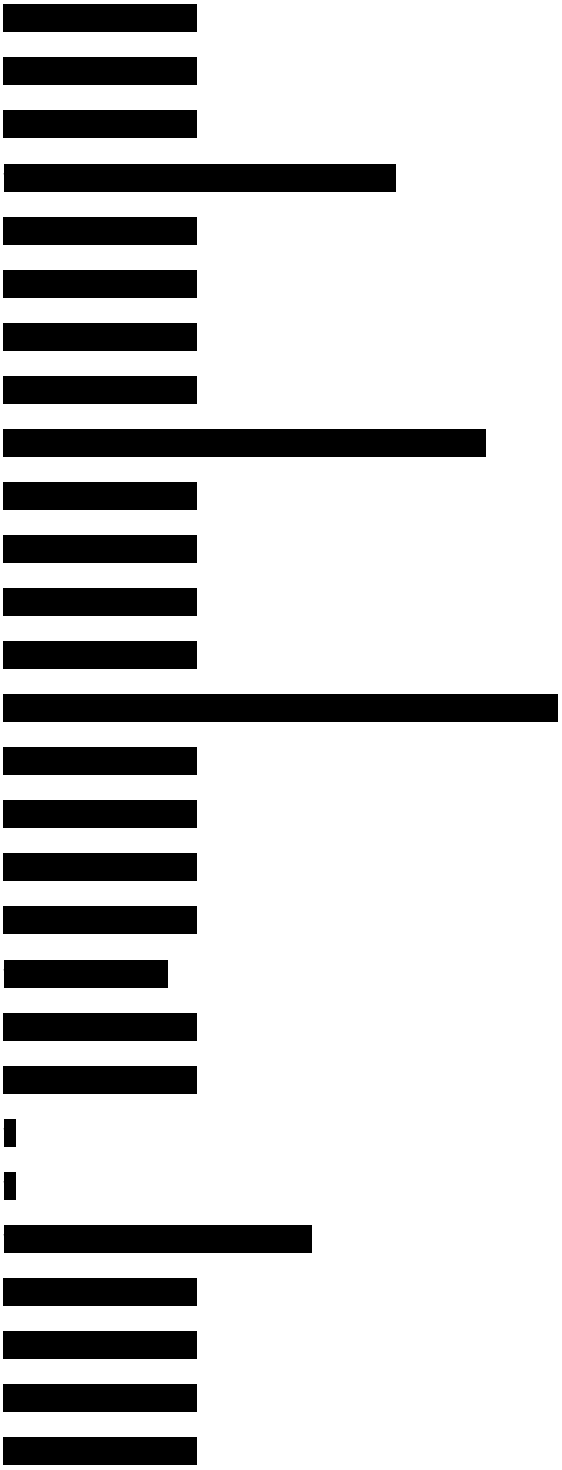
[redacted]

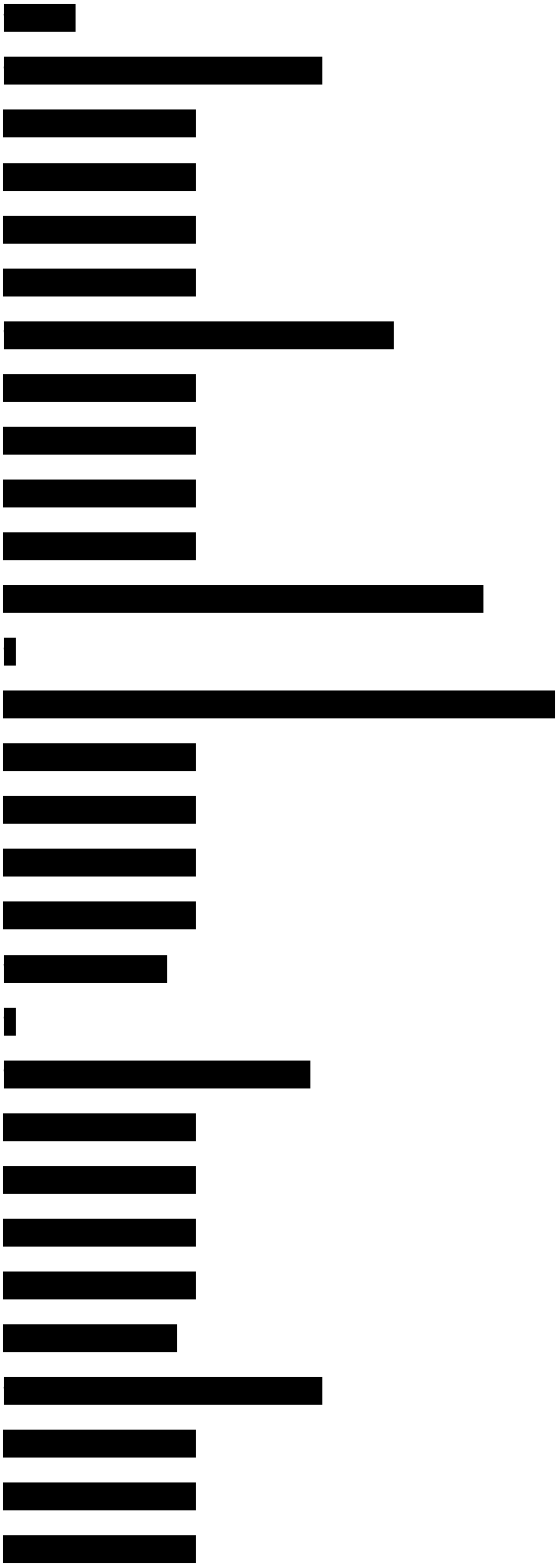
[redacted]

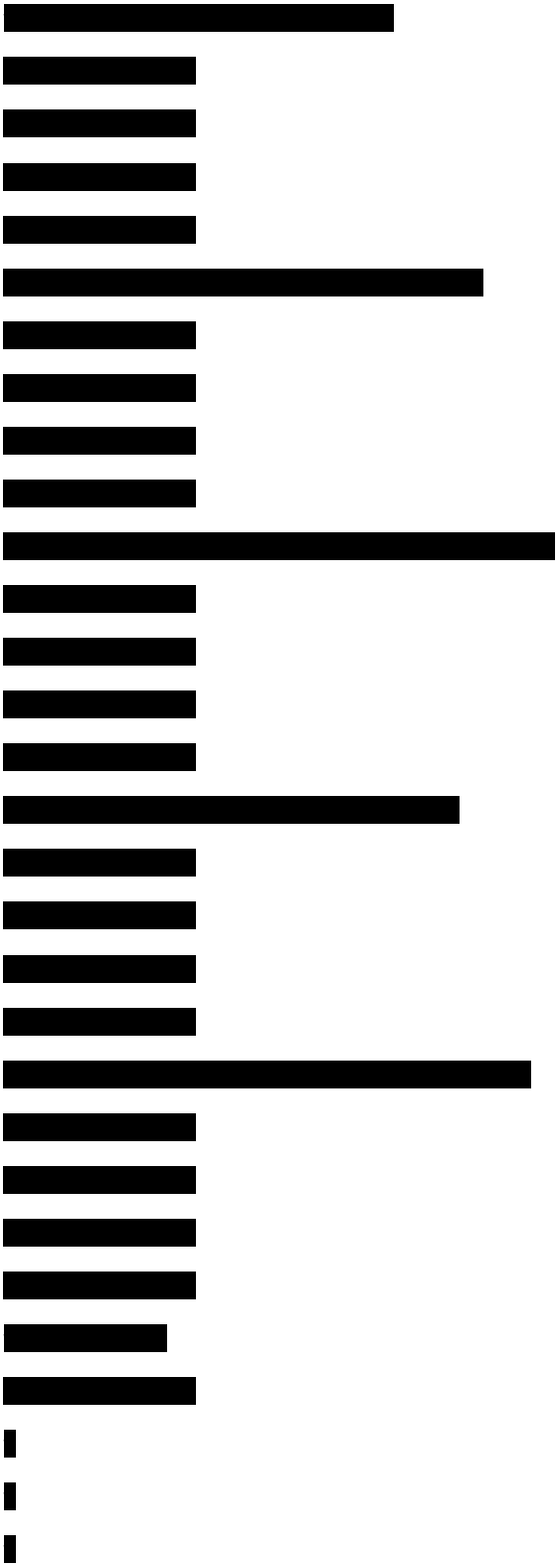
[redacted]

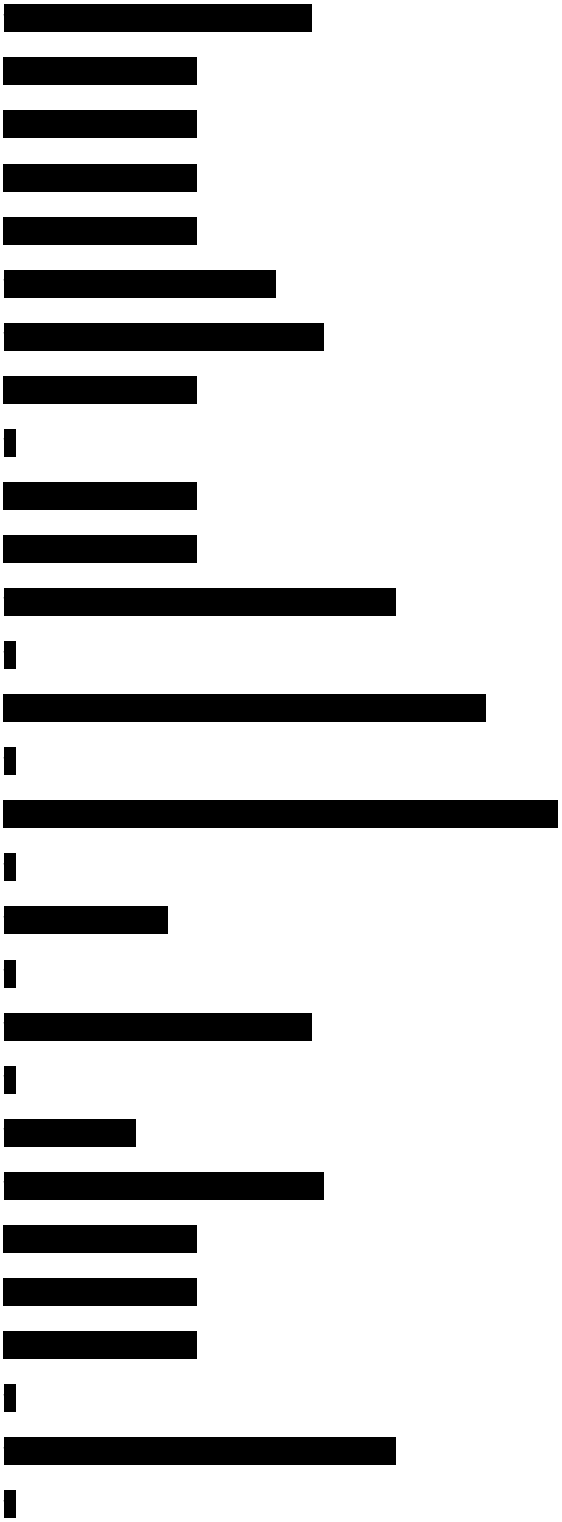


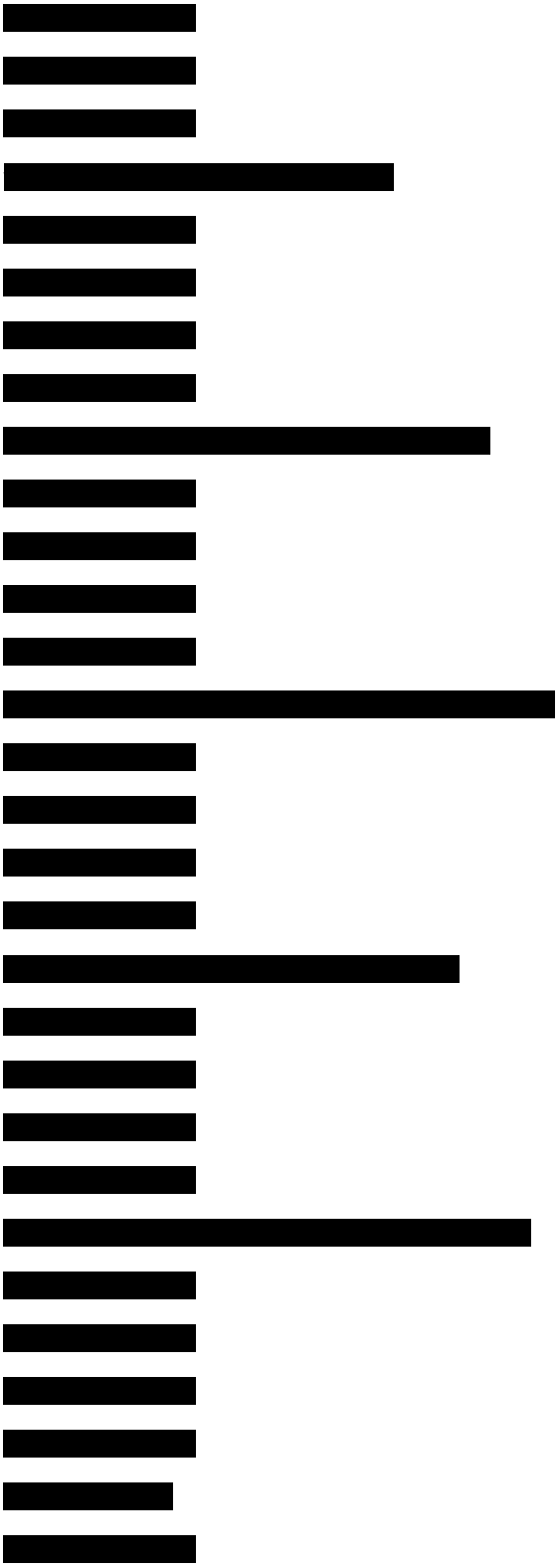


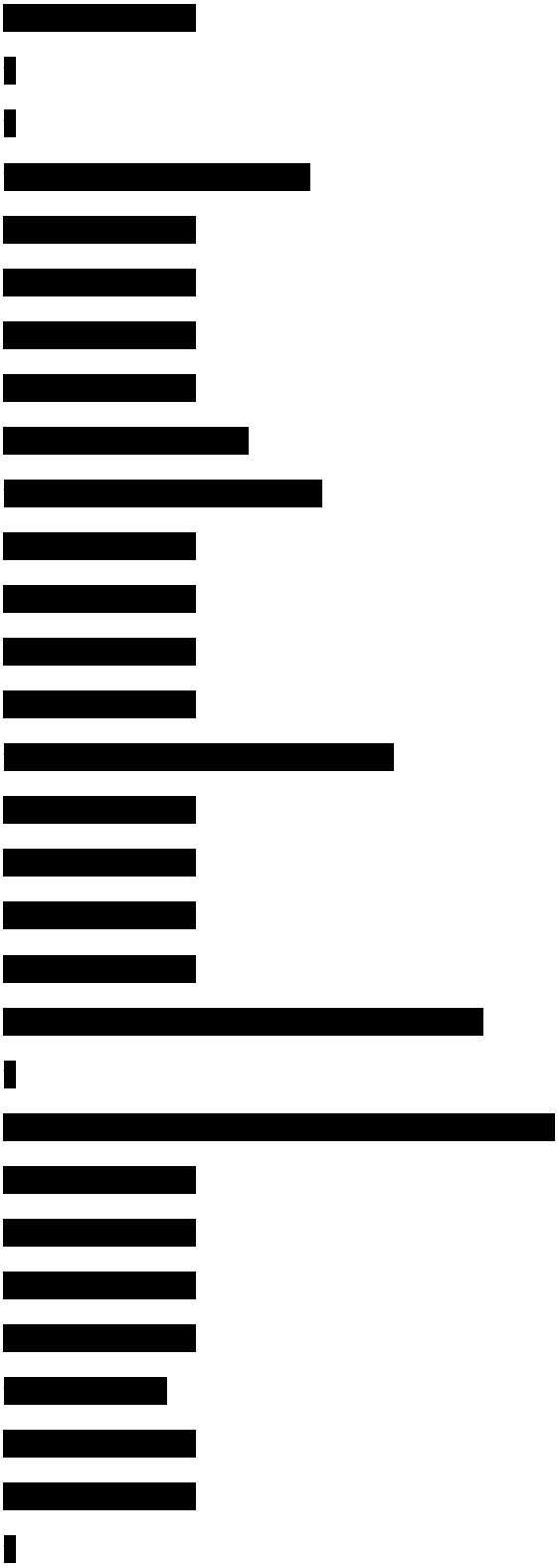


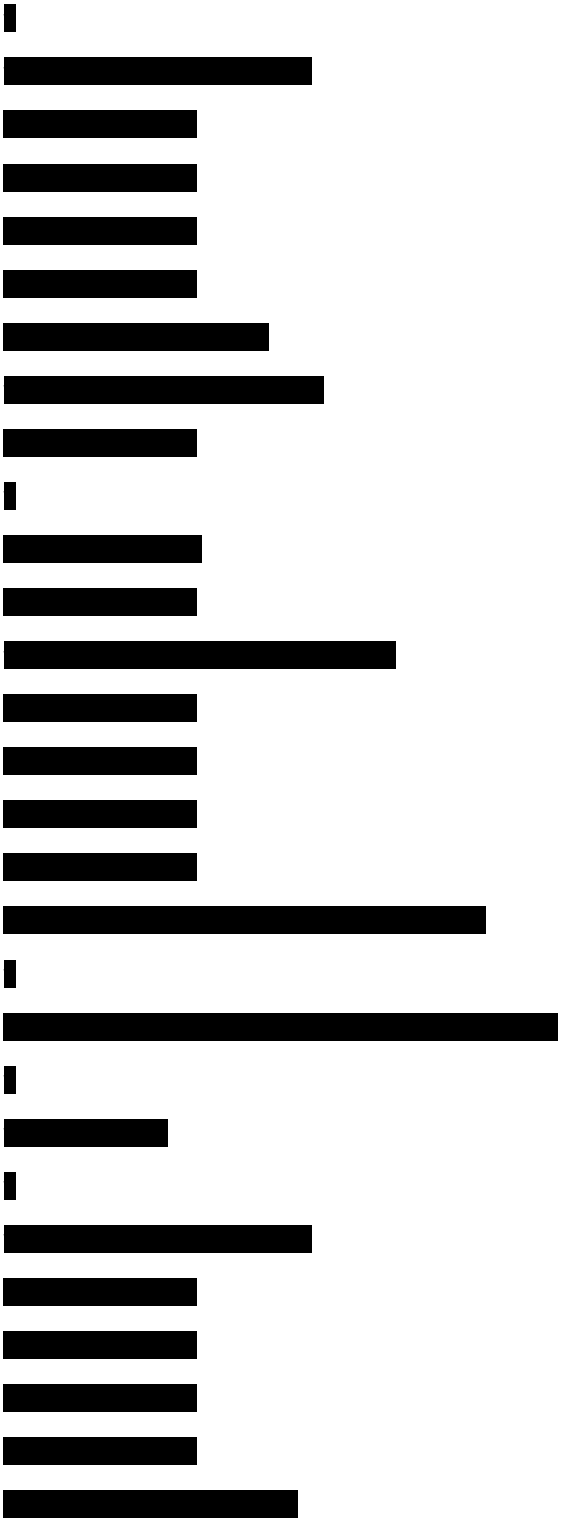


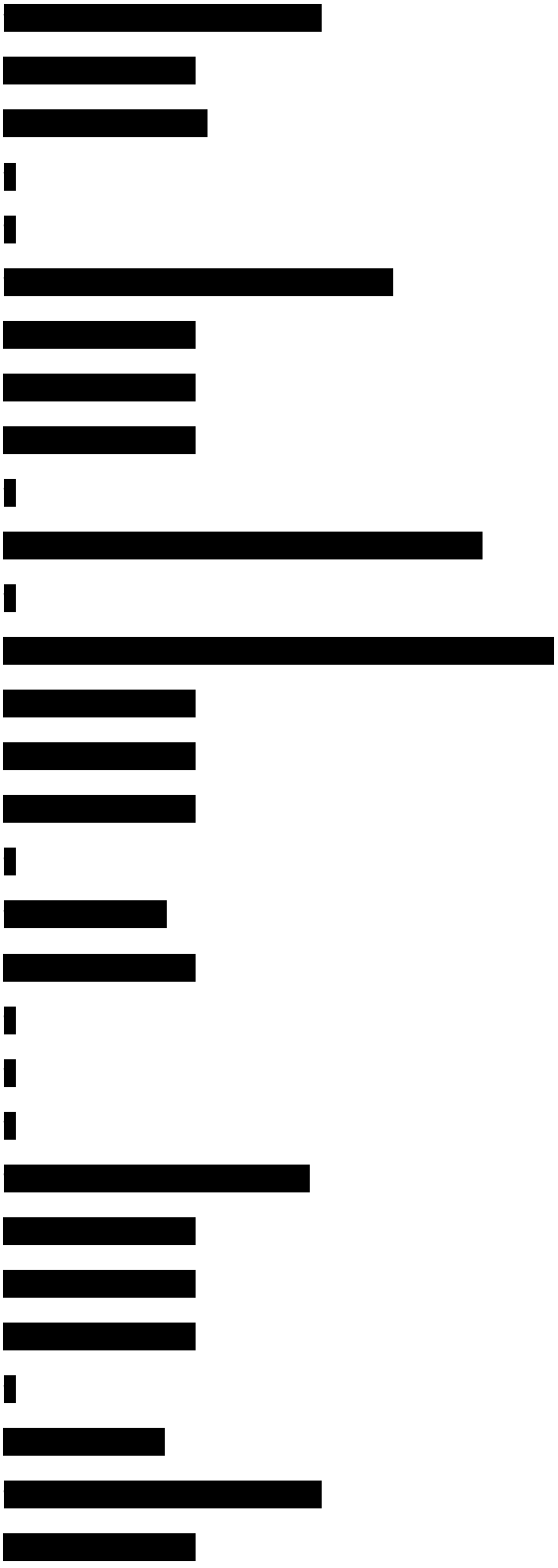


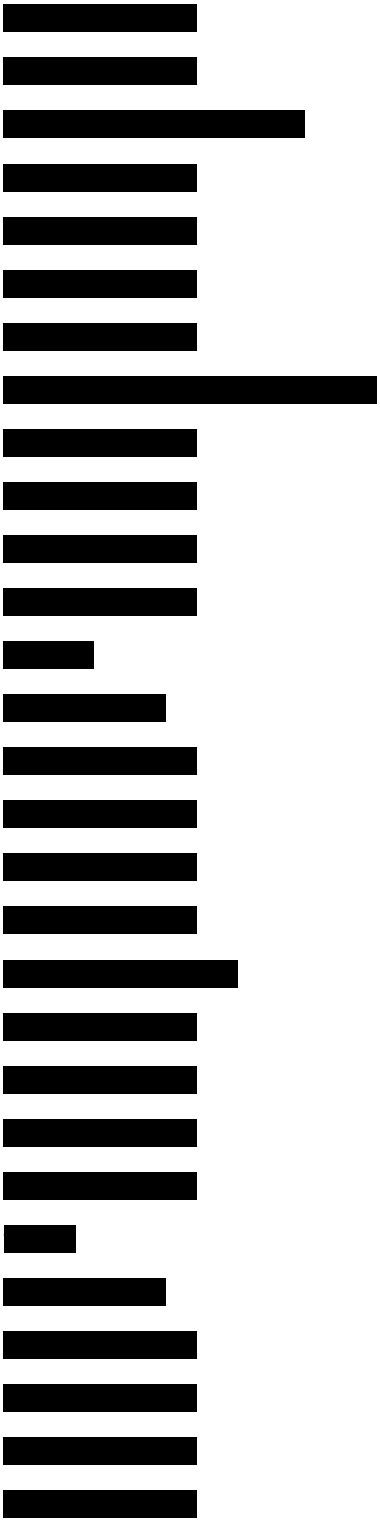


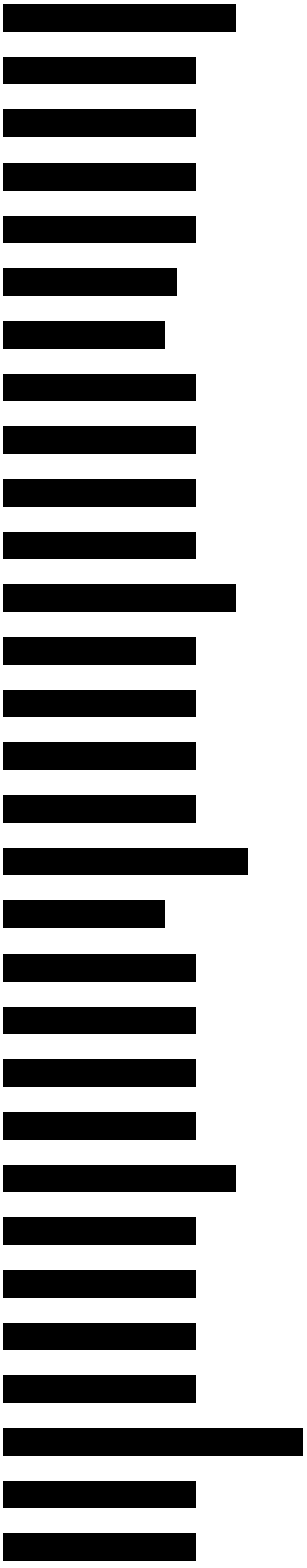


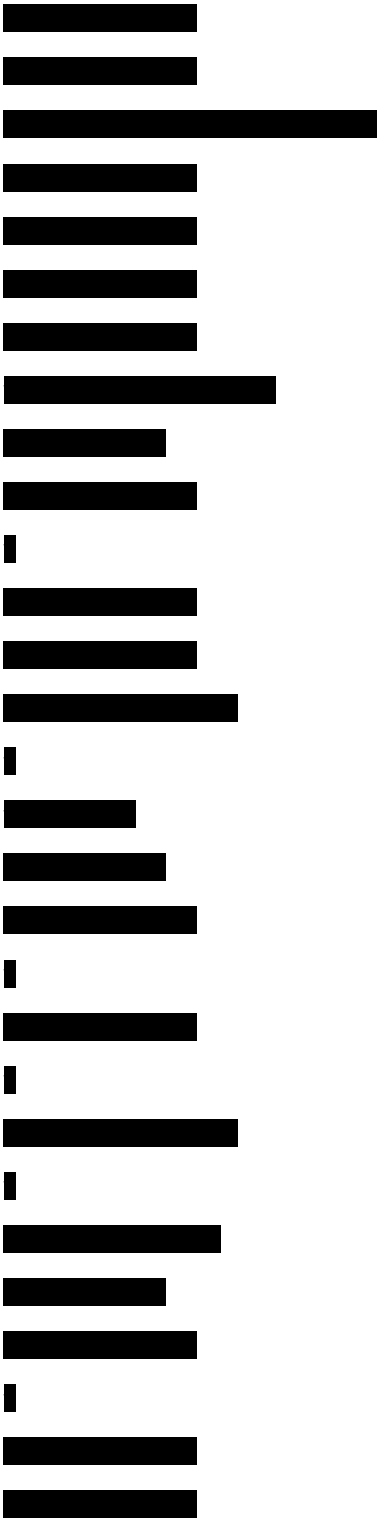


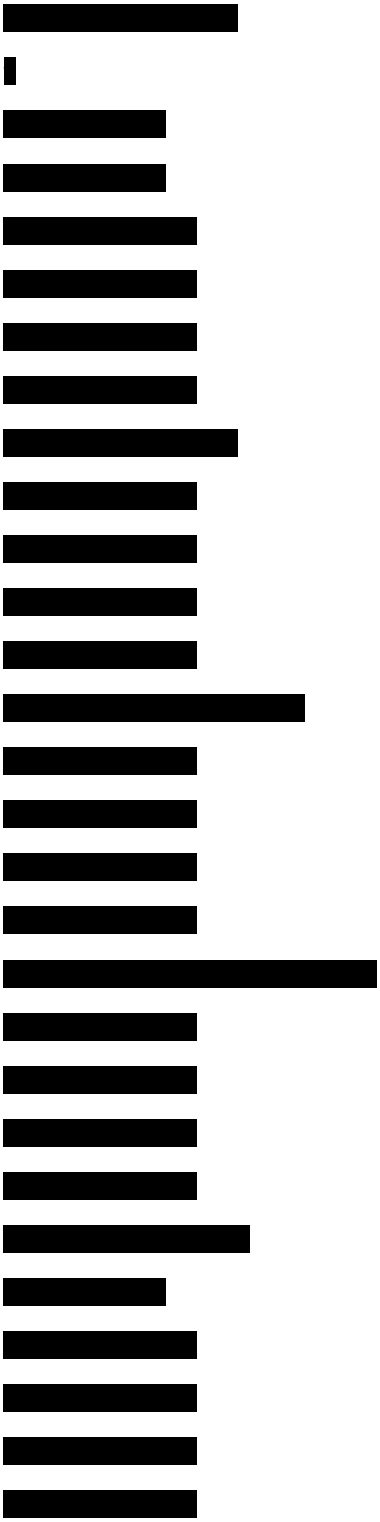


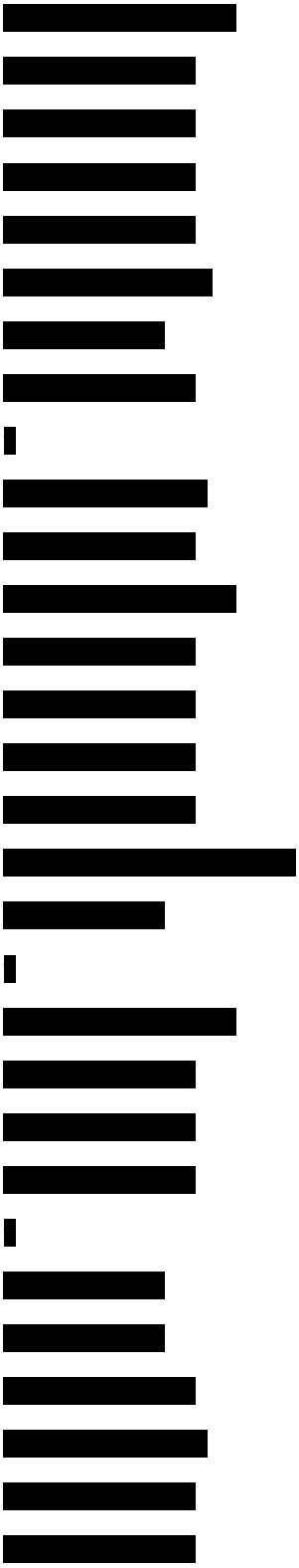


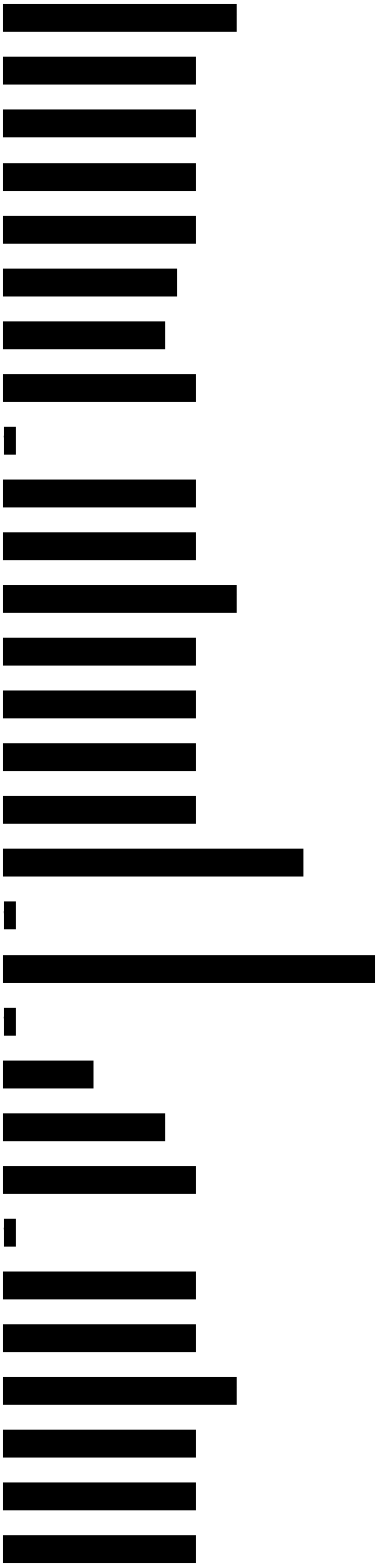


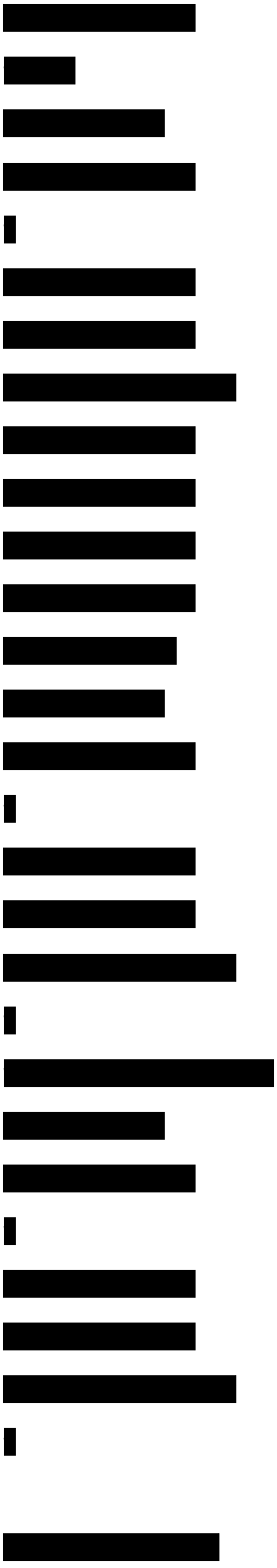












[redacted]

[redacted]

References

1. Coronary artery disease - A guide for patients and families. Ottawa: Ottawa Heart Institute; 2012: https://www.ottawaheart.ca/sites/default/files/uploads/coronary-artery-disease-patient-guide.pdf. Accessed 2018 Aug 11.
2. Cassar A, Holmes DR, Rihal CS, Gersh BJ. Chronic Coronary Artery Disease: Diagnosis and Management. *Mayo Clin Proc.* 2009;84(12):1130-1146.
3. Khoury H, Lavoie L, Welner S, Folkerts K. The Burden of Major Adverse Cardiac Events and Antiplatelet Prevention in Patients with Coronary or Peripheral Arterial Disease. *Cardiovascular therapeutics.* 2016;34(2):115-124.
4. Morley R, Sharma A, Horsch A. Peripheral artery disease. London: British Medical Journal Publishing Group; 2018: https://www.bmj.com/content/360/bmj.j5842. Accessed 2018-02-01.
5. Table: 13-10-0394-01 - Leading causes of death, total population, by age group. Ottawa: Statistics Canada; 2018: https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310039401. Accessed 2018 Aug 20.
6. Steg PG, Bhatt DL, Wilson PW, et al. One-year cardiovascular event rates in outpatients with atherothrombosis. *Jama.* 2007;297(11):1197-1206.
7. Canadian Cardiovascular Society Guidelines for the Diagnosis and Management of Stable Ischemic Heart Disease - Canadian Journal of Cardiology. 2018.
8. Gerhard-Herman M, Gornick H, Barrett C, et al. 2016 AHA/ACC Guideline on the management of patients with lower extremity peripheral artery disease: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation.* 2017;135(12):e686-e725. https://www.ahajournals.org/doi/abs/10.1161/CIR.0000000000000470. Accessed 2018 Aug 20.
9. Xarelto (rivaroxaban): 10 mg, 15 mg and 20 mg tablets [product monograph]. Mississauga (ON): Bayer Inc.; 2018 May.
10. Plavix (clopidogrel): 75 and 300 mg tablets [product monograph]. Laval (QC): sanofi-aventis Canada Inc.; 2018 March.
11. Brilinta (ticagrelor): 60 and 90 mg tablets [product monograph]. Mississauga (ON): AstraZeneca Canada Inc.; 2016 May.
12. Effient (prasugrel (as prasugrel hydrochloride)): 10 mg tablets [product monograph]. Toronto (ON): Eli Lilly Canada Inc.; 2014 June.
13. Coumadin (warfarin sodium): 1, 2, 2.5, 3, 4, 5, 6 and 10 mg tablets [product monograph]. Montreal (QC): Bristol-Myers Squibb Canada; 2018 May.
14. Anand SS, Caron F, Eikelboom JW, et al. Major Adverse Limb Events and Mortality in Patients With Peripheral Artery Disease: The COMPASS Trial. *J Am Coll Cardiol.* 2018;71(20):2306-2315.
15. Connolly SJ, Eikelboom JW, Bosch J, et al. Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial.[Erratum appears in Lancet]. *Lancet.* 2017;10:10.
16. Anand SS, Bosch J, Eikelboom JW, et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet.* 2017;10:10.
17. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. *N Engl J Med.* 2017;377(14):1319-1330.
18. Clinical Study Report: PH-39342: A randomized controlled trial of rivaroxaban for the prevention of major cardiovascular events in patieuts with coronary or peripheral artery disease (COMPASS- Cardiovascular OutcoMes for People using Anticoagulation StrategieS) [**CONFIDENTIAL** internal manufacturer's report]. Leverkusen (DE): Bayer AG; 2017.
19. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Nature Reviews Cardiology.* 2012;9(11):620.
20. Higgins JP AD, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011;343:d5928
21. Campbell CL, Smyth S, Montalescot G, Steinhubl SR. Aspirin Dose for the Prevention of Cardiovascular Disease: A Systematic Review. *Jama.* 2018;297(18):2018-2024.
22. Lettino M, Leonardi S, De Maria E, Halvorsen S. Antiplatelet and antithrombotic treatment for secondary prevention in ischaemic heart disease. *Eur J Prev Cardiolog.* 2017;24(3_suppl):61-70.
23. Guyatt GB, M.; Glasziou, P.; et al. Problems of stopping trials early. *BMJ.* 2012(344):e3863.
24. Darmon A, Bhatt DL, Elbez Y, et al. External applicability of the COMPASS trial: An analysis of the reduction of atherothrombosis for continued health (REACH) registry. *European Heart Journal.* 2018;39(9):750-757.
25. Stable coronary artery disease (management of): ESC clinical practice guidelines. Sophia Antipolis (FR): European Society of Cardiology; 2018: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Stable-Coronary-Artery-Disease-Management-of. Accessed 2018 Aug 20.
26. 2018 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology focused update of the guidelines for the use of antiplatelet therapy. *Can J Cardiol.* 2018;34(3):214–233.
27. Anand SS, Yusuf S. Oral anticoagulants in patients with coronary artery disease. *J Am Coll Cardiol.* 2003;41(4 Suppl S):62s-69s.
28. Mann D, Zipes D, Libby P, Bonow P. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine.* 10 ed: Elsevier; 2014.
29. WHO. *World Health Organization.* 2018.

30. Borzak S. In stable CVD, rivaroxaban plus aspirin reduced CV events and increased bleeding compared with aspirin alone. *Ann Intern Med.* 2017;167(10):JC52.

31. Bosch J, Eikelboom JW, Connolly SJ, et al. Rationale, Design and Baseline Characteristics of Participants in the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) Trial. *Can J Cardiol.* 2017;33(8):1027-1035.

32. Capell WH, Bonaca MP, Nehler MR, et al. Rationale and design for the Vascular Outcomes study of ASA along with rivaroxaban in endovascular or surgical limb revascularization for peripheral artery disease (VOYAGER PAD). *Am Heart J.* 2018;199:83-91.

33. Fanaroff AC, Hasselblad V, Roe MT, et al. Antithrombotic agents for secondary prevention after acute coronary syndromes: A systematic review and network meta-analysis. *Int J Cardiol.* 2017;241:87-96.

34. Kohlman-Trigoboff D. Review of article: Rivaroxaban with or without aspirin in stable cardiovascular disease. Eikelboom JW, Connolly SJ, Bosch J, et al. for the COMPASS investigators. *J Vasc Nurs.* 2017;35(4):221-223.

35. Kruger PC, Eikelboom JW, Yusuf S. Rivaroxaban with or without aspirin for prevention of cardiovascular disease. *Coron Artery Dis.* 2018;17:17.

36. Olinic DM, Tataru DA, Homorodean C, Spinu M, Olinic M. Antithrombotic treatment in peripheral artery disease. *Vasa.* 2018;47(2):99-108.

37. Gibson CM, Chakrabarti AK, Mega J, et al. Reduction of stent thrombosis in patients with acute coronary syndromes treated with rivaroxaban in ATLAS-ACS 2 TIMI 51. *J Am Coll Cardiol.* 2013;62(4):286-290.

38. Gibson CM, Mega JL, Burton P, et al. Rationale and design of the Anti-Xa therapy to lower cardiovascular events in addition to standard therapy in subjects with acute coronary syndrome-thrombolysis in myocardial infarction 51 (ATLAS-ACS 2 TIMI 51) trial: a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of rivaroxaban in subjects with acute coronary syndrome. *Am Heart J.* 2011;161(5):815-821.e816.

39. Mant J. Rivaroxaban plus aspirin, compared with aspirin alone, reduced cardiovascular events in patients with stable peripheral or carotid artery disease, but increased the risk of major bleeding. *BMJ Evid Based Med.* 2018;12:12.

40. Mega JL, Braunwald E, Wiviott SD, et al. Comparison of the efficacy and safety of two rivaroxaban doses in acute coronary syndrome (from ATLAS ACS 2-TIMI 51). *Am J Cardiol.* 2013;112(4):472-478.

41. Ohman EM, Roe MT, Steg PG, et al. Clinically significant bleeding with low-dose rivaroxaban versus aspirin, in addition to P2Y12 inhibition, in acute coronary syndromes (GEMINI-ACS-1): a double-blind, multicentre, randomised trial. *Lancet.* 2017;389(10081):1799-1808.

42. Shah R, Hellkamp A, Lokhnygina Y, et al. Use of concomitant aspirin in patients with atrial fibrillation: Findings from the ROCKET AF trial. *Am Heart J.* 2016;179:77-86.

43. Brooks R. EuroQol: the current state of play. *Health policy (Amsterdam, Netherlands).* 1996;37(1):53-72.

44. EuroQol - a new facility for the measurement of health-related quality of life. *Health policy (Amsterdam, Netherlands).* 1990;16(3):199-208.

45. Network meta-analyses on efficacy/safety of rivaroxaban in patients with stable coronary artery disease (CAD) or peripheral artery disease (PAD). In: CDR submission: Xarelto (rivaroxaban) 2.5 mg film coated tablets.Company: Bayer AG [**CONFIDENTIAL** manufacturer's submission]. 2018 Apr.

46. Systematic literature review of randomised clinical trials in patients with chronic coronary artery disease (CAD) and peripheral artery disease (PAD): In CDR submission: Xarelto (rivaroxaban) 2.5 mg film coated tablets. [**CONFIDENTIA**L manufacturer's submission]. 2017 Apr.

47. Systematic reviews: CRD's guidance for undertaking reviews in health. York [GB]: Centre for Reviews and Dissemination, University of York; 2009: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf. Accessed 2018 Aug 20.

48. Dias S, Sutton A, Ades A, et al. A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. *Med Decis Making.* 2013;33(5):607-617.

49. Spiegelhalter D, Abrams K, Miles J. Bayesian approaches to clinical trials and health-care evaluation. Chichester [GB]: John Wiley & Sons Ltd; 2004: https://pdfs.semanticscholar.org/d689/7974c441cf239ef2896d37fd328f4724dbdd.pdf. Accessed 2018 Aug 20.

50. Jansen J, Devine B, Itzler R, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: Report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: Part 1. *Value Health.* 2011 Jun;14(4):417-428.