
# Additive Therapies for Cardiovascular Disease: Effectiveness and Value

**Final Evidence Report**

**October 17, 2019**

**Prepared for**

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Daniel A. Ollendorf served as the lead author for the report. Patricia Synnott, Serina Herron-Smith, and Katherine Fazioli led the systematic review and authorship of the comparative clinical effectiveness section. R. Brett McQueen and Jonathan D. Campbell developed the cost-effectiveness model, and along with Taryn Quinlan, authored the corresponding sections of the report. Rick Chapman and Remziye Zaim were responsible for oversight of the cost-effectiveness analyses and developed the budget impact model. Ellie Adair authored the section on coverage policies and clinical guidelines, and managed the timeline and public process, and performed quality controls. David Rind and Steve Pearson provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Laura Cianciolo for her contributions to this report.

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*In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following clinical experts provided input that helped guide the ICER team as we shaped our scope and report. None of these individuals is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.*

*For a complete list of stakeholders from whom we requested input, please visit: https://icer-review.org/material/cvd-stakeholder-list/.*

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# Table of Contents

## List of Acronyms Used in this Report

| | |
|---|---|
| **ACS** | Acute coronary syndrome |
| **ACCF** | American College of Cardiology Foundation |
| **ADA** | American Diabetes Association |
| **AE** | Adverse event |
| **AHA** | American Heart Association |
| **AHRQ** | Agency for Healthcare Research and Quality |
| **ALI** | Acute limb ischemia |
| **ASA** | Aspirin or acetylsalicylic acid |
| **BCBSKC** | Blue Cross Blue Shield of Kansas City |
| **BI** | Budget impact |
| **CAD** | Coronary artery disease |
| **CE** | Cost effectiveness |
| **CI** | Confidence interval |
| **CMS** | Centers for Medicare and Medicaid Services |
| **COPD** | Chronic obstructive pulmonary disease |
| **CV** | Cardiovascular |
| **CVD** | Cardiovascular disease |
| **DAPT** | Dual antiplatelet therapy |
| **eGFR** | Estimated glomerular filtration rate |
| **EPA** | Eicosapentaenoic acid |
| **EQ-5D** | European Quality of Life-5 Dimensions |
| **ESC** | European Society of Cardiology |
| **FDA** | United States Food and Drug Administration |
| **GDP** | Gross domestic product |
| **GI** | Gastrointestinal |
| **HR** | Hazard ratio |
| **hsCRP** | High-sensitivity C-reactive protein |
| **ISTH** | International Society on Thrombosis and Haemostasis |
| **LCD** | Local coverage determination |
| **LDL** | Low-density lipoprotein |
| **LY** | Life year |
| **MI** | Myocardial infarction |
| **mRS** | Modified Rankin Scale |
| **NCD** | National coverage determination |
| **NMA** | Network meta-analysis |
| **PAD** | Peripheral artery disease |
| **PCI** | Percutaneous coronary intervention |
| **PICOTS** | Population, Intervention, Comparator, Outcome, Timing, Setting |
| **PPI** | Proton pump inhibitor |
| **PRISMA** | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| **QALY** | Quality-adjusted life year |
| **RCT** | Randomized controlled trial |
| **SAE** | Serious adverse event |
| **TEAE** | Treatment-emergent adverse event |
| **TG** | Triglyceride |
| **TIMI** | Thrombolysis in myocardial infarction |
| **US** | United States |
| **USPSTF** | United States Preventive Services Task Force |
| **WAC** | Wholesale acquisition cost |
| **WTP** | Willingness to pay |

# Executive Summary

## Background

The term cardiovascular disease (CVD) defines a complex, burdensome, and highly prevalent set of conditions. Three of the major types of CVD, coronary artery disease (CAD), peripheral artery disease (PAD), and cerebrovascular disease, result most frequently from atherosclerosis, a chronic degenerative process involving increasing buildup of plaque formed by fat- and cholesterol-based deposits. Over time, these deposits result in arterial narrowing and wall hardening, which in turn can result in angina, claudication, myocardial infarction (MI), stroke, heart failure, and death, among other problems. In total, CVD is estimated to affect one-half of adults in the United States (US), and is the leading cause of death across all races and ethnicities, with approximately 850,000 deaths annually.[2] CVD also imposes a substantial financial burden, with annual direct and indirect costs estimated to total $351 billion; projected annual costs are expected to exceed $1 trillion by 2035.[2] Hypertension, hypercholesterolemia, diabetes, and smoking are well-established risk factors for atherosclerotic CVD, and overweight/obesity, poor diet, physical inactivity, and excessive alcohol use may also contribute to its development.[3]

In addition to mortality risks and financial burden associated with CVD, major adverse cardiovascular events can result in long-term disability and complicate care for other conditions. For example, an analysis of linked data from the US Health and Retirement Study and Medicare claims found significant increases in the number of functional limitations on activities of daily living following hospitalization for MI or stroke; in addition, those hospitalized for stroke had a fourfold increase in the odds of moderate-to-severe cognitive impairment, even after controlling for pre-hospitalization cognition.[4]

The management of CVD has commonly consisted of behavioral and lifestyle changes (i.e., diet, weight reduction, physical activity, smoking cessation) to interrupt atherosclerotic processes, as well as risk factor management, including blood pressure control, treatment with lipid-lowering agents such as statin medications and PCSK9 inhibitors, antiplatelet therapy, and when necessary, management of diabetes as well as surgical or percutaneous revascularization. Although low-dose acetylsalicylic acid (aspirin, or ASA) and statins have become cornerstone therapies with proven benefit for patients with established CVD, this population remains at high residual risk of cardiovascular events.[5] In addition, those without documented CVD but with established risk factors such as diabetes and comorbid hypertension or hypercholesterolemia are also at elevated risk of major cardiovascular events. For these patients, there is clinical interest in exploring other types of medical management in addition to the strategies.

## Interventions

***Rivaroxaban***

Rivaroxaban (Xarelto®, Janssen Pharmaceuticals, Inc.) is an oral direct and selective inhibitor of factor Xa in the blood coagulation pathway. Rivaroxaban was first approved for the prevention of deep vein thrombosis in patients undergoing major orthopedic surgery and is commonly used in the management of atrial fibrillation and venous thromboembolic disease. In October 2018, rivaroxaban 2.5 mg taken twice daily with aspirin received an indication for the prevention of major cardiovascular events in patients with CAD or PAD.[6]

***Icosapent Ethyl***

Icosapent ethyl (Vascepa®, Amarin Pharma, Inc.) is a purified ethyl ester of the omega-3 fatty acid known as eicosapentaenoic acid (EPA), which was initially approved in 2012 as an adjunct to diet to treat severe hypertriglyceridemia (triglyceride levels ≥500 mg/dL). The manufacturer has filed for an expanded indication for management of patients with established CVD or at high risk of CV events. Initially, a decision from the Food and Drug Administration (FDA) was expected by September 28, 2019,[7] however an FDA advisory committee meeting has been scheduled for November 14, 2019.[8] Icosapent ethyl's mechanism of action in cardioprotection is not fully known.[9] It is taken twice daily with food (total daily dose: 4 g).

## Insights Gained from Discussions with Patients and Patient Groups

ICER engaged with patients, patient groups, and clinical experts to understand the specific challenges associated with ongoing management of CVD from the patient perspective. There was acknowledgment that the high rate of recurrent events, even in CVD patients whose risk factors are optimally managed, continues to concern clinicians. Still, caution was urged in considering further additions to the current armamentarium, given the need to balance the potential for additional clinical benefit against the risk of major bleeding and other harms, as well as the inconsistent track record of previous antithrombotic regimens and omega-3 preparations respectively in reducing the rate of recurrent cardiovascular events. Despite these concerns, there was enthusiasm expressed around the potential for new treatments to further reduce event risks in these high-risk populations.

We also heard that medication adherence might be a challenge in this population, given already high rates of polypharmacy and comorbidity in older patients likely to be candidates for add-on therapy. Indeed, patients expressed trepidation with an increased therapeutic burden, citing concerns with both the daily complexity of treatment and increased financial responsibility for ongoing treatment. Patients also mentioned that the value and risk of adding new treatments to an already complex treatment regimen is not necessarily clearly and consistently communicated. Indeed, prior research in this clinical area suggests that patients tend to significantly overestimate both their event and bleeding risks relative to their quantified risk scores.[10] Other feedback included the need to tailor the physician-patient conversation to

reflect the patient's specific situation—for example, a family history of CVD, management of comorbid conditions, or the benefits of lifestyle and behavioral changes in addition to medical management.

## Comparative Clinical Effectiveness

To inform our analysis of the comparative clinical effectiveness of additive therapies for the management of CVD, we sought evidence related to low-dose rivaroxaban + ASA compared to ASA alone or in combination with another antiplatelet agent (i.e., dual antiplatelet therapy [DAPT]). Separately, we also evaluated the clinical evidence for icosapent ethyl compared to optimal medical management alone. Our review focused on clinical benefits (i.e., reduction in cardiovascular events, mortality, and quality of life), as well as potential harms (i.e., bleeding and other drug-related AEs). We did not attempt to indirectly compare rivaroxaban to icosapent ethyl, as the two key Phase III trials that were the focus of our review differed in terms of target population and definitions of key outcomes. Key findings are summarized by drug in the sections that follow.

### Rivaroxaban

***Compared to treatment with ASA alone, rivaroxaban + ASA reduced the composite risk of cardiovascular death, stroke, or MI in patients with stable CVD. Patients treated with rivaroxaban + ASA experienced significantly fewer strokes (including disabling or fatal strokes), less cardiovascular death, and fewer cardiovascular-related hospitalizations. No significant effect of rivaroxaban on hemorrhagic stroke or MI was observed. Patients treated with rivaroxaban + ASA experienced a significant increase in major bleeding events, which led to permanent discontinuation of therapy in approximately 3% of patients. Most major bleeding events occurred in the GI tract.***

Our review of rivaroxaban was primarily informed by the Phase III COMPASS trial,[11] which randomized approximately 27,000 patients to receive rivaroxaban 2.5 mg twice daily and 100 mg once daily of ASA, 5 mg twice daily of rivaroxaban alone, or 100 mg once daily of ASA alone. The FDA-approved indication is for rivaroxaban only in combination with ASA, however; as such, evidence from the rivaroxaban alone arm is not summarized here. Based on a planned interim analysis, the COMPASS trial was stopped early (after a mean of 23 months of follow-up) due to evidence of significant clinical benefit.

#### Clinical Benefits

*Major Adverse Cardiovascular Events*

The primary outcome of the COMPASS trial was a composite endpoint consisting of the first occurrence of cardiovascular death, stroke, or MI.[11] In the time to event analysis, the hazard ratio for the primary outcome was 0.76 (95% CI: 0.66, 0.86; p<0.001). Patients treated with rivaroxaban + ASA had statistically significantly fewer primary outcome events (4.1%) compared

to patients in the ASA alone group (5.4%); for the ASA alone group, this translates into an annual event rate of approximately 3%, suggesting a relatively high-risk population.

*Individual Events*

Individual components of the primary and secondary composite outcomes are presented in Table 3.3 in Section 3. Patients treated with rivaroxaban + ASA experienced significantly fewer strokes, and less cardiovascular death, death from coronary heart disease, and death from any cause. In an exploratory analysis, rivaroxaban + ASA reduced the risk of disabling or fatal strokes (i.e., strokes defined as a score between 3 and 6 on the modified Rankin Scale) by 42% (HR 0.58; 95% CI: 0.37 to 0.89; p=0.01).[12-14] Hemorrhagic strokes occurred in more patients in the rivaroxaban + ASA group but differences did not reach statistical significance.

*Other Benefits*

Hospitalization for cardiovascular causes (Appendix Table D4) occurred less in patients randomized to rivaroxaban + ASA versus ASA alone (14.2% vs. 15.3%; HR 0.92; 95% CI: 0.86 to 1.00; p=0.04). The non-cardiovascular-related hospitalization rate was not statistically different between arms. Although the European Quality of Life-5 Dimensions (EQ-5D) scale was measured in the COMPASS trial, no results have been published or presented as of the publication of this Evidence Report.

***Harms***

Major bleeding events occurred in significantly more patients treated with rivaroxaban + ASA compared to ASA alone (3.1% vs. 1.9%; HR 1.70; 95% CI: 1.40 to 2.05; p<0.001); 2.7% of patients in the rivaroxaban + ASA group permanently discontinued treatment due to bleeding, compared to 1.2% in the ASA alone group.[6,11] The most common bleeding site was the GI tract (1.5% vs. 0.7%; HR 2.15; 95% CI: 1.60 to 2.89; p<0.0001). Selected bleeding outcomes are presented in Table ES1 and all bleeding outcomes are reported in Appendix Table D5.

**Table ES1. Selected Bleeding Outcomes in COMPASS**

| Outcome | Rivaroxaban + ASA | ASA | Hazard Ratio (95% CI) | P-Value |
|---|---|---|---|---|
| Major Bleeding | 288 (3.1) | 170 (1.9) | 1.70 (1.40-2.05) | <0.001 |
| Fatal Bleeding | 15 (0.2) | 10 (0.1) | 1.49 (0.67-3.33) | 0.32 |
| Non-Fatal Symptomatic Intracranial Bleeding | 21 (0.2) | 19 (0.2) | 1.10 (0.59-2.04) | 0.77 |
| Other Major Bleeding | 210 (2.3) | 112 (1.2) | 1.88 (1.49-2.36) | <0.001 |
| Minor Bleeding | 838 (9.2) | 503 (5.5) | 1.70 (1.52-1.90) | <0.001 |

ASA: aspirin, CI: confidence interval

Serious adverse events (SAEs) occurred in 7.9% of patients in the rivaroxaban + ASA arm versus 7.3% of patients on ASA alone; discontinuation due to non-bleeding AEs was not reported.

## Clinical Benefits and Safety of Dual Antiplatelet Therapy (DAPT)

Our literature search did not identify any studies directly comparing rivaroxaban + ASA to DAPT in the population of focus. Although we did not systematically review DAPT versus ASA alone, we searched for RCTs that evaluated new initiation of DAPT (as opposed to continuation of current DAPT therapy) in patients with stable CVD. We identified two RCTs of ticagrelor + ASA and clopidogrel + ASA, respectively.[15-18] These trials are summarized in Appendix D for context. We also indirectly compared DAPT to rivaroxaban + ASA through an NMA of major adverse cardiovascular events in patients with a recent MI (see below).

### *NMA*

We performed an NMA in the subgroup of patients with a recent MI (i.e., in the two years prior to randomization for the studies of rivaroxaban and ticagrelor, and at a median of two years prior to randomization for the study of clopidogrel) to compare ticagrelor + ASA and clopidogrel + ASA with rivaroxaban + ASA. The analysis estimated the comparative risk of a composite endpoint of cardiovascular death, stroke, or MI between each of the regimens of focus. The results of our NMA, presented in Table ES2, do not reveal statistical differences between therapies. However, given the elevated risk of major bleeding that is associated with each of the regimens, any analysis of comparative effectiveness is incomplete without an accompanying analysis of comparative safety. We endeavored to also compare the incidence of major bleeding between therapies but were unable to quantitatively synthesize the data due to the use of important differences in definitions of major bleeding.

**Table ES2. NMA Results Comparing the Risk of Cardiovascular Death, Stroke, or MI in Patients Treated with Antithrombotic Therapy for Stable CVD**

| | | | |
|---|---|---|---|
| **Rivaroxaban + ASA** | | | |
| 0.91<br>(0.61 to 1.36) | **Ticagrelor + ASA** | | |
| 0.91<br>(0.58 to 1.40) | 1.00<br>(0.75 to 1.32) | **Clopidogrel + ASA** | |
| 0.70<br>(0.48 to 1.02) | **0.77**<br>**(0.66 to 0.90)** | **0.77**<br>**(0.61 to 0.98)** | **ASA** |

Each box represents the estimated hazard ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain one.

## Icosapent Ethyl

***Compared to optimal medical management alone (i.e., placebo), icosapent ethyl reduced the risk of a composite outcome of cardiovascular death, stroke, MI, coronary revascularization, or unstable angina in patients with established CVD or diabetes mellitus and additional risk factors, as well as each individual component and the composite secondary outcome of cardiovascular death, MI, or stroke. A treatment benefit was also observed in analyses of the first, subsequent, and total major adverse cardiovascular events. Rates of serious adverse events and events leading to treatment discontinuation were similar between arms. A greater proportion of patients treated with icosapent ethyl experienced serious bleeding-related disorders, as well as peripheral edema, constipation, and atrial fibrillation.***

Evidence on icosapent ethyl was primarily derived from the Phase III REDUCE-IT trial,[19] which randomized patients at increased risk of ischemic events (either established CVD or primary prevention in patients age ≥50 with diabetes and at least one additional risk factor) to 2 g twice daily of icosapent ethyl (n=4089) or a placebo (n=4090) that contained mineral oil to resemble the color and consistency of icosapent ethyl. Patients were required to have elevated fasting triglyceride levels (≥135 and <500 mg/dL) and well-controlled LDL cholesterol levels (>40 and ≤100 mg/dL) while on a stable dose of statins for at least four weeks. At baseline, 71% of patients had established CVD and 29% made up the high-risk primary prevention cohort.[19] Patients were followed for a median of 4.9 years.

### *Clinical Benefits*

*Major Adverse Cardiovascular Events*

As noted above, the REDUCE-IT trial evaluated a composite of cardiovascular death, MI, stroke, coronary revascularization, or unstable angina as its primary endpoint. In the time-to-event analysis, icosapent ethyl reduced the risk of a primary endpoint event by 25% (HR 0.75; 95% CI: 0.68 to 0.83; p<0.001).[19] At a median follow-up of 4.9 years (maximum 6.2 years), 17.2% of patients treated with icosapent ethyl and 22.0% treated with placebo had a first primary endpoint event. The annual event rate in the placebo arm was approximately 4.4%, suggesting a very high-risk population.

The REDUCE-IT trial's key secondary endpoint (cardiovascular death, MI, or stroke) also occurred in fewer patients treated with icosapent ethyl compared to those receiving placebo (11.2% vs. 14.8%, respectively; HR 0.74; 95% CI: 0.65-0.83; p<0.001).[19]

*Individual and Total Events*

Icosapent ethyl reduced the risk of cardiovascular death by 20%, nonfatal MI by 30%, nonfatal stroke by 29%, coronary revascularization by 34%, and hospitalization for unstable angina by 32%; however, a 13% reduction in all-cause mortality was not statistically significant. The effect of icosapent ethyl on total events (first and subsequent) was examined in a pre-specified analysis using a negative binomial regression model.[20] The risk of total primary endpoint events,

including cardiovascular death, MI, stroke, revascularization, and unstable angina, was reduced by 30% with icosapent ethyl compared to placebo (rate ratio (RR): 0.70; 95% CI: 0.62, 0.78). Treatment with icosapent ethyl resulted in a 28% risk reduction compared to placebo (RR: 0.72; 95% CI: 0.63-0.82) on the REDUCE-IT trial's key secondary endpoint of cardiovascular death, stroke, or MI.

***Harms***

The incidence of serious treatment-emergent adverse events (TEAEs) was similar in the icosapent ethyl and placebo arms of the REDUCE-IT trial (30.6% vs. 30.7%, respectively).[19] Serious TEAEs leading to death occurred in 2.3% of patients treated with icosapent ethyl and 2.5% of patients who received placebo. Serious bleeding-related disorders, identified using the Medical Dictionary for Regulatory Activities (MedDRA), occurred in a greater proportion of patients treated with icosapent ethyl, although the difference was not statistically significant (2.7% vs. 2.1%, p=0.06). No fatal bleeding events occurred in either group and rates of hemorrhagic stroke, central nervous system bleeding, and GI bleeding did not statistically differ. TEAEs that occurred in proportionately more patients treated with icosapent ethyl included peripheral edema (6.5% vs. 5.0%, p=0.002), constipation (5.4% vs. 3.6%, p<0.001), and atrial fibrillation (5.3% vs. 3.9%, p=0.003).[19] Hospitalization for atrial fibrillation or flutter was significantly higher in the icosapent ethyl arm compared to placebo (3.1% vs. 2.1%; p=0.004).

Approximately 11% of patients randomized to placebo and 10% randomized to icosapent ethyl discontinued the study early.[9] The rate of TEAEs leading to discontinuation of the study drug was similar for patients treated with icosapent ethyl and placebo (7.9% vs 8.2%, respectively) as was the rate of drug discontinuation due to serious TEAEs (2.2% vs 2.3%, respectively).

## Controversies and Uncertainties

***Rivaroxaban***

The generalizability of the COMPASS trial population is subject to a number of uncertainties. For one, study entry criteria of stable CAD and PAD as well as documentation of atherosclerosis in at least two vascular beds among patients age <65 years ensured a population at high risk of recurrent cardiovascular events, but exclusion of patients at high bleeding risk and further exclusion of 8% patients not tolerating or adherent to run-in ASA therapy likely resulted in a sample at reduced bleeding risk relative to the potential candidate population for rivaroxaban.[21,22] In addition, we cannot exclude the possibility that the clinical benefits observed in COMPASS are somewhat overstated due to the trial having been stopped early for benefit after a mean of 23 months of follow-up. [23] In addition, the decision to separately randomize patients to receive the proton-pump inhibitor (PPI) pantoprazole or placebo within the rivaroxaban + ASA, rivaroxaban alone, and ASA alone groups is a puzzling one, given that clinical guidelines recommend routine use of PPIs for gastroprotection in patients receiving combination anticoagulation + ASA therapy[24] but not for anticoagulants or ASA alone.

Finally, while the indications for combination treatment with rivaroxaban and DAPT with a $P2Y_{12}$ inhibitor do not completely overlap, there is a large subset of patients with a recent MI event who could conceivably be candidates for either treatment approach. Indeed, some clinicians have called for further research comparing DAPT to combination therapy with ASA and a factor Xa inhibitor (e.g., rivaroxaban).[25,26] In the absence of head-to-head trials at the time of this report's publication, we attempted to compare the regimens indirectly through a network meta-analysis. However, while only small differences exist in the definitions of clinical events across the major trials of these regimens, the same cannot be said for definitions of major bleeding, which differed substantially across trials; in some cases, a common definition was used but modified to enough of an extent that we could not attempt quantitative comparisons with any confidence. While this is a source of frustration for producers of comparative effectiveness research, the real harm done is to the patient-clinician shared decision.

***Icosapent Ethyl***

As noted previously, the placebo vehicle used in the REDUCE-IT trial (as well as earlier trials of icosapent ethyl) contained mineral oil to mimic the viscosity of the active agent. Biomarker changes observed in the trial raise the possibility that the mineral oil used was not biologically inert, however; patients in the placebo arm experienced a threefold-higher percentage increase in LDL-C at year one (10.2% vs. 3.1% for icosapent ethyl, $p<0.001$ for between-group difference) and a substantial increase in the inflammation marker hsCRP at year two (32.9% vs. -13.9%, $p<0.001$), adding to documented concerns regarding the mineral oil's potential interference with statin absorption.[9] The manufacturer conducted a post-hoc analysis, the results of which suggested a consistent risk reduction with icosapent ethyl irrespective of whether LDL-C increased in the placebo arm.[9] However, it is difficult to interpret analyses of effects utilizing on-treatment response subgroups, and so residual concerns remain about a potentially biologically active "placebo" and the possibility that the true effect of icosapent ethyl may be attenuated from that observed in the REDUCE-IT trial.

We also note that the results of this trial stand apart from many prior studies of omega-3 preparations that showed little to no cardiovascular benefit.[27] Indeed, when a Bayesian approach is taken to the overall evidence base, the interpretation of REDUCE-IT's findings will differ depending on whether prior expectations for these results are pessimistic, realistic, or optimistic.[28] It is worth noting that reductions in cardiovascular events of approximately 20% were observed in a prior EPA-only trial (JELIS), which randomized approximately 19,000 Japanese patients to 1.8 g of EPA in addition to statin therapy versus statins alone over a mean of 4.6 years of follow-up.[29] However, the JELIS trial was open-label and showed no reductions in cardiovascular death, so its relevance to the results of REDUCE-IT is unclear. The JELIS trial was also conducted in a Japanese population with a much higher baseline consumption of fish than is typically seen in the US; very few patients in REDUCE-IT were from the Asia-Pacific region making comparisons across trials difficult.[30,31]

Regardless of issues of trial design or interpretation, the greatest uncertainty may be in how generalizable the REDUCE-IT results are and therefore what the most appropriate target

population will be. As with COMPASS, the patients enrolled in REDUCE-IT were at very high risk of cardiovascular events, as illustrated by a placebo event rate of approximately 4.4% per year over the 4.9-year median duration of follow-up.[9] Patients also were on statin therapy, and it is unclear whether icosapent ethyl would be effective in patients not treated with statins. How the benefits of icosapent ethyl translate to an eligible population that is certain to be both broader and at lower risk than the trial population remains to be seen.

## Summary and Comment

### *Rivaroxaban + ASA versus ASA Alone*

Compared to ASA alone, rivaroxaban + ASA significantly reduced the risk of cardiovascular death, stroke, or MI in patients with stable CVD. Patients treated with rivaroxaban + ASA experienced significantly fewer strokes (including disabling or fatal strokes), less cardiovascular death, less all-cause mortality, fewer major adverse limb events, and fewer cardiovascular-related hospitalizations. Bleeding events of greatest severity—i.e., fatal bleeding, symptomatic bleeding into a critical organ, and nonfatal symptomatic intracranial hemorrhages—were not significantly increased by adding rivaroxaban to ASA. We therefore have high certainty that rivaroxaban + ASA provides a small-to-substantial net health benefit in patients with CAD, PAD, or both conditions ("B+").

### *Rivaroxaban + ASA versus DAPT*

We did not identify any head-to-head studies that directly compared rivaroxaban + ASA to DAPT in patients with stable CVD. Although an indirect comparison of the risk of major adverse cardiovascular events in patients with a recent MI suggested that DAPT may provide a similar cardioprotective benefit to rivaroxaban + ASA, clinically significant differences in the way major bleeding was defined in the clinical trials of focus precluded a companion analysis of relative bleeding risks. We also note that those with a recent MI represented a relatively small subset of patients in the COMPASS trial, so the comparative benefits and risks of these two strategies in the remaining CAD and PAD population are unknown. We therefore have low certainty of whether rivaroxaban + ASA provides a negative, comparable, or positive net health benefit compared to DAPT in patients with CAD or PAD ("I").

### *Icosapent Ethyl versus Optimal Medical Management*

Icosapent ethyl reduced the risk of major adverse cardiovascular events in patients with established CVD or diabetes mellitus and additional risk factors compared to optimal medical management alone (i.e., placebo). The therapy was generally well-tolerated, despite a slight increase in the incidence of major bleeding disorders. However, over 4.9 years of follow-up, no fatal bleeding events occurred, and rates of TEAEs were comparable between the icosapent ethyl and placebo arms. Although we are uncertain whether the use of mineral oil may have caused some harm to the placebo group, we do not believe that this theory can account for the entire benefit observed in the REDUCE-IT trial. We believe that the results of REDUCE-IT likely

apply across a range of baseline triglyceride levels but are uncertain whether the results generalize to patients not treated with statins. For adults with established CVD or at high risk of cardiovascular events who are being treated with statins, we have high certainty that icosapent ethyl provides a small-to-substantial net health benefit ("B+").

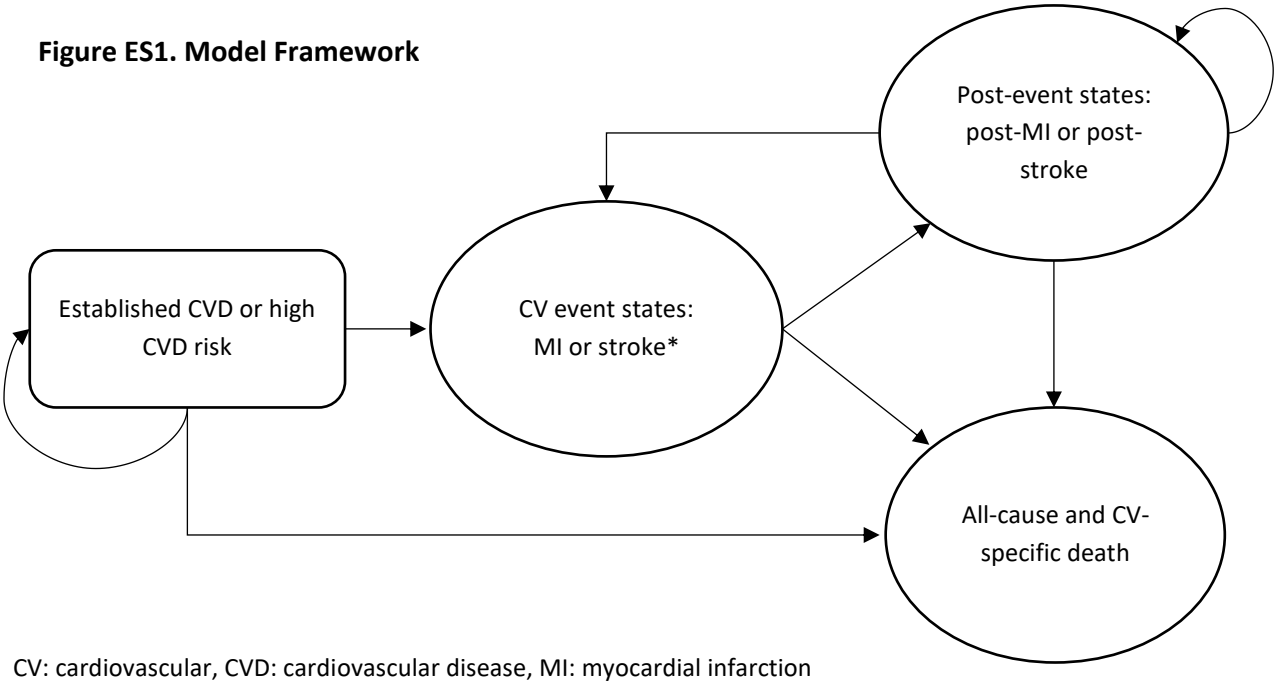
# Long-Term Cost Effectiveness

## Overview and Methods

The primary aim of this analysis was to estimate the cost effectiveness of rivaroxaban and icosapent ethyl as additive therapies to optimal medical management in patients with established CVD, and in the case of icosapent ethyl, also in patients without evidence of CVD but with diabetes and at least one additional risk factor. A Markov cohort model was constructed to compare the addition of rivaroxaban to ASA therapy to ASA alone and to compare the addition of icosapent ethyl to optimal medical management (including statins) to optimal medical management (including statins) alone. Rivaroxaban and icosapent ethyl were modeled separately but shared a similar overall model structure. Patient survival, quality-adjusted survival, and health care costs from a health care sector perspective were estimated over a lifetime time horizon for each intervention and comparator. Costs and outcomes were discounted at 3% per year. While the base-case analysis took a health care sector perspective, productivity losses to the patient and caregiver were considered in a scenario analysis using a modified societal perspective.

Individuals in the CVD cohort began on treatment and could stay in that state, pass into event states of MI or stroke, or could die (Figure ES1). Patients who experienced a cardiovascular event moved into post-event health states, where they may have had higher likelihood for death as compared to the general CVD prevention population. Patients remained in the model until they died. All patients could transition to death from all-causes from any of the alive health states. Death could have occurred from all-cause or cardiovascular event/post-event related morality.

**Figure ES1. Model Framework**




CV: cardiovascular, CVD: cardiovascular disease, MI: myocardial infarction
Other treatment-specific modeled events include major adverse limb events and other SAEs.
*Other CV events such as revascularization and unstable angina included in scenario analysis.

For both drugs, we obtained net pricing estimates from SSR Health, LLC,[32] which combine data on unit sales with publicly-disclosed US sales figures that are net of discounts, rebates, concessions to wholesalers and distributors, and patient assistance programs to derive a net price (Table ES3).

**Table ES3. Drug Cost Inputs**

| Drug | WAC per Tablet/Capsule | Net Price per Tablet/Capsule | Discount from WAC | Net Price per Year |
|---|---|---|---|---|
| **Rivaroxaban (Xarelto®, Janssen)** | $7.47 per 2.5 mg tablet | $3.03 | 59.41% | $2,215 |
| **Icosapent Ethyl (Vascepa®, Amarin Pharma)** | $2.53 per 1 g capsule | $1.11 | 56.04% | $1,625 |

WAC: wholesale acquisition cost

WAC per Redbook®; net pricing estimates from SSR Health.[32,33]

## Model Validation

We used several approaches to validate the model. First, we provided preliminary methods and results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model. Second, we varied model input parameters to evaluate face validity of changes in results. We performed model verification for model calculations using internal reviewers. As part of ICER's efforts to increase modeling transparency, we also shared the model with relevant manufacturers for external verification and feedback shortly after publishing the draft report for this review. Finally, we compared results to other cost-effectiveness models in this therapy area.

## Base-Case Results

Base-case discounted costs and outcomes from the model are listed in Table ES4 for rivaroxaban and in Table ES5 for icosapent ethyl. Rivaroxaban was associated with approximately $17,000 in discounted lifetime intervention costs, whereas icosapent ethyl was associated with $15,000 in lifetime intervention costs. Average discounted life years, equal value life years gained (evLYG) (a measure that evenly values any gains in length of life, regardless of the impact on patients' quality of life), and QALYs were higher for both interventions as compared to optimal medical management alone.

**Table ES4. Base-Case Discounted Results for Rivaroxaban Compared to Optimal Medical Management including ASA**

| Treatment | Intervention Costs | Non-Intervention Costs | Total Costs | Life Years | evLYG | QALYs |
|---|---|---|---|---|---|---|
| Rivaroxaban | $17,000 | $20,000 | $38,000 | 10.86 | 9.07 | 9.06 |
| Medical Management | $200 | $24,000 | $24,000 | 10.45 | 8.69 | 8.69 |

evLYG: equal value of life years gained, QALY: quality-adjusted life year

**Table ES5. Base-Case Discounted Results for Icosapent Ethyl Compared to Optimal Medical Management including Statins**

| Treatment | Intervention Costs | Non-Intervention Costs | Total Costs | Life Years | evLYG | QALYs |
|---|---|---|---|---|---|---|
| Icosapent Ethyl | $15,000 | $25,000 | $40,000 | 12.26 | 10.21 | 10.19 |
| Medical Management | $800 | $30,000 | $31,000 | 11.73 | 9.69 | 9.69 |

evLYG: equal value of life years gained, QALY: quality-adjusted life year

Base-case discounted incremental results are shown in Table ES6, with rivaroxaban versus optimal medical management yielding $36,000 per QALY gained. Icosapent ethyl versus optimal medical management yields $18,000 per QALY gained. Discounted incremental life year results were slightly lower than the incremental cost-per-QALY findings. Results for the incremental evLYG were slightly more favorable than the cost-per-QALY findings given there is a life extension to each therapy over medical management. The incremental cost per major adverse cardiovascular event avoided should be interpreted with caution, given that this metric does not have a known threshold for an understanding of value and does not include the differential timing or the differential importance of major adverse cardiovascular events. Note that the intervention-specific incremental findings are modeled using intervention-specific populations and therefore should not be directly compared across treatments.

**Table ES6. Base-Case Incremental Results**

| Intervention* | Incr. Costs | Incr. LYs | Incr. evLYG | Incr. QALYs | Cost per LY | Cost per evLYG | Cost per QALY | Cost per MACE Avoided |
|---|---|---|---|---|---|---|---|---|
| **Rivaroxaban vs. Medical Management** | $13,000 | 0.41 | 0.38 | 0.37 | $32,000 per LY gained | $35,000 per evLYG gained | $36,000 per QALY gained | $120,000 per MACE avoided |
| **Icosapent Ethyl vs. Medical Management** | $9,000 | 0.54 | 0.52 | 0.50 | $17,000 per LY gained | $17,000 per evLYG gained | $18,000 per QALY gained | $53,000 per MACE avoided |

ICER: incremental cost-effectiveness ratio, Incr.: Incremental LY: life year, MACE: major cardiovascular event, QALY: quality adjusted life year

*Modeled populations differed across interventions; results for the interventions are not directly comparable.

## Sensitivity Analyses

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes in cost per additional QALY in deterministic sensitivity analyses. Key drivers of uncertainty for both comparisons (rivaroxaban versus optimal medical management and icosapent ethyl versus optimal medical management) included the clinical event hazard ratios for MI, stroke, and cardiovascular death, with smaller impacts observed from uncertainty in utility and cost inputs. In probabilistic sensitivity analyses, in which all important parameters were varied simultaneously, 92% of iterations suggested that rivaroxaban met the $50,000/QALY threshold. Icosapent ethyl results suggested that nearly 100% of iterations met the $50,000/QALY threshold. Both interventions achieved 100% of iterations meeting the $100,000/QALY and $150,000/QALY thresholds.

## Threshold Analyses

We estimated threshold treatment prices that would reflect an incremental cost-per-QALY of $50,000, $100,000, and $150,000. The findings suggest that both treatments' net prices were below the price needed to achieve $50,000 per QALY (Table ES7).

**Table ES7. Threshold Analysis Results**

| | WAC per Tablet/Capsule | Annual WAC | Net Price per Tablet/ Capsule | Net Price per Year | Annual Price to Achieve $50,000 per QALY | Annual Price to Achieve $100,000 per QALY | Annual Price to Achieve $150,000 per QALY |
|---|---|---|---|---|---|---|---|
| Rivaroxaban | $7.47 per 2.5 mg tablet | $5,457 | $3.03 | $2,215 | $2,849 | $5,223 | $7,597 |
| Icosapent Ethyl | $2.53 per 1 g capsule | $3,699 | $1.11 | $1,625 | $3,433 | $6,282 | $9,204 |

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

Table ES8 presents the threshold results for each drug at thresholds of $50,000, $100,000, and $150,000 per equal value life year gained (evLYG). An analysis of the evLYG is included to complement the cost per QALY calculations and provide policymakers with a broader view of cost effectiveness.

**Table ES8. Cost per evLYG Threshold Analysis Results**

| | WAC per Tablet/Capsule | Annual WAC | Net Price per Tablet/ Capsule | Net Price per Year | Annual Price to Achieve $50,000 per evLYG | Annual Price to Achieve $100,000 per evLYG | Annual Price to Achieve $150,000 per evLYG |
|---|---|---|---|---|---|---|---|
| Rivaroxaban | $7.47 per 2.5 mg tablet | $5,457 | $3.03 | $2,215 | $2,922 | $5,369 | $7,780 |
| Icosapent Ethyl | $2.53 per 1 g capsule | $3,699 | $1.11 | $1,625 | $3,506 | $6,501 | $9,423 |

evLYG: equal value life year gained, WAC: wholesale acquisition cost

## Summary and Comment

Our base-case results suggest that the use of rivaroxaban (plus ASA) and icosapent ethyl (in patients receiving statins) both provide clinical benefit in terms of gains in quality-adjusted survival and overall survival compared to optimal medical management alone in the adult, established CVD cohort, and in the case of icosapent ethyl also for adults without known CVD but at high risk for cardiovascular events. This translated into incremental cost-effectiveness estimates that fell below commonly cited cost-effectiveness thresholds under the assumptions used in this analysis. The results were relatively robust to parameter uncertainties in the one-way and probabilistic sensitivity analyses. Further, the results were robust to a number of scenario analyses including the modified societal perspective and others.

Our analyses had important limitations and assumptions. We assumed three-component major adverse cardiovascular events, MI, stroke, and cardiovascular death, to form the base-case health states within the model structure for both rivaroxaban and for icosapent ethyl. A scenario analysis that broadened major adverse cardiovascular events to include other events

suggested similar but lower cost-effectiveness findings for icosapent ethyl. An additional limitation of this analysis was the model calibration to the observed clinical trial event rates for optimal medical management. Many unknowns were a part of the model calibration exercise. Finally, it is important to note that randomized controlled trial findings may not generalize or translate to observed signals within the real world (i.e., efficacy does not equal effectiveness). Given that the cost-effectiveness findings relied on randomized controlled trials for estimates of clinical benefit and harm, the findings should be interpreted with caution when estimating whether these interventions would achieve similar value for money in actual practice.

In conclusion, the findings of our analysis suggest that the additive CVD therapies of focus for this review provide gains in quality-adjusted survival and overall survival over optimal medical management. Assuming clinical signals within the trial hold for patients treated with these interventions and current net prices, the base-case results suggest that costs for treatment with either rivaroxaban or icosapent ethyl would fall below commonly cited thresholds for cost effectiveness. The results were relatively robust to sensitivity and scenario analyses.

## Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in the table below.

### Potential Other Benefits

**Table ES9. Potential Other Benefits**

| Other Benefits | Description |
|---|---|
| This intervention offers reduced complexity that will significantly improve patient outcomes. | Most candidate patients are older and already taking multiple classes of medication, so the potential is for *increased* complexity. |
| This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories. | N/A |
| This intervention will significantly reduce caregiver or broader family burden. | N/A |
| This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed. | Icosapent ethyl may complement other commonly-prescribed therapies for CVD that have different mechanism of action. |
| This intervention will have a significant impact on improving return to work and/or overall productivity. | N/A |
| Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention. | N/A |

## Contextual Considerations

**Table ES10. Potential Contextual Considerations**

| Contextual Consideration | Description |
|---|---|
| This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life. | Both drugs were studied in high-risk populations suggestive of significant unmet need. |
| This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness. | CVD is both prevalent and associated with a high lifetime burden of illness. |
| This intervention is the first to offer any improvement for patients with this condition. | N/A |
| Compared to "the comparator," there is significant uncertainty about the long-term risk of serious side effects of this intervention. | The early termination of the COMPASS trial introduces significant uncertainty regarding the long-term safety of rivaroxaban. |
| Compared to "the comparator," there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention. | The early termination of the COMPASS trial introduces some uncertainty regarding the long-term benefits of rivaroxaban. Uncertainty around icosapent ethyl revolves around the previous track record of other omega-3 preparations. |
| There are additional contextual considerations that should have an important role in judgments of the value of this intervention. | N/A |

# Value-Based Benchmark Prices

Annual value-based price benchmarks (VBPBs) of rivaroxaban and icosapent ethyl are presented in Table ES11. The value-based benchmark price for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY (or evLYG) gained.

For rivaroxaban, price changes of approximately 4% discount to 39% over the list price (WAC) would be required to reach the $100,000 to $150,000 per QALY threshold prices, respectively. For icosapent ethyl, prices approximately 70% to 149% above WAC would achieve $100,000 to $150,000 per QALY threshold prices. The cost per evLYG price range is quite similar to the cost per QALY range for both rivaroxaban and icosapent ethyl.

**Table ES11. Value-Based Price Benchmarks for Rivaroxaban and Icosapent Ethyl**

| | Annual WAC | Annual Price at $100,000 Threshold | Annual Price at $150,000 Threshold | Change from WAC to Reach Threshold Prices |
|---|---|---|---|---|
| **Rivaroxaban** | | | | |
| **Per QALY Gained** | $5,457 | $5,223 | $7,597 | -4% to +39% |
| **Per evLYG** | | $5,369 | $7,780 | -2% to +43% |
| **Icosapent Ethyl** | | | | |
| **Per QALY Gained** | $3,699 | $6,282 | $9,204 | +70% to +149% |
| **Per evLYG** | | $6,501 | $9,423 | +76% to +155% |

WAC: wholesale acquisition cost; evLYG: equal value life year gained; QALY: quality-adjusted life year

## Potential Budget Impact

We used results from the model to inform our budget impact estimates. For rivaroxaban, the candidate population was estimated to be approximately 6.7% of the US population age ≥20, or approximately 16.9 million individuals in total (~3.4 million per year over five years). For icosapent ethyl, the candidate population included both the CAD estimate used for rivaroxaban as well as estimates of individuals with prior stroke and those age ≥50 with diabetes and at least one additional risk factor. The resulting estimate was approximately 33.5 million individuals, or 6.7 million per year over five years.

As shown in Figures ES2 and ES3, despite both therapies meeting common cost-effectiveness thresholds, only a small portion of the eligible populations could be treated with crossing the ICER budget impact threshold of $819 million per year because so many patients are potentially eligible. When using net prices, only approximately 6% and 4% of eligible patients could be treated in a given year with rivaroxaban and icosapent ethyl respectively without crossing the ICER budget impact threshold.

**Figure ES2. Potential Budget Impact of Rivaroxaban at Various Prices**

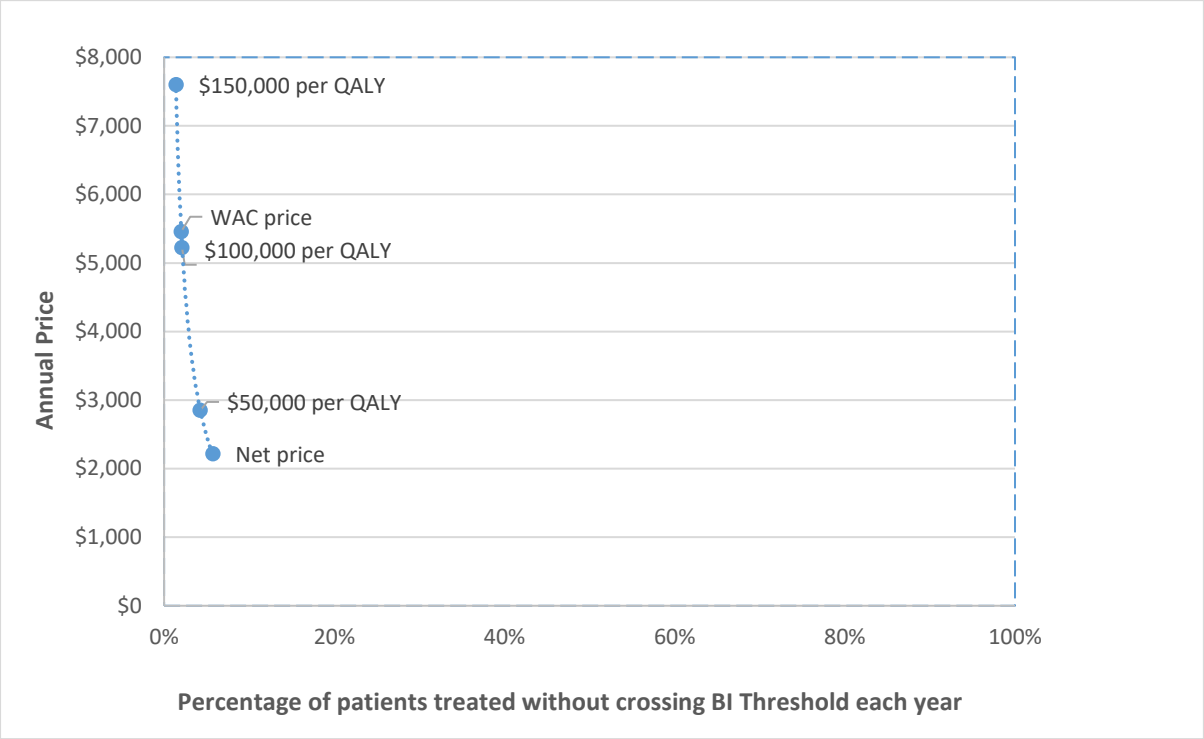
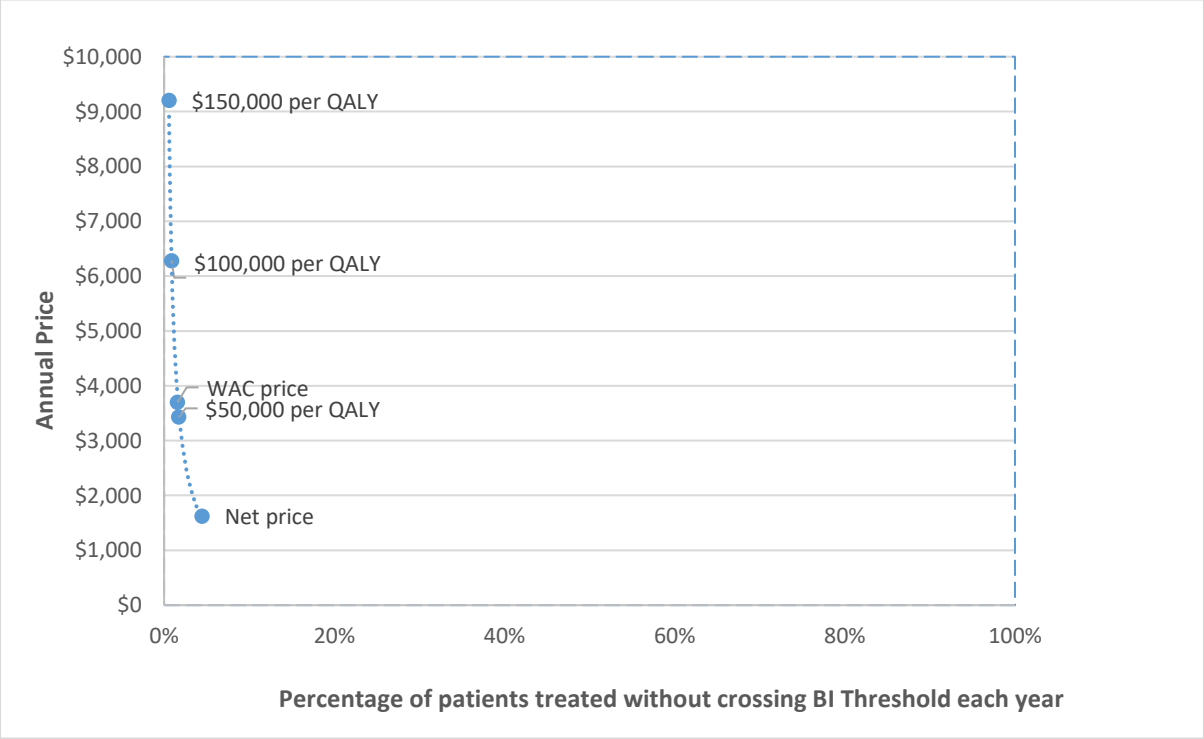



**Figure ES3. Potential Budget Impact of Icosapent Ethyl at Various Prices**



## Access and Affordability Alert

ICER is issuing an access and affordability alert for both rivaroxaban and icosapent ethyl. For rivaroxaban, at the net price of $2,215 per year, approximately 6% of eligible patients could be treated in a given year without crossing the ICER potential budget impact threshold of $819 million, while clinical experts at the Public Meeting stated that they would consider using rivaroxaban in approximately 30% of eligible patients. For icosapent ethyl, at the net price of $1,625 per year, approximately 4% of eligible patients could be treated in a given year without crossing the ICER potential budget impact threshold of $819 million. Clinical experts at the Public Meeting stated that they believe that the majority of eligible patients would want to be on icosapent ethyl. The purpose of an ICER affordability and access alert is to signal to stakeholders and policy makers that the amount of added health care costs associated with a new service may be difficult for the health care system to absorb over the short term without displacing other needed services or contributing to rapid growth in health care insurance costs. Thus, there is a risk to sustainable access to high-value care for all patients if managing these issues is not appropriately planned for.

# Midwest CEPAC Votes

The Midwest CEPAC Panel deliberated on key questions raised by ICER's report at a public meeting on September 26, 2019. The results of these votes are presented below, and additional information on the deliberation surrounding the votes can be found in the full report.

1. **Is the evidence adequate to demonstrate that the net health benefit of rivaroxaban plus ASA is superior to that provided by ASA alone?**

| | |
|---|---|
| ***Yes: 10 votes*** | No: 1 vote |

2. **Is the evidence adequate to demonstrate that the net health benefit of rivaroxaban plus ASA is superior to that provided by ASA as part of dual antiplatelet therapy (DAPT) with an oral $P2Y_{12}$ inhibitor (e.g., ticagrelor or clopidogrel)?**

| | |
|---|---|
| Yes: 0 votes | ***No: 11 votes*** |

3. **Is the evidence adequate to demonstrate that the net health benefit of icosapent ethyl added to optimal medical management (including statin therapy) is superior to that provided by optimal medical management (including statin therapy) alone?**

| | |
|---|---|
| ***Yes: 9 votes*** | No: 2 votes |

4. **Does treating patients with rivaroxaban plus ASA offer one or more of the following potential "other benefits or disadvantages" compared to ASA alone? (Select all that apply).**

| | |
|---|---|
| This intervention will significantly reduce caregiver or broader family burden. | **1/11** |
| This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed. | **6/11** |
| This intervention will have a significant impact on improving patients' ability to return to work and/or their overall productivity. | **1/11** |
| There are other important benefits or disadvantages that should have an important role in judgements of the value of this intervention. | No vote |

5. **Does treating patients with icosapent ethyl offer one or more of the following potential "other benefits or disadvantages" compared to optimal medical management (including statin therapy) alone? (Select all that apply).**

| | |
|---|---|
| This intervention will significantly reduce caregiver or broader family burden. | 0/11 |
| This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed. | **7/11** |
| This intervention will have a significant impact on improving patients' ability to return to work and/or their overall productivity. | 0/11 |
| There are other important benefits or disadvantages that should have an important role in judgements of the value of this intervention. | No vote |

6. **Are any of the following contextual considerations important in assessing the long-term value for money of rivaroxaban plus ASA? (Select all that apply).**

| | |
|---|---|
| This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life. | **6/11** |
| This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness. | **6/11** |
| There is significant uncertainty about the long-term risk of serious side effects of this intervention. | **9/11** |
| There is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention. | **9/11** |
| There are additional contextual considerations that should have an important role in judgements of the value of this intervention. | No vote |

7. **Are any of the following contextual considerations important in assessing the long-term value for money of icosapent ethyl? (Select all that apply).**

| | |
|---|---|
| This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life. | **6/11** |
| This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness. | **6/11** |
| There is significant uncertainty about the long-term risk of serious side effects of this intervention. | **5/11** |

| | |
|---|---|
| There is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention. | **7/11** |
| There are additional contextual considerations that should have an important role in judgements of the value of this intervention. | No vote |

### Long-Term Value for Money

As described in ICER's value assessment framework, questions on long-term value for money are subject to a value vote when incremental cost-effectiveness ratios for the interventions of interest are between $50,000 and $175,000 per QALY in the primary "base-case" analysis. The base-case estimates of the cost per QALY for both rivaroxaban + ASA and icosapent ethyl are below the lower end of this range, and therefore the treatment is deemed "high long-term value for money" without a vote unless the CEPAC determines in its discussion that the Evidence Report base-case analysis does not adequately reflect the most probable incremental cost-effectiveness ratio for either treatment.

ICER's value assessment framework also describes that the CEPAC does not take Long-Term Value for Money votes on treatments for which the evidence is considered inadequate during the Clinical Vote. Such is the case for rivaroxaban + ASA versus DAPT therapy. Thus, no Value vote was taken for rivaroxaban + ASA versus DAPT therapy (e.g. clopidogrel).

## Key Policy Implications

Following its deliberation on the evidence, the Midwest CEPAC Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on rivaroxaban and icosapent ethyl to policy and practice associated with the treatment of CVD. The policy roundtable members included two patients, two clinical experts, two payers, and one representative from a pharmaceutical manufacturer. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The top-line policy implications are presented below, and additional information can be found in Section 8 of the full report.

### Payers

1. Evidence to compare rivaroxaban to dual-action platelet therapy (DAPT) plus aspirin is limited by lack of head-to-head trials and differing outcome measures. Additionally, clinical experts do not view these two treatment options as interchangeable given their different mechanisms of action and risk profiles, therefore DAPT should not be considered an appropriate candidate in a step therapy protocol as a first step prior to receiving coverage for rivaroxaban.
2. Icosapent ethyl has not yet received FDA approval and therefore the specific language of the label is unknown. While awaiting the FDA decision, payers should consider parameters of coverage criteria related to the eligibility criteria of the pivotal trial: a)

definition of risk for coronary artery disease; b) concurrent use of statins; and c) triglyceride level of 135-499 mg/dL.

## Providers

3. Clinicians, when thinking about the apparent benefit of rivaroxaban in the clinical trial, should remember that patients at high risk of bleeding were excluded.
4. Develop options to help patients navigate complex medication regimens.

## Clinical and Specialty Societies

5. Develop a decision algorithm and/or tool for clinicians to use in determining the most appropriate additive therapies to consider for a given patient.
6. Ensure that any clinical guideline statements regarding rivaroxaban clearly warn against assuming a class effect for direct oral anticoagulants.

## Manufacturers

7. Conduct additional studies of icosapent ethyl in patients not on statin therapy.
8. Ensure that future trial recruitment reflects the demographics of the CVD population.

## Regulators

9. The FDA, manufacturers, and the clinical research community should work to solidify a common, single, outcomes definitions for key outcomes -- such as major bleeding -- so clinicians and patients have the information they need to make informed decisions.

## Researchers

10. Researchers should develop explicit head-to-head evidence of the comparative benefits and risks of rivaroxaban + aspirin versus dual antiplatelet therapy in patients who have completed an initial course of DAPT (12-30 months).
11. Researchers should conduct a real-world observational study to confirm the benefits of icosapent ethyl.

# 1. Introduction

## 1.1 Background

The term cardiovascular disease (CVD) defines a complex, burdensome, and highly prevalent set of conditions. Three of the major types of CVD, coronary artery disease (CAD), peripheral artery disease (PAD), and cerebrovascular disease, result most frequently from atherosclerosis, a chronic degenerative process involving increasing buildup of plaque formed by fat- and cholesterol-based deposits. Over time, these deposits result in arterial narrowing and wall hardening, which in turn can result in angina, claudication, myocardial infarction (MI), stroke, heart failure, and death, among other problems. In total, CVD is estimated to affect one-half of adults in the United States (US), and is the leading cause of death across all races and ethnicities, with approximately 850,000 deaths annually.[2] CVD also imposes a substantial financial burden, with annual direct and indirect costs estimated to total $351 billion; projected annual costs are expected to exceed $1 trillion by 2035.[2] Hypertension, hypercholesterolemia, diabetes, and smoking are well-established risk factors for atherosclerotic CVD, and overweight/obesity, poor diet, physical inactivity, and excessive alcohol use may also contribute to its development.[3]

In addition to mortality risks and financial burden associated with CVD, major adverse cardiovascular events can result in long-term disability and complicate care for other conditions. For example, an analysis of linked data from the US Health and Retirement Study and Medicare claims found significant increases in the number of functional limitations on activities of daily living following hospitalization for MI or stroke; in addition, those hospitalized for stroke had a fourfold increase in the odds of moderate-to-severe cognitive impairment, even after controlling for pre-hospitalization cognition.[4]

The management of CVD has commonly consisted of behavioral and lifestyle changes (i.e., diet, weight reduction, physical activity, smoking cessation) to interrupt atherosclerotic processes, as well as risk factor management, including blood pressure control, treatment with lipid-lowering agents such as statin medications and PCSK9 inhibitors, antiplatelet therapy, and when necessary, management of diabetes as well as surgical or percutaneous revascularization. Although low-dose acetylsalicylic acid (aspirin, or ASA) and statins have become cornerstone therapies with proven benefit for patients with established CVD, this population remains at high residual risk of cardiovascular events.[5] In addition, those without documented CVD but with established risk factors such as diabetes and comorbid hypertension or hypercholesterolemia are also at elevated risk of major cardiovascular events. For these patients, there is clinical interest in exploring other types of medical management in addition to the strategies.

## Interventions

### *Rivaroxaban*

Rivaroxaban (Xarelto®, Janssen Pharmaceuticals, Inc.) is an oral direct and selective inhibitor of factor Xa in the blood coagulation pathway. This process also results in inhibition of prothrombinase,[6] an enzyme essential not only to hemostasis but to complex biologic processes such as angiogenesis, cell proliferation, and inflammation; it therefore plays a role in the development and progression of atherosclerosis, cancer, and other chronic inflammatory diseases.[34]

Rivaroxaban, first approved for the prevention of deep vein thrombosis in patients undergoing major orthopedic surgery, is commonly used in the management of atrial fibrillation and venous thromboembolic disease. It received an indication for the prevention of major cardiovascular events in patients with chronic CAD or PAD in October 2018, and is the latest in a line of antithrombotic regimens that have been tested as alternatives or additions to ASA, including vitamin K antagonists, antiplatelet therapies, and thrombin receptor antagonists.[21] The recommended dosage for prevention of cardiovascular events is 2.5 mg twice daily with or without food, in combination with ASA (75-100 mg) once daily.[6]

### *Icosapent Ethyl*

Icosapent ethyl (Vascepa®, Amarin Pharma, Inc.) is a purified ethyl ester of the omega-3 fatty acid known as eicosapentaenoic acid (EPA), which was initially approved in 2012 as an adjunct to diet to treat severe hypertriglyceridemia (triglyceride levels ≥500 mg/dL). Following the completion of a Phase III trial in patients with established CVD or at high risk of cardiovascular events,[9] the manufacturer filed for an expanded indication in March of 2019, with an expected FDA decision date of September 28, 2019.[7] On August 8, 2019, the company announced that they had received notification from the FDA that an advisory committee meeting had been scheduled for November 14, 2019, with extension of the deadline for an FDA decision to late December.[35] At the time of publication of this report, no details are currently available regarding the reasons for an advisory committee or specific questions or concerns posed by the FDA.

Icosapent ethyl's mechanism of action in cardioprotection is not fully known; while hypertriglyceridemia increases the risk of ischemic events, reduction in these levels with icosapent ethyl may only partially explain the treatment effects observed in the trial. Other mechanisms, such as antithrombotic effects and stabilization and regression of coronary plaque have also been hypothesized.[9] The current recommended dosage of 2 g twice daily with food for hypertriglyceridemia was also the dose tested in the cardiovascular prevention trial.

## 1.2 Scope of the Assessment

This project assesses both the comparative clinical effectiveness and economic impacts of rivaroxaban + ASA and icosapent ethyl for the management of CVD. Evidence was collected from available randomized controlled trials and non-randomized clinical trials. We did not restrict studies according to number of patients or study setting. We supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see https://icer-review.org/methodology/icersmethods/icer-value-assessment-framework/grey-literature-policy/).

### Populations

The population of focus for the review is adults with established CVD who are currently treated with optimal medical management. For the assessment of icosapent ethyl, we also reviewed evidence for patients without known CVD but at high risk for cardiovascular events.

Where data were available, we examined evidence for key subgroups suggested by clinical experts, including the following:

1. Diagnosis of diabetes mellitus
2. Diagnosis of CAD alone versus CAD and concomitant PAD (rivaroxaban only)
3. Levels of high-sensitivity C-reactive protein (hsCRP) at baseline (i.e., ≤2 mg/l or >2 mg/l) as well as changes in hsCRP from baseline to follow-up
4. Subgroups defined by level of cardiovascular risk at baseline
5. Renal dysfunction
6. Diagnosis of heart failure

### Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which drugs to include. The full list of interventions is as follows:

1. Rivaroxaban + ASA
    - Patients are assumed to also be receiving optimal medical management
2. Icosapent ethyl
    - Patients are assumed to also be receiving optimal medical management including statins

### Comparators

Comparators were defined to reflect the input of clinicians and other stakeholders on treatment strategies that would be considered relevant alternatives for the overall population of interest or a prominent subset, as well as the comparators as defined in major clinical studies of icosapent ethyl and rivaroxaban.

1. Rivaroxaban comparators:
    - optimal medical management including ASA without an additional antiplatelet agent
    - optimal medical management including ASA as part of dual antiplatelet therapy (DAPT) with an oral $P2Y_{12}$ inhibitor (e.g., clopidogrel)
2. Icosapent ethyl comparator:
    - Optimal medical management including statin therapy

## Outcomes

The outcomes of interest are described in Table 1.1 below.

**Table 1.1. Outcomes and Harms**

| Outcomes | Key Harms |
|---|---|
| All-cause mortality | TEAEs |
| Cardiovascular mortality | Discontinuation due to TEAEs |
| MI | Serious TEAEs |
| Stroke | Major bleeding events |
| Coronary revascularization | |
| Unstable angina | |
| Heart failure | |
| Venous thromboembolism | |
| Health-related quality of life | |
| Cardiovascular hospitalization | |
| Major adverse limb events | |

MI: myocardial infarction, TEAE: treatment-emergent adverse event

## Timing

Evidence on intervention effectiveness were derived from studies of at least one year's duration and evidence on harms from studies of at least three month's duration.

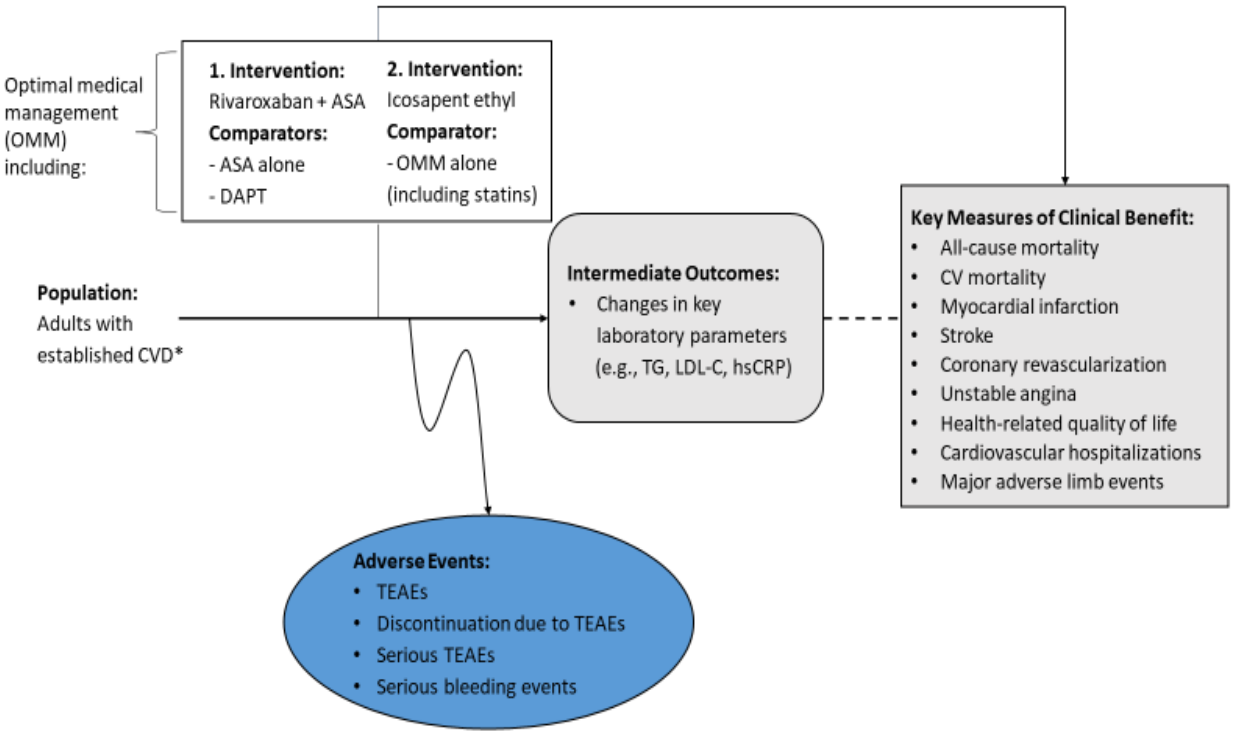
## Settings

All relevant settings were considered, with a focus on outpatient management in the US.

## Analytic Framework

The analytic framework for this assessment is depicted in Figure 1.1.

**Figure 1.1. Analytic Framework: Rivaroxaban and Icosapent Ethyl for CVD**




ASA: aspirin, CV: cardiovascular, CVD: cardiovascular disease, DAPT: dual antiplatelet therapy, hsCRP: high-sensitivity C-reactive protein, LDL-C: low-density lipoprotein cholesterol, OMM: optimal medical management, TEAE: treatment-emergent adverse event, TG: triglyceride

*For the assessment of icosapent ethyl, we will also review evidence for patients without known CVD but at high risk for CV events.

The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific clinical or health outcomes. Outcomes are listed in the shaded boxes: those within the rounded boxes are intermediate outcomes (e.g., change in blood pressure), and those within the squared-off boxes are key measures of clinical benefit (e.g., health-related quality of life). The key measures of clinical benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the AEs of an action (typically treatment), which are listed within the blue ellipsis.[1]

## 1.3 Definitions

**International Society on Thrombosis and Haemostasis (ISTH) major bleeding**: Fatal bleeding, symptomatic bleeding into a critical area or organ, bleeding that causes a decrease in hemoglobin ≥2 g/dL, or bleeding that requires a transfusion of ≥2 units of whole blood or red cells.[21,36]

> **Modified ISTH major bleeding (used in COMPASS trial of rivaroxaban):** Fatal bleeding, symptomatic bleeding into a critical organ, bleeding into a surgical site requiring reoperation, and bleeding that led to a visit to an acute care facility with or without an overnight stay.[21]

**Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) severe bleeding:** Fatal bleeding events, intracranial hemorrhages, or bleeding that causes hemodynamic compromise requiring blood or fluid replacement, inotropic support, or surgical intervention.[17]

**Thrombolysis in Myocardial Infarction (TIMI) major bleeding:** Intracranial bleeding, clinically overt signs of hemorrhage (drop in hemoglobin ≥5 g/dL or fall in hematocrit ≥15%), or a bleeding event that led to death within seven days.[15]

**Rankin Scale:** A 6-point scale used to measure disability in individuals who have suffered a stroke or other cause of neurologic disability. Scores range from 0, indicating no symptoms or disability, to 6, indicating death; a score of 3 represents moderate disability.[12-14]

**Ischemic stroke:** Occurs when a blood vessel supplying blood to the brain becomes obstructed.[37]

**Hemorrhagic stroke:** Occurs when a blood vessel in the brain leaks or ruptures.[37]

## 1.4 Insights Gained from Discussions with Patients and Patient Groups

ICER engaged with patients, patient groups, and clinical experts to understand the specific challenges associated with ongoing management of CVD from the patient perspective. There was acknowledgment that the high rate of recurrent events, even in CVD patients whose risk factors are optimally managed, continues to concern clinicians. Still, caution was urged in considering further additions to the current armamentarium, given the need to balance the potential for additional clinical benefit against the risk of major bleeding and other harms, as well as the inconsistent track record of previous antithrombotic regimens and omega-3 preparations respectively in reducing the rate of recurrent cardiovascular events. Despite these concerns, there was enthusiasm expressed around the potential for new treatments to further reduce event risks in these high-risk populations.

We also heard that medication adherence might be a challenge in this population, given already high rates of polypharmacy and comorbidity in older patients likely to be candidates for add-on therapy. Indeed, patients expressed trepidation with an increased therapeutic burden, citing concerns with both the daily complexity of treatment and increased financial responsibility for ongoing treatment. Patients also mentioned that the value and risk of adding new treatments to an already complex treatment regimen is not necessarily clearly and consistently communicated. Indeed, prior research in this clinical area suggests that patients tend to significantly overestimate both their event and bleeding risks relative to their quantified risk scores.[10] Other feedback included the need to tailor the physician-patient conversation to reflect the patient's specific situation—for example, a family history of CVD, management of comorbid conditions, or the benefits of lifestyle and behavioral changes in addition to medical management.

## 1.5 Potential Cost-Saving Measures in the Management of CVD

As described in its Final Value Assessment Framework for 2017-2019, ICER now includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/final-vaf-2017-2019/). These services are ones that would not be directly affected by rivaroxaban + ASA or icosapent ethyl (e.g., reduction cardiovascular events), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of CVD beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with CVD that could be reduced, eliminated, or made more efficient. ICER has not received any such suggestions at the time of posting this Evidence Report.

# 2. Summary of Coverage Policies and Clinical Guidelines

## 2.1 Coverage Policies

To understand the insurance landscape for the interventions and comparators in this report, we reviewed National and Local Coverage Determinations (NCDs and LCDs) from the Centers for Medicare and Medicaid Services (CMS), and publicly available coverage policies from representative public plans (MO HealthNet and Illinois Medicaid) and national and regional private payers (Aetna, Cigna, and Blue Cross Blue Shield of Kansas City). We also looked at Aetna's standard Medicare plan to see if Medicare coverage differed from its standard national plan. We surveyed the coverage policies for the currently approved indications of icosapent ethyl and rivaroxaban, understanding these coverage policies may change for icosapent ethyl should this intervention receive Food and Drug Administration (FDA) approval for its new indication being reviewed for this report. We also reviewed coverage policies for two agents used in DAPT, clopidogrel and ticagrelor, which are included in this report as comparators to rivaroxaban.

We were unable to identify any NCDs or LCDs relating to the use of any of these therapies.[38] A summary of our other findings is as follows:

**Rivaroxaban**

Rivaroxaban is listed as "preferred" on the preferred drug list of both surveyed Medicaid plans.[38,39] Minnesota based payer, HealthPartners, lists rivaroxaban as a tier three drug on its standard private plan and BCBSKC lists it as a tier-two drug—neither require prior authorization.[39,40] Aetna and Cigna's standard national plans both list rivaroxaban as a preferred brand on their respective drug lists.[41,42] It is also a preferred brand on Aetna's standard Medicare plan.[43]

**Clopidogrel and Ticagrelor**

Clopidogrel, a generic anti-platelet agent, and ticagrelor, a brand anti-platelet agent, are the preferred generic and preferred brand drugs respectively on both surveyed Medicaid plans.[38] As the generic option, clopidogrel is consistently a tier one or preferred generic drug, while ticagrelor is a tier two or three drug, or the preferred brand drug, on all surveyed private plans, both regional and national, and on Aetna's standard Medicare plan. None of these plans listed any prior authorization criteria for either drug, although members are alerted that they may pay more for the brand drug should they forego the generic.[39-43]

**Icosapent Ethyl**

Icosapent ethyl is listed as "non-preferred" on the preferred drug list of both surveyed Medicaid plans.[38] HealthPartners lists icosapent ethyl as a "non-formulary" drug on its standard private plan, explaining that depending on an individual's plan this medication is either not covered, or covered at a higher out-of-pocket cost. If it is covered, it requires a prior authorization stating: "reserved for patients with an inadequate response to two or more preferred products, such as generic Lovaza, gemfibrozil, and fenofibrate."[39]

BCBSKC lists icosapent ethyl as a tier-two drug but requires no prior authorization.[40] Cigna's standard national plans lists it as a tier-three, non-preferred brand drug.[42] Aetna's standard national plan lists icosapent ethyl on its preferred brand drug list, with no additional information[41], but it's standard Medicare plan lists it as a non-preferred brand.[43]

## 2.2 Clinical Guidelines

Treatment guidelines for secondary prevention are many and large. This report focuses on only those guidelines pertaining to the use of anticoagulation, DAPT, and fish oil in patients with established CVD.

**American Heart Association (AHA) and the American College of Cardiology Foundation (ACCF)**

The AHA/ACCF guidelines for secondary prevention in patients with coronary or other atherosclerotic vascular disease state that all patients with CAD should take daily ASA unless contraindicated. DAPT (which refers to ASA plus a $PY2_{12}$ inhibitor such as clopidogrel and ticagrelor) is recommended for patients after acute coronary syndrome (ACS) and for patients with symptomatic PAD. The guidelines also state that DAPT may be considered in patients with stable CAD.[44]

In 2016, AHA/ACCF published a focused update on guidelines for the use and duration DAPT. The guidelines state that for patients with ACS, regardless of whether or not they have been treated with revascularization or fibrinolytic therapy, DAPT therapy should continue for no fewer than 12 months and if is well tolerated without bleeding complications, it may be reasonable to continue DAPT for longer than 12 months. For patients with non-ST elevation ACS treated with medical therapy alone, and in patients with ACS treated with DAPT after coronary stent implantation, the guidelines state it is reasonable to prefer ticagrelor to clopidogrel for $P2Y_{12}$ maintenance therapy.[45]

The AHA/ACCF guidelines for secondary prevention in patients with CAD note that "it may be reasonable" to recommend omega-3 fatty acids from fish oil or capsules to patients whose non-HDL cholesterol levels remain elevated despite appropriate statin therapy. They also note that omega-3 fatty acids from fish oil or capsules may be used to reduce the risk of CVD in all patients.[44]

**American Heart Association (AHA)**

In August of 2019, the American Heart Association released a "Science Advisory" stating that four grams per day of prescription omega-3 fatty acids (EPA+DHA or EPA-only) is effective therapy for reducing triglycerides, either as monotherapy or in conjunction with lipid-lowering agents. The advisory noted that, in contrast to other cited perspectives, the EPA+DHA formulation only raises low-density (LDL) lipoprotein in the setting of very high triglycerides (≥500 mg/dL). The advisory also counseled against patients self-treating with fish oil supplements not approved by the FDA.[46]

**The American Diabetes Association (ADA)**

The ADA's Standards of Medical Care in Diabetes guidelines recommend that all patients with diabetes and a history of atherosclerotic CVD take ASA as part of their secondary prevention strategy. They also state that DAPT is reasonable for a year after ACS.

The guidelines were also recently updated to include the recommendation that icosapent ethyl be considered in patients with diabetes and atherosclerotic CVD, or other cardiac risk factors, who have controlled low-density lipoprotein (LDL) cholesterol on a statin, but whose triglycerides remain elevated.[47]

**The European Society of Cardiology (ESC)**

The ESC's 2013 Guidelines on the Management of Stable Coronary Artery Disease recommend low dose ASA for all patients with established CAD. These guidelines also note that N-3 polyunsaturated fatty acids, consumed mainly through fish oil, could have potential benefit on cardiac risk factors, but trial results have shown mixed results for reducing cardiovascular events.[48]

In 2017, the ESC released a focused update on guidelines for DAPT stating that for patients with stable CAD, there is no indication for DAPT (unless overridden by a concomitant or prior indication). For patients with ACS who have been treated with percutaneous coronary intervention (PCI) or who are managed with medical therapy alone, DAPT is recommended to continue for 12 months. If the patient is at high risk for bleeding, DAPT is recommended for six months.[49]

In 2019, the ESC released an updated guideline that incorporated results from the REDUCE-IT trial. The update recommends that treatment with omega-3 fatty acids, including icosapent ethyl 2 g twice daily, in combination with statins should be considered for high-risk patients with triglycerides between 135 and 499 mg/dL.[50]

# 3. Comparative Clinical Effectiveness

## 3.1 Overview

To inform our analysis of the comparative clinical effectiveness of additive therapies for the management of CVD, we sought evidence related to low-dose rivaroxaban + ASA compared to ASA alone or in combination with another antiplatelet agent (i.e., DAPT). Separately, we also evaluated the clinical evidence for icosapent ethyl compared to optimal medical management alone. Our review focused on clinical benefits (i.e., reduction in cardiovascular events, mortality, and quality of life), as well as potential harms (i.e., bleeding and other drug-related AEs). We did not attempt to indirectly compare rivaroxaban to icosapent ethyl given differences in target population and definitions of key outcomes. Methods and findings of our review of the clinical evidence are described in the sections that follow.

## 3.2 Methods

### Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on additive therapies for CVD followed established best research methods.[51,52] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[53] The PRISMA guidelines include a checklist of 27 items, which are described further in Appendix Table A1.

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

## Study Selection

Subsequent to the literature search and removal of duplicate citations, references went through two levels of screening at both the abstract and full-text levels. Two reviewers independently screened the titles and abstracts of all publications identified using DistillerSR (Evidence Partners, Ottawa, Canada); a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus.

Citations accepted during abstract-level screening were reviewed as full text. The review followed the same procedures as the title/abstract screening. Reasons for exclusion were categorized according to the PICOTS elements.

## Data Extraction and Quality Assessment

Two reviewers extracted key information from the full set of accepted studies (See Appendix D). Elements included a description of patient populations, sample size, duration of follow-up, study design features (e.g., double-blind), interventions (agent, dosage, dosing frequency, method of administration), results, and quality assessment for each study. Extracted data were reviewed for logic and were validated by a third investigator for additional quality assurance.

We used criteria employed by the US Preventive Services Task Force ([USPSTF], see Appendix D) to assess the quality of clinical trials and comparative cohort studies, using the categories "good," "fair," or "poor."[54]

## Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit for rivaroxaban + ASA and icosapent ethyl relative to the comparators of focus.[55]

## Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for newer treatments, we performed an assessment of publication bias for rivaroxaban + ASA and icosapent ethyl using the ClinicalTrials.gov database of trials. We scanned the site to identify studies completed more than two years ago that would have met our inclusion criteria and for which no findings have been published. Any such studies may indicate whether there is bias in the published literature. For this review, we did not find evidence of any study completed more than two years ago that has not subsequently been published.

### Data Synthesis and Statistical Analyses

Data on relevant outcomes were abstracted into evidence tables (see Appendix Tables D1-D15) and are described in the text below. Data informing the comparison of rivaroxaban + ASA to DAPT were also synthesized quantitatively in a network meta-analysis (NMA) with a focus on prevention of cardiovascular events. The NMA included data from the subgroup of patients with a MI within two years of randomization. An NMA extends pairwise meta-analyses by simultaneously combining both the direct estimates (i.e., estimates obtained from head-to-head comparisons) and indirect estimates (i.e., estimates obtained from common comparator[s]). The NMA was conducted in a Bayesian framework with fixed effects on the treatment parameter using the gemtc package in R.[56] A fixed effects approach was taken given the small size of the evidence network (i.e., single-study connections throughout). The log hazard ratios for the composite outcome of cardiovascular death, stroke, or MI were analyzed using a normal likelihood and identity link. Inputs used for the analysis are reported in Appendix Table D9. Tabular results are presented for the treatment effects (hazard ratio) of each intervention versus ASA along with 95% credible intervals (95% CrI) in Section 3.3. Note that we attempted an NMA specification for major bleeding events, but differences in definitions of this outcome across relevant clinical trials precluded such an analysis.

## 3.3 Results

### Study Selection

Our literature search identified 808 potentially relevant references, of which 10 met the full PICOTS criteria (Appendix A, Figure A1). The primary reasons for exclusion included study population outside of our scope (e.g., acute coronary syndromes), dosing or combination therapy outside of the FDA-labeled indication (e.g., >2.5 mg BID of rivaroxaban, rivaroxaban + DAPT), and lack of outcomes of interest (e.g., studies that only reported on changes in laboratory parameters).

Of the 10 included references, eight publications[11,14,57-62] related to a single randomized controlled trial (RCT) of rivaroxaban and two references corresponded to a single RCT of icosapent ethyl.[19,20]

Although we did not systematically review the available literature on DAPT, we searched for RCTs that evaluated the initiation of DAPT with ticagrelor or clopidogrel in combination with ASA. We selected two DAPT initiation trials in patients with established CVD for inclusion in an NMA of cardiovascular outcomes. Results of the NMA are presented in the sections that follow; evidence from four references related to the two DAPT RCTS are additionally summarized for context in Appendix D.

## Quality of Selected Studies

We rated the two key studies of rivaroxaban and icosapent ethyl, respectively, to be of good quality using criteria from the USPSTF (Appendix D). The trials had adequate blinding of patients, investigators, and outcome assessors. The groups were comparable at baseline and there was non-differential follow-up.

## Key Studies of Rivaroxaban

Our review of rivaroxaban was primarily informed by the Phase III COMPASS trial.[11] Patients were eligible to participate in the trial if they had CAD, PAD, or both. Patients with CAD under the age of 65 were also required to have documented atherosclerosis in at least two vascular beds or to have at least two additional risk factors (e.g., diabetes mellitus, heart failure). Key exclusion criteria included a high bleeding risk, recent stroke, severe heart failure, advanced kidney disease, and the use of other antithrombotic therapies. Additional inclusion and exclusion criteria can be found in Appendix Table D2.

Eligible patients (n=28,275) first entered a 30-day run-in period during which they received 100 mg of ASA once daily in combination with placebo twice daily; 8.2% (2,320) of patients were excluded after the run-in phase, with 729 withdrawing consent and 1,645 citing adherence concerns. Patients who recently underwent coronary artery bypass graft (CABG) (n=1,448), were exempt from the run-in phase and randomized within four to 14 days of the procedure.

Following the run-in, patients who adhered to therapy and who did not have any AEs were randomized 1:1:1 to combination therapy with rivaroxaban 2.5 mg twice daily and 100 mg once daily of ASA (n=9,152), 100 mg once daily of ASA alone (n=9,126), or 5 mg twice daily of rivaroxaban alone (n=9,117); in a second randomization, the COMPASS trial also compared pantoprazole, a proton-pump inhibitor (PPI), to placebo to assess upper gastrointestinal (GI) complications.[61] Pantoprazole randomization occurred equally across the rivaroxaban + ASA, rivaroxaban alone, and ASA alone treatment groups. As rivaroxaban was only approved in combination with ASA for patients with CAD or PAD, evidence pertaining to the rivaroxaban alone arm of COMPASS was not summarized in this review.

At baseline, 91% of patients had documented CAD and 27% had a history of PAD.[11] Approximately 62% of patients had a prior MI, 4% had a previous stroke, 38% had diabetes mellitus, and 22% had heart failure. Patients were on a number of other background medications, including angiotensin-converting enzymes and angiotensin-receptor blockers (71%), beta-blockers (70%), and lipid-lowering agents (90%). Based on a planned interim analysis, the COMPASS trial was stopped early (after a mean of 23 months of follow-up) due to evidence of significant clinical benefit. Key characteristics of the COMPASS trial are summarized in Table 3.1 below.

**Table 3.1. Summary of the COMPASS Trial[11]**

| | Treatment Groups | Patient Characteristics | Primary Outcome | Key Safety Outcome |
|---|---|---|---|---|
| **COMPASS Phase III Double-Blind**<br><br>**Mean Follow-Up: 23 Months** | 1. Rivaroxaban (2.5 mg BID) + ASA (100 mg QD)<br><br>2. ASA (100 mg QD) | n=27,395<br>Age: 68.2±7.9<br>Previous stroke: 343 (3.8)<br>Previous MI: 5,687.5 (62.2)<br>CAD: 8,287 (90.6)<br>PAD: 2,498 (27.3) | A composite of CV death, stroke, or MI | Major bleeding:* fatal bleeding, symptomatic bleeding into a critical organ, bleeding into a surgical site requiring reoperation, and bleeding that led to hospitalization or presentation to an acute care facility |

ASA: aspirin, CAD: coronary artery disease, CV: cardiovascular, MI: myocardial infarction, PAD: peripheral artery disease

*COMPASS also evaluated 5 mg twice daily of rivaroxaban alone, however only the FDA approved dose is represented here. Modified criteria from ISTH.

The COMPASS trial's primary endpoint was a composite of cardiovascular death, stroke, or MI; major bleeding, which was defined using modified criteria from ISTH, was a key safety outcome. Additional secondary and tertiary outcomes included individual components of the primary composite endpoint, acute limb ischemia, hospitalization, revascularization, and limb amputation.

## Clinical Benefits of Rivaroxaban

**Summary*: Compared to treatment with ASA alone, rivaroxaban + ASA reduced the risk of cardiovascular death, stroke, or MI in patients with stable CVD. Patients treated with rivaroxaban + ASA experienced significantly fewer strokes (including disabling or fatal strokes), less cardiovascular death, and fewer cardiovascular-related hospitalizations. No significant effect of rivaroxaban on hemorrhagic stroke or MI was observed.***

### *Major Adverse Cardiovascular Events*

*Time-to-First Event Composite Endpoints*

As noted above, the primary outcome of the COMPASS trial was a composite endpoint consisting of the first occurrence of cardiovascular death, stroke, or MI.[11] In the time to event analysis, the hazard ratio for the primary outcome was 0.76 (95% CI: 0.66, 0.86; p<0.001; number needed to treat [NNT]: 77). Patients treated with rivaroxaban + ASA had statistically significantly fewer primary outcome events (4.1%) compared to patients in the ASA alone group (5.4%); for the ASA alone group, this translates into an annual event rate of approximately 3%, suggesting a relatively high-risk population. As mentioned above, these results led the independent data and safety monitoring board to recommend early termination of the trial after the first formal interim analysis (50% of planned events) for efficacy.

Two secondary composite outcomes, comprised of ischemic stroke, MI, acute limb ischemia, and either death from coronary heart disease or cardiovascular death, also occurred in fewer patients treated with rivaroxaban + ASA versus ASA alone (Table 3.2).

**Table 3.2. Primary and Secondary Composite Outcomes in COMPASS[11]**

| | | Rivaroxaban + ASA n (%) | ASA n (%) | Hazard Ratio (95% CI) | P-Value |
|---|---|---|---|---|---|
| Primary Endpoint | CV Death, Stroke, or MI | 379 (4.1) | 496 (5.4) | 0.76 (0.66-0.86) | <0.001 |
| Secondary Endpoints | Ischemic Stroke, MI, ALI, or Death from CHD | 329 (3.6) | 450 (4.9) | 0.72 (0.63-0.83) | <0.001 |
| | Ischemic Stroke, MI, ALI, or CV Death | 389 (4.3) | 516 (5.7) | 0.74 (0.65-0.85) | <0.001 |

ALI: acute limb ischemia, ASA: aspirin, CHD: coronary heart disease, CI: confidence interval, CV: cardiovascular, MI: myocardial infarction

*Individual Events*

Individual components of the primary and secondary composite outcomes are presented in Table 3.3. Patients treated with rivaroxaban + ASA experienced significantly fewer strokes, and less cardiovascular death, death from coronary heart disease, and death from any cause. In an exploratory analysis, rivaroxaban + ASA reduced the risk of disabling or fatal strokes (i.e., strokes defined as a score between 3 and 6 on the modified Rankin Scale) by 42% (HR 0.58; 95% CI: 0.37 to 0.89; p=0.01).[12-14] Hemorrhagic strokes occurred in more patients in the rivaroxaban + ASA group but differences did not reach statistical significance.

**Table 3.3. Individual Event Rates in COMPASS[11,14]**

| | Rivaroxaban + ASA n (%) | ASA n (%) | Hazard Ratio (95% CI) | P-Value |
|---|---|---|---|---|
| Stroke | 83 (0.9) | 142 (1.6) | 0.58 (0.44-0.76) | <0.001 |
| Ischemic Stroke | 64 (0.7) | 125 (1.4) | 0.51 (0.38-0.69) | <0.0001 |
| Hemorrhagic Stroke | 15 (0.2) | 10 (0.1) | 1.49 (0.67-3.31) | 0.33 |
| MI | 178 (1.9) | 205 (2.2) | 0.86 (0.70-1.05) | 0.14 |
| CV Death | 160 (1.7) | 203 (2.2) | 0.78 (0.64-0.96) | 0.02 |
| Non-CV Death | 153 (1.7) | 175 (1.9) | 0.87 (0.70-1.08) | 0.20 |
| Death from Coronary Heart Disease | 86 (0.9) | 117 (1.3) | 0.73 (0.55-0.96) | 0.03 |
| All-Cause Death | 313 (3.4) | 378 (4.1) | 0.82 (0.71-0.96) | 0.01 |
| Revascularization* | 530 (6%) | 553 (7%) | 0.95 (0.84-1.07) | 0.39 |

ASA: aspirin, CI: confidence interval, CV: cardiovascular, MI: myocardial infarction
*Reported in CAD subgroup.

***Other Benefits of Rivaroxaban***

*Hospitalization*

Hospitalization for cardiovascular causes (Appendix Table D4) occurred less in patients randomized to rivaroxaban + ASA versus ASA alone (14.2% vs. 15.3%; HR 0.92; 95% CI: 0.86 to 1.00; p=0.04). The non-cardiovascular-related hospitalization rate was not statistically different between arms.

*Quality of Life*

We did not identify any evidence related to quality of life for rivaroxaban + ASA, although the European Quality of Life-5 Dimensions (EQ-5D) was implemented as a tertiary outcome in the COMPASS trial. As of the time of this report, these data have not been published or presented publicly.

## Harms of Rivaroxaban

**Summary**: ***Patients treated with rivaroxaban + ASA experienced a significant increase in major bleeding events, which led to permanent discontinuation of therapy in approximately 3% of patients. Most major bleeding events occurred in the GI tract; proton pump inhibitor therapy (PPI) had a protective effect on gastroduodenal bleeding (although not upper GI bleeding), which was not statistically different between patients randomized to rivaroxaban + ASA and ASA alone.***

The COMPASS trial's primary safety endpoint was major bleeding, which was assessed using a modified definition from ISTH. The modified ISTH criteria included fatal bleeding, symptomatic bleeding into a critical organ, bleeding into a surgical site requiring reoperation, or bleeding leading to hospitalization (or an acute care visit that did not require an overnight stay); bleeding events that did not meet the ISTH criteria were counted as minor. The most severe bleeding event was recorded among patients with more than one event; the rate of total bleeding events was not reported.

Major bleeding events occurred in significantly more patients treated with rivaroxaban + ASA compared to ASA alone (3.1% vs. 1.9%; HR 1.70; 95% CI: 1.40 to 2.05; p<0.001); 2.7% of patients in the rivaroxaban + ASA group permanently discontinued treatment due to bleeding, compared to 1.2% in the ASA alone group.[6,11] Selected bleeding outcomes are presented in Table 3.4 and all bleeding outcomes are reported in Appendix Table D5.

**Table 3.4. Selected Bleeding Outcomes in COMPASS**

| Outcome | Rivaroxaban + ASA | ASA | Hazard Ratio (95% CI) | P-Value |
|---|---|---|---|---|
| Major Bleeding | 288 (3.1) | 170 (1.9) | 1.70 (1.40-2.05) | <0.001 |
| Fatal Bleeding | 15 (0.2) | 10 (0.1) | 1.49 (0.67-3.33) | 0.32 |
| Non-Fatal Symptomatic Intracranial Bleeding | 21 (0.2) | 19 (0.2) | 1.10 (0.59-2.04) | 0.77 |
| Other Major Bleeding | 210 (2.3) | 112 (1.2) | 1.88 (1.49-2.36) | <0.001 |
| Minor Bleeding | 838 (9.2) | 503 (5.5) | 1.70 (1.52-1.90) | <0.001 |

ASA: aspirin, CI: confidence interval

The most common bleeding site was the GI tract (1.5% vs. 0.7%; HR 2.15; 95% CI: 1.60 to 2.89; p<0.0001). As previously noted, the COMPASS trial evaluated whether the addition of a PPI, pantoprazole (40 mg once daily), could reduce the risk of upper GI bleeding.[61] Clinically significant upper GI bleeding was defined as a composite of overt bleeding (i.e., hematemesis and/or melena) with a gastroduodenal lesion (peptic ulcer or neoplasia), overt upper GI bleeding of unknown origin, occult bleeding (drop in hemoglobin of 2 g per deciliter or more), symptomatic gastroduodenal ulcer with at least three days of GI pain, or at least five gastroduodenal erosions with at least three days of GI pain, and upper GI obstruction or perforation. Statistical differences in the occurrence of clinically significant upper GI bleeding were not observed between the pantoprazole and placebo arms on the composite bleeding endpoint, although pantoprazole did reduce the risk of gastroduodenal bleeding events (0.2% vs. 0.4% for the pantoprazole and placebo groups, respectively; HR 0.52; 95% CI: 0.28 to 0.94). There was no statistically significant interaction between pantoprazole and randomization to rivaroxaban + ASA or ASA alone. Additional results from this study are reported in Appendix Table D6.

Serious adverse events (SAEs) occurred in 7.9% of patients in the rivaroxaban + ASA arm versus 7.3% of patients on ASA alone; discontinuation due to non-bleeding AEs was not reported. The FDA label for rivaroxaban carries a black box warning for premature discontinuation and spinal/epidural hematoma.[6] The warning states that discontinuing any oral anticoagulant, including rivaroxaban, increases the risk of thrombotic events. Patients who are receiving neuraxial anesthesia or are undergoing spinal puncture are at increased risk of epidural or spinal hematomas, which may result in long-term paralysis. Data related to these warnings were not reported in the COMPASS trial. The FDA label also includes a warning for serious and fatal bleeding, and advises that an agent to reverse the anti-factor Xa activity of rivaroxaban is available.

## Net Clinical Benefit

To evaluate the balance or benefits and bleeding risk, COMPASS trial investigators assessed a net-clinical-benefit outcome, which they defined as cardiovascular death, stroke, MI, fatal bleeding, or symptomatic bleeding into a critical organ. The risk of this composite outcome was lower with rivaroxaban + ASA than with ASA alone (HR 0.80; 95% CI: 0.70 to 0.91; p<0.001).[11]

However, these results should be interpreted with discretion, as they did not account for the full primary safety endpoint of major bleeding.

## Subgroup Analyses

**Summary**: ***Subgroup analyses in patients with CAD, PAD, renal dysfunction, mild-to-moderate heart failure, recent CABG surgery, and in patients with high-risk features demonstrated a consistent benefit for rivaroxaban + ASA as well as a consistently elevated risk of major bleeding. In patients with PAD, rivaroxaban + ASA reduced the risk of major adverse limb events, including major amputations.***

*CAD and PAD*

Patients with CAD comprised 91% of the COMPASS trial and patients with PAD represented 27% of the trial population; rivaroxaban + ASA reduced the risk of major adverse cardiac events and increased the risk of bleeding in both subgroups.

In patients with PAD, rivaroxaban + ASA significantly lowered the risk of major adverse limb events, defined as the development of acute or chronic limb ischemia during trial follow-up (HR 0.54; 95% CI: 0.35 to 0.84; p=0.0054).[57,59] Rivaroxaban + ASA also reduced the risk of major amputations by approximately 70% (HR 0.30; 95% CI: 0.11 to 0.80; p=0.011).

**Table 3.5. Clinical Benefit and Safety of Rivaroxaban + ASA in CAD and PAD Subgroups[11,57,58,63]**

| | Overall COMPASS Population | CAD Subgroup | CAD Alone Subgroup | PAD Subgroup | PAD Alone Subgroup | Concomitant CAD and PAD Subgroup |
|---|---|---|---|---|---|---|
| | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| ***Primary Endpoint*** | | | | | | |
| **CV Death, Stroke, or MI** | 0.76 (0.66-0.86) | 0.74 (0.65-0.86) | 0.77 (0.66-0.91) | 0.72 (0.57-0.90) | 0.89 (0.55-1.44) | 0.67 (0.52-0.87) |
| ***Secondary Endpoint*** | | | | | | |
| **Ischemic Stroke, MI, ALI, or Death from CHD** | 0.72 (0.63-0.83) | 0.72 (0.62-0.83) | 0.75 (0.63-0.90) | 0.68 (0.53-0.86) | 0.78 (0.48-1.25) | NR |
| **Ischemic Stroke, MI, ALI, or CV Death** | 0.74 (0.65-0.85) | 0.73 (0.64-0.84) | 0.77 (0.65-0.90) | 0.71 (0.57-0.88) | 0.88 (0.57-1.34) | NR |
| ***Major Bleeding*** | | | | | | |
| **Fatal Bleeding, Symptomatic Bleeding into a Critical Organ, Bleeding into a Surgical Site Requiring Reoperation, and Bleeding that Led to a Hospital Visit** | 1.70 (1.40-2.05) | 1.66 (1.37-2.03) | NR | 1.61 (1.12-2.31) | NR | NR |

ALI: acute limb ischemia, CAD: coronary artery disease, CHD: coronary heart disease, CI: confidence interval, CV: cardiovascular disease, HR: hazard ratio, MI: myocardial infarction, PAD: peripheral artery disease

*Renal Function*

A statistically-significant reduction in the primary composite efficacy endpoint from the COMPASS trial (i.e., cardiovascular death, stroke, or MI) was observed in patients with and without moderate renal dysfunction (defined by an estimated glomerular filtration rate [eGFR] of <60 ml/min or ≥60 ml/min, respectively; Table 3.6); results were consistent in patients with greater renal dysfunction (eGFR <30 ml/min, HR 0.73; 95% CI: 0.28 to 1.91).[60] The occurrence of major bleeding events was similar in groups stratified by level of renal function.

**Table 3.6. Clinical Benefit and Safety of Rivaroxaban Subgroups Defined by Renal Function[60]**

| | | Overall COMPASS Population | Normal Renal Function (eGFR≥60 ml/min) | Moderate Renal Dysfunction (eGFR<60 ml/min) |
|---|---|---|---|---|
| | | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| **Primary Endpoint** | CV death, stroke, or MI | 0.76 (0.66-0.86) | 0.76 (0.64-0.90) | 0.75 (0.60-0.94) |
| **Major Bleeding** | Fatal bleeding, symptomatic bleeding into a critical organ, bleeding into a surgical site requiring reoperation, and bleeding that led to a hospital visit | 1.70 (1.40-2.05) | 1.81 (1.44-2.28) | 1.47 (1.05-2.07) |

ALI: acute limb ischemia, ASA: aspirin, CHD: coronary heart disease, CI: confidence interval, CV: cardiovascular, HR: hazard ratio, MI: myocardial infarction

*Mild-to-Moderate Heart Failure*

Patients with mild or moderate heart failure represented 22% of the COMPASS trial's population; patients with severe heart failure (i.e. left ventricular ejection fraction <30% or New York Heart Association Class III or IV symptoms) were not eligible to participate. In prespecified subgroup analyses in patients with and without a diagnosis of heart failure, rivaroxaban + ASA significantly reduced the risk of the composite primary endpoint of cardiovascular death, stroke, or MI (Table 3.7; p=0.28 for interaction).[62] Rivaroxaban + ASA reduced the risk of death from any cause compared to ASA alone (HR 0.66; 95% CI: 0.50 to 0.86) in patients *with* heart failure but statistical differences were not observed in patients who did not have a history of heart failure (p-value for interaction=0.05). The risk of major bleeding was increased in both subgroups treated with rivaroxaban + ASA.

**Table 3.7. Clinical Benefit and Safety of Rivaroxaban Subgroups Defined by Diagnosis of Heart Failure[62]**

| | | Overall COMPASS Population | No Heart Failure | Mild to Moderate Heart Failure |
|---|---|---|---|---|
| | | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| **Primary Endpoint** | CV death, stroke, or MI | 0.76 (0.66-0.86) | 0.79 (0.68-0.93) | 0.68 (0.53-0.86) |
| **Major Bleeding** | Fatal bleeding, symptomatic bleeding into a critical organ, bleeding into a surgical site requiring reoperation, and bleeding that led to a hospital visit | 1.70 (1.40-2.05) | 1.79 (1.45-2.21) | 1.36 (0.88-2.09) |

ALI: acute limb ischemia, ASA: aspirin, CHD: coronary heart disease, CI: confidence interval, CV: cardiovascular, HR: hazard ratio, MI: myocardial infarction

*Additional Subgroups*

Additional subgroup analyses focusing on patients randomized following CABG surgery or those with one or more high-risk features such as diabetes, ≥2 vascular beds affected, and renal insufficiency, suggest treatment effects that are similar to or greater than those in the overall population.[64,65]

## Clinical Benefits and Safety of DAPT

Our literature search did not identify any studies directly comparing rivaroxaban + ASA to DAPT in the population of focus. Although we did not systematically review DAPT versus ASA alone, we searched for RCTs that evaluated new initiation of DAPT (as opposed to continuation of current DAPT therapy) in patients with stable CVD. We identified two RCTs of ticagrelor + ASA and clopidogrel + ASA, respectively.[15-18] These trials are summarized in Appendix D for context. We also indirectly compared DAPT to rivaroxaban + ASA through an NMA of major adverse cardiovascular events in patients with a recent MI (see below).

***NMA***

We performed an NMA in the subgroup of patients with a recent MI (i.e., in the two years prior to randomization for the studies of rivaroxaban and ticagrelor, and at a median of two years prior to randomization for the study of clopidogrel) to compare ticagrelor + ASA and clopidogrel + ASA with rivaroxaban + ASA. The analysis estimated the comparative risk of a composite endpoint of cardiovascular death, stroke, or MI between each of the regimens of focus. The results of our NMA, presented in Table 3.8, do not reveal statistical differences between therapies. However, given the elevated risk of major bleeding that is associated with each of the regimens, any analysis of comparative effectiveness is incomplete without an accompanying analysis of comparative safety. We endeavored to also compare the incidence of major bleeding between therapies but were unable to quantitatively synthesize the data due to the use of important differences in definitions of major bleeding. Data informing the NMA as well as a network diagram are reported in Appendix D.

**Table 3.8. NMA Results Comparing the Risk of Cardiovascular Death, Stroke, or MI in Patients Treated with Antithrombotic Therapy for Stable CVD**

| Rivaroxaban + ASA | | | |
|---|---|---|---|
| 0.91<br>(0.61 to 1.36) | Ticagrelor + ASA | | |
| 0.91<br>(0.58 to 1.40) | 1.00<br>(0.75 to 1.32) | Clopidogrel + ASA | |
| 0.70<br>(0.48 to 1.02) | **0.77**<br>**(0.66 to 0.90)** | **0.77**<br>**(0.61 to 0.98)** | ASA |

Each box represents the estimated hazard ratio and 95% credible interval for the combined direct and indirect comparisons between two drugs. Estimates in bold signify that the 95% credible interval does not contain one.

## Key Studies of Icosapent Ethyl

Evidence on icosapent ethyl was primarily derived from the REDUCE-IT trial.[19] REDUCE-IT was a multinational, double-blind, Phase III trial that randomized patients at increased risk of ischemic events to 2 g twice daily of icosapent ethyl (n=4089) or a placebo (n=4090) that contained mineral oil to resemble the color and consistency of icosapent ethyl. Patients were eligible to enroll in the trial if they were at least 45 years of age with established CVD (secondary prevention cohort) or at least 50 years of age with diabetes mellitus and at least one additional risk factor for CVD (primary prevention cohort). Patients were required to have elevated fasting triglyceride levels (≥135 and <500 mg/dL) and well-controlled LDL cholesterol levels (>40 and ≤100 mg/dL) while on a stable dose of statins for at least four weeks. Key exclusion criteria included severe heart failure, severe liver disease, planned coronary intervention, glycated hemoglobin >10%, acute or chronic pancreatitis, or known hypersensitivity to fish or shellfish. Additional inclusion and exclusion criteria can be found in Appendix Table D11.

At baseline, 71% of patients had established CVD and 29% made up the high-risk primary prevention cohort.[19] Approximately 58% of included patients had type 2 diabetes mellitus, 87% had hypertension, and 48% had a prior MI. Most patients (93%) were receiving moderate-to-high intensity statin therapy. Patients were followed for a median of 4.9 years. Additional baseline characteristics are reported in Appendix Table D12.

The primary endpoint of the REDUCE-IT trial was a composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, and unstable angina in a time-to-event analysis. Per suggestions from the FDA, a protocol amendment in 2016 designated a composite of cardiovascular death, nonfatal MI, and nonfatal stroke as a key secondary endpoint. Additional endpoints included time-to-event analyses of the individual components of the composite endpoints as well as all-cause mortality. The effect of icosapent ethyl on total events (first plus subsequent) was examined in prespecified analyses for both the primary and key secondary composite endpoints.[20]

**Table 3.9. Summary of the Reduction of Cardiovascular Events with Icosapent Ethyl—Intervention Trial (REDUCE-IT)**

| Study Design | Treatment Groups* | Patient Characteristics | Primary Efficacy Endpoint | Key Secondary Efficacy Endpoint |
|---|---|---|---|---|
| **Phase III, double-blind RCT**<br><br>**Median follow-up: 4.9 years** | 1. Icosapent ethyl 4 g/day<br><br>2. Placebo | N=8179<br>Median age: 64.0<br>Secondary prevention, %: 70.7<br>Primary prevention, %: 29.3<br>Median TG: 216.0 mg/dL<br>Median LDL-C: 75.0 mg/dL | A composite of CV death, stroke, MI, hospitalization for unstable angina, or coronary revascularization | A composite of CV death, stroke, or MI |

CV: cardiovascular, LDL-C: low density lipoprotein-cholesterol, mg/dL: milligram per deciliter, MI: myocardial infarction, RCT: randomized controlled trial, TG: triglyceride

*Patients were also receiving a stable dose of statins in each treatment group.

## Clinical Benefits of Icosapent Ethyl

**Summary*: Compared to optimal medical management alone (i.e., placebo), icosapent ethyl reduced the risk of a composite outcome of cardiovascular death, stroke, MI, coronary revascularization, or unstable angina in patients with established CVD or diabetes mellitus and additional risk factors. Icosapent ethyl significantly reduced the risk of all individual components of the primary composite endpoint as well as the composite secondary outcome of cardiovascular death, MI, or stroke. A treatment benefit was also observed in analyses of the first, subsequent, and total major adverse cardiovascular events.***

### *Major Adverse Cardiovascular Events*

*Time-to-First Event Composite Endpoints*

As noted above, the REDUCE-IT trial evaluated a composite of cardiovascular death, MI, stroke, coronary revascularization, or unstable angina as its primary endpoint. In the time-to-event analysis, icosapent ethyl reduced the risk of a primary endpoint event by 25% (HR 0.75; 95% CI: 0.68 to 0.83; p<0.001).[19] At a median follow-up of 4.9 years (maximum 6.2 years), 17.2% of patients treated with icosapent ethyl and 22.0% treated with placebo had a first primary endpoint event (number needed to treat [NNT]: 21; 95% CI: 15 to 33). The annual event rate in the placebo arm was approximately 4.4%, suggesting a very high-risk population.

The REDUCE-IT trial's key secondary endpoint (cardiovascular death, MI, or stroke) also occurred in fewer patients treated with icosapent ethyl compared to those receiving placebo (11.2% vs. 14.8%, respectively; HR 0.74; 95% CI: 0.65-0.83; p<0.001; NNT: 28; 95% CI: 20 to 47).[19]

*Individual Events*

Individual components of the primary composite endpoint are presented in Table 3.10. Icosapent ethyl significantly reduced the risk of cardiovascular death by 20%, nonfatal MI by

30%, nonfatal stroke by 29%, coronary revascularization by 34%, and hospitalization for unstable angina by 32%. Icosapent ethyl treatment did not result in a statistically significant reduction in the risk of all-cause mortality.

**Table 3.10. Key Efficacy Endpoints in REDUCE-IT[19]**

| Endpoint | Icosapent Ethyl, n (%) | Placebo, n (%) | HR (95% CI) | P-Value |
|---|---|---|---|---|
| **Primary Composite** ***CV Death, Nonfatal MI, Nonfatal Stroke, Revascularization, and Unstable Angina*** | 705 (17.2) | 901 (22.0) | 0.75 (0.68–0.83) | <0.001 |
| **Key Secondary Composite** ***CV Death, Nonfatal MI, Nonfatal Stroke*** | 459 (11.2) | 606 (14.8) | 0.74 (0.65–0.83) | <0.001 |
| **CV Death** | 174 (4.3) | 213 (5.2) | 0.80 (0.66–0.98) | 0.03 |
| **Nonfatal MI** | 237 (5.8) | 332 (8.1) | 0.70 (0.59-0.82) | NR |
| **Nonfatal Stroke** | 85 (2.1) | 118 (2.9) | 0.71 (0.54-0.94) | NR |
| **Coronary Revascularization** | 376 (9.2) | 544 (13.3) | 0.66 (0.58-0.76) | NR |
| **Hospitalization for Unstable Angina** | 108 (2.6) | 157 (3.8) | 0.68 (0.53-0.87) | 0.002 |
| **All-Cause Mortality** | 274 (6.7) | 310 (7.6) | 0.87 (0.74–1.02) | NS |

CI: confidence interval, CV: cardiovascular, HR: hazard ratio, MI: myocardial infarction, NR: not reported, NS: not specified

*Total Events*

The effect of icosapent ethyl on total events (first and subsequent) was examined in a pre-specified analysis using a negative binomial regression model.[20] A hierarchical approach was used for event identification, in which a cardiovascular death superseded nonfatal events occurring on the same day, and multiple nonfatal events occurring on the same day were counted as one event.

The risk of total primary endpoint events, including cardiovascular death, MI, stroke, revascularization, and unstable angina, was reduced by 30% with icosapent ethyl compared to placebo (rate ratio (RR): 0.70; 95% CI: 0.62, 0.78). Treatment with icosapent ethyl resulted in a 28% risk reduction compared to placebo (RR: 0.72; 95% CI: 0.63-0.82) on the REDUCE-IT trial's key secondary endpoint of cardiovascular death, stroke, or MI.

In a prespecified supportive analysis, hazard ratios for the time to first, second, and third events were calculated using the Wei-Lin-Weissfeld method, and the rate ratio for fourth or subsequent events was calculated using the negative binomial regression model. Icosapent ethyl reduced the risk of first primary endpoint events by 25%, second primary endpoint events by 32%, third primary endpoint events by 31%, and fourth or subsequent primary endpoint events by 48%; in contrast, the hazard ratios for secondary endpoint events remained relatively consistent across the event sequence (Table 3.11).[20]

**Table 3.11. Hazard/Rate Ratios for Total and Subsequent Ischemic Events[20]**

| Endpoint | Total Events RR (95% CI) | First Event HR (95% CI) | Second Event HR (95% CI) | Third Event HR (95% CI) | ≥Fourth Event RR (95% CI) |
|---|---|---|---|---|---|
| Primary Composite CV Death, Nonfatal MI, Nonfatal Stroke, Revascularization, and Unstable Angina | 0.70 (0.62-0.78) | 0.75 (0.68-0.83) | 0.68 (0.60-0.78) | 0.69 (0.59-0.82) | 0.52 (0.38-0.70) |
| Key Secondary Composite CV Death, Nonfatal MI, and Nonfatal Stroke | 0.72 (0.63-0.82) | 0.74 (0.65-0.83) | 0.75 (0.63-0.89) | 0.79 (0.65-0.96) | Not reported |

CI: confidence interval, CV: cardiovascular, HR: hazard ratio, RR: rate ratio

## Harms of Icosapent Ethyl

**Summary:** ***Rates of serious TEAEs were similar in patients treated with icosapent ethyl and placebo. A greater proportion of patients treated with icosapent ethyl experienced serious bleeding-related disorders, as well as peripheral edema, constipation, and atrial fibrillation. The incidence of serious and non-serious TEAEs leading to treatment discontinuation was similar for both treatment arms.***

The incidence of serious TEAEs was similar in the icosapent ethyl and placebo arms of the REDUCE-IT trial (30.6% vs. 30.7%, respectively).[19] Serious TEAEs leading to death occurred in 2.3% of patients treated with icosapent ethyl and 2.5% of patients who received placebo. Serious bleeding-related disorders, identified using the Medical Dictionary for Regulatory Activities (MedDRA), occurred in a greater proportion of patients treated with icosapent ethyl, although the difference was not statistically significant (2.7% vs. 2.1%, p=0.06). No fatal bleeding events occurred in either group and rates of hemorrhagic stroke, central nervous system bleeding, and GI bleeding did not statistically differ. TEAEs that occurred in proportionately more patients treated with icosapent ethyl included peripheral edema (6.5% vs. 5.0%, p=0.002), constipation (5.4% vs. 3.6%, p<0.001), and atrial fibrillation (5.3% vs. 3.9%, p=0.003).[19] Hospitalization for atrial fibrillation or flutter was significantly higher in the icosapent ethyl arm compared to placebo (3.1% vs. 2.1%; p=0.004).

Approximately 11% of patients randomized to placebo and 10% randomized to icosapent ethyl discontinued the study early.[9] The rate of TEAEs leading to discontinuation of the study drug was similar for patients treated with icosapent ethyl and placebo (7.9% vs 8.2%, respectively) as was the rate of drug discontinuation due to serious TEAEs (2.2% vs 2.3%, respectively). The rate of all-cause study drug discontinuation was not reported for the entire trial population but was reported for patients who had a primary endpoint event. At the time of a first primary endpoint event, 18.7% of patients randomized to icosapent ethyl and 18.2% of patients randomized to placebo had discontinued the study drug.[20]

Although we did not consider earlier trials of icosapent ethyl in patients with elevated triglyceride levels (i.e., MARINE[66] and ANCHOR[67]) as part of our core study set, we also reviewed safety data from these studies as they evaluated the same dose of icosapent ethyl as the REDUCE-IT trial. Over 12 weeks of treatment in both trials, 35-45% of patients treated with 4 g daily of icosapent ethyl experienced a TEAE. Most TEAEs were determined to be of mild or moderate severity and were not considered related to the study drug. The only TEAEs occurring in numerically more patients treated with icosapent ethyl 4 g/d in either trial was arthralgia in the ANCHOR trial (1.7% vs 0.4%; see Appendix Table D15).

## Subgroup Analyses

**Summary**: ***Analyses of the primary and key secondary endpoints from the REDUCE-IT trial did not reach statistical significance in the primary prevention subgroup. A consistent treatment benefit was observed for icosapent ethyl in subgroups of patients with and without diabetes mellitus, with and without renal dysfunction, with and without elevated triglyceride levels, and with and without elevated levels of the inflammation marker hsCRP.***

### *Subgroups Defined by Baseline Characteristics*

The effect of icosapent ethyl on the risk of primary and key secondary composite endpoint events were reported for various subgroups of interest (Table 3.12). For patients with established CVD at baseline (secondary prevention cohort), icosapent ethyl statistically-significantly reduced the risk of the composite primary endpoint of cardiovascular death, MI, stroke, revascularization, or unstable angina by 27%. The risk of the key secondary composite endpoint, cardiovascular death, MI, or stroke, was reduced 28% with icosapent ethyl in the secondary prevention cohort (Table 3.12).[9] For patients in the primary prevention cohort, there were no statistically significant risk reductions for either the primary or key secondary composite endpoints (Table 3.12). At a prespecified alpha level of 0.15, there was evidence of a significant differential effect between the secondary and primary prevention subgroups on the primary composite endpoint (p-value for interaction=0.14) but not the secondary composite endpoint.

A consistent treatment benefit was observed for both the primary and key secondary composite endpoints in subgroups with and without diabetes mellitus, with and without renal dysfunction (eGFR<60 vs. ≥60 mL/min/1.73$^2$), with and without elevated triglyceride levels (≥150 vs. <150 mg/dL and ≥200 vs. <200 mg/dL), and in subgroups stratified by hsCRP level at baseline (≤2 vs >2 mg/L) (Table 3.12).[9]

**Table 3.12. Primary and Key Secondary Composite Endpoints for Key Subgroups Defined by Baseline Characteristics[9]**

| Subgroup | | Primary Composite *CV Death, MI, Stroke, Revascularization, and Unstable Angina* | Key Secondary Composite *CV Death, MI, and Stroke* |
|---|---|---|---|
| | | HR (95% CI) | HR (95% CI) |
| CV Risk | Secondary Prevention | 0.73 (0.65–0.81) | 0.72 (0.63–0.82) |
| | Primary Prevention | 0.88 (0.70–1.10) | 0.81 (0.62–1.06) |
| Diabetes Mellitus | Yes | 0.77 (0.68–0.87) | 0.70 (0.60–0.81) |
| | No | 0.73 (0.62–0.85) | 0.80 (0.65–0.98) |
| eGFR | <60 mL/min/1.73 $m^2$ | 0.71 (0.59–0.85) | 0.71 (0.57–0.88) |
| | ≥60 to <90 mL/min/1.73 $m^2$ | 0.80 (0.70–0.92) | 0.77 (0.64–0.91) |
| | ≥90 mL/min/1.73 $m^2$ | 0.70 (0.56–0.89) | 0.70 (0.52–0.94) |
| hsCRP | ≤2 mg/L | 0.68 (0.58–0.79) | 0.73 (0.61–0.89) |
| | >2 mg/L | 0.81 (0.71–0.93) | 0.73 (0.63–0.86) |
| Triglycerides | ≥150 mg/dL | 0.75 (0.68-0.83) | 0.74 (0.65-0.84) |
| | <150 mg/dL | 0.79 (0.57-1.09) | 0.66 (0.44-0.99) |
| | ≥200 mg/dL | 0.73 (0.64–0.83) | 0.75 (0.65–0.88) |
| | <200 mg/dL | 0.79 (0.67–0.93) | 0.71 (0.58–0.86) |

CI: confidence interval, CV: cardiovascular, eGFR: estimated glomerular filtration rate, HR: hazard ratio, hsCRP: highly sensitive C-reactive protein, MI: myocardial infarction

### *Subgroups Defined by On-Treatment Changes*

As stated earlier, the placebo used in REDUCE-IT contained mineral oil to resemble the color and consistency of icosapent ethyl. Patients receiving placebo had marked increases in LDL cholesterol (LDL-C) levels at year one compared to icosapent ethyl (median percent change: 10.2% vs. 3.1%, p<0.001) and in hsCRP levels at year two (32.3% vs. -13.9%, p<0.001). These unexpected increases may indicate that the mineral oil used was not biologically inert and may have resulted in an overstated treatment effect of icosapent ethyl relative to placebo. In response to these concerns, the manufacturer posted the results of a post-hoc analysis on their website, which stratified patients with and without on-trial increases in LDL-C in the placebo arm.[68] The post-hoc analysis suggested that treatment with icosapent ethyl resulted in significant reductions in the risk for both the primary and key secondary composite endpoints, irrespective of whether patients in the placebo arm experienced an increase in LDL-C (Table 3.13). To the best of our knowledge, however, similar analyses have not been performed in relation to changes in hsCRP from baseline.

**Table 3.13. Subgroup Analysis by Change in LDL-C at Year One**

| Post-Hoc Analysis | Primary Composite *CV Death, MI, Stroke, Revascularization, and Unstable Angina* HR (95% CI) | Key Secondary Composite *CV Death, MI, and Stroke* HR (95% CI) |
|---|---|---|
| Icosapent ethyl vs. placebo LDL-C **Increase** | 0.79 (0.70 to 0.88) | 0.80 (0.70 to 0.93) |
| Icosapent ethyl vs. placebo LDL-C **No change/decrease** | 0.79 (0.69 to 0.91) | 0.74 (0.63 to 0.88) |
| Placebo LDL- increase vs. placebo LDL-C **No change/decrease** | 1.01 (0.87 to 1.17) | 0.92 (0.77 to 1.10) |

CI: confidence interval, CV: cardiovascular, HR: hazard ratio, LDL: low-density lipoprotein, MI: myocardial infarction

## Controversies and Uncertainties

While the available evidence for both rivaroxaban and icosapent ethyl is indicative of a potential net clinical benefit, there are several concerns with the design and results of these trials that should be considered along with data on clinical outcomes and potential harms of these treatments. Concerns are organized by intervention of interest in the sections that follow.

### *Rivaroxaban*

The generalizability of the COMPASS trial population is subject to a number of uncertainties. For one, study entry criteria of stable CAD and PAD as well as documentation of atherosclerosis in at least two vascular beds among patients age <65 years ensured a population at high risk of recurrent cardiovascular events, but exclusion of patients at high bleeding risk and further exclusion of 8% patients not tolerating or adherent to run-in ASA therapy likely resulted in a sample at reduced bleeding risk relative to the potential candidate population for rivaroxaban.[21,22]

In addition, we cannot exclude the possibility that the clinical benefits observed in COMPASS are somewhat overstated due to the trial having been stopped early for benefit after a mean of 23 months of follow-up.[23] The Kaplan-Meier estimates provide some reassurance that benefits observed after approximately one year of follow-up continued until the trial was stopped[21], but the balance of event reduction and bleeding risks beyond this point is currently unknown.

Relatedly, while the trial considered a measure of "net benefit" that included both cardiovascular and bleeding events and found a statistically-significant 20% reduction in risk, this definition only included fatal bleeding and symptomatic bleeding into a critical organ, and no other definitions of major bleeding that comprised the primary safety outcome. Our own calculations of risk-benefit using the full event definitions indicate an NNT of 77 for

cardiovascular events and a number needed to harm (NNH) of 83 for bleeding events, suggesting a much smaller net benefit on average than that reported in COMPASS. To be sure, the individual calculus may be clear for avoiding a severe MI or disabling stroke relative to a treatable bleed at an acute care facility without an overnight stay, but the calculus for avoiding a moderately symptomatic MI with increased troponin levels relative to a critical organ bleed would be very different.[22]

The decision to separately randomize patients to receive the PPI pantoprazole or placebo within the rivaroxaban + ASA, rivaroxaban alone, and ASA alone groups is a puzzling one, given that clinical guidelines recommend routine use of PPIs for gastroprotection in patients receiving combination anticoagulation + ASA therapy[24] but not for anticoagulants or ASA alone. Recently-reported results from COMPASS suggest that pantoprazole does not reduce the risk of upper GI bleeding but does reduce bleeding from gastroduodenal lesions relative to placebo, and that this finding is consistent regardless of the anticoagulation strategy used.[69] It is unclear how this finding would change clinical practice, however, given the well-established benefit-risk profile and generic availability of PPIs.[70-72]

Finally, while the indications for combination treatment with rivaroxaban and DAPT with a $P2Y_{12}$ inhibitor do not completely overlap, there is a large subset of patients with a recent MI event who could conceivably be candidates for either treatment approach. Indeed, some clinicians have called for further research comparing DAPT to combination therapy with ASA and a factor Xa inhibitor (e.g., rivaroxaban).[25,26] In the absence of head-to-head trials at the time of this report's publication, we attempted to compare the regimens indirectly through a network meta-analysis. However, while only small differences exist in the definitions of clinical events across the major trials of these regimens, the same cannot be said for definitions of major bleeding, which differed substantially across trials; in some cases, a common definition was used but modified to enough of an extent that we could not attempt quantitative comparisons with any confidence. While this is a source of frustration for producers of comparative effectiveness research like us, the real harm done is to the patient-clinician shared decision. Patients, in particular, deserve to know how the major benefits and risks compare for treatments they expect to receive over a lifetime. Standard and well-accepted definitions of both cardiovascular events and bleeding risks exist, and the fact that they have not been used consistently and without modification in as important a clinical area as this is a disservice to patients and the clinicians who care for them.

### *Icosapent Ethyl*

As noted previously, the placebo vehicle used in the REDUCE-IT trial (as well as earlier trials of icosapent ethyl) contained mineral oil to mimic the viscosity of the active agent. Biomarker changes observed in the trial raise the possibility that the mineral oil used was not biologically inert, however; patients in the placebo arm experienced a threefold-higher percentage increase in LDL-C at year one (10.2% vs. 3.1% for icosapent ethyl, $p<0.001$ for between-group difference) and a substantial increase in the inflammation marker hsCRP at year two (32.9% vs. -13.9%, $p<0.001$), adding to documented concerns regarding the mineral oil's potential interference

with statin absorption.[9] As described above, the manufacturer conducted a post-hoc analysis, which stratified patients with and without on-trial increases in LDL-C in the placebo arm.[68] The results of this analysis suggested a consistent risk reduction with icosapent ethyl irrespective of whether LDL-C increased in the placebo arm.[9] However, it is difficult to interpret analyses of effects utilizing on-treatment response subgroups, and so residual concerns remain about a potentially biologically active "placebo" and the possibility that the true effect of icosapent ethyl may be attenuated from that observed in the REDUCE-IT trial. To the best of our knowledge, similar analyses have not been performed in relation to changes in hsCRP from baseline.

Other findings from REDUCE-IT give rise to additional uncertainties. For example, a separate publication described a larger effect size for icosapent ethyl when total ischemic events (rather than time to first event) are considered, as well as improved levels of risk reduction with each subsequent event.[20] This type of analysis is controversial, however, given the relation that often exists between event types (e.g., nonfatal MI followed by revascularization or death) and the consequent inflation of event rates.[73] The authors addressed this by bundling multiple events occurring on the same day into one and specifying multiple statistical models. Subsequent events were evaluated using the Wei-Lin-Weissfeld model, however, which has been previously criticized for overstating the population at risk of subsequent events, which may lead to overestimates of reductions in the risk of these events.[74,75] Other model specifications not subject to this form of bias, such as the Prentice-Williams-Petersen and kinetic modeling techniques,[73,75] were not employed in this analysis.

We also note that the results of this trial stand apart from many prior studies of omega-3 preparations that showed little to no cardiovascular benefit.[27] Indeed, when a Bayesian approach is taken to the overall evidence base, the interpretation of REDUCE-IT's findings will differ depending on whether prior expectations for these results are pessimistic, realistic, or optimistic.[28]

Several possible explanations for differences between REDUCE-IT's conclusions and those of previous studies have been posited, including use of an EPA-only formulation. Docosahexaenoic acid (DHA), another common component of omega-3 preparations, has been found to increase LDL-C levels when used alone or in combination with EPA,[76] although findings from a recent AHA science advisory indicate this is only the case in patients with very high triglycerides, and recommend prescription forms of EPA+DHA and EPA alone for triglyceride reduction.[46] Other possible reasons include a higher daily dose than previously studied, and the possibility of metabolic effects of EPA other than triglyceride-lowering alone.[9] Indeed, patients in the REDUCE-IT trial had baseline elevations in triglyceride levels, but subgroup analyses suggested that the effect of icosapent ethyl may be similar across triglyceride categories.

It is worth noting that reductions in cardiovascular events of approximately 20% were observed in a prior EPA-only trial (JELIS), which randomized approximately 19,000 Japanese patients to 1.8 g of EPA in addition to statin therapy versus statins alone over a mean of 4.6 years of follow-up.[29] However, the JELIS trial was open-label and showed no reductions in cardiovascular death, so its relevance to the results of REDUCE-IT is unclear. The JELIS trial was also conducted in a

Japanese population with a much higher baseline consumption of fish than is typically seen in the US; very few patients in REDUCE-IT were from the Asia-Pacific region making comparisons across trials difficult.[30,31]

Regardless of issues of trial design or interpretation, the greatest uncertainty may be in how generalizable the REDUCE-IT results are and therefore what the most appropriate target population will be. As with COMPASS, the patients enrolled in REDUCE-IT were at very high risk of cardiovascular events, as illustrated by a placebo event rate of approximately 4.4% per year over the 4.9-year median duration of follow-up.[9] Patients also were on statin therapy, and it is unclear whether icosapent ethyl would be effective in patients not treated with statins. How the benefits of icosapent ethyl translate to an eligible population that is certain to be both broader and at lower risk than the trial population remains to be seen.

## 3.4 Summary and Comment

Using the ICER Evidence Matrix (Figure 3.1), we assigned evidence ratings to rivaroxaban + ASA and icosapent ethyl relative to the comparators of interest for this review (Table 3.14).

**Figure 3.1. ICER Evidence Rating Matrix**

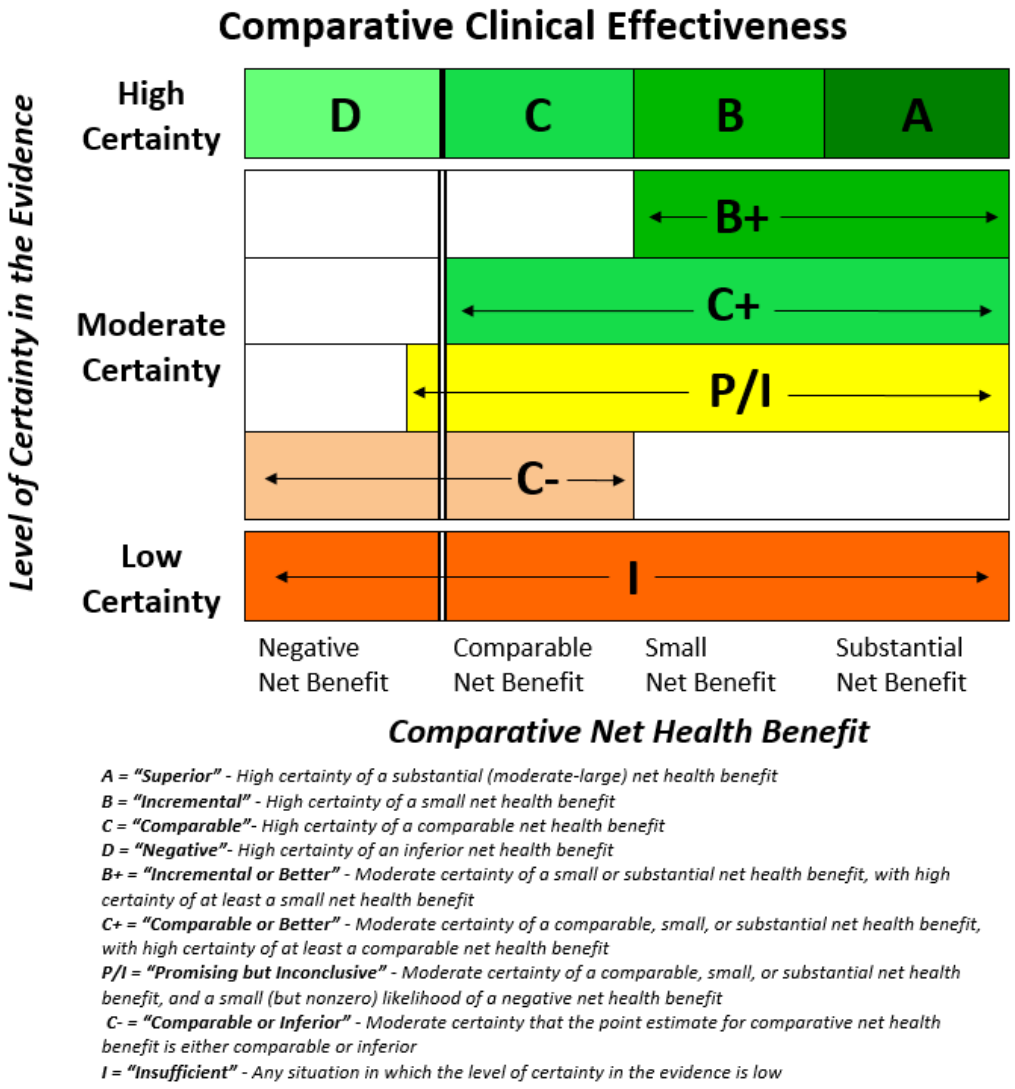



**Table 3.14. ICER Evidence Ratings**

| Intervention | Comparator | ICER Evidence Rating |
|---|---|---|
| Rivaroxaban + ASA | ASA | B+ |
| Rivaroxaban + ASA | DAPT | I |
| Icosapent Ethyl | Optimal medical management | B+ |

ASA: aspirin, DAPT: dual antiplatelet therapy

## Rivaroxaban + ASA versus ASA Alone

Compared to ASA alone, rivaroxaban + ASA significantly reduced the risk of cardiovascular death, stroke, or MI in patients with stable CVD. Patients treated with rivaroxaban + ASA experienced significantly fewer strokes (including disabling or fatal strokes), less cardiovascular death, less all-cause mortality, fewer major adverse limb events, and fewer cardiovascular-related hospitalizations. Although rivaroxaban + ASA significantly increased the risk of major bleeding events, the COMPASS trial's inclusion of bleeds leading to presentation at an acute care facility in its primary safety analysis of major bleeding may have led to the inclusion of both consequential and somewhat inconsequential bleeding events in this analysis. Bleeding events of greatest severity—i.e., fatal bleeding, symptomatic bleeding into a critical organ, and nonfatal symptomatic intracranial hemorrhages—were not significantly increased by adding rivaroxaban to ASA. We therefore have high certainty that rivaroxaban + ASA provides a small-to-substantial net health benefit in patients with CAD, PAD, or both conditions ("B+").

## Rivaroxaban + ASA versus DAPT

We did not identify any head-to-head studies that directly compared rivaroxaban + ASA to DAPT in patients with stable CVD. Although an indirect comparison of the risk of major adverse cardiovascular events in patients with a recent MI suggested that DAPT may provide a similar cardioprotective benefit as rivaroxaban + ASA, clinically significant differences in the way major bleeding was defined in the clinical trials of focus precluded a companion analysis of relative bleeding risks. We also note that those with a recent MI represented a relatively small subset of patients in the COMPASS trial, so the comparative benefits and risks of these two strategies in the remaining CAD and PAD population are unknown. We therefore have low certainty of whether rivaroxaban + ASA provides a negative, comparable, or positive net health benefit compared to DAPT in patients with CAD or PAD ("I").

## Icosapent Ethyl versus Optimal Medical Management

Icosapent ethyl reduced the risk of major adverse cardiovascular events in patients with established CVD or diabetes mellitus and additional risk factors compared to optimal medical management alone (i.e., placebo). The therapy was generally well-tolerated, despite a slight increase in the incidence of major bleeding disorders. However, over 4.9 years of follow-up, no fatal bleeding events occurred, and rates of TEAEs were comparable between the icosapent ethyl and placebo arms. Although we are uncertain whether the use of mineral oil may have caused some harm to the placebo group, we do not believe that this theory can account for the entire benefit observed in the REDUCE-IT trial. We believe that the results of REDUCE-IT likely apply across a range of baseline triglyceride levels but are uncertain whether the results generalize to patients not treated with statins. For adults with established CVD or at high risk of cardiovascular events who are being treated with statins, we have high certainty that icosapent ethyl provides a small-to-substantial net health benefit ("B+").

# 4. Long-Term Cost Effectiveness

## 4.1 Overview

The primary aim of this analysis was to estimate the cost effectiveness of rivaroxaban and icosapent ethyl as additive therapies to optimal medical management in patients with established CVD, and in the case of icosapent ethyl, also in patients without evidence of CVD but with diabetes and at least one additional risk factor. A Markov cohort model was constructed to compare the addition of rivaroxaban to ASA therapy to ASA alone and to compare the addition of icosapent ethyl to optimal medical management (including statins) to optimal medical management (including statins) alone. Rivaroxaban and icosapent ethyl were modeled separately but shared a similar overall model structure. Patient survival, quality-adjusted survival, and health care costs from a health care sector perspective were estimated over a lifetime time horizon for each intervention and comparator. Costs and outcomes were discounted at 3% per year. While the base-case analysis took a health care sector perspective, productivity losses to the patient and caregiver were considered in a scenario analysis using a modified societal perspective.

## 4.2 Methods

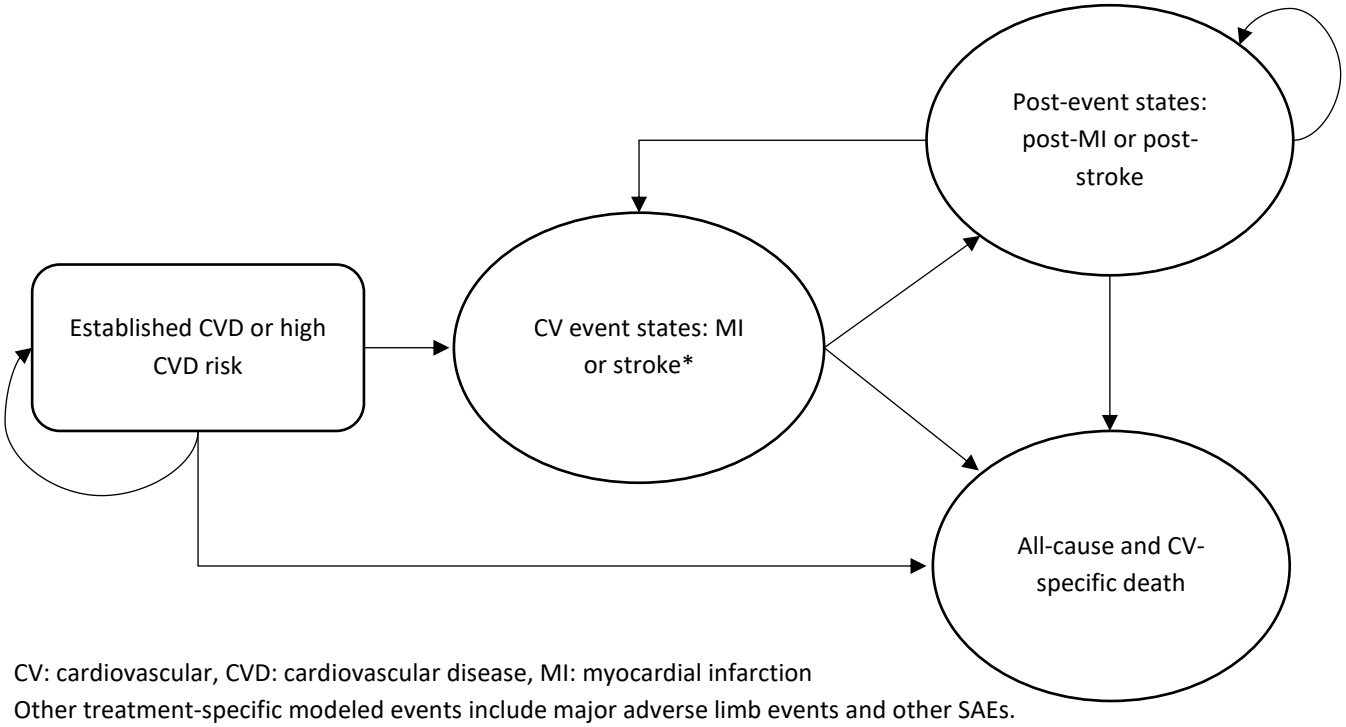
### Model Structure

The Markov model focused on an intention to treat analysis, with a hypothetical cohort of adult patients with established CVD (or at high CVD risk) being treated with optimal medical management entering the model. The model included health states that define the pathways of CVD and that have been used in previous modeling efforts.[77-81] The base-case health states included major cardiovascular events of MI and stroke, as well as post-event health states and death (from cardiovascular and other causes). A scenario analysis included other cardiovascular events beyond MI and stroke (e.g., revascularization or unstable angina) in the event and post-event health states. Additional consequences such as major adverse limb events for rivaroxaban, as well as SAEs, were tracked in the model. For these additional consequences, we assumed event probabilities were equal for all living health states and therefore did not require additional health states in the model structure.

Specifically, the CVD cohort began on treatment and could stay in that state, pass into event states of MI or stroke, or death (Figure 4.1). Patients who experienced a cardiovascular event moved into post-event health states, where they may have had higher likelihood for death as compared to the general CVD prevention population. Patients remained in the model until they died. All patients could transition to death from all-causes from any of the alive health states. Death could have occurred from all-cause or cardiovascular event/post-event related morality. As patients moved through the model over the course of their lifetime, they collected costs and health utility weights related to the management and treatment of specific cardiovascular

conditions. The cumulative sum of costs, survival time and utility weights produced model outputs such as lifetime costs, life years (LYs), quality-adjusted life years (QALYs), and equal value of life years gained (evLYG). An analysis of the incremental cost per evLYG is included in this report to complement the cost per QALY calculations and provide policymakers with a broader view of cost effectiveness. A description of the methodology used to derive the evLYG can be found in Appendix E. Other outputs of the model included cumulative incidence of cardiovascular events and cardiovascular events avoided. The model was developed in Microsoft Excel 2016 (Redmond, WA).

**Figure 4.1. Model Framework**




CV: cardiovascular, CVD: cardiovascular disease, MI: myocardial infarction
Other treatment-specific modeled events include major adverse limb events and other SAEs.
*Other CV events such as revascularization and unstable angina included in scenario analysis.

## Target Population

The population of focus was adults with established CVD being treated with optimal medical management. For the assessment of icosapent ethyl, patients without known CVD but at high risk for cardiovascular events were also considered. The modeled populations' characteristics were consistent with the average across trial arms in the pivotal trials (Tables 4.1 and 4.2). The population of study for rivaroxaban was, on average, 68 years old, 78% male, 21% with smoking history, 38% with diabetes, 62% with prior MI, 4% with prior stroke, 22% with heart failure, and with a number of commonly prescribed therapies as part of their medical management. The population of study for icosapent ethyl was, on average, 64 years old, 71% male, 15% with smoking history, 58% with diabetes, and 71% with prior CVD events. These model characteristics have limited impact within the model, by influencing the time-varying clinical event rate estimates (see *Transition Probabilities*).

**Table 4.1. Base-Case Model Patient Characteristics for Rivaroxaban Evaluation**

| Characteristic | Overall | Source |
|---|---|---|
| Age, Years, Mean (SD) | 68.2 (7.9) | 82,83 |
| Male (%) | 78.0 | |
| Total Cholesterol, mmol/liter | 4.3 (3.5) | |
| Systolic Blood Pressure, mmHg | 135.5 (17.57) | |
| Smoking (% Yes) | 21.4 | 82 |
| Diabetes (% Yes) | 37.9 | 82,83 |
| Prior MI (% Yes) | 62.1 | |
| Prior Stroke (% Yes) | 3.8 | |
| Heart Failure (% Yes) | 21.5 | |
| CAD (% Yes) | 90.6 | |
| PAD (% Yes) | 27.3 | |
| ACE Inhibitor or ARBs (% Yes) | 70.8 | |
| Calcium-Channel Blocker (% Yes) | 26.8 | |
| Diuretic (% Yes) | 28.5 | |
| Beta-Blocker (% Yes) | 70.0 | |
| Lipid-Lowering Agent (% Yes) | 89.7 | |

ACE: angiotensin-converting-enzyme, ARB: angiotensin II receptor blocker, CAD: coronary artery disease, MI: myocardial infarction, PAD: peripheral artery disease, SD: standard deviation

**Table 4.2. Base-Case Model Patient Characteristics for Icosapent Ethyl Evaluation**

| Characteristic | Overall | Source |
|---|---|---|
| Age, Years, Median (IQR) | 64.0 | 19 |
| Male (%) | 71.2 | |
| High-Density Lipoprotein, mg/dL, Median (IQR) | 40.0 | |
| Low-Density Lipoprotein, mg/dL, Median (IQR) | 75.0 | |
| Triglycerides, mg/dL, Median (IQR) | 216 | |
| Smoking (% Yes) | 15.2 | 84 |
| Diabetes – Type 2 (% Yes) | 57.8 | 19,84 |
| Prior CVD Events (% Yes) | 70.7 | 19 |

CVD: cardiovascular disease, IQR: interquartile range

*Data not available in publicly disclosed sources.

## Treatment Strategies

### *Interventions*

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers. The full list of interventions is as follows:

1. Rivaroxaban + ASA
    - Patients are assumed to also be receiving optimal medical management.
2. Icosapent ethyl
    - Patients are assumed to also be receiving optimal medical management, including statins.

***Comparators***

Comparators were defined to reflect the input of clinicians and other stakeholders on treatment strategies that would be considered relevant alternatives for the overall population of interest or a prominent subset, as well as the comparators as defined in major clinical studies of rivaroxaban and icosapent ethyl.

1. Rivaroxaban comparators:
    - Optimal medical management including ASA without an additional antiplatelet agent.
    - DAPT with clopidogrel (scenario analysis only).
2. Icosapent ethyl comparator:
    - Optimal medical management including statin therapy.

## Key Model Characteristics and Assumptions

Model cycle length was one year, based on what was observed in prior published economic models and clinical data. The base-case analysis assumed a lifetime horizon, consistent with the ICER Value Framework. The base-case analysis took a health care sector perspective and thus focused on direct medical care and drug costs only. Costs and outcomes were discounted at 3% per year. Key model assumptions are described in Table 4.3.

**Table 4.3. Key Model Assumptions**

| Assumption | Rationale |
|---|---|
| **Individual hazard ratios were used for each subcomponent of composite endpoints observed in the clinical trials. Endpoint subcomponents included the common major adverse CV events: MI, stroke, and CV death. Other CV events (e.g., revascularization and unstable angina) were evaluated in a scenario analysis.** | Given differences across the severity of endpoints in terms of cost, disutility, or likelihood of CV death, endpoint subcomponents were tracked in the model. Relative reductions in other CV events such as revascularization and unstable angina were not included in the base case due to potential associations and double counting issues with MI and stroke events. |
| **Subsequent CV events (second, third, and fourth events) had the same overall HR as the first CVD event.** | Based on the clinical review critique, time to first event analyses were the statistical analyses of primary focus in trials, and there were statistical concerns regarding correlations between subsequent event types. The model was calibrated to the overall CV event rate observed in the control arm (MI, stroke, and CV death), with the HR applied to events associated with the modeled intervention. |
| **Patients could have more than one event in the same cycle, with costs and disutilities for multiple events assumed to be additive.** | This cohort-level model allowed for multiple events within a model cycle by assuming that the costs and disutility of one event (stroke or MI) could be added to that of the costs and disutility of another event (MI or stroke). |

| Assumption | Rationale |
|---|---|
| **There was a higher risk of CV death for patients in a CV event or post-event health state.** | Literature-based evidence.[85-90] |
| **Model event rate was consistent with control arm first event rates (for MI, stroke, and CV death) from clinical trials.** | Because the trial evidence suggested high-risk populations, the model was calibrated to the trial populations in terms of first MI, stroke, and CV death events. |
| **Patients continued on treatment after first event in the model.** | Patients continuing on therapy after an event was consistent with the trial evidence. |
| **Patients who discontinued treatment were not re-treated with the same initiating therapy. Discontinuation rates mirrored trial evidence and were forecasted based on annualized discontinuation due to SAEs.** | Patients discontinuing therapy did not re-initiate in the trials for both therapies. After the average trial duration, the model assumed an annualized discontinuation rate consistent with discontinuation due to SAEs from the trials. |

CV: cardiovascular, CVD: cardiovascular disease, HR: hazard ratio, MI: myocardial infraction, SAE: serious adverse event

## Model Inputs

Model inputs were estimated from the evidence review, published literature, and information provided by stakeholders. The inputs that informed the models for rivaroxaban and icosapent ethyl are described below.

### *Clinical Inputs*

Key clinical inputs for the model included validated CVD risk prediction models, baseline trial-based clinical markers (e.g., cholesterol, triglycerides), baseline comorbid conditions (e.g., diabetes), and other baseline factors (e.g., smoking, event history, etc.).

#### *Transition Probabilities*

Cardiovascular events included in the base-case model were: MI, stroke, and cardiovascular-related mortality. Validated cardiovascular risk calculators[91] were used to estimate time-varying annualized event rates within the control arm (Table 4.4). The control arm's 10-year risk of cardiovascular events was calibrated such that the model produced consistent first cardiovascular events observed over the same period as within the trial.

For rivaroxaban, the model calibration varied baseline risk while holding constant the proportion of MI (59% of non-fatal first events restricted to MI and stroke only), stroke (41% of non-fatal first events restricted to MI and stroke only), and death derived from first event trial-based results (37% of non-fatal MI, non-fatal stroke, and cardiovascular death). For rivaroxaban, the mean treatment follow-up duration was 23 months. At the beginning of the model, the control arm's annualized cardiovascular event rate was determined by comparing the observed first cardiovascular event and cardiovascular death over an average of 23 months to that of the model's estimates at the end of two years (24 months). These annualized rates in the model varied with time based on the validated cardiovascular risk calculators.[91]

For icosapent ethyl, the model calibration varied baseline risk while holding constant the distribution of MI (73% of non-fatal first events restricted to MI and stroke only), stroke (26% of non-fatal first events restricted to MI and stroke only), and death derived from first event trial-based results (32% of non-fatal MI, non-fatal stroke, and cardiovascular death). For icosapent ethyl, the median follow-up duration was 58.8 months. At the beginning of the model, the control arm's annualized cardiovascular event rate was determined by comparing the observed first cardiovascular event and cardiovascular death over an average of 58.8 months to that of the model's estimates at the end of five years (60 months). These annualized rates in the model varied with time based on the validated cardiovascular risk calculators.[91]

Subsequent events were included in the model as well as first events. We assumed that the risk of subsequent events would be the same as that of first events even if the risk calculator[91] suggested lower likelihood of non-fatal cardiovascular events, given the relatively high severity of the populations in the COMPASS and REDUCE-IT trials and the challenges inherent in evaluating subsequent event risks in situations with event types that are not independent from one another. Once calibrated to the trial's control arm first observed events, these same risk calculator parameters were also used in the model's treatment arm in combination with the treatment- and event-specific hazard ratios.

**Table 4.4. Sources for Baseline Risk Equations for First Future Events, Subsequent Events, and Mortality**

| Baseline Risk Equations | Values | Source |
|---|---|---|
| **First Future Event (MI or Stroke)** | Varies by age and risk factors | 91 |
| **Subsequent Future Events (MI or Stroke)** | Varies by age and risk factors | |
| **Event-Specific Mortality** | Calibrated to death from first event using trial-based results from standard of care arms | *Multiple sources[20,21,85-90,92] |
| **Mortality Post-MI or Stroke** | Increased mortality relative risk of 2.5 | |
| **Mortality, All-Cause** | Varies by age | US Life Tables[93] |

* An earlier version of this report incorrectly detailed these sources. It has been corrected here.
MI: myocardial infarction

The treatment- and event-specific hazard ratios for endpoints from the treatment-specific clinical trials were applied to baseline risk estimates to model the transition from the established CVD to the cardiovascular event health states at the end of each model cycle (each year). Efficacy estimates for each intervention are detailed in Tables 4.5 and 4.6. The base case assumed efficacy estimates from time to first event. Alternatives such as the relative risk of total events and the inclusion of other cardiovascular events (revascularization and unstable angina) were evaluated in a scenario analysis.

**Table 4.5. Efficacy Estimates for Rivaroxaban**

| Parameter | Rivaroxaban + ASA n (%) | ASA Alone n (%) | HR (95% CI) | *P*-Value | Source |
|---|---|---|---|---|---|
| Composite Primary Outcome: Stroke, CV Death, MI* | 379 (4.1) | 496 (5.4) | 0.76 (0.66-0.86) | <0.001 | 83 |
| Stroke† | 83 (0.9) | 142 (1.6) | 0.58 (0.44-0.76) | <0.001 | |
| CV Death† | 160 (1.7) | 203 (2.2) | 0.78 (0.64-0.96) | 0.02 | |
| MI† | 178 (1.9) | 205 (2.2) | 0.86 (0.70-1.05) | 0.14 | |
| MALE‡ | 30 (1) | 56 (2) | 0.54 (0.35-0.84) | 0.0054 | 57 |

ASA: aspirin, CI: confidence interval, CV: cardiovascular, HR: hazard ratio, MALE: major adverse limb event, MI: myocardial infarction

*Only *p*-values for the primary outcome are confirmatory.

†As the statistical analysis plan for the trial did not specify modifications to the pre-specified control of multiple testing of other efficacy outcomes in the case of early termination of the study, any HRs, corresponding CIs, and *P*-values reported for other efficacy outcomes cannot be interpreted as statistically significant.

‡MALE was defined as acute or chronic limb ischemia and included all major amputations. MALE was a pre-specified outcome for patients with PAD in the COMPASS trial.

**Table 4.6. Efficacy Estimates for Icosapent Ethyl**

| Parameter | Icosapent Ethyl n (%) | Comparator/ Placebo n (%) | HR (95% CI) | *P*-Value | Source |
|---|---|---|---|---|---|
| Composite Outcome: CV Death, Nonfatal Stroke, Nonfatal MI | 459 (11.2) | 606 (14.8) | 0.74 (0.65-0.83) | <0.001 | 19 |
| Secondary Prevention | 559 (19.3) | 738 (25.5) | 0.73 (0.65-0.81) | | |
| Primary Prevention | 146 (12.2) | 163 (13.6) | 0.88 (0.70-1.10) | | |
| Non-Fatal Stroke | 85 (2.1) | 118 (2.9) | 0.71 (0.54-0.94) | 0.01 | |
| CV Death | 174 (4.3) | 213 (5.2) | 0.80 (0.66-0.98) | 0.03 | |
| Non-Fatal MI | 237 (5.8) | 332 (8.1) | 0.70 (0.59-0.82) | <0.001 | |
| Total Events (Primary Composite Endpoint) | 1076 | 1546 | 0.70 (0.62-0.78) | <0.0001 | 20 |

CI: confidence interval, CV: cardiovascular, HR: hazard ratio, MI: myocardial infarction

*Discontinuation*

Treatment discontinuation rates were based on trial-specific data for each comparison. For rivaroxaban, 16.5% of patients in the rivaroxaban + ASA arm had permanently discontinued treatment at the final study visit (mean follow-up duration of 23 months).[83]

For icosapent ethyl, after an average follow-up of approximately two years, 18.7% of patients in the icosapent ethyl arm had discontinued treatment at the time of a first event.[20]

Beyond two years duration in the model for rivaroxaban and five years duration for icosapent ethyl, we assumed an annualized discontinuation based on SAE-related discontinuation of 2.7% for rivaroxaban and 2.2% for icosapent ethyl. The observed trial-based hazard ratios were assigned for all patients in the first two or five years of the model (no matter the discontinuation status, i.e., consistent with an intention to treat analysis) for rivaroxaban and icosapent ethyl, respectively. For model cycles beyond two years (rivaroxaban) and five years (icosapent ethyl), the proportion remaining on active treatment were assigned the observed trial-based hazard ratios whereas the proportion who discontinued treatment were assigned the costs and outcomes consistent with optimal medical management.

*Utilities*

To adjust for quality of life, health state utilities were derived from publicly available literature and applied to health states. Utility values were primarily from a study on preference-based EQ-5D index scores for chronic conditions, based on survey results for a nationally representative sample of the US adult population.[94] We used consistent health state utility values across both comparisons. We assigned higher disutilities to MI and stroke events compared to the post-event states, consistent with prior studies (Table 4.7). Disutilities for AEs were applied to the proportion of the cohort with an event within each cycle.

Since the severity of stroke can differ with patients experiencing a wide range of symptoms and disability, we compared the disutility values for stroke listed in Table 4.7 to a weighted average stroke utility value that incorporates stroke severity. The Modified Rankin Scale (mRS) is a commonly used clinical outcome measure to classify strokes based on symptom severity, with severity ranging from 0 (no symptoms) to 6 (dead). The COMPASS trial classified the severity of all stroke events using the mRS, and the associated utilities for each stroke category have been published in the literature[95] (Appendix Table E5). We weighted the utility values for mRS categories by the proportion of patients in the COMPASS control arm who experienced a stroke in each mRS category to estimate a weighted average stroke utility (Appendix Table E5). This weighted average utility value is 0.6615, which is higher than the utility value applied to a patient in our model cohort who experiences an event cycle stroke (0.5976). While the severity differed for COMPASS patients who experienced a stroke, the risk reduction for stroke with rivaroxaban + ASA versus ASA alone was consistent across all mRS categories.[14]

**Table 4.7. Utility and Disutility Values for Health States**

| Parameter | Value | Source |
|---|---|---|
| Treated Population without Observed Events | 0.854* | 96,97 |
| Post-Event MI (Disutility Applied to State) | -0.150 | 94 |
| Post-Event Stroke (Disutility Applied to State) | -0.204 | |
| Event Cycle MI (Disutilities Applied to Event) | -0.0409 + -0.150 | |
| Event Cycle Stroke (Disutilities Applied to Event) | -0.0524 + -0.204 | |
| Severe Atrial Fibrillation (Disutility Applied to Event) | -0.164 | 98 |
| Major Bleeding (Disutility Applied to Event) | -0.181 | 99 |
| Acute Non-Fatal MALE (Disutility Applied to Event) | -0.220 | 78 |

MALE: major adverse limb event, MI: myocardial infarction

*Based on average utilities of coronary heart disease patients who had undergone coronary artery bypass grafting (CABG) and PCI and later stabilized. (CABG=0.847, PCI=0.861).

*Adverse Events*

The model included all reported treatment-related SAEs and bleeding events for each of the two comparisons. Each SAE had an associated cost and disutility (if available) that was applied for each occurrence of the event. Inputs related to SAEs for each intervention are detailed in Tables 4.8 and 4.9.

For the rivaroxaban comparison, major bleeding events occurred more frequently in patients in the rivaroxaban + ASA group than in the ASA alone group (3.1% vs. 1.9%). The annualized probability for each treatment arm was used within the model.[83]

**Table 4.8. Bleeding Event Parameter for Rivaroxaban Evaluation**

| Parameter | Rivaroxaban + ASA | ASA Alone | HR (95% CI) | *P*-Value | Source |
|---|---|---|---|---|---|
| Modified ISTH Major Bleeding* | 288 (3.1) | 170 (1.9) | 1.70 (1.40-2.05) | <0.001 | 83 |

ASA: aspirin, CI: confidence interval, HR: hazard ratio, ISTH: International Society on Thrombosis and Haemostasis

*Modified ISTH bleeding was defined as a composite of fatal bleeding, symptomatic bleeding into a critical organ, bleeding into a surgical site requiring reoperation, and bleeding that led to hospitalization (including presentation to an acute care facility without an overnight stay).

For the icosapent ethyl comparison, overall AE rates were low in both treatment arms and none of the AEs were fatal. There was an observed trend toward increased serious bleeding in the icosapent ethyl arm. The evidence on icosapent ethyl did not suggest significant increases in serious central nervous system bleeding, GI bleeding, or adjudicated hemorrhagic stroke and therefore no difference in major bleeding was assumed within the model. There was a small, statistically significant increase in hospitalization for atrial fibrillation or flutter endpoints that was included in the model.[20]

**Table 4.9. Adverse Event Parameters for Icosapent Ethyl Evaluation**

| Parameter | Icosapent Ethyl | Comparator/Placebo | *P*-Value | Source |
|---|---|---|---|---|
| Serious TEAE (%) | 30.6 | 30.7 | 0.98 | 20 |
| Hospitalization for Atrial Fibrillation or Flutter (%) | 3.1 | 2.1 | 0.004 | |
| Bleeding-Related Disorders (%) | 2.7 | 2.1 | 0.06 | |

TEAE: treatment-emergent adverse event

*Drug Utilization*

The following inputs were used to model drug utilization and associated costs for each intervention:

- Duration of treatment
- Schedule of doses for each drug

**Table 4.10. Treatment Regimens**

| Characteristic | Rivaroxaban + ASA | ASA Alone | Icosapent Ethyl |
|---|---|---|---|
| Recommended Dose | Rivaroxaban 2.5 mg twice daily + ASA 100 mg once daily | ASA 100 mg once daily | 2 g twice daily |
| Route of Administration | Oral | Oral | Oral, with food |

ASA: aspirin

***Economic Inputs***

*Drug Acquisition Costs*

For both drugs, we obtained net pricing estimates from SSR Health, LLC,[32] which combine data on unit sales with publicly-disclosed US sales figures that are net of discounts, rebates, concessions to wholesalers and distributors, and patient assistance programs to derive a net price. We estimated net prices by comparing the four-quarter averages (i.e., 2nd quarter of 2018 through 1st quarter of 2019) of both net prices and wholesale acquisition cost (WAC) per unit to calculate a mean discount from WAC for the drug. Finally, we applied this average discount to the most recently available WAC (July 1, 2019) to arrive at an estimated net price per unit.

Rivaroxaban's WAC is $7.47 per 2.5 mg tablet. The average discount from WAC was 59.41% for rivaroxaban, leading to an estimated net price of $3.03 per dose.

Icosapent ethyl's WAC for a one-month supply of 4 g/day is $303.65 (each bottle contains 120 each of 1 g capsules). The average discount from WAC was 56.04% for icosapent ethyl, leading to an estimated net price of $1.11 per dose.

**Table 4.11. Drug Cost Inputs**

| Drug | WAC per Tablet/Capsule | Net Price per Tablet/Capsule | Discount from WAC | Net Price per Year |
|---|---|---|---|---|
| Rivaroxaban (Xarelto®, Janssen) | $7.47 per 2.5mg tablet | $3.03 | 59.41% | $2,215 |
| Icosapent Ethyl (Vascepa®, Amarin Pharma) | $2.53 per 1g capsule | $1.11 | 56.04% | $1,625 |

WAC: wholesale acquisition cost

WAC per Redbook®; net pricing estimates from SSR Health.[32,33]

Please refer to the ICER Reference Case for more details on drug pricing.

*Non-Drug Costs*

Health state costs were derived from literature-based estimates. Indirect costs were not included in the base-case analysis but were included in a scenario analysis. All costs were inflated to year 2019 levels using the health care component of the personal consumption expenditure index,[100] in accordance with the ICER Reference Case.[101]

**Table 4.12. Non-Drug Cost Inputs**

| Input | 2019 USD Mean Value* | Source |
|---|---|---|
| MI Treatment and Event Year Cost | $55,316 | [102] and supporting references |
| Stroke Treatment and Event Year Cost | $58,932 | |
| Post-MI Annual Cost (Assumed Same as Subsequent Years of Coronary Heart Disease) | $2,728 | |
| Post-Stroke Annual Cost | $5,742 | |
| CV Death Cost | $18,341 | [103] |
| Major Bleeding Cost (Applied to Event Year) | $3,367 | [78] |
| Acute Non-Fatal MALE Cost (Applied to Event) | $17,979 | |
| Hospitalization for Atrial Fibrillation | $9,957 | [104] |

CV: cardiovascular, MALE: major adverse limb event, MI: myocardial infarction, USD: United States dollar

*Estimates varied in sensitivity analyses using the 2.5th and 97.5th percentiles of evidence-based probability distributions where available.

## Sensitivity Analyses

We ran one-way sensitivity analyses to identify the key drivers of model outcomes, using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges for each input described in the model inputs section above. Probabilistic sensitivity analyses were also performed by jointly varying all model parameters over 5,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. Additionally, we performed a threshold analysis by systematically altering the price of rivaroxaban and icosapent

ethyl to estimate the maximum prices that would correspond to willingness to pay (WTP) thresholds of $50,000/QALY, $100,000/QALY, and $150,000/QALY.

## Scenario Analyses

Multiple scenario analyses were conducted to evaluate the impact of key model choices and assumptions on the robustness of the results and conclusions. First, the perspective was expanded to a modified/restricted societal one that included productivity losses. Evidence suggests that workers have workplace absenteeism and short-term disability equal to 13.6 hours per month within the first year after a cardiovascular event, but no differences beyond the first year.[105] We assumed these first-year annualized hours, 163.2 hours, would apply to all individuals in the model who experienced a cardiovascular event.[106] The average hourly wage of $27.71 was assumed to apply to all hours no matter the working status of the individual. Second, the addition of other cardiovascular events, such as revascularization and unstable angina, were included in the cardiovascular event health state within the model. Coronary revascularization and unstable angina requiring hospitalization were pre-specified subcomponents of the primary composite endpoint in the icosapent ethyl trial. Third, the composite primary endpoints and corresponding hazard ratios from the intervention-specific trials were modeled instead of the individual subcomponents of the primary endpoints. Fourth, DAPT with clopidogrel was modeled as a comparator to rivaroxaban + ASA (Appendix Table E2-E4). Due to differences in severe bleeds, the clinical review was not able to produce a hazard ratio that indirectly compared the rates of major bleeding with DAPT with clopidogrel to rivaroxaban + ASA. The annualized bleeding rate for the ASA alone arm of the "CAPRIE-like subgroup" (documented prior MI, ischemic stroke, or symptomatic PAD) from CHARISMA was 0.0065.[18] Rate ratios between 1 and 5 (for rivaroxaban + ASA versus DAPT with clopidogrel) were modeled and compared versus commonly cited thresholds. Finally, we estimated the potential cost effectiveness of the interventions versus their respective optimal medical management comparator by assuming the same baseline cardiovascular risk through averaging the baseline risk across the two interventions' trial populations, but assuming the same intervention-specific hazard ratios.

## Model Validation

We used several approaches to validate the model. First, we provided preliminary methods and results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model. Second, we varied model input parameters to evaluate face validity of changes in results. We performed model verification for model calculations using internal reviewers. As part of ICER's efforts to increase modeling transparency, we will also share the model with relevant manufacturers for external verification and feedback shortly after publishing the draft report for this review. Finally, we compared results to other cost-effectiveness models in this therapy area.

## 4.3 Results

### Base-Case Results

The base-case lifetime undiscounted clinical events are found in Tables 4.13 and 4.14 for rivaroxaban and icosapent ethyl, respectively. Over a lifetime horizon, we present the percentage of the modeled cohort who experienced their first modeled event as an MI or as a stroke. Separately, we present the proportion of the modeled cohort who experienced death due to CVD or due to all other causes. Further, we present the cumulative incidence of cardiovascular events (MI, stroke, and cardiovascular death). The column percentage sum of death due to CVD and all other causes approximates to 100 but may differ slightly due to rounding. For both rivaroxaban and icosapent ethyl, lower lifetime first MI, first stroke, and death due to CVD were observed. The major adverse cardiovascular event cumulative incidence including MI, stroke, and cardiovascular-related death was lower for both interventions as compared to optimal medical management alone. Note that subsequent events were also tracked within the model alongside associated costs and disutilities but are not reported here.

**Table 4.13. Rivaroxaban Long-Run Clinical Outcomes (Lifetime Horizon, Undiscounted)**

| Lifetime Events | | | |
|---|---|---|---|
| **Event** | **Intervention** | **Medical Management** | **Absolute Difference** |
| **First Event MI** | 20% | 21% | -1% |
| **First Event Stroke** | 10% | 14% | -4% |
| **Death (CV)** | 30% | 35% | -5% |
| **Cumulative CV events (MI, Stroke, and CV Death)** | 61% | 72% | -11% |
| **Death (All Other Cause)** | 70% | 64% | N/A |

CV: cardiovascular, MI: myocardial infarction

**Table 4.14. Icosapent Ethyl Long-Run Clinical Outcomes (Lifetime Horizon, Undiscounted)**

| Lifetime Events | | | |
|---|---|---|---|
| **Event** | **Intervention** | **Medical Management** | **Absolute Difference** |
| **First Event MI** | 29% | 35% | -6% |
| **First Event Stroke** | 9% | 11% | -2% |
| **Death (CV)** | 38% | 46% | -8% |
| **Cumulative CV events (MI, Stroke, and CV Death)** | 81% | 98% | -17% |
| **Death (All Other Cause)** | 61% | 54% | N/A |

CV: cardiovascular, MI: myocardial infarction

Base-case discounted costs and outcomes from the model are listed in Table 4.15 for rivaroxaban and in Table 4.16 for icosapent ethyl. Rivaroxaban was associated with approximately $17,000 in discounted lifetime intervention costs, whereas icosapent ethyl was associated with $15,000 in lifetime intervention costs. Although additional medical management intervention and non-intervention costs are likely within the modeled cohorts,

such costs were assumed to be equal across treatment arms, and therefore not included within this analysis. Average discounted life years and QALYs were higher for both interventions as compared to optimal medical management alone. The items included within the health care sector base-case results as well as those included within the modified societal perspective are listed in the impact inventory (Appendix Table E1).

**Table 4.15. Base-Case Discounted Results for Rivaroxaban Compared to Optimal Medical Management including ASA**

| Treatment | Intervention Costs | Non-Intervention Costs | Total Costs | Life Years | evLYG | QALYs |
|---|---|---|---|---|---|---|
| Rivaroxaban | $17,000 | $20,000 | $38,000 | 10.86 | 9.07 | 9.06 |
| Medical Management | $200 | $24,000 | $24,000 | 10.45 | 8.69 | 8.69 |

evLYG: equal value of life years gained, QALY: quality-adjusted life year

**Table 4.16. Base-Case Discounted Results for Icosapent Ethyl Compared to Optimal Medical Management including Statins**

| Treatment | Intervention Costs | Non-Intervention Costs | Total Costs | Life Years | evLYG | QALYs |
|---|---|---|---|---|---|---|
| Icosapent Ethyl | $15,000 | $25,000 | $40,000 | 12.26 | 10.21 | 10.19 |
| Medical Management | $800 | $30,000 | $31,000 | 11.73 | 9.69 | 9.69 |

evLYG: equal value of life years gained, QALY: quality-adjusted life year

Base-case discounted incremental results are shown in Table 4.17, with rivaroxaban versus optimal medical management yielding $36,000 per QALY gained. Icosapent ethyl versus optimal medical management yields $18,000 per QALY gained. Discounted incremental life year results were slightly lower than the incremental cost-per-QALY findings. Discounted incremental equal value life years gained (evLYG) evenly measures any gains in length of life, regardless of the impact on patients' quality of life. Results for the incremental evLYG were slightly lower than the cost-per-QALY findings given there is a life extension to each therapy over medical management. Incremental cost per major adverse cardiovascular event avoided could be interpreted as the expected costs to achieve one less major adverse cardiovascular event (MI, stroke, or cardiovascular death) when treating a population with rivaroxaban versus optimal medical management or separately, when treating a population with icosapent ethyl versus optimal medical management. The incremental cost per major adverse cardiovascular event avoided should be interpreted with caution, given that this metric does not have a known threshold for an understanding of value and does not include the differential timing or the differential importance of major adverse cardiovascular events. Note that the intervention-specific incremental findings are modeled using intervention-specific populations and therefore should not be directly compared across treatments.

**Table 4.17. Base-Case Incremental Results**

| Intervention* | Incr. Costs | Incr. LYs | Incr. evLYG | Incr. QALYs | Cost per LY | Cost per evLYG | Cost per QALY | Cost per MACE Avoided |
|---|---|---|---|---|---|---|---|---|
| Rivaroxaban vs. Medical Management | $13,000 | 0.41 | 0.38 | 0.37 | $32,000 per LY gained | $35,000 per evLYG gained | $36,000 per QALY gained | $120,000 per MACE avoided |
| Icosapent Ethyl vs. Medical Management | $9,000 | 0.54 | 0.52 | 0.50 | $17,000 per LY gained | $17,000 per evLYG gained | $18,000 per QALY gained | $53,000 per MACE avoided |

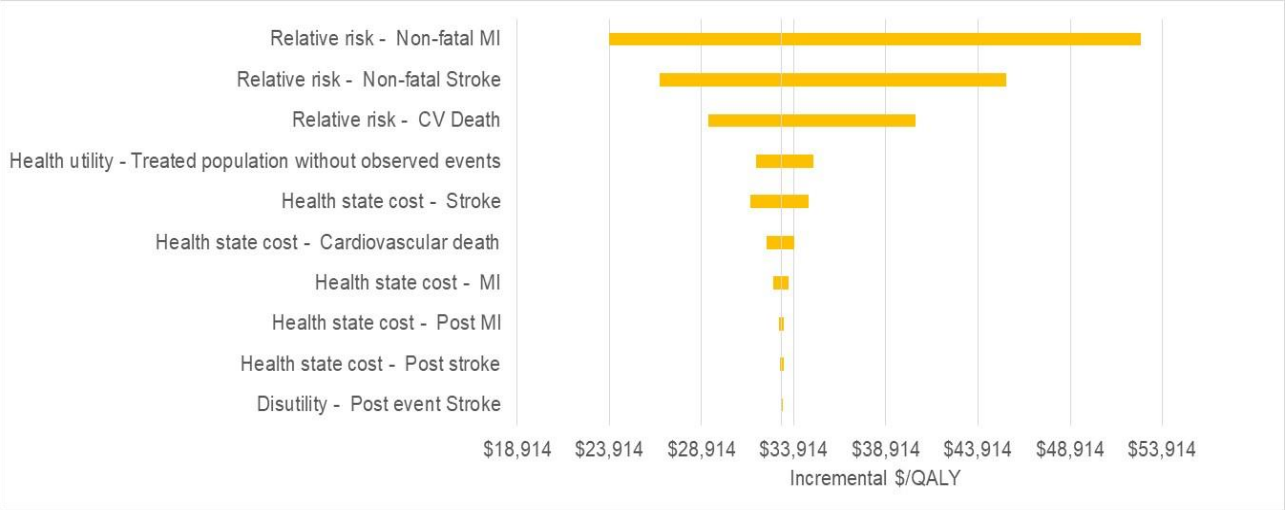
ICER: incremental cost-effectiveness ratio, Incr.: Incremental, LY: life year, MACE: major cardiovascular event, QALY: quality adjusted life year

*Modeled populations differed across interventions; results for the interventions are not directly comparable.

## Sensitivity Analysis Results

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes in cost per additional QALY. Key drivers of uncertainty for rivaroxaban versus optimal medical management included the clinical event hazard ratios for MI, stroke, and cardiovascular death, with smaller impacts observed from uncertainty in utility and cost inputs (Figure 4.2). Similarly, key drivers of uncertainty for icosapent ethyl versus optimal medical management included the clinical event hazard ratios for MI, stroke, and cardiovascular death, with smaller impacts observed from uncertainty in utility and cost inputs (Figure 4.3).

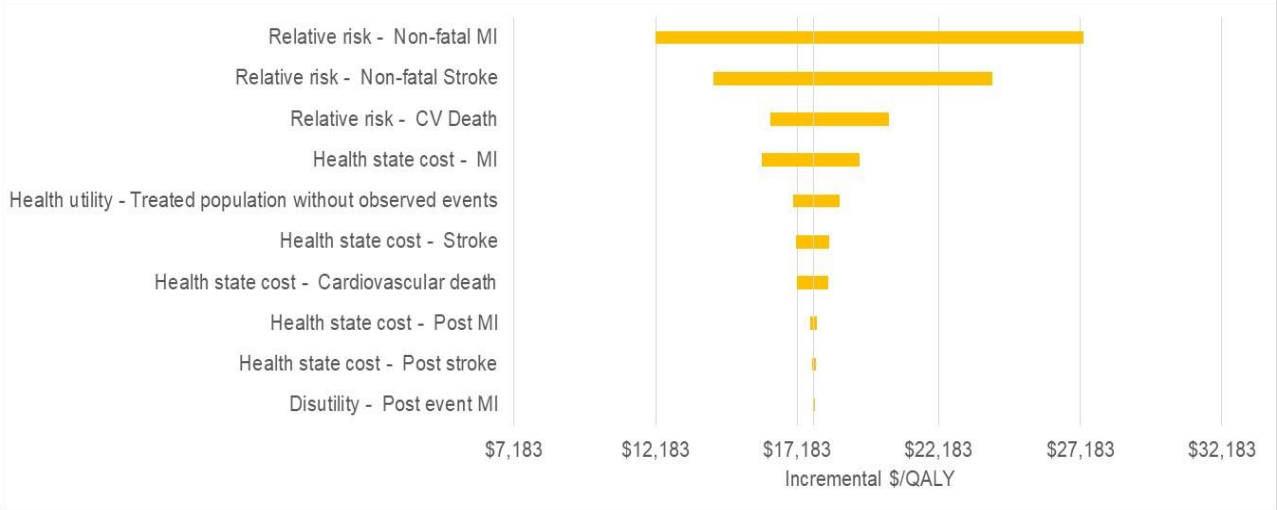
**Figure 4.2. Tornado Diagram for One-Way Sensitivity Analyses of Rivaroxaban versus Medical Management (Accompanied Values Below)**




| Input Name | Lower Input ICER | Upper Input ICER | Lower Input | Upper Input |
|---|---|---|---|---|
| **Relative Risk – Non-Fatal MI** | $23,914 | $52,746 | 0.70 | 1.05 |
| **Relative Risk – Non-Fatal Stroke** | $26,651 | $45,463 | 0.44 | 0.76 |
| **Relative Risk – CV Death** | $29,304 | $40,500 | 0.64 | 0.96 |
| **Health Utility – Treated Population without Observed Events** | $34,981 | $31,854 | 0.81 | 0.89 |
| **Health State Cost – Stroke** | $34,698 | $31,582 | $42,894 | $77,477 |
| **Health State Cost – CV Death** | $33,937 | $32,461 | $13,350 | $24,113 |
| **Health State Cost – MI** | $33,647 | $32,797 | $40,262 | $72,724 |
| **Health State Cost – Post MI** | $33,131 | $33,394 | $1,986 | $3,586 |
| **Health State Cost – Post Stroke** | $33,349 | $33,142 | $4,179 | $7,549 |
| **Disutility – Post Event Stroke** | $33,302 | $33,202 | 0.19 | 0.21 |

CV: cardiovascular, MI: myocardial infarction, ICER: incremental cost-effectiveness ratio

**Figure 4.3. Tornado Diagram for One-Way Sensitivity Analyses of Icosapent Ethyl versus Medical Management (Accompanied Values Below)**




| Input Name | Lower Input Incremental Result | Upper Input Incremental Result | Lower Input | Upper Input |
|---|---|---|---|---|
| **Hazard Ratio – Non-Fatal MI** | $12,183 | $27,305 | 0.59 | 0.82 |
| **Hazard Ratio – Non-Fatal Stroke** | $14,223 | $24,083 | 0.54 | 0.94 |
| **Hazard Ratio – CV Death** | $16,232 | $20,434 | 0.66 | 0.98 |
| **Health State Cost – MI** | $19,383 | $15,918 | $40,262 | $72,723 |
| **Health Utility – Treated Population without Observed Events** | $18,674 | $17,048 | 0.81 | 0.89 |
| **Health State Cost – Stroke** | $18,314 | $17,155 | $42,894 | $77,477 |
| **Health State Cost – CV Death** | $18,292 | $17,181 | $13,350 | $24,113 |
| **Health State Cost – Post MI** | $17,878 | $17,658 | $1,986 | $3,586 |
| **Health State Cost – Post Stroke** | $17,839 | $17,704 | $4,179 | $7,549 |
| **Disutility – Post Event MI** | $17,808 | $17,744 | 0.14 | 0.16 |

CV: cardiovascular, MI: myocardial infarction

Ninety two percent of iterations suggested that rivaroxaban met the $50,000/QALY threshold. Icosapent ethyl results suggested that nearly 100% of iterations met the $50,000/QALY threshold (Table 4.18). Both interventions achieved 100% of iterations that met the $100,000/QALY and $150,000/QALY thresholds.

**Table 4.18. Probabilistic Sensitivity Analysis Results**

| Comparison* | Cost-Effective at $50,000 per QALY | Cost-Effective at $100,000 per QALY | Cost-Effective at $150,000 per QALY |
|---|---|---|---|
| Rivaroxaban vs. Medical Management | 92% | 100% | 100% |
| Icosapent Ethyl vs. Medical Management | 100% | 100% | 100% |

QALY: quality-adjusted life year

*Modeled populations differed across interventions; results for the interventions are not directly comparable.

## Scenario Analyses Results

### *Modified Societal Perspective*

We conducted a scenario analysis by assigning an annualized productivity-related cost of $4,522 to each cardiovascular event in the model. This scenario did not discriminate against those who were not working as it assigned the same cost to all individuals who experienced an event. The rounded incremental results did not materially differ from the base-case findings (Table 4.19).

**Table 4.19. Incremental Results for Modified Societal Perspective**

| Comparison* | Incremental Costs | Incremental LYs | Incremental QALYs | CE Ratio per LY | CE Ratio per QALY |
|---|---|---|---|---|---|
| Rivaroxaban vs. Medical Management | $13,000 | 0.41 | 0.37 | $32,000 per LY | $35,000 per QALY |
| Icosapent Ethyl vs. Medical Management | $9,000 | 0.54 | 0.50 | $16,000 per LY | $17,000 per QALY |

CE: cost effectiveness, LY: life year, QALY: quality-adjusted life year

*Modeled populations differed across interventions; results for the interventions are not directly comparable.

### *Other Cardiovascular Events Health State*

A scenario analysis was conducted with the addition of other cardiovascular events such as revascularization and unstable angina included in the cardiovascular event health state within the icosapent ethyl evaluation. This broader inclusion of other cardiovascular events shifted the incremental cost per QALY from $18,000/QALY (base-case) to $16,000/QALY (Table 4.20).

**Table 4.20. Incremental Results for Other Cardiovascular Events Health State**

| Comparison | Incremental Costs | Incremental LYs | Incremental QALYs | CE Ratio per LY | CE Ratio per QALY |
|---|---|---|---|---|---|
| Icosapent Ethyl vs. Medical Management | $8,000 | 0.56 | 0.50 | $14,000 per LY | $16,000 per QALY |

CE: cost effectiveness, LY: life year, QALY: quality-adjusted life year

### *Composite Primary Endpoints*

A scenario analysis was conducted using the composite primary endpoints instead of individual primary endpoints from the intervention-specific trials. This scenario yielded higher but similar incremental cost-per-QALY findings (Table 4.21).

**Table 4.21. Incremental Results for Composite Primary Endpoints**

| Comparison* | Incremental Costs | Incremental LYs | Incremental QALYs | CE Ratio per LY | CE Ratio per QALY |
|---|---|---|---|---|---|
| Rivaroxaban vs. Medical Management | $14,000 | 0.41 | 0.36 | $34,000 per LY | $38,000 per QALY |
| Icosapent Ethyl vs. Medical Management | $10,000 | 0.52 | 0.47 | $19,000 per LY | $21,000 per QALY |

CE: cost effectiveness, LY: life year, QALY: quality-adjusted life year

*Modeled populations differed across interventions; results for the interventions are not directly comparable.

### *DAPT with Clopidogrel Comparator for Rivaroxaban*

A scenario analysis was conducted comparing rivaroxaban + ASA to DAPT with clopidogrel + ASA. We present the incremental findings assuming the ASA annualized major bleed rate of 0.0065 (Table 4.22) for both rivaroxaban + ASA as well as for DAPT with clopidogrel (i.e., assuming this rate did not differ between treatment strategies). Further, we present the incremental findings assuming the ASA annualized major bleed rate of 0.0065 for DAPT with clopidogrel and solved for the rate ratio that would generate an incremental cost-effectiveness ratio per QALY of $100,000 (rivaroxaban + ASA vs. DAPT with clopidogrel). The rate ratio for major bleed was 2.83 (rivaroxaban + ASA vs. DAPT with clopidogrel) to generate an incremental cost-effectiveness ratio of $100,000 per QALY (results not shown).

**Table 4.22. Incremental Results for DAPT with Clopidogrel Comparator**

| Comparison | Incremental Costs | Incremental LYs | Incremental QALYs | CE Ratio per LY | CE Ratio per QALY |
|---|---|---|---|---|---|
| Rivaroxaban vs. DAPT with Clopidogrel | $14,000 | 0.16 | 0.16 | $89,000 per LY | $86,000 per QALY |

CE: cost effectiveness, DAPT: dual antiplatelet therapy, LY: life year, QALY: quality-adjusted life year

### *Same Baseline Cardiovascular Risk Assumption*

We estimated the potential cost effectiveness of the interventions versus their respective optimal medical management comparator by assuming the same baseline cardiovascular risk by averaging the baseline risk across the two interventions' trial populations but assuming the base-case intervention-specific hazard ratios. The incremental results for both treatments move toward one another with rivaroxaban's incremental cost-per-QALY of $33,000/QALY and icosapent ethyl's incremental cost-per-QALY of $19,000/QALY. However, given the lack of formal direct or indirect treatment comparisons, the results for the interventions may not be directly comparable.

**Table 4.23. Incremental Results for Same Baseline Cardiovascular Risk**

| Comparison | Incremental Costs | Incremental LYs | Incremental QALYs | CE Ratio per LY | CE Ratio per QALY |
|---|---|---|---|---|---|
| Rivaroxaban vs. Medical Management | $13,000 | 0.43 | 0.40 | $30,000 per LY | $33,000 per QALY |
| Icosapent Ethyl vs. Medical Management | $9,000 | 0.51 | 0.48 | $18,000 per LY | $19,000 per QALY |

CE: cost effectiveness, LY: life year, QALY: quality-adjusted life year

### *Threshold Analyses Results*

We estimated threshold treatment prices that would reflect an incremental cost-per-QALY of $50,000, $100,000, and $150,000. The findings suggest that both treatments' net prices were below the price needed to achieve $50,000 per QALY (Table 4.24). Interestingly, the annual price to achieve $100,000/QALY was slightly lower but approximated the WAC annualized price for rivaroxaban. The annual price to achieve $50,000/QALY was slightly lower but approximated the WAC annualized price for icosapent ethyl.

**Table 4.24. Cost per QALY Threshold Analysis Results**

| | WAC per Tablet/Capsule | Annual WAC | Net Price per Tablet/ Capsule | Net Price per Year | Annual Price to Achieve $50,000 per QALY | Annual Price to Achieve $100,000 per QALY | Annual Price to Achieve $150,000 per QALY |
|---|---|---|---|---|---|---|---|
| Rivaroxaban | $7.47 per 2.5 mg tablet | $5,457 | $3.03 | $2,215 | $2,849 | $5,223 | $7,597 |
| Icosapent Ethyl | $2.53 per 1 g capsule | $3,699 | $1.11 | $1,625 | $3,433 | $6,282 | $9,204 |

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

Table 4.25 presents the threshold results for each drug at thresholds of $50,000, $100,00 and $150,000 per equal value life year gained (evLYG). An analysis of the evLYG is included to

complement the cost per QALY calculations and provide policymakers with a broader view of cost effectiveness. The cost per evLYG considers any extension of life at the same "weight" no matter what treatment is being evaluated.

**Table 4.25. Cost per evLYG Threshold Analysis Results**

| | WAC per Tablet/Capsule | Annual WAC | Net Price per Tablet/ Capsule | Net Price per Year | Annual Price to Achieve $50,000 per evLYG | Annual Price to Achieve $100,000 per evLYG | Annual Price to Achieve $150,000 per evLYG |
|---|---|---|---|---|---|---|---|
| **Rivaroxaban** | $7.47 per 2.5 mg tablet | $5,457 | $3.03 | $2,215 | $2,922 | $5,369 | $7,780 |
| **Icosapent Ethyl** | $2.53 per 1 g capsule | $3,699 | $1.11 | $1,625 | $3,506 | $6,501 | $9,423 |

evLYG: equal value life year gained, WAC: wholesale acquisition cost

## Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

We reported on the model calibration findings to suggest that over a time horizon consistent with the randomized controlled trials, the model produced first event MI, first event stroke, and cardiovascular death rates within small margins of error of the randomized controlled trial findings (Appendix Table E7-Table E8).

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments. Fonarow et al. evaluated the cost effectiveness of evolocumab in patients with atherosclerotic CVD when added to standard background therapy.[107] They used a Markov cohort state-transition model from a US societal perspective assuming a lifetime time horizon to capture the progression of atherosclerotic CVD in adults. We used inputs from this study in our model to validate against the Fonarow model findings and achieved agreeable estimates (Appendix Table E6).

### *Prior Economic Models*

In our review of prior economic models, Fonarow et al. evaluated the cost effectiveness of the proprotein convertase subtilisin/kexin type 9 inhibitor evolocumab in patients with atherosclerotic cardiovascular disease when added to standard background therapy.[107] A Markov cohort state-transition model was used, integrating US population-specific

demographics, risk factors, background therapy, and event rates, along with trial-based event risk reduction. In the base case, using patients with atherosclerotic cardiovascular disease, evolocumab had an ICER of approximately $269,000 per QALY gained (approximately $166,000 using a discounted price based on an average rebate of 29% for branded pharmaceuticals).[107] Sensitivity and scenario analyses demonstrated ICERs ranging from approximately $100,000 to $489,000 per QALY, with an ICER of approximately $414,000 per QALY when using trial patient characteristics. At its list price of $14,523, the addition of evolocumab to standard background therapy in patients with atherosclerotic cardiovascular disease exceeded generally accepted cost-effectiveness thresholds.[107]

A study by Kazi et al. estimated the cost effectiveness of PCSK9 inhibitors in patients with heterozygous familial hypercholesterolemia (FH) or atherosclerotic cardiovascular disease (ASCVD).[102] A simulation model of US adults aged 35 to 94 years, called the Cardiovascular Disease Policy Model, was used to evaluate the cost effectiveness of PCSK9 inhibitors or ezetimibe in heterozygous FH or ASCVD.[102] Adding PCSK9 inhibitors to statins in heterozygous FH was estimated to prevent 316,300 MACE at a cost of $503,000 per QALY gained compared with adding ezetimibe to statins (80% uncertainty interval [UI], $493,000-$1,737,000).[102] In ASCVD, adding PCSK9 inhibitors to statins was estimated to prevent 4.3 million MACE compared with adding ezetimibe, at $414,000 per QALY (80% UI, $277,000-$1,539,000).[102] In this study, PCSK9 inhibitor use in patients with heterozygous FH or ASCVD did not meet generally acceptable incremental cost-effectiveness thresholds.[102]

Two studies assessed the cost effectiveness of rivaroxaban and aspirin compared to aspirin alone in patients with stable cardiovascular disease and in patients with peripheral or carotid artery disease from the Australian perspective.[78,79] Ademi et al. developed a Markov model using input data from the COMPASS trial. Compared to aspirin alone, rivaroxaban plus aspirin was estimated to have an ICER of AUD$31,436/QALY gained.[79] The authors concluded that compared to aspirin, rivaroxaban in combination with aspirin is likely to be cost-effective in preventing recurrent cardiovascular events in patients with stable atherosclerotic vascular disease.[79] Similarly, Zomer et al. estimated that rivaroxaban plus aspirin therapy prevented 143 non-fatal cardiovascular disease events, 118 major adverse limb events and 10 deaths compared to aspirin therapy alone, resulting in an ICER of AUD$26,769 per QALY.[78] The authors concluded that in patients with peripheral artery disease or carotid artery disease, rivaroxaban plus aspirin therapy was cost-effective in the prevention of recurrent cardiovascular disease compared to aspirin therapy alone.[78]

Other published economic evaluations included the assessment of eicosapentaenoic acid (EPA) in CVD prevention in the settings of the US and Japan.[80,81] The results of the US model showed that combining EPA with statin therapy for secondary prevention of cardiovascular disease may be a cost-saving option compared to statin monotherapy.[81] In the Japanese assessment, EPA plus statin combination therapy showed acceptable cost effectiveness for secondary prevention, but not primary prevention, of CVD in patients with hypercholesterolemia.[80]

Lastly, Jiang et al. assessed the cost effectiveness of 30-month vs 12-month dual antiplatelet therapy (DAPT) with clopidogrel and aspirin after drug-eluting stents in patients with acute coronary syndrome.[77] Continuation of DAPT appears to be cost-effective in acute coronary syndrome patients who were event-free for 12-month DAPT after drug-eluting stents. However, the cost effectiveness of DAPT for 30 months was highly subject to the odds ratios of nonfatal stroke and death.

## 4.4 Summary and Comment

Our base-case results suggest that the use of rivaroxaban (plus ASA) and icosapent ethyl (in patients receiving statins) both provide clinical benefit in terms of gains in quality-adjusted survival and overall survival compared to optimal medical management alone in the adult, established CVD cohort, and in the case of icosapent ethyl also for adults without known CVD but at high risk for cardiovascular events. This translated into incremental cost-effectiveness estimates that fell below commonly cited cost-effectiveness thresholds under the assumptions used in this analysis. The results were relatively robust to parameter uncertainties in the one-way and probabilistic sensitivity analyses. Further, the results were robust to a number of scenario analyses including the modified societal perspective and others. When comparing rivaroxaban + ASA to generic clopidogrel + ASA (DAPT), the incremental results were between $85,000 and $100,000 per QALY assuming plausible (but unknown) relative risks of major bleeding.

### Limitations

Our analyses had important limitations and assumptions. We assumed three-component major adverse cardiovascular events, MI, stroke, and cardiovascular death, to form the base-case health states within the model structure for both rivaroxaban and for icosapent ethyl. Acknowledging that other potential cardiovascular events are problematic to model due to potential double-counting and competing events, we did not cost out or apply disutilities to any other potential differences in cardiovascular events such as revascularization. This model structure was consistent with prior ICER evaluations within established CVD.[108] A scenario analysis that broadened major adverse cardiovascular events to include other events suggested similar but lower cost-effectiveness findings for icosapent ethyl. For all evaluated treatments, the evidence was more uncertain when quantifying the cumulative incidence of subsequent events as well as the relative impacts that the treatments had on subsequent events. Base-case assumptions held treatment-specific first-event relative reductions constant for subsequent events. Icosapent ethyl trial evidence suggested this assumption is appropriate or slightly conservative for the purposes of estimating cost effectiveness. Patient-level projections of trial evidence could aid in supporting or refuting our model assumptions surrounding ASA cumulative incidence of subsequent events as well as the relative impact of treatment.

An additional limitation of this analysis was the model calibration to the observed clinical trial event rates for optimal medical management. Many unknowns were a part of the model calibration exercise. We opted to calibrate the model to first MI, first stroke and cardiovascular

death. Alternative calibration options were tested with similar incremental lifetime findings (results not reported). Finally, it is important to note that randomized controlled trial findings may not generalize or translate to observed signals within the real world (i.e., efficacy does not equal effectiveness). Given that the cost-effectiveness findings relied on randomized controlled trials for estimates of clinical benefit and harm, the findings should be interpreted with caution when estimating whether these interventions would achieve similar value for money in actual practice.

## Conclusions

In conclusion, the findings of our analysis suggest that the additive CVD therapies of focus for this review provide gains in quality-adjusted survival and overall survival over optimal medical management. Assuming clinical signals within the trial hold for patients treated with these interventions and current net prices, the base-case results suggest that costs for treatment with either rivaroxaban or icosapent ethyl would fall below commonly cited thresholds for cost effectiveness. The results were relatively robust to sensitivity and scenario analyses. When comparing rivaroxaban + ASA to clopidogrel + ASA, the incremental results are more uncertain, but generally fall below $100,000/QALY.

# 5. Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. We also recognize that there may be broader contextual issues related to the severity of the condition, whether other treatments are available, and ethical, legal, or other societal priorities that influence the relative value of illnesses and interventions. These general elements are listed in the table below, and the subsequent text provides detail about the elements that are applicable to the comparisons of icosapent ethyl and rivaroxaban to optimal medical management. We sought input from stakeholders, including individual patients, patient advocacy organizations, clinicians, and manufacturers, to inform the contents of this section.

Each ICER review culminates in a public meeting of an independent voting Council of clinicians, patients, and health services researchers. As part of their deliberations, Council members will judge whether a treatment may substantially impact the considerations listed in Table 5.1. The presence of substantial other benefits or contextual considerations may shift a council member's vote on an intervention's long-term value for money to a different category than would be indicated by the clinical evidence and cost-effectiveness analyses alone. For example, a council member may initially consider a therapy with an incremental cost-effectiveness ratio of $150,000 per QALY to represent low long-term value for money. However, the Council member may vote for a higher value category if they consider the treatment to bring substantial other benefits or contextual considerations. Conversely, disadvantages associated with a treatment may lead a Council member to vote for a lower value category. A Council member may also determine that there are no other benefits or contextual considerations substantial enough to shift their vote. All factors that are considered in the voting process are outlined in ICER's value assessment framework. The content of these deliberations is described in the last chapter of ICER's Final Evidence Report, which is released after the public meeting.

This section, as well as the Council's deliberation, provides stakeholders with information to inform their decisions on a range of issues, including shared decision-making between patients and clinicians, coverage policy development, and pricing negotiations.

**Table 5.1. Potential Other Benefits or Contextual Considerations (Not Specific to Any Disease or Therapy)**

| Potential Other Benefits |
|---|
| This intervention offers reduced complexity that will significantly improve patient outcomes. |
| This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories. |
| This intervention will significantly reduce caregiver or broader family burden. |
| This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed. |
| This intervention will have a significant impact on improving return to work and/or overall productivity. |
| Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention. |
| **Potential Other Contextual Considerations** |
| This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life. |
| This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness. |
| This intervention is the first to offer any improvement for patients with this condition. |
| Compared to optimal medical management alone, there is significant uncertainty about the long-term risk of serious side effects of this intervention. |
| Compared to optimal medical management alone, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention. |
| There are additional contextual considerations that should have an important role in judgments of the value of this intervention. |

## 5.1 Potential Other Benefits

The majority of patients in the target populations for icosapent ethyl and rivaroxaban (i.e., established CVD or patients with multiple risk factors for CVD) are older individuals already taking multiple classes of medication for risk factor control. Accordingly, we see the potential for *increased* treatment complexity and patient/family burden rather than reductions.

Because both agents represent new mechanisms of action, they represent important treatment options that may be complementary to existing treatment mechanisms (e.g., PCSK9 inhibition), and may offer benefit if adherence to existing treatment is sub-optimal. They also appear to offer further risk reductions in patients already optimally managed on other medications, however, an important consideration given the high residual risk of cardiovascular events in those with established disease.

There are no expected benefits with regard to reduction in disparities, return to work, or other aspects of disease management and treatment.

## 5.2 Contextual Considerations

As noted previously, CVD is both prevalent and associated with a high lifetime burden of illness. In addition, both icosapent ethyl and rivaroxaban were studied in CVD populations at particularly high risk of recurrent events, suggesting a significant level of unmet need. That being said, utilization of these therapies may ultimately include lower-risk individuals, with risk-benefit tradeoffs that are more uncertain.

While icosapent ethyl and rivaroxaban represent new treatment mechanisms for CVD, there are multiple other options available, including antithrombotics and multiple classes of lipid-lowering agents and antihypertensives, many of which are available in generic form. The incremental benefit of adding either of these two treatments to current medical management relative to adding another relatively new treatment such as a PCSK9 inhibitor is unclear, as are the potential benefits of all of these agents in combination.

The Phase III COMPASS trial of rivaroxaban was stopped early due to evidence of clinical benefit, so the evidence base is limited to a median of approximately two years of follow-up. While this introduces a fair degree of uncertainty to the assessment of long-term clinical benefits, uncertainty around long-term risks is likely greater. For example, guideline statements for long-term use of dual antiplatelet therapy use cautionary language specifically because of the relatively short-term nature of clinical trials and concerns regarding bleeding risks over the long-term.[109] In contrast, the Phase III REDUCE-IT trial of icosapent ethyl included a median of nearly five years of follow-up. Residual uncertainty among the clinical community is primarily focused on the poor previous track record of other omega-3-based products in reducing cardiovascular risks.

The benefits of rivaroxaban were robust among most patient subgroups, except for the very elderly (≥75 years) as well as those with PAD only and without baseline dyslipidemia, although these were small subsets of the COMPASS trial.[21] Similarly, icosapent ethyl's effects were relatively consistent across subgroups, although the 95% confidence interval around the hazard ratio estimate did include 1.0 in primary-prevention patients, those receiving ezetimibe, and patients with baseline triglycerides <150 mg/dL; again, the latter two subsets were quite small.[9] As mentioned above, however, the major challenge in interpretation of the trial data is in generalizability, as patients were at very high risk of recurrent CVD events and optimally managed on current therapy, conditions unlikely to be replicated with real-world use.

# 6. Value-Based Price Benchmarks

Annual value-based price benchmarks (VBPBs) of rivaroxaban and icosapent ethyl are presented in Table 6.1. The value-based benchmark price for a drug is defined as the price range that would achieve incremental cost-effectiveness ratios between $100,000 and $150,000 per QALY (or evLYG) gained.

For rivaroxaban, price changes of approximately 4% discount to 39% over the list price (WAC) would be required to reach the $100,000 to $150,000 per QALY threshold prices, respectively. For icosapent ethyl, prices approximately 70% to 149% above WAC would achieve $100,000 to $150,000 per QALY threshold prices (Table 6.1).

**Table 6.1. Value-Based Price Benchmarks for Rivaroxaban and Icosapent Ethyl**

| | Annual WAC | Annual Price at $100,000 Threshold | Annual Price at $150,000 Threshold | Change from WAC to Reach Threshold Prices |
|---|---|---|---|---|
| **Rivaroxaban** | | | | |
| **Per QALY Gained** | $5,457 | $5,223 | $7,597 | -4% to +39% |
| **Per evLYG** | | $5,369 | $7,780 | -2% to +43% |
| **Icosapent Ethyl** | | | | |
| **Per QALY Gained** | $3,699 | $6,282 | $9,204 | +70% to +149% |
| **Per evLYG** | | $6,501 | $9,423 | +76% to +155% |

WAC: wholesale acquisition cost; evLYG: equal value life year gained; QALY: quality-adjusted life year

We are including results for price per evLYG to ensure that policymakers are aware of the complementary information these results can provide to the cost per QALY findings. The annual price at which rivaroxaban meets the $100,000 to $150,000 per evLYG range for use in these patients is $5,369 to $7,780. For icosapent ethyl, the relevant cost per evLYG price range is $6,501 to $9,423 for the $100,000 to $150,000 per evLYG thresholds. The cost per evLYG price range is quite similar to the cost per QALY range for both rivaroxaban and icosapent ethyl.

# 7. Potential Budget Impact

## 7.1 Overview

We used the cost-effectiveness model to estimate the potential total budgetary impacts of rivaroxaban and icosapent ethyl as additive therapies to optimal medical management in patients (age ≥20) with established CVD, and in the case of icosapent ethyl, also in patients without evidence of CVD but with diabetes (age ≥50) and at least one additional risk factor.

## 7.2 Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new technology for the eligible population in this indication, calculated as differential health care costs (including drug costs) minus any offsets in these costs from avoided treatments and averted health care events. We assumed that patients matching those in the respective trials would be eligible for rivaroxaban and icosapent ethyl. All costs were undiscounted and estimated over a five-year time horizon, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with these new therapies.

For rivaroxaban, to estimate the size of the eligible prevalent population, we used a baseline estimate for CAD of 6.7% of the US population (age≥20) based on a recent update from the AHA in conjunction with the National Institutes of Health and other agencies.[2] We then applied this estimate to the average of the projected 2019 to 2023 US population (age≥20) to derive the eligible population over the next five years. This resulted in an eligible population size for rivaroxaban of approximately 16,908,000 patients over five years, or an estimated 3,385,000 patients each year.

For icosapent ethyl, to estimate the secondary prevention group, we used the same baseline estimate for CAD of 6.7% of the US population (age≥20).[2] In addition, we accounted for the prevalence of patients with stroke (2.5%).[2] To estimate the primary prevention population with diabetes and one additional risk factor, we used an estimate of diabetes mellitus prevalence in the US population of 9.8%[2] and assumed 87% of these patients would have an additional risk factor, based on the estimated proportion of diabetes patients with metabolic syndrome.[110] We applied these estimated proportions for patients in the secondary prevention group and for patients of age ≥50 years in the primary prevention group to the projected average of the 2019 to 2023 US population to derive the estimated eligible population over the next five years. This resulted in an eligible population size for icosapent ethyl of approximately 33,522,000 patients over five years, or an estimated 6,704,000 patients each year.

ICER's methods for estimating potential budget impact are described in detail elsewhere[111] and have been recently updated. ICER recalculates the potential budget impact threshold each

calendar year, using the most recent inputs available. In the recalculation of ICER's potential budget impact threshold for calendar year 2019, we extended the time period over which we average the annual number of drugs approved by the FDA from two to five years to reduce fluctuations in the threshold due to this variable. The intent of our revised approach to budgetary impact is to document the percentage of patients who could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy. For 2019-2020, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $819 million per year for new drugs.

To estimate potential budget impact, we evaluate a new therapy that would take market share from one or more existing therapies and calculate the blended budget impact associated with displacing use of existing therapies with the new intervention. For this analysis, we evaluated the potential budget impact of rivaroxaban and icosapent ethyl as additive therapies to optimal medical management in patients with established CVD, and in the case of icosapent ethyl, also in patients without evidence of CVD but with diabetes and at least one additional risk factor. For each treatment, we assumed equal uptake over five years, with treatment duration ranging from one year (for the year-five cohort) to five years (for the year-one cohort). In other words, patients initiating therapy in year one would accrue all drug costs and cost offsets over the full five years, but those initiating in other years would only accrue a proportional amount of the five-year costs. Note that the purpose of these analyses is to estimate the *potential* budget impact, not to predict actual uptake or expected budget impact.

## 7.3 Results

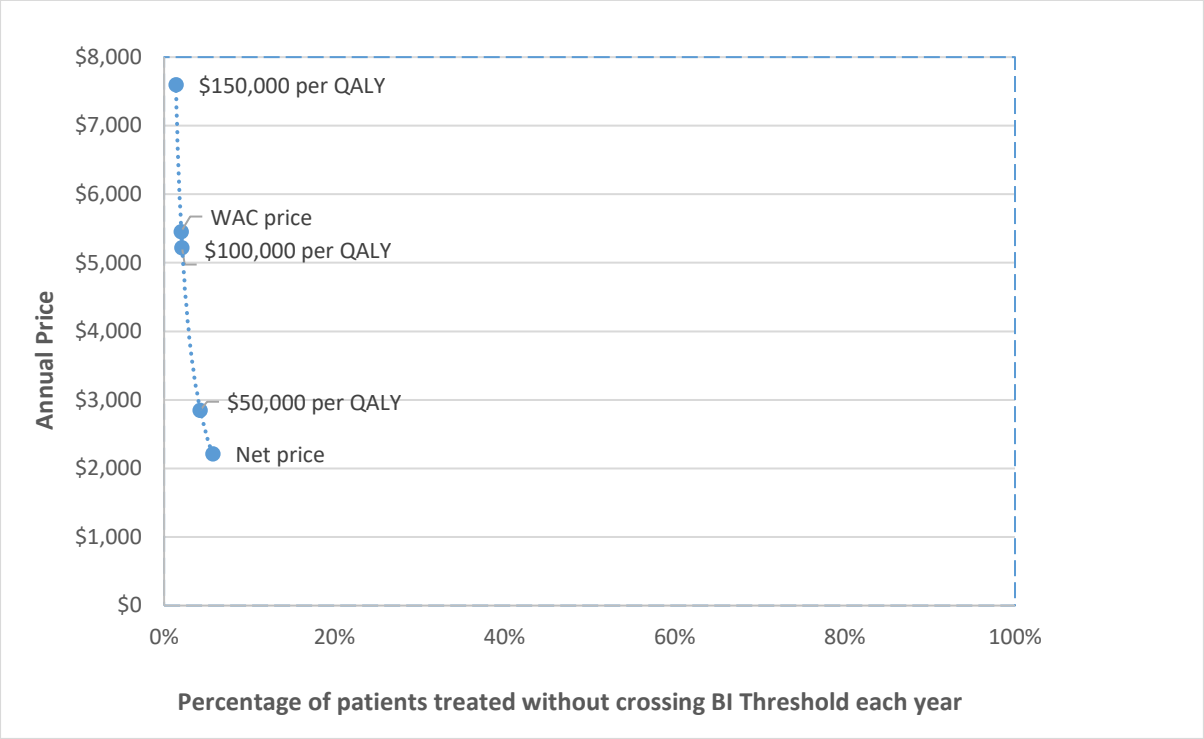
For rivaroxaban, per-patient budget impact calculations are based on the WAC price of $5,457 per year, the net price of $2,215 per year, and the prices to reach $150,000, $100,000, and $50,000 per QALY thresholds (at $7,597, $5,223, and $2,849 per year, respectively).

The average five-year annualized per patient potential budgetary impact when using the WAC price and the net price were approximately $3,800 and $1,450, respectively. The average five-year annualized potential budgetary impact at the three cost-effectiveness threshold prices ranged from approximately $5,900 per patient using the annual price to achieve $150,000 per QALY to approximately $2,000 using the annual price to achieve a $50,000 per QALY cost-effectiveness threshold.

As shown in Figure 7.1, the ICER budget impact threshold of $819 million would be crossed if greater than approximately 2% of eligible patients were treated in a given year with rivaroxaban at the WAC price. When using the net price, the threshold would be reached when approximately 6% of eligible patients were treated in a given year with rivaroxaban. Approximately 1%, 2% and 4% of patients could be treated in a given year without crossing the budget impact threshold at the $150,000, $100,000, and $50,000 per QALY threshold prices. Although the per patient budget impact is relatively small, due to the very large population of

patients potentially eligible for treatment, the threshold is reached even at prices that would meet standard cost-effectiveness thresholds.

**Figure 7.1. Potential Budget Impact of Rivaroxaban at Various Prices**

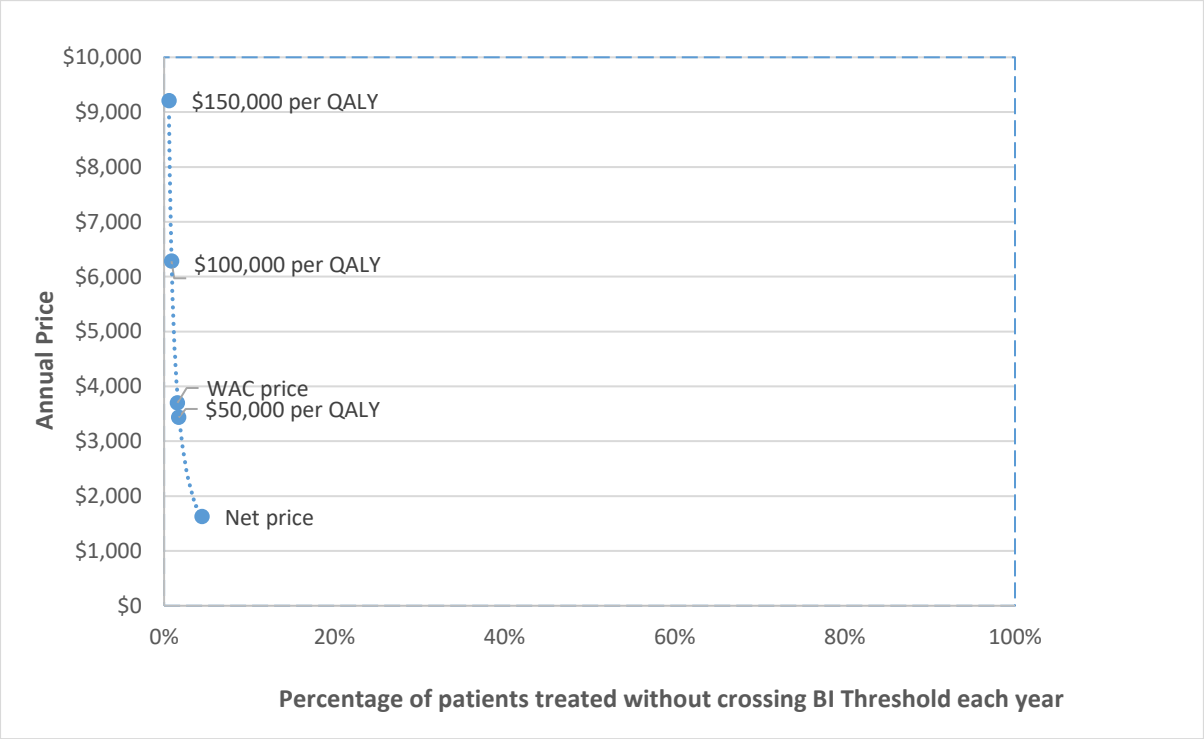



For icosapent ethyl, per-patient budget impact calculations are based on the WAC price of $3,699 per year, the net price of $1,625 per year, and the prices to reach $150,000, $100,000, and $50,000 per QALY thresholds (at $9,204, $6,282, and $3,433 per year, respectively).

The average five-year annualized per patient potential budgetary impact when using the WAC price and the net price were approximately $2,500 and $960, respectively. The average five-year annualized potential budgetary impact at the three cost-effectiveness threshold prices ranged from approximately $7,200 per patient using the annual price to achieve $150,000 per QALY to approximately $2,450 using the annual price to achieve a $50,000 per QALY cost-effectiveness threshold.

As shown in Figure 7.2, the ICER budget impact threshold of $819 million would be crossed if greater than approximately 2% of eligible patients were treated in a given year with icosapent ethyl at the WAC price. When using the net price, the threshold would be reached if approximately 4% of eligible patients were treated in a given year with icosapent ethyl. Between 1% and 2% of patients could be treated in a given year without crossing the budget impact threshold at the $150,000, $100,000, and $50,000 per QALY threshold prices. As with rivaroxaban, the relatively small budget impact per patient, when combined with the very large population of patients potentially eligible for treatment, has the potential to exceed the budget impact threshold.

**Figure 7.2. Potential Budget Impact of Icosapent Ethyl at Various Prices**




## 7.4 Access and Affordability Alert

ICER is issuing an access and affordability alert for both rivaroxaban and icosapent ethyl. For rivaroxaban, at the net price of $2,215 per year, approximately 6% of eligible patients could be treated in a given year without crossing the ICER potential budget impact threshold of $819 million, while clinical experts at the Public Meeting stated that they would consider using rivaroxaban in approximately 30% of eligible patients. For icosapent ethyl, at the net price of $1,625 per year, approximately 4% of eligible patients could be treated in a given year without crossing the ICER potential budget impact threshold of $819 million. Clinical experts stated at the Public Meeting that they believe that the majority of eligible patients would want to be on icosapent ethyl. The purpose of an ICER affordability and access alert is to signal to stakeholders and policy makers that the amount of added health care costs associated with a new service may be difficult for the health care system to absorb over the short term without displacing other needed services or contributing to rapid growth in health care insurance costs. Thus, there is a risk to sustainable access to high-value care for all patients if managing these issues is not appropriately planned for.

# 8. Summary of the Votes and Considerations for Policy

## 8.1 About the Midwest CEPAC Process

During Midwest CEPAC public meetings, the Midwest CEPAC Panel deliberates and votes on key questions related to the systematic review of the clinical evidence, an economic analysis of the applications of treatments under examination, and the supplementary information presented. Panel members are not pre-selected based on the topic being addressed and are intentionally selected to represent a range of expertise and diverse perspectives.

Acknowledging that any judgment of evidence is strengthened by real-life clinical and patient perspectives, subject matter experts are recruited for each meeting topic and provide input to Midwest CEPAC Panel members before the meeting to help clarify their understanding of the different interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the Midwest CEPAC Panel during their deliberation and help to shape recommendations on ways the evidence can apply to policy and practice.

After the Midwest CEPAC Panel votes, a policy roundtable discussion is held with the Midwest CEPAC Panel, clinical experts, patient advocates, payers, and when feasible, manufacturers. The goal of this discussion is to bring stakeholders together to apply the evidence to guide patient education, clinical practice, and coverage and public policies. Participants on policy roundtables are selected for their expertise on the specific meeting topic, are different for each meeting, and do not vote on any questions.

At the September 26, 2019 meeting, the Midwest CEPAC Panel discussed issues regarding the application of the available evidence to help patients, clinicians, and payers address important questions related to the use of rivaroxaban and icosapent ethyl. Following the evidence presentation and public comments (public comments from the meeting can be accessed [https://www.youtube.com/watch?v=2LFCTqW_hSc&feature=youtu.be], starting at minute [1:28:55]), the Midwest CEPAC Panel voted (votes from the meeting can be accessed [https://www.youtube.com/watch?v=ATMvwRQ_RPk&feature=youtu.be], starting at minute [0:02:23]), on key questions concerning the comparative clinical effectiveness, and potential other benefits and contextual considerations related to rivaroxaban and icosapent ethyl. These questions are developed by the ICER research team for each assessment to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice, medical policy decisions, and patient decision-making. The voting results are presented below, along with specific considerations mentioned by Midwest CEPAC Panel members during the voting process.

In its deliberations and votes related to value, the Midwest CEPAC Panel considered the individual patient benefits, and incremental costs to achieve such benefits, from a given intervention over the long term.

There are four elements to consider when deliberating on long-term value for money (see Figure 8.1 below):

- Comparative clinical effectiveness is a judgment of the overall difference in clinical outcomes between two interventions (or between an intervention and placebo), tempered by the level of certainty possible given the strengths and weaknesses of the body of evidence. Midwest CEPAC uses the ICER Evidence Rating Matrix as its conceptual framework for considering comparative clinical effectiveness.

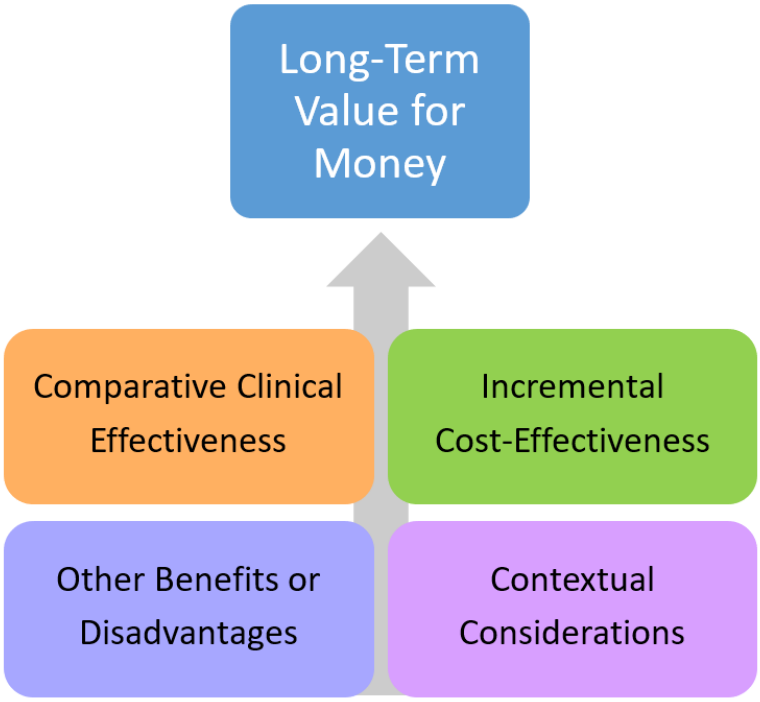
- Estimated incremental cost effectiveness is the average incremental cost per patient of one intervention compared to another to achieve a desired "health gain," such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms of cost per unit of effectiveness, and the resulting comparison is presented as a cost-effectiveness ratio. Relative certainty in the cost and outcome estimates continues to be a consideration. As a measure of cost effectiveness, the Midwest CEPAC voting panel follows common academic and health technology assessment standards by using cost per quality-adjusted life year (QALY), with formal voting on "long-term value for money" when the base-case incremental cost-effectiveness ratio is between $50,000 per QALY and $175,000 per QALY.

- Potential other benefits refer to any significant benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples of potential other benefits include better access to treatment centers, mechanisms of treatment delivery that require fewer visits to the clinician's office, treatments that reduce disparities across various patient groups, and new potential mechanisms of action for treating clinical conditions that have demonstrated low rates of response to currently available therapies. Other disadvantages could include increased burden of treatment on patients or their caregivers. For each intervention evaluated, it will be open to discussion whether potential other benefits or disadvantages such as these are important enough to factor into the overall judgment of long-term value for money. There is no quantitative measure for potential other benefits or disadvantages.

- Contextual considerations include ethical, legal, or other issues (but not cost) that influence the relative priority of illnesses and interventions. Examples of contextual considerations include whether there are currently any existing treatments for the condition, whether the condition severely affects quality of life or not, and whether

there is significant uncertainty about the magnitude of benefit or risk of an intervention over the long term. There is no quantitative measure for contextual considerations.

**Figure 8.1. Conceptual Structure of Long-term Value for Money**




## 8.2 Voting Results

### Midwest CEPAC Votes

***Clinical Evidence***

**a) Is the evidence adequate to demonstrate that the net health benefit of rivaroxaban plus ASA is superior to that provided by ASA alone?**

| | |
|---|---|
| ***Yes: 10 votes*** | No: 1 vote |

A majority of the Council determined that the evidence was adequate to demonstrate that the net health benefit of rivaroxaban plus ASA is superior to that provided by ASA alone**.**

The Council member who voted in the negative was concerned that the absolute difference between the two options was quite small, and there is no certainty that the benefit would be maintained over a lifetime. In addition, given the inclusion criteria in the COMPASS trial, the bleeding risk of patients in the trial is likely substantially lower than that of patients in the real world.

**b) Is the evidence adequate to demonstrate that the net health benefit of rivaroxaban plus ASA is superior to that provided by ASA as part of dual antiplatelet therapy (DAPT) with an oral $P2Y_{12}$ inhibitor (e.g., ticagrelor or clopidogrel)?**

| | |
|---|---|
| Yes: 0 votes | ***No: 11 votes*** |

The Council unanimously judged that the evidence was inadequate to demonstrate a superior net health benefit of rivaroxaban plus ASA compared to that provided by ASA as part of dual antiplatelet therapy (DAPT) with an oral $P2Y_{12}$ inhibitor (e.g., ticagrelor or clopidogrel) in patients with cardiovascular disease**.** Given the lack of head-to-head trials and the different ways that bleeding was measured across trials, panelists concluded there was not yet evidence to make a determination on rivaroxaban plus ASA compared to DAPT.

**c) Is the evidence adequate to demonstrate that the net health benefit of icosapent ethyl added to optimal medical management (including statin therapy) is superior to that provided by optimal medical management (including statin therapy) alone?**

| | |
|---|---|
| ***Yes: 9 votes*** | No: 2 votes |

A majority of the Council determined that the evidence was adequate to demonstrate a net health benefit of icosapent ethyl added to optimal medical management (including statin therapy)**.**

The Council members who voted in the negative expressed concerns regarding the unexpected results in the REDUCE-IT trial compared to the many previous studies investigating fish oil that showed no benefit to cardiovascular health, and questioned whether these results could be replicated. One council member argued that the potential benefit of icosapent ethyl is relatively small when considering absolute effects. The other dissenting voter was concerned about the confounding factor of mineral oil being used in the placebo arm and potentially inflating the results. Council members did discuss the specific DHA and EPA composition of icosapent ethyl as it compares with other fish oil interventions currently on the market, as this composition may be responsible for the divergent results produced by the REDUCE-IT trial. However, they agreed that additional study is required to gain any certainty on this question.

*Other Benefits and Disadvantages, and Contextual Considerations*

**d) Does treating patients with rivaroxaban plus ASA offer one or more of the following potential "other benefits or disadvantages" compared to ASA alone? (Select all that apply).**

| | |
|---|---|
| This intervention will significantly reduce caregiver or broader family burden. | **1/11** |
| This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed. | **6/11** |
| This intervention will have a significant impact on improving patients' ability to return to work and/or their overall productivity. | **1/11** |
| There are other important benefits or disadvantages that should have an important role in judgements of the value of this intervention. | No vote |

Approximately half of the council judged that treating patients with rivaroxaban plus ASA offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed. One Council member felt that treating patients with rivaroxaban plus ASA will significantly reduce caregiver or broader family burden, and one member voted that it will have a significant impact on improving patients' ability to return to work and/or their overall productivity. Prior to voting, one Council member reiterated that, given the inclusion criteria in the COMPASS trial, the bleeding risk of patients in the trial is likely substantially lower than that of patients in the real world. The Council decided that this issue pertains to generalizability and clinical effectiveness and does not represent an important disadvantage that should have an important role in judgements of the value of this intervention. Another council member mentioned that rivaroxaban's introduction to the market could increase the decision-making burden for patients and caregivers, as it is a potential addition to patients' already long and complex list of drug therapies. However, the Council agreed that this is not a disadvantage specific to rivaroxaban plus ASA. No other important benefits or disadvantages were raised, and the council did not vote on the final question.

**e) Does treating patients with icosapent ethyl offer one or more of the following potential "other benefits or disadvantages" compared to optimal medical management (including statin therapy) alone? (Select all that apply).**

| | |
|---|---|
| This intervention will significantly reduce caregiver or broader family burden. | 0/11 |
| This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed. | **7/11** |
| This intervention will have a significant impact on improving patients' ability to return to work and/or their overall productivity. | 0/11 |
| There are other important benefits or disadvantages that should have an important role in judgements of the value of this intervention. | No vote |

Approximately half of the Council judged that treating patients with icosapent ethyl offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed. One Council member stated his opinion that icosapent ethyl may offer a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed; however, due to the nature of cardiovascular disease, it likely will not significantly reduce caregiver burden or have a significant impact on improving patients' ability to return to work.

**f) Are any of the following contextual considerations important in assessing the long-term value for money of rivaroxaban plus ASA? (Select all that apply).**

| | |
|---|---|
| This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life. | **6/11** |
| This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness. | **6/11** |
| There is significant uncertainty about the long-term risk of serious side effects of this intervention. | **9/11** |
| There is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention. | **9/11** |
| There are additional contextual considerations that should have an important role in judgements of the value of this intervention. | **No vote** |

The Council considered cardiovascular disease to represent a condition of high severity with a high lifetime burden of illness. One Council member noted the particularly large proportion of Americans diagnosed with cardiovascular disease compared with those affected by other, less prevalent diseases, as a possible contextual consideration of this intervention. Most Council members agreed that there is significant uncertainty about the long-term risk of serious side effects and the magnitude or durability of the long-term benefits of rivaroxaban plus ASA. Bleeding risk is one long-term serious side effect that can change with age and comorbidity status. Although the Council did not vote on additional contextual considerations, members noted that less than 1% of participants in the COMPASS trial self-identified as black Americans, a population that is at greater risk for cardiovascular disease and stroke than white Americans. They also discussed rivaroxaban plus ASA's potential for good in large populations, as well as its potential for harm.

**g) Are any of the following contextual considerations important in assessing the long-term value for money of icosapent ethyl? (Select all that apply).**

| | |
|---|---|
| This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life. | **6/11** |
| This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness. | **6/11** |
| There is significant uncertainty about the long-term risk of serious side effects of this intervention. | **5/11** |
| There is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention. | **7/11** |
| There are additional contextual considerations that should have an important role in judgements of the value of this intervention. | No vote |

The Council considered cardiovascular disease to represent a condition of high severity with a high lifetime burden of illness. Five Council members voted that there is significant uncertainty about the long-term risk of serious side effects and the magnitude or durability of the long-term benefits of icosapent ethyl .

***Long-Term Value for Money***

As described in ICER's value assessment framework, questions on long-term value for money are subject to a value vote when incremental cost-effectiveness ratios for the interventions of interest are between $50,000 and $175,000 per QALY in the primary "base-case" analysis. The base-case estimates of the cost per QALY for both rivaroxaban + ASA and icosapent ethyl are below the lower end of this range, and therefore the treatment is deemed "high long-term value for money" without a vote unless the CEPAC determines in its discussion that the Evidence Report base-case analysis does not adequately reflect the most probable incremental cost-effectiveness ratio for either treatment.

ICER's value assessment framework also describes that the CEPAC does not take Long-Term Value For Money votes on treatments for which the evidence is considered inadequate during the Clinical Vote. Such is the case for rivaroxaban + ASA versus DAPT therapy. Thus, no Value vote was taken for rivaroxaban + ASA versus DAPT therapy (e.g. clopidogrel).

## 8.3 Roundtable Discussion and Key Policy Implications

Following its deliberation on the evidence, the Midwest CEPAC Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on rivaroxaban and icosapent ethyl to policy and practice associated with the treatment of CVD. The policy roundtable members included two patients, two clinical experts, two payers, and one representative from a pharmaceutical manufacturer. discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. The names of the Policy Roundtable participants are shown below, and conflict of interest disclosures for all meeting participants can be found in Appendix G.

**Table 8.3 Policy Roundtable Members**

| Name | Title and Affiliation |
|---|---|
| **Andrea Baer, MS, BCPA** | Executive Director, Mended Hearts |
| **Chester "Bernie" Good, MD, MPH** | Senior Medical Director, UPMC Health Plan |
| **Craig Granowitz, MD, PhD** | Senior Vice President, Chief Medical Officer, Amarin Corporation |
| **Kayla Leeser, PharmD** | Clinical Pharmacist, IngenioRx |
| **Jeremy Sussman, MD, MS** | Associate Professor, University of Michigan |
| **Marie Warshauer, MS** | Support Network |
| **Jason Wasfy, MD** | Director of Quality and Analytics, Massachusetts General Hospital Heart Center |

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

## Payers

***1. Evidence to compare rivaroxaban to dual-action platelet therapy (DAPT) plus aspirin is limited by lack of head-to-head trials and differing outcome measures. Additionally, clinical experts do not view these two treatment options as interchangeable given their different mechanisms of action and risk profiles, therefore DAPT should not be considered an appropriate candidate in a step therapy protocol as a first step prior to receiving coverage for rivaroxaban.***

Although subgroups in trials of rivaroxaban were comparable to some trial populations in which DAPT was evaluated, looking at these subgroups limited the population size and increased imprecision in results. Additionally, bleeding outcomes were reported differently and were not comparable. ICER concluded the evidence was insufficient to compare the net benefits of rivaroxaban and DAPT.

***Other considerations for key prior authorization criteria for rivaroxaban are shown below:***

**Patient Eligibility Criteria**:

a. **Severity of disease:** The FDA indication for rivaroxaban allows for treatment in a broader population than the high-risk patients enrolled in COMPASS, yet there is no strong evidence-based approach to defining a narrower set of eligibility criteria for coverage.

b. **Bleeding risk**: Patients at high risk of major bleeding were excluded from the COMPASS trial of rivaroxaban. Payers might consider instituting coverage criteria requiring clinicians to attest that patients have not had a prior major bleed and/or are not currently at high risk for future bleeds. However, balancing bleeding risk with CV event

risk needs to be an individualized decision, and payers may wish to frame coverage language without any determination of bleeding risk.

**Provider Criteria:**

1) Specialist prescribing should not be viewed as a necessary part of a coverage policy. While payers might consider limiting prescribing to cardiologists or in consultation with a cardiologist, many non-specialists have experience prescribing rivaroxaban for conditions such as atrial fibrillation, deep venous thrombosis, and pulmonary embolism. The dose of rivaroxaban for CV risk reduction is much lower than that used for these other conditions, and so non-specialists may be comfortable prescribing rivaroxaban for this indication as well.

***2. Icosapent ethyl has not yet received FDA approval and therefore the specific language of the label is unknown. While awaiting the FDA decision, payers should consider parameters of coverage criteria related to the eligibility criteria of the pivotal trial: a) definition of risk for coronary artery disease; b) concurrent use of statins; and c) triglyceride level of 135-499 mg/dL.***

a. **Definition of risk of CAD:** Patients in the REDUCE-IT trial were required to either have established CVD or be 50 or older with diabetes and at least one additional risk factor. Many primary prevention patients would have a constellation of risk factors creating a similar risk to that in the primary prevention cohort of the trial, and the evidence does not strongly support the use of the specific trial criteria around risk. Payers may wish to consider coverage criteria based on total risk rather than based on the trial criteria.

b. **Concurrent use of statins:** The REDUCE-IT trial required patients to be on a stable dose of a statin and to have an LDL-cholesterol level of 41-100 mg/dL. Given uncertainties around the mechanism of benefit of icosapent ethyl and whether it would be effective in patients not receiving statins, payers may consider requiring that patients be taking statin therapy when prescribed icosapent ethyl. Payers face a challenging situation for patients who are statin intolerant—they could limit eligibility, or they could use this as an opportunity to get patients on a statin, since many patients felt to be statin "intolerant" are able to take statins with appropriate clinical support.

c. **Triglyceride level greater than 135**: The REDUCE-IT trial did not suggest that the benefits of icosapent ethyl were related to baseline triglyceride level, and other evidence has also suggested that therapies that reduce triglycerides do not necessarily reduce CV risk. As such, there is no strong reason to believe that icosapent ethyl is more effective at reducing CV risk for patients with triglyceride levels meeting the entry criteria for the trial. While payers could decide to limit icosapent ethyl coverage to match the trial eligibility criteria, if the FDA label does not include a triglyceride level requirement, then plans may choose also not to have a criterion related to triglyceride level.

## Providers

***3. Clinicians, when thinking about the apparent benefit of rivaroxaban in the clinical trial, should remember that patients at high risk of bleeding were excluded.***

Clinicians should individualize decisions about adding treatments that decrease CV risk but increase risk of bleeding based on patients' individual risks for these events. Patients at high risk of bleeding are likely to have a different net benefit from what was seen in the COMPASS trial of rivaroxaban.

***4. Develop options to help patients navigate complex medication regimens.***

Patients with CVD are already treated with many medications each with their own regimens and side effects. Medications include statins, aspirin or DAPT, angiotensin-converting-enzyme (ACE) inhibitors, beta blockers, and potentially many more medications for comorbidities such as diabetes. In this milieu, adding one or two additional therapies may be overwhelming for patients. Shared decision making and patient support through education, caregivers, and potentially the use of health coaches may assist in mitigating the cognitive and emotional burden on patients from having so many therapies to manage.

## Clinical and Specialty Societies

***5. Develop a decision algorithm and/or tool for clinicians to use in determining the most appropriate additive therapies to consider for a given patient.***

In addition to the therapies evaluated in this report, treatments that can be considered for residual CV risk include PCSK9 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors, among others. There is overlap in the populations eligible for many of these therapies, and evidence-based guidance around how to order considerations of these treatments for different patients could standardize decision making and improve outcomes.

***6. Ensure that any clinical guideline statements regarding rivaroxaban clearly warn against assuming a class effect for direct oral anticoagulants.***

While there are other direct oral anticoagulants (DOACs) available on the market, none currently share rivaroxaban's indication for prevention of cardiovascular events. The DOACs also vary significantly in terms of dosing, and an observational study conducted in a Medicare population suggests that the benefit-risk profile of these agents also differs when used for stroke prevention in atrial fibrillation.[112] Clinical societies should therefore direct clinicians to consider only low-dose rivaroxaban for cardioprotection until similar evidence is available for other DOACs.

## Manufacturers

***7. Conduct additional studies of icosapent ethyl in patients not on statin therapy.***

Given the nature and findings of REDUCE-IT, payers may require patients to be on statin therapy concurrently with icosapent ethyl. Yet many patients, if not strictly statin-intolerant, are unwilling to take statins, and such a requirement might exacerbate this problem and prevent some patients from receiving what could be a promising intervention. The manufacturer should conduct additional clinical trials to assess the clinical performance of icosapent ethyl in patients not receiving statins.

***8. Ensure that future trial recruitment reflects the demographics of the CVD population.***

COMPASS and REDUCE-IT were large, multicenter clinical trials, yet trial patients were not reflective of the CVD population at large in important ways. For example, African Americans are 35% more likely to develop CVD than their white counterparts[113] and have rates of stroke that are twice as high.[114] Yet only 1% of COMPASS participants were black. Enrollment of more representative CVD populations will not only increase generalizability but can also potentially provide reassurance that treatment effects persist across appropriately sized and pre-specified subgroups.

## Regulators

***9. The FDA, manufacturers, and the clinical research community should work to solidify a common, single, outcomes definitions for key outcomes -- such as major bleeding -- so clinicians and patients have the information they need to make informed decisions.***

As noted in the report and discussed during the roundtable, standard definitions of key outcomes such as major bleeding have been developed, yet they have been modified to such an extent that formal indirect comparisons of results from clinical trials of competing treatment options were not possible. This represents a disservice to patients and clinicians, who need to understand how to best weigh the risks and benefits of the alternatives available to them. Given that these standard definitions exist, regulators, manufacturers, and the research community should come together to identify a core outcome definition that can be used across trials and treatments.

## Researchers

***10. Researchers should develop explicit head-to-head evidence of the comparative benefits and risks of rivaroxaban + ASA versus dual antiplatelet therapy in patients who have completed an initial course of DAPT (12-30 months).***

There is an important need for head-to head comparative analyses of DAPT and rivaroxaban + ASA. Prolonged use (i.e., 12-30 months) of dual antiplatelet therapy (DAPT) after an MI is currently standard clinical practice. After an initial course of DAPT, some patients may benefit

from indefinite treatment. However, low-dose rivaroxaban + ASA is also now a potential option rather than ongoing DAPT. How the balance of clinical benefits and bleeding risks compares between these two alternatives is an open question in the absence of direct comparative evidence. Subtle but important factors in populations presenting for treatment might introduce selection bias in an observational setting, therefore an observational analysis is unlikely to provide persuasive findings and a randomized trial is needed. The Patient-Centered Outcomes Research Institute (PCORI) or the National Institute of Health (NIH) are well-suited to sponsor this kind of trial to provide critical information for clinicians and patients that will remain unanswered otherwise.

***11. Researchers should conduct a real-world observational study to confirm the benefits of icosapent ethyl.***

The results of REDUCE-IT, while impressive, have not eliminated uncertainty regarding the potential effects of the placebo composition in the trial, as well as the largely unimpressive evidence from prior omega-3 studies. In addition, the FDA is unlikely to require a second confirmatory clinical trial for this indication. A rigorous prospective observational study of icosapent ethyl that had results consistent with those seen in the REDUCE-IT trial would help alleviate concerns, while a conflicting result would suggest the need for a second randomized trial.

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This is the first ICER review of rivaroxaban and icosapent ethyl for CVD.

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# APPENDICES

# Appendix A. Search Strategies and Results

**Table A1. PRISMA 2009 Checklist**

| | # | Checklist Item |
|---|---|---|
| **TITLE** | | |
| **Title** | 1 | Identify the report as a systematic review, meta-analysis, or both. |
| **ABSTRACT** | | |
| **Structured Summary** | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. |
| **INTRODUCTION** | | |
| **Rationale** | 3 | Describe the rationale for the review in the context of what is already known. |
| **Objectives** | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). |
| **METHODS** | | |
| **Protocol and Registration** | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. |
| **Eligibility Criteria** | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. |
| **Information Sources** | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. |
| **Search** | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. |
| **Study Selection** | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). |
| **Data Collection Process** | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. |
| **Data Items** | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. |
| **Risk of Bias in Individual Studies** | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. |

| | # | Checklist Item |
|---|---|---|
| **Summary Measures** | 13 | State the principal summary measures (e.g., risk ratio, difference in means). |
| **Synthesis of Results** | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. |
| **Risk of Bias across Studies** | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). |
| **Additional Analyses** | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. |
| **RESULTS** | | |
| **Study Selection** | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. |
| **Study Characteristics** | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. |
| **Risk of Bias within Studies** | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). |
| **Results of Individual Studies** | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. |
| **Synthesis of Results** | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. |
| **Risk of Bias across Studies** | 22 | Present results of any assessment of risk of bias across studies (see Item 15). |
| **Additional Analysis** | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). |
| **DISCUSSION** | | |
| **Summary of Evidence** | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). |
| **Limitations** | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). |
| **Conclusions** | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. |
| **FUNDING** | | |
| **Funding** | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. |

**From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097**

**Table A2. Search Strategy of MEDLINE and Cochrane Central Register of Controlled Trials (via Ovid)***

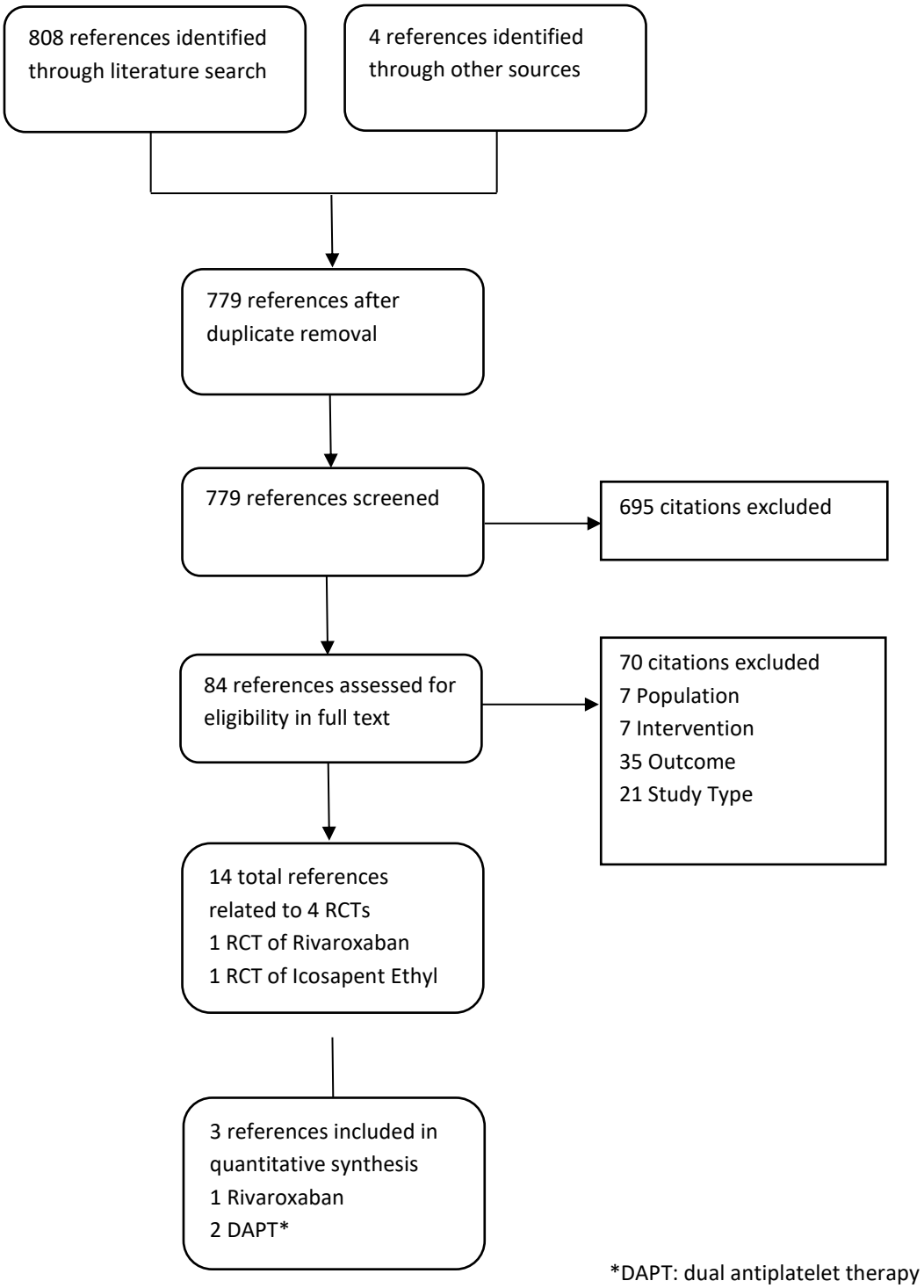
| | |
|---|---|
| **1** | **((cardiovascular or heart or coronary or atherosclero$ or isch?emic or peripheral or arter$ or cerebrovascular) adj2 (diseas$ or disorder$ or syndrome$ or atherosclero$)).ti,ab.** |
| **2** | ('icosapent ethyl' or vascepa or amr101).ti,ab. |
| **3** | exp rivaroxaban/ or (rivaroxaban or Xarelto).ti,ab. |
| **4** | 2 or 3 |
| **5** | 1 and 4 |
| **6** | (animals not (humans and animals)).sh. |
| **7** | 5 not 6 |
| **8** | (addresses or autobiography or bibliography or biography or case reports or classical article or clinical conference or clinical trial, phase i or comment or congresses or consensus development conference or consensus development conference, nih or dataset or dictionary or directory or duplicate publication or editorial or equivalence trial or "expression of concern" or guideline or historical article or interactive tutorial or interview or introductory journal article or lectures or legal cases or legislation or letter or news or newspaper article or overall or patient education handout or periodical index or personal narratives or portraits or practice guideline or "published erratum review" or "scientific integrity review" or technical report or twin study or validation studies or video-audio media or webcasts).pt. |
| **9** | 7 not 8 |
| **10** | limit 9 to english language |

*Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present

**Table A3. Search Strategy of EMBASE**

| | |
|---|---|
| **1** | **((cardiovascular OR heart OR coronary OR atherosclero* OR isch*emic OR peripheral OR arter* OR cerebrovascular) NEAR/2 (diseas* OR disorder* OR syndrome* OR atherosclero*)):ti,ab** |
| **2** | 'icosapentaenoic acid ethyl ester'/exp OR 'icosapent ethyl':ti,ab OR vascepa:ti,ab OR amr101:ti,ab |
| **3** | 'rivaroxaban'/exp OR rivaroxaban:ti,ab OR xarelto:ti,ab |
| **4** | #2 OR #3 |
| **5** | #1 AND #4 |
| **6** | ('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp |
| **7** | #5 NOT #6 |
| **8** | #7 AND ('case report'/de OR 'in vitro study'/de OR 'chapter'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it) |
| **9** | #7 NOT #8 |
| **10** | #9 NOT [medline]/lim |
| **11** | #10 AND [english]/lim |

**Figure A1. PRISMA Flow Chart Showing Results of Literature Search for Rivaroxaban and Icosapent Ethyl**




*DAPT: dual antiplatelet therapy

# Appendix B. Previous Systematic Reviews and Technology Assessments

We identified two completed technology assessment of rivaroxaban for CVD, which is summarized below. We also identified one ongoing, but temporarily suspended technology assessment of icosapent ethyl, and a peer-reviewed systematic review of DAPT for secondary prevention.

**Canadian Agency for Drugs and Technologies in Health (CADTH) Common Drug Review: Rivaroxaban (Xarelto) 2019**

Although Health Canada approved rivaroxaban + ASA for CAD with or without PAD, CADTH recommended that rivaroxaban be reimbursed only for patients with concomitant CAD and PAD. CADTH's reimbursement recommendation was informed by a review of the COMPASS trial,[21] a manufacturer-provided NMA comparing rivaroxaban to DAPT, and a manufacturer-submitted cost-utility analysis. Based on this analysis, CADTH concluded that rivaroxaban + ASA is cost-effective in patients with concomitant CAD and PAD compared with ASA alone, at an incremental cost-effectiveness ratio of Can$17,764 per QALY gained. Reviewers noted a few gaps in the available evidence, including uncertainties about the generalizability of the COMPASS trial results, the long-term efficacy and safety of rivaroxaban + ASA, the optimal duration of therapy, whether rivaroxaban + ASA improves health-related quality of life or daily function, and the comparative efficacy and safety of rivaroxaban + ASA versus DAPT.

**NICE: Rivaroxaban for Preventing Major Cardiovascular Events in People with Coronary or Peripheral Artery Disease [ID1397], Expected publication date August 28, 2019**

NICE recommends the use of rivaroxaban plus aspirin within its marketing authroitization, as an option for preventing atherothrombotic events in adults with coronary artery disease or symptomatic peripheral artery disease who are at high risk for ischemic events. Additionally, NICE recommends assessing a person's risk for bleeding before considering rivaroxaban.

**Canadian Agency for Drugs and Technologies in Health (CADTH) Common Drug Review: Icosapent Ethyl [SR0619-000], Review temporarily suspended.**

CADTH is currently evaluating the clinical and cost effectiveness of icosapent ethyl for the prevention of ischemic events in statin-treated patients with elevated triglyceride levels with CVD or at high risk for CVD, however the review has been temporarily suspended pending receipt and review of information.

**Udell JA, et al. Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials. European Heart Journal. 2015;37(4):390-399.[115]**

We identified a meta-analysis evaluating DAPT for the secondary prevention of cardiovascular events in patients with a prior MI.[115] Six trials that randomized patients to DAPT (n=20,203) or ASA alone (n=13,232) for at least one year were included. One trial was conducted exclusively in patients with a prior MI, and the other five trials were conducted in high-risk populations and reported on subgroups of patients with a prior MI. Two trials compared the initiation of DAPT to treatment with ASA alone, and the other four trials compared continuation of DAPT versus discontinuation of the P2Y12 inhibitor (i.e., treatment with ASA alone). The primary outcome in all six trials was a composite of cardiovascular death, MI, or stroke. The mean duration of follow-up was 31 months.

At baseline, the mean age across studies was 64.0 years, 23.6% were female, 83.9% underwent or had a history of PCI, and 29.6% had diabetes.[115] Results from the meta-analysis showed treatment with DAPT reduced the risk of the primary composite endpoint (cardiovascular death, MI, or stroke) by 22% compared to ASA alone (6.4% vs. 7.5%, respectively, risk ratio [RR] 0.78; 95% CI: 0.67 to 0.90; p=0.0001). Patients treated with DAPT also experienced a significant reduction in cardiovascular death (RR 0.85; 95% CI: 0.74 to 0.98; p=0.03), MI (RR 0.70; 95% CI: 0.55 to 0.88; p=0.003), and stroke (RR 0.81; 95% CI 0.68 to 0.97; p=0.02).

The six trials measured the incidence of major bleeding using a variety of definitions; three trials used the TIMI definition, two trials used the GUSTO definition, and one trial used the STEEPLE definition. Nevertheless, the investigators conducted a meta-analysis of major bleeding endpoints and found treatment with DAPT significantly increased the risk of major bleeding compared to ASA alone (1.9% vs. 1.1%; RR: 1.73; 95% CI: 1.19 to 2.50, p=0.004), but not fatal bleeding (0.14% vs 0.17%; RR 0.91; 95% CI: 0.53 to 1.58; p=0.75) or intracranial hemorrhage (0.41% vs. 0.31%; RR 1.34; 95% CI: 0.89 to 2.02; p=0.17).

# Appendix C. Ongoing Studies

| Title/Trial Sponsor | Study Design | Arms | Patient Population | Primary Outcome | Estimated Completion Date |
|---|---|---|---|---|---|
| **Xarelto® (Rivaroxaban)** | | | | | |
| **Efficacy and Safety of Rivaroxaban in Reducing the Risk of Major Thrombotic Vascular Events in Subjects with Symptomatic Peripheral Artery Disease Undergoing Peripheral Revascularization Procedures of the Lower Extremities (VOYAGER PAD)**<br><br>**Bayer and Janssen Research & Development, LLC**<br><br>**NCT02504216** | Phase III, randomized, double-blind, parallel assignment<br><br>Enrollment: 6564 | Arm 1: Rivaroxaban 2.5 mg twice daily<br><br>Arm 2: Placebo | Inclusion<br>• Age ≥50<br>• Moderate to severe symptomatic lower extremity PAD<br>• Peripheral revascularization distal to the external iliac artery for symptomatic PAD within the last 10 days<br><br>Exclusion<br>• Patients undergoing revascularization for asymptomatic PAD<br>• Prior revascularization on the index leg within 10 days of the qualifying revascularization<br>• Planned use of additional antiplatelet agent other than clopidogrel and ASA | Time from randomization to the first occurrence of any of the following major thrombotic vascular events: MI, ischemic stroke, CV death, acute limb ischemia, and major amputation | October 2019 |

| Title/Trial Sponsor | Study Design | Arms | Patient Population | Primary Outcome | Estimated Completion Date |
|---|---|---|---|---|---|
| **Switching for DAPT to Dual Pathway Inhibition With Low-Dose Rivaroxaban in Adjunct to Aspirin in Patients With Coronary Artery Disease (SWAP-AC)**<br><br>**University of Florida & Janssen, LP**<br><br>**NCT04006288** | Phase IV, randomized, open label, parallel assignment<br><br>Enrollment: 90 | Arm 1: ASA + clopidogrel → continued DAPT<br><br>Arm 2: ASA + clopidogrel → ASA + rivaroxaban<br><br>Arm 3: ASA + prasugrel → continued DAPT<br><br>Arm 4: ASA + prasugrel → ASA + rivaroxaban<br><br>Arm 5: ASA + ticagrelor → continued DAPT<br><br>Arm 6: ASA + ticagrelor → ASA + rivaroxaban | Inclusion:<br>• Age ≥18<br>• Known CAD and have completed their required duration of care DAPT and still be on treatment: ≥6 months after an elective PCI, ≥12 months after experiencing an ACS<br>Exclusion:<br>• Deemed to be at high risk of bleeding, active bleeding, or history of major bleeding<br>• Estimated GFR <15 ml/min by MDRD equation<br>• Known non-CVD that is associated with poor prognosis | Maximal platelet aggregation by light transmittance aggregometry at 30 days | December 2020 |

| Title/Trial Sponsor | Study Design | Arms | Patient Population | Primary Outcome | Estimated Completion Date |
|---|---|---|---|---|---|
| **Vascepa® (Icosapent Ethyl)** | | | | | |
| **Effect of Vascepa on Improving Coronary Atherosclerosis in People with High Triglycerides Taking Statin Therapy (EVAPORATE)**<br><br>**Los Angeles Biomedical Research Institute**<br><br>**NCT02926027** | Phase IV, randomized, double blind, parallel assignment<br><br>Enrollment: 80 | Arm 1: Icosapent ethyl (4 g/day)<br><br>Arm 2: Placebo | Inclusion<br>• Age ≥30<br>• Elevated triglycerides (fasting value between 200-499 mg/dL)<br>• LDL-C >40 mg/dL and ≤115 mg/dL<br>• Stable diet + exercise<br>• Stable treatment with statin for at least four weeks<br><br>Exclusion<br>• A contraindication to fish or fish oils<br>• Use of non-study lipid altering medications or supplements<br>• Bleeding disorder<br>• Uncontrolled hypertension<br>• MI, stroke, life-threatening arrhythmia within prior six months | Change in baseline in low attenuation plaque at 18 months | September 2019 |

| Title/Trial Sponsor | Study Design | Arms | Patient Population | Primary Outcome | Estimated Completion Date |
|---|---|---|---|---|---|
| **Other Ongoing Trials of Omega-3 Fatty Acids** | | | | | |
| **Randomized Trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy - Statin and Eicosapentaenoic Acid (RESPECT-EPA)**<br><br>**UMIN000012069**<br><br>**Japan Heart Foundation** | Phase IV, randomized, open-label, parallel assignment<br><br>Target enrollment: 3900 | Arm 1: Eicosapentaenoic acid (1.8 g/day)<br><br>Arm 2: Placebo | Inclusion:<br>• Age ≥20<br>• CAD, defined by having either 1) history of acute coronary system; 2) history of coronary revascularization; or 3): diagnosis of ischemic heart disease and severe coronary artery stenosis (≥75%)<br>• Stable treatment with statin for at least four weeks<br><br>Exclusion:<br>• Acute coronary syndrome or coronary revascularization within prior three months<br>• Planned coronary revascularization or angiography<br>• Inadequately controlled diabetes mellitus<br>• Active bleeding or bleeding tendency | Time from randomization to the first occurrence of any of the following major CV events: CV death, non-fatal MI, non-fatal cerebral infarction, unstable angina requiring emergent hospitalization and coronary revascularization, and coronary revascularization | October 2021 |

| Title/Trial Sponsor | Study Design | Arms | Patient Population | Primary Outcome | Estimated Completion Date |
|---|---|---|---|---|---|
| **Outcomes Study to Assess Statin Residual Risk Reduction With Epanova in High CV Risk Patients With Hypertriglyceridemia (STRENGTH)**<br><br>**NCT02104817**<br><br>**AstraZeneca** | Phase III, randomized, double-blind, parallel assignment<br><br>Enrollment: 13086 | Arm 1: Omega-3-carboxylic acids<br><br>Arm 2: Placebo | Inclusion:<br>• Age ≥18<br>• High risk for CV events, defined as 1) CVD; 2) men age ≥40 or women age ≥50 with diabetes mellitus and at least one additional risk factor; or 3) men age>50 or women age>60 with at least one additional risk factor<br>• Stable treatment with statin for at least four weeks<br>• LDL-C <100 mg/dL<br>• TG level ≥180 and <500 mg/dL<br><br>Exclusion:<br>• Use of fibrates, bile acid sequestrants, or niacin within four weeks | Time from randomization to the first occurrence of any of the following major CV events: CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina | September 2020 |

Sources: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies); UMIN Clinical Trials Registry (UMIN-CTR) https://www.umin.ac.jp/ctr/index.htm

# Appendix D. Comparative Clinical Effectiveness Supplemental Information

## US Preventive Services Task Force (USPSTF) Criteria for the Quality Assessment of Clinical Trials and Comparative Cohort Studies

***Good:*** *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

***Fair:*** *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

***Poor:*** *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

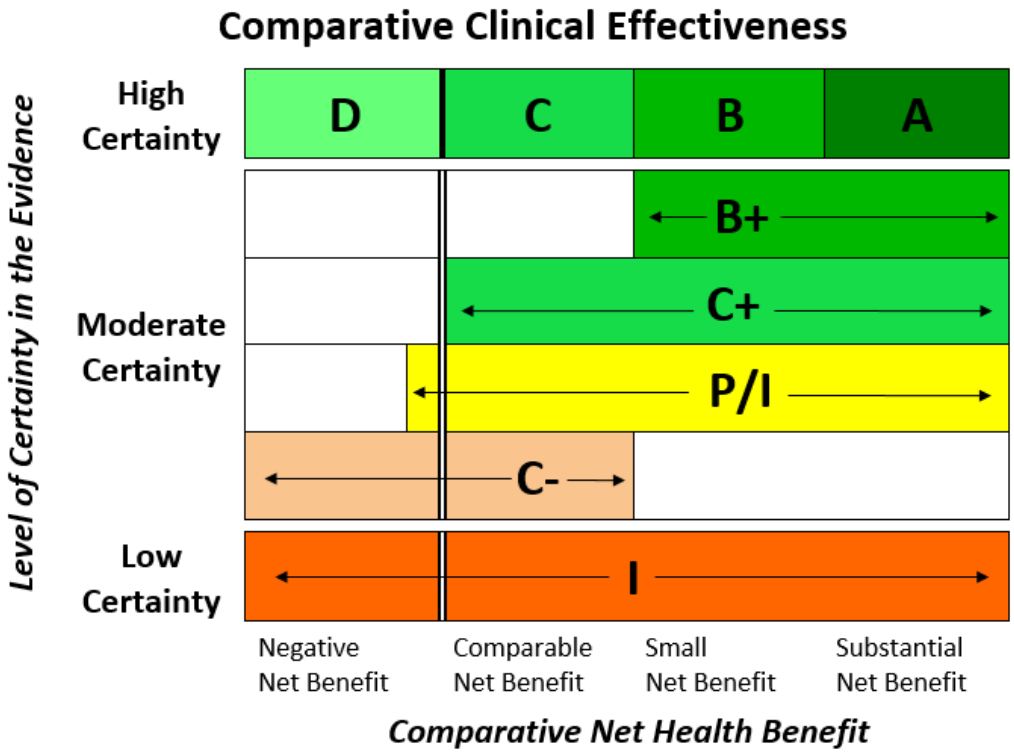
Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality.

## ICER Evidence Rating

We used the ICER Evidence Rating Matrix (see Figure D1) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
The level of **certainty** in the best point estimate of net health benefit.[55]

**Figure D1. ICER Evidence Rating Matrix**




***A* = *"Superior"*** *- High certainty of a substantial (moderate-large) net health benefit*
***B* = *"Incremental"*** *- High certainty of a small net health benefit*
***C* = *"Comparable"*** *- High certainty of a comparable net health benefit*
***D* = *"Negative"*** *- High certainty of an inferior net health benefit*
***B+* = *"Incremental or Better"*** *- Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
***C+* = *"Comparable or Better"*** *- Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
***P/I* = *"Promising but Inconclusive"*** *- Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit*
***C-* = *"Comparable or Inferior"*** *- Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior*
***I* = *"Insufficient"*** *- Any situation in which the level of certainty in the evidence is low*

**Table D1. Study Quality of COMPASS**

| Study | Comparable Groups | Adequate Randomization | Patient Blinding | Physician Blinding | Outcome Adjudication Blinding | Non-Differential Follow-Up | ITT Analysis | Appropriate Handling of Missing Data | Overall Quality |
|---|---|---|---|---|---|---|---|---|---|
| **COMPASS** | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Good |

ITT: intent-to-treat

**Table D2. Study Design of COMPASS**

| Study | COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) |
|---|---|
| **Design** | Multicenter, double-blind, placebo-controlled, double-dummy, randomized trial. Patients were randomized 1:1:1 to received rivaroxaban (2.5 mg twice daily) + ASA (100 mg daily), rivaroxaban (5 mg twice daily), or ASA (100 mg once daily) and stratified according to center and use of PPI at the time of randomization. Eligible patients were also randomly assigned 1:1 to receive pantoprazole (40 mg daily) or matched placebo. |
| **Inclusion Criteria** | ○ CAD or PAD<br>Patients with CAD must also meet at least one of the following<br>○ Age ≥65, or<br>○ Age <65 and documented atherosclerosis or revascularization involving at least two vascular beds, or at least two additional risk factors |
| **Exclusion Criteria** | ○ High risk of bleeding<br>○ Need for DAPT, other non-ASA antiplatelet therapy or oral anticoagulant therapy<br>○ Stroke within one month or any history of hemorrhagic or lacunar stroke<br>○ Severe heart failure with known ejection fraction <30% or New York heart Association (NYHA) class III or IV symptoms<br>○ Estimated glomerular filtration rate (eGFR) <15 mL/min |
| **N** | 27,395 |
| **Interventions** | • 2.5 mg twice daily rivaroxaban + ASA (n=9,152)<br>• 5 mg twice daily rivaroxaban (n=9,117)<br>• 100 mg twice daily ASA (n=9,126) |
| **Follow-Up** | Mean follow-up of 23 months |
| **Outcomes** | • ***Primary Endpoint:*** A composite of CV death, stroke, or MI<br>• ***Secondary Endpoints:***<br>○ A composite of ischemic stroke, MI, acute limb ischemia, or death from CAD<br>○ A composite of ischemic stroke, MI, acute limb ischemia, or CV death<br>○ Death from any cause<br>• ***Tertiary Endpoints:***<br>○ Individual components of primary and secondary endpoints<br>○ Hospitalization for CV causes<br>○ Revascularization<br>○ Limb amputation<br>○ Stent thrombosis<br>○ Angina<br>○ Heart failure<br>○ Resuscitated cardiac arrest<br>○ Venous thromboembolism<br>○ New diagnosis of cancer |

ASA: aspirin, CAD: coronary artery disease, CV: cardiovascular, DAPT: dual antiplatelet therapy, MI: myocardial infarction, PPI: a proton-pump inhibitor, PAD: peripheral artery disease

**Table D3. Key Baseline Characteristics of COMPASS*[11,57,58]**

| Study | Overall COMPASS | | CAD Subgroup | | PAD Subgroup | |
|---|---|---|---|---|---|---|
| Intervention | RV + ASA | ASA | RV + ASA | ASA | RV + ASA | ASA |
| N | 9152 | 9216 | 8313 | 8261 | 2492 | 2504 |
| Age, Mean (SD) | 68.3 (7.9) | 68.2 (8.0) | 69 (65-73)† | 69 (65-73)† | 67.9 (8.45) | 67.8 (8.47) |
| Body Mass Index, Mean (SD) | 28.3 (4.8) | 28.4 (4.7) | 28.4 (4.7) | 28.5 (4.7) | 28.3 (5.0) | 28.4 (5.0) |
| Blood Pressure, Mean (SD) | 136 (17) systolic; 77 (10) diastolic | 136 (18) systolic; 78 (10) diastolic | 135 (17) systolic; 77 (10) diastolic | 135 (17) systolic; 78 (10) diastolic | 138.9 (18.5) systolic; 77.7 (10.1) diastolic | 138.6 (18.2) systolic; 77.8 (10.3) diastolic |
| Prior Stroke, No. (%) | 351 (3.8) | 335 (3.7) | 279 (3) | 268 (3) | 171 (6.9) | 154 (6.2) |
| Prior MI, No. (%) | 5654 (61.8) | 5721 (62.7) | 5654 (68) | 5721 (69) | NR | NR |
| Heart Failure, No. (%) | 1963 (21.4) | 1979 (21.7) | 1909 (23) | 1912 (23) | NR | NR |
| CAD, No. (%) | 8313 (90.8) | 8261 (90.5) | -- | -- | 1656 (66.5) | 1641 (65.5) |
| PAD, No. (%) | 2492 (27.2) | 2504 (27.4) | 1656 (20) | 1641 (20) | Symptomatic: 2026 (81.3)‡ | Symptomatic: 2039 (81.4)‡ |
| Diabetes, No. (%) | 3448 (37.7) | 3474 (38.1) | 3043 (37) | 3040 (37) | 1100 (44.1) | 1104 (44.1) |
| Smoking Status, No. (%) | 1944 (21.2) tobacco use | 1972 (21.6) tobacco use | 1679 (20) current smoker; 3944 (47) former smoker | 1687 (20) current smoker; 3908 (47) former smoker | 682 (27.4) current; 1147 (46) former; 663 (26.6) never | 685 (27.4) current; 1143 (45.6) former; 676 (27) never |
| *Concomitant Medications* | | | | | | |
| ACE Inhibitor or ARB, No. (%) | 6475 (70.7) | 6462 (70.8) | 5970 (72) | 5939 (72) | 1715 (68.8) | 1765 (70.5) |
| Beta-Blocker, No. (%) | 6389 (69.8) | 6394 (70.1) | 6124 (74) | 6154 (75) | 1477 (59.3) | 1485 (59.3) |
| Lipid-Lowering Agent, No. (%) | 8239 (90.0) | 8158 (89.4) | 7667 (92) | 7573 (92) | 2088 (83.8) | 2074 (82.8) |
| NSAID, No. (%) | 531 (5.8) | 473 (5.2) | NR | NR | NR | NR |

ACE: angiotensin-converting-enzyme, ARB: angiotensin II receptor blocker, ASA: aspirin, CAD: coronary artery disease, MI: myocardial infarction, No.: number of patients, NSAID: nonsteroidal anti-inflammatory drug, PAD: peripheral artery disease, RV: rivaroxaban; SD: standard deviation

*Only reporting the results of the FDA approved 2.5 mg dose of rivaroxaban.

†Median (IQR).

‡Symptomatic PAD (the sum of systematic PAD of the lower extremities and carotid artery disease).

**Table D4. Key Efficacy Outcomes in COMPASS at a Mean of 23 Months of Follow-Up*[11,14,57-60,116]**

| Study | Overall COMPASS | | CAD Subgroup | | PAD Subgroup | | Renal Dysfunction | | | | Heart Failure | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Intervention | RV + ASA | ASA | RV + ASA | ASA | RV + ASA | ASA | RV eGFR <60 ml | ASA <60 | RV eGFR ≥60 ml | ASA ≥60 | RV + ASA No HF | ASA No HF | RV + ASA HF | ASA HF |
| N | 9152 | 9126 | 8313 | 8261 | 2492 | 2504 | 2054 | 2114 | 7094 | 7012 | 7189 | 7147 | 1963 | 1979 |
| ***Primary Outcome*** | | | | | | | | | | | | | | |
| CV Death, Stroke, or MI, No. (%) | 379 (4.1) | 496 (5.4) | 347 (4) | 460 (6) | 126 (5) | 174 (7) | 132 (6.4) | 177 (8.4) | 247 (3.5) | 319 (4.5) | 271 (3.8) | 339 (4.7) | 108 (5.5) | 157 (7.9) |
| HR (95% CI) P-Value | 0.76 (0.66-0.86) p<0.001 | | 0.74 (0.65-0.86) p<0.0001 | | 0.72 (0.57-0.90) p=0.0047 | | 0.75 (0.60-0.94) p=0.01 | | 0.76 (0.64-0.90) p=0.001 | | 0.79 (0.68-0.93) -- | | 0.68 (0.53-0.86) -- | |
| ***Secondary Outcomes*** | | | | | | | | | | | | | | |
| Ischemic Stroke, MI, ALI, Death from CHD, No. (%) | 329 (3.6) | 450 (4.9) | 299 (4) | 411 (5) | 115 (5) | 169 (7) | NR | NR | NR | NR | NR | NR | NR | NR |
| HR (95%CI) P-Value | 0.72 (0.63-0.83) p<0.001 | | 0.72 (0.62-0.83) p<0.0001 | | 0.68 (0.53-0.86) p=0.0011 | | NR | NR | NR | NR | NR | NR | NR | NR |
| Ischemic Stroke, MI, ALI or CV Death, No. (%) | 389 (4.3) | 516 (5.7) | 349 (4) | 470 (6) | 142 (6) | 198 (8) | NR | NR | NR | NR | NR | NR | NR | NR |
| HR (95%CI) P-Value | 0.74 (0.65-0.85) p<0.001 | | 0.73 (0.64-0.84) p<0.0001 | | 0.71 (0.57-0.88) p=0.0019 | | NR | NR | NR | NR | NR | NR | NR | NR |
| ***Other Outcomes*** | | | | | | | | | | | | | | |
| CV Death, No. (%) | 160(1.7) | 203 (2.2) | 139 (2) | 184 (2) | 64 (3) | 78 (3) | 71 (3.5) | 83 (3.9) | 89 (1.3) | 120 (1.7) | NR | NR | NR | NR |
| HR (95%CI) P-Value | 0.78 (0.64-0.96) p=0.02 | | 0.75 (0.60-0.93) p=0.010 | | 0.82 (0.59-1.14) -- | | 0.88 (0.64-1.20) p=0.41 | | 0.73 (0.56-0.96) p=0.02 | | NR | NR | NR | NR |
| Non-CV Death, No. (%) | 153 (1.7) | 175 (1.9) | 123 (2) | 155 (2) | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| HR (95%CI) P-Value | 0.87 (0.70-1.08) p=0.20 | | 0.79 (0.62-1.00) p=0.048 | | NR | | NR | NR | NR | NR | NR | NR | NR | NR |

| Study | Overall COMPASS | | CAD Subgroup | | PAD Subgroup | | Renal Dysfunction | | | | Heart Failure | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Death from CHD, No. (%) | 86 (0.9) | 117 (1.3) | 8 (1.0) | 107 (1.3) | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| HR (95%CI) P-Value | 0.73 (0.55-0.96) p=0.03 | | 0.74 (0.55-0.99) p=0.04 | | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| MI, No. (%) | 178 (1.9) | 205 (2.2) | 169 (2) | 195 (2) | 51 (2) | 67 (3) | 53 (2.6) | 73 (3.5) | 125 (1.8) | 132 (1.9) | NR | NR | NR | NR |
| HR (95%CI) P-Value | 0.86 (0.70-1.05) p=0.14 | | 0.86 (0.70-1.05) p=0.15 | | 0.76 (0.53-1.09) -- | | 0.73 (0.51-1.04) p=0.08 | | 0.93 (0.73-1.19) p=0.57 | | NR | NR | NR | NR |
| Stroke, No. (%) | 83 (0.9) | 142 (1.6) | 74 (1) | 130 (2) | 25 (1) | 47 (2) | 20 (1.0) | 49 (2.3) | 63 (0.9) | 93 (1.3) | NR | NR | NR | NR |
| HR (95% CI) P-Value | 0.58 (0.44-0.76) p<0.001 | | 0.56 (0.42-0.75) p<0.0001 | | 0.54 (0.33-0.87) -- | | 0.42 (0.25-0.70) p=0.0007 | | 0.67 (0.48-0.92) p=0.01 | | NR | NR | NR | NR |
| Ischemic Stroke, No. (%) | 64 (0.7) | 132 (1.4) | 60 (1) | 120 (2) | NR | NR | 14 (0.7) | 46 (2.2) | 54 (0.8) | 86 (1.2) | NR | NR | NR | NR |
| HR (95% CI) P-Value | 0.51 (0.38-0.68) p<0.001 | | 0.50 (0.36-0.67) p<0.0001 | | NR | NR | 0.31 (0.17-0.57) p<0.0001 | | 0.62 (0.44-0.87) p=0.005 | | NR | NR | NR | NR |
| Hemorrhagic Stroke, No. (%) | 15 (0.2) | 10 (0.1) | 14 (<1) | 10 (<1) | NR | NR | 6 (0.3) | 3 (0.1) | 9 (0.1) | 7 (<0.1) | NR | NR | NR | NR |
| HR (95% CI) P-Value | 1.49 (0.67-3.31) p=0.33 | | 1.39 (0.62-3.32) p=0.43 | | NR | NR | 2.01 (0.50-8.06) p=0.31 | | 1.26 (0.47-3.39) p=0.64 | | NR | NR | NR | NR |
| Heart Failure, No. (%) | 197 (2.2) | 192 (2.1) | 178 (2) | 182 (2) | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| HR (95% CI) P-Value | 1.02 (0.84-1.24) p=0.84 | | 0.97 (0.79-1.19) p=0.78 | | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| Hospitalization for CV Cause, No. (%) | 1303 (14.2) | 1394 (15.3) | 1189 (14) | 1270 (15) | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| HR (95% CI) P-Value | 0.92 (0.86-1.00) p=0.04 | | 0.92 (0.85-1.00) p=0.046 | | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| Hospitalization for non-CV Cause, No. (%) | 1701 (18.6) | 1624 (17.8) | 1552 (19) | 1481 (18) | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |

| Study | Overall COMPASS | | CAD Subgroup | | PAD Subgroup | | Renal Dysfunction | | | | Heart Failure | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| HR (95% CI) P-Value | 1.05 (0.98-1.13) p=0.14 | | 1.05 (0.98-1.13) p=0.18 | | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| Hospitalization for HF, No. (%) | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | 98 (1.4) | 76 (1.1) | 57 (2.9) | 69 (3.5) |
| HR (95% CI) P-Value | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | 1.29 (0.95-1.74) -- | | 0.82 (0.58-1.16) -- | |
| MALE, No. (%) | NR | NR | NR | NR | 30 (1) | 56 (2) | NR | NR | NR | NR | NR | NR | NR | NR |
| HR (95%CI) P-Value | NR | NR | NR | NR | 0.54 (0.35-0.84) p=0.0054 | | NR | NR | NR | NR | NR | NR | NR | NR |
| Major Amputation, No. (%) | NR | NR | NR | NR | 5 (<1) | 17 (1) | NR | NR | NR | NR | NR | NR | NR | NR |
| HR (95%CI) P-Value | NR | NR | NR | NR | 0.30 (0.11-0.80) p=0.011 | | NR | NR | NR | NR | NR | NR | NR | NR |
| Vascular Amputation, No. (%) | NR | NR | NR | NR | 11 (<1) | 28 (1) | NR | NR | NR | NR | NR | NR | NR | NR |
| HR (95%CI) P-Value | NR | NR | NR | NR | 0.40 (0.20-0.79) p=0.0069 | | NR | NR | NR | NR | NR | NR | NR | NR |

ALI: acute limb ischemia, ASA: aspirin, CAD: coronary artery disease, CHD: coronary heart disease, CI: confidence interval, CV: cardiovascular, eGFR: estimated glomerular filtration rate, HF: heart failure, HR: hazard ratio, MALE: major adverse limb event, MI: myocardial infarction, No.: number of patients, NR: not reported, PAD: peripheral artery disease, RV: rivaroxaban

*Only reporting the results of the FDA approved 2.5 mg dose of rivaroxaban.

**Table D5. Key Safety Events in COMPASS at a Mean of 23 Months of Follow-Up*[11,57,58,116]**

| Study | Overall COMPASS | | CAD Subgroup | | PAD Subgroup | | Renal Dysfunction | | | | Heart Failure | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Intervention | RV + ASA | ASA | RV + ASA | ASA | RV + ASA | ASA | RV eGFR <60 ml | ASA <60 | RV eGFR ≥60 ml | ASA ≥60 | RV + ASA No HF | ASA No HF | RV + ASA HF | ASA HF |
| N | 9152 | 9126 | 8313 | 8261 | 2492 | 2504 | 2054 | 2114 | 7094 | 7012 | 7189 | 7147 | 1963 | 1979 |
| Any SAE, No. (%) | 721 (7.9) | 662 (7.3) | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| Major Bleeding, No. (%) | 288 (3.1) | 170 (1.9) | 263 (3) | 158 (2) | 77 (3) | 48 (2) | 81 (3.9) | 57 (2.7) | 206 (2.9) | 113 (1.6) | 239 (3.3) | 134 (1.9) | 49 (2.5) | 36 (1.8) |
| P-Value | p<0.001 | | p<0.001 | | p=0.0089 | | p=0.02 | | p<0.0001 | | -- | | -- | |
| Fatal Bleeding, No. (%) | 15 (02) | 10 (0.1) | 14 (<1) | 9 (<1) | 4 (<1) | 3 (<1) | 5 (0.2) | 4 (0.2) | 10 (0.1) | 6 (<0.1) | NR | NR | NR | NR |
| P-Value | p=0.32 | | p=0.30 | | -- | | p=0.74 | | p=0.34 | | NR | NR | NR | NR |
| Nonfatal ICH, No. (%) | 21 (0.2) | 19 (0.2) | 19 (<1) | 19 (<1) | 4 (<1) | 8 (<1) | NR | NR | NR | NR | NR | NR | NR | NR |
| P-Value | p=0.77 | | p=0.98 | | -- | | NR | NR | NR | NR | NR | NR | NR | NR |
| Nonfatal Non-ICH, No. (%) | 42 (0.5) | 29 (0.3) | 36 (<1) | 25 (<1) | 13 (1) | 8 (<1) | NR | NR | NR | NR | NR | NR | NR | NR |
| P-Value | p=0.14 | | p=0.18 | | -- | | NR | NR | NR | NR | NR | NR | NR | NR |
| *Site of Major Bleeding* | | | | | | | | | | | | | | |
| GI, No. (%) | 140 (1.5) | 65 (0.7) | 130 (2) | 61 (1) | 41 (2) | 18 (1) | NR | NR | NR | NR | NR | NR | NR | NR |
| P-Value | p<0.001 | | p<0.0001 | | p=0.0027 | | NR | NR | NR | NR | NR | NR | NR | NR |
| Intracranial, No. (%) | 28 (0.3) | 24 (0.3) | 26 (<1) | 23 (<1) | 5 (<1) | 9 (< 1) | 11 (0.5) | 7 (0.3) | 17 (0.2) | 17 (0.2) | 19 (0.3) | 18 (0.3) | 9 (0.5) | 6 (0.3) |
| P-Value | p=0.60 | | p=0.69 | | -- | | p=0.33 | | p=0.95 | | -- | | -- | |
| Skin or Injection Site, No. (%) | 28 (0.3) | 12 (0.1) | 25 (<1) | 10 (<1) | 5 (<1) | 8 (<1) | NR | NR | NR | NR | NR | NR | NR | NR |
| P-Value | p=0.01 | | p=0.012 | | -- | | NR | NR | NR | NR | NR | NR | NR | NR |
| Urinary, No. (%) | 13 (0.1) | 21 (0.2) | 13 (<1) | 21 (<1) | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| P-Value | p=0.16 | | p=0.16 | | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| *Other* | | | | | | | | | | | | | | |

| Study | Overall COMPASS | | CAD Subgroup | | PAD Subgroup | | Renal Dysfunction | | | | Heart Failure | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Minor Bleeding, No. (%)** | 838 (9.2) | 503 (5.5) | 775 (9) | 454 (6) | 198 (8) | 141 (6) | NR | NR | NR | NR | NR | NR | NR | NR |
| **P-Value** | p<0.001 | | p<0.0001 | | p=0.0011 | | NR | NR | NR | NR | NR | NR | NR | NR |
| ***Net-Clinical-Benefit Outcome, n (%)*** | | | | | | | | | | | | | | |
| **CV Death, Stroke, MI, Fatal Bleeding, or Symptomatic Bleeding into Critical Organ** | 431 (4.7) | 534 (5.9) | 392 (5) | 494 (6) | 140 (6) | 185 (7) | 147 (7.2) | 188 (8.9) | 284 (4.0) | 346 (4.9) | 315 (4.4) | 369 (5.2) | 116 (5.9) | 165 (8.3) |
| **HR (95% CI)**<br>**P-Value** | 0.80 (0.70-0.91)<br>p<0.001 | | 0.78 (0.69-0.90)<br>p=0.0003 | | 0.75 (0.60-0.94)<br>p=0.011 | | 0.79 (0.64-0.98)<br>p=0.03 | | 0.81 (0.69-0.94)<br>p=0.007 | | 0.85 (0.73-0.99) -<br>-- | | 0.69 (0.55-0.88)<br>-- | |

AE: Adverse event, ASA: aspirin, eGFR: estimated glomerular filtration rate, HF: heart failure, ICH: intracranial hemorrhage, MI: myocardial infarction, RV: rivaroxaban, SAE: serious adverse event

*Only reporting the results of the FDA approved 2.5 mg dose of rivaroxaban.

**Table D6. Summary of Pantoprazole to Prevent Gastroduodenal Events[61]**

| Study and Population | Patient Characteristics | | Pantoprazole, No. (%) | Placebo, No. (%) | Between Group Differences |
|---|---|---|---|---|---|
| **Pantoprazole to Prevent Gastroduodenal Events in Patients Receiving Rivaroxaban and/or Aspirin in a Randomized, Double-Blind, Placebo-Controlled Trial**<br><br>**COMPASS Moayyedi 2019** | **Pantoprazole (n=8791)**<br>Age, median: 68<br>Female sex, no. (%): 1937 (22)<br>Previous MI, no. (%): 5403 (62)<br>Previous stroke, no. (%): 350 (4)<br>Previous cancer, no. (%): 450 (5)<br>Diabetes, no. (%): 3363 (38)<br>Heart failure, no. (%): 2181 (25)<br><br>Medication<br>NSAID, no. (%): 425 (5)<br>SSRIs, no. (%): 257 (3)<br>ACE inhibitors/arbs, no. (%): 6269 (71)<br>Beta blockers, no. (%): 6137 (70)<br>Lipid-lowering agents, no. (%): 7775 (88) | **Placebo (n=8807)**<br>Age, median: 68<br>Female sex, no. (%): 1869 (21)<br>Previous MI, no. (%): 5404 (61)<br>Previous stroke, no. (%): 366 (4)<br>Previous cancer, no. (%): 491 (6)<br>Diabetes no. (%): 3369 (38)<br>Heart failure no. (%): 2138 (24)<br><br>Medication<br>NSAID, no. (%): 447 (5)<br>SSRI, no. (%): 258 (3)<br>ACE inhibitors/ARBs, no. (%): 6286 (71)<br>Beta blockers, no. (%): 6122 (70)<br>Lipid-lowering agents, no. (%): 7823 (89) | ***Primary outcome:* clinically significant upper GI events*:** 102 (1.2) | 116 (1.3) | **HR (95% CI):** 0.88 (0.67-1.15) p=0.35 |
| | | | **Overt bleeding of gastroduodenal organ:** 16†(0.2) | 31 (0.4) | **HR (95% CI):** 0.52 (0.28-0.94) p=0.03 |
| | | | **Overt upper GI bleeding of unknown origin:** 50 (0.6) | 45 (0.5) | **HR (95% CI):** 1.09 (0.73-1.63) p=0.68 |
| | | | **Bleeding of presumed occult upper GI tract w/ documented decrease in Hb ≥2 g/dL:** 10 (0.1) | 10 (0.1) | **HR (95% CI):** 1.00 (0.42-2.40) p=0.99 |
| | | | **Symptomatic gastroduodenal ulcer:** 8 (<0.1) | 17 (0.2) | **HR (95% CI):** 0.47 (0.20-1.09) p=0.07 |
| | | | **GI pain with underlying multiple gastroduodenal erosions:** 4 (<0.1) | 7 (<0.1) | **HR (95% CI):** 0.57 (0.17-1.95) p=0.37 |
| | | | **Upper GI obstruction or peroration:** 21 (0.2) | 16 (0.2) | **HR (95% CI):** 1.32 (0.69-2.52) p=0.41 |

ACE: angiotensin-converting-enzyme, ARB: angiotensin II receptor blocker, GI: gastrointestinal, Hb: hemoglobin, HR: hazard ratio, MI: myocardial infarction, NSAID: nonsteroidal anti-inflammatory drug, SSRI: selective serotonin reuptake inhibitor

*Composite of overt bleeding of gastroduodenal organ confirmed by endoscopy or radiography, overt upper GI bleeding of unknown origin, bleeding of presumed occult upper GI tract origin with documented decrease in Hb of 2 g/dL, symptomatic gastroduodenal ulcer, GI pain with underlying multiple gastroduodenal erosions, and upper GI obstruction/perforation.

†Includes one gastric cancer in pantoprazole group, no upper GI cancers in the placebo group.

## Summary of Key DAPT Trials Incorporated into NMA

### *Ticagrelor + ASA*

PEGASUS-TIMI 54 was a Phase III randomized controlled trial that evaluated the efficacy and safety of DAPT with ticagrelor (90 mg or 60 mg) + ASA compared to ASA alone.[15] Patients were eligible to participate if they had had a MI one to three years before enrollment, were at least 50 years of age, and had at least one additional risk factor, including ≥65 years of age, diabetes mellitus, a second prior MI, multivessel CAD, or chronic renal dysfunction. Eligible patients were randomized 1:1:1 to receive 90 mg of ticagrelor orally (n=7050), 60 mg of ticagrelor orally (n=7045), or placebo (n=7067); all patients received 75-150 mg of ASA daily. At baseline, patients had a mean age of 65, 32% had diabetes, 60% had multivessel CAD, and the median time since the qualifying MI was 1.7 years. Background medications at baseline included statins (93%), beta-blockers (82%), and ACE inhibitors or ARBs (81%). Patients were followed for a median of 33 months (IQR 28-37).[15]

The two ticagrelor doses (90 mg and 60 mg) significantly reduced the risk of the composite primary endpoint of cardiovascular death, MI, or stroke. In a pooled analysis of both ticagrelor doses versus placebo, ticagrelor reduced the risk of the composite endpoint by 16% (HR: 0.84; 95% CI (0.76 to 0.94); p=0.001); results for each dose arm compared to ticagrelor are reported in Table D6.[15] When stratified by time from MI (<2 years vs. ≥2 years), patients whose MI occurred <2 years before enrollment appeared to derive a greater benefit from ticagrelor (60 mg) than those who had a MI ≥2 years prior to enrollment (p-value for interaction=0.09; Table D6); results for the 90 mg dose of ticagrelor were similar in these subgroups.[15,16]

**Table D7. PEGASUS-TIMI 54 Summary Results[15]**

| | Ticagrelor (90 mg) + ASA | Ticagrelor (60 mg) + ASA | ASA | Ticagrelor (90 mg) + ASA vs. ASA | Ticagrelor (60 mg) + ASA vs. ASA |
|---|---|---|---|---|---|
| | 3-Yr Kaplan-Meier Event Rate | 3-Yr Kaplan-Meier Event Rate | 3-Yr Kaplan-Meier Event Rate | HR (95% CI) P-Value | HR (95% CI) P-Value |
| **Composite of CV Death, MI, or Stroke** | | | | | |
| **All Patients** | 7.9% | 7.8% | 9.0% | 0.85 (0.75-0.96) p=0.008 | 0.84 (0.74-0.95) p=0.004 |
| ***Subgroup: MI <2 Years before Enrollment*** | 8.2% | 7.8% | 9.7% | 0.83 (0.71-0.96) p=NR | 0.77 (0.66-0.90) p=NR |
| ***Subgroup: MI ≥2 Years before Enrollment*** | 7.3% | 7.8% | 7.9% | 0.89 (0.73-1.08) p=NR | 0.96 (0.79-1.17) p=NR |
| **TIMI Major Bleeding** | | | | | |
| **All Patients** | 2.6% | 2.3% | 1.1% | 2.69 (1.96-3.70) p<0.001 | 2.32 (1.68-3.21) p<0.001 |
| ***Subgroup: MI <2 Years before Enrollment*** | 2.4% | 2.4% | 1.2% | 2.18 (1.48-3.23) | 2.05 (1.38-3.03) |
| ***Subgroup: MI ≥2 Years before Enrollment*** | 2.9% | 2.2% | 0.7% | 4.15 (2.34-7.36) | 3.17 (1.76-5.70) |

ASA: aspirin, HR: hazard ratio, CI: confidence interval, CV: cardiovascular, MI: myocardial infarction, NR: not reported, TIMI: Thrombolysis in Myocardial Infarction

The PEGASUS trial's primary safety endpoint was Thrombolysis in Myocardial Infarction (TIMI) major bleeding, defined as intracranial bleeding, clinically overt signs of hemorrhage (drop in hemoglobin ≥5 g/dL or fall in hematocrit ≥15%), or a bleeding event that led to death within seven days.[15] Both doses of ticagrelor significantly increased the rate of major bleeding (90mg: 2.6%; 60mg: 2.3%) versus ASA (1.1%; p<0.001 for both comparisons, see Table D6). Bleeding led to the discontinuation of study drug in significantly more patients treated with ticagrelor (7.8% and 6.2% for the 90 mg and 60 mg arms, respectively) versus ASA (1.5%; p<0.001 for both comparisons).

### *Clopidogrel + ASA*

CHARISMA was a Phase III, multicenter, double-blind study evaluating the efficacy and safety of 75 mg of clopidogrel + ASA (75-162 mg/day; n=7802) versus ASA alone (n=7801).[17] Patients were eligible for the study if they were at least 45 years of age and had multiple atherothrombotic risk factors, documented coronary disease, cerebrovascular disease, or symptomatic PAD. At baseline, the median age of patients was 64, 42% had diabetes, 78% had documented vascular disease, and 34% had a prior MI. Background medications at baseline included statins (77%), beta-blockers (55%), ACE inhibitors (46%), and ARBs (26%). Patients were followed for a median of 28 months.

Clopidogrel + ASA did not significantly reduce the risk of the primary endpoint, a composite of MI, stroke, or cardiovascular death, in the overall trial population (Table D7). However, in a post hoc subgroup analysis of higher-risk patients (i.e., patients with a prior MI, stroke, or symptomatic PAD) the rate of MI, stroke or cardiovascular death was statistically significantly lower with clopidogrel + ASA (7.8%) versus ASA alone (8.8%; HR: 0.83; 95% CI 0.72 to 0.96; p=0.010); results were consistent in the subgroup with a prior MI (Table D7).[18]

The CHARISMA trial's primary safety endpoint was Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO)-defined severe bleeding; fatal bleeding events, intracranial hemorrhages, or bleeding that caused hemodynamic compromise requiring blood or fluid replacement, inotropic support, or surgical intervention were considered severe.[17] The rate of severe bleeding was 1.7% for clopidogrel + ASA versus 1.3% for ASA alone (relative risk [RR] 1.25 (95% CI 0.97 to 1.61; p=0.09); moderate bleeding, i.e., bleeding that led to a transfusion and a statistically significant increase in moderate bleeding but did not meet the severe definition, occurred in 2.1% of the clopidogrel + ASA arm and 1.3 % of the ASA alone arm (RR: 1.62; 95% CI 1.25 – 2.08; p<0.001).

**Table D8. CHARISMA Trial Summary Results[17,18]**

| | Clopidogrel + ASA | ASA | Clopidogrel + ASA vs. ASA |
|---|---|---|---|
| | % | % | HR (95% CI)<br>P-Value |
| **Composite of CV Death, MI, or Stroke** | | | |
| **All Patients** | 6.8% | 7.3% | [RR] 0.93 (0.83-1.05)<br>p=0.22 |
| ***Subgroup: Prior MI, Stroke, or Symptomatic PAD*** | 7.8% | 8.8% | 0.83 (0.72-0.96)<br>p=0.010 |
| ***Subgroup: Prior MI*** | 6.6% | 8.3% | 0.77 (0.61-0.98)<br>p=0.031 |
| **Severe of Life-Threatening Bleeding** | | | |
| **All Patients** | 1.7% | 1.3% | [RR] 1.25 (0.91-1.61)<br>p=0.09 |
| ***Subgroup: Prior MI, Stroke, or Symptomatic PAD*** | 1.7% | 1.5% | 1.11 (0.81-1.54)<br>p=0.509 |

## NMA Supplemental Information

**Table D9. Data Inputs for NMA of Composite Cardiovascular Death, MI, or Stroke in Patients with a Recent MI**

| Trial | Regimen | Hazard Ratio | 95% CI |
|---|---|---|---|
| COMPASS[58] | Rivaroxaban + ASA vs. ASA | 0.70 | 0.48-1.01 |
| PEGASUS[15] | Ticagrelor (60 mg) + ASA vs. ASA | 0.77 | 0.66-0.90 |
| CHARISMA[18] | Clopidogrel + ASA vs. ASA | 0.77 | 0.61-0.98 |

**Figure D1. Network Diagram for NMA in Patients with a Recent MI**

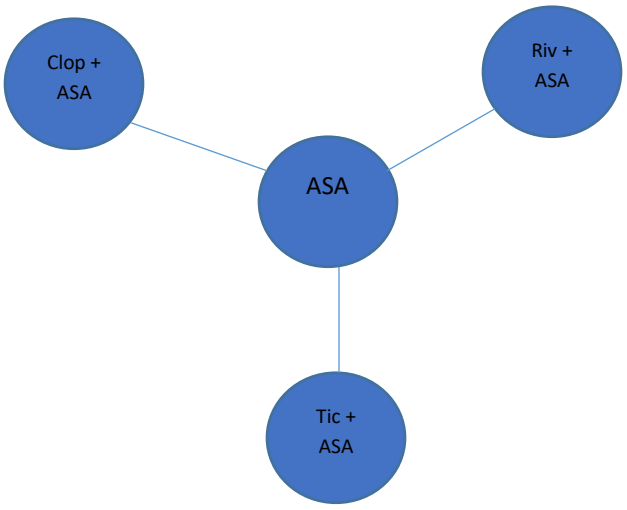


**Table D10. Study Quality of REDUCE-IT**

| Study | Comparable Groups | Adequate Randomization | Patient Blinding | Physician Blinding | Outcome Adjudication Blinding | Non-Differential Follow-Up | ITT Analysis | Appropriate Handling of Missing Data | Overall Quality |
|---|---|---|---|---|---|---|---|---|---|
| REDUCE-IT | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Good |

ITT: intention-to-treat

**Table D11. Study Design of REDUCE- IT**

| Study | REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl—Intervention Trial) |
|---|---|
| **Design** | Phase IIIb, multicenter, double-blind, placebo-controlled, randomized trial with parallel assignment |
| **Inclusion Criteria** | ***General Criteria***<br>• ≥45 years with established CVD (Secondary Prevention Cohort) OR ≥50 years with diabetes mellitus and ≥1 additional risk factor for CVD (Primary Prevention Cohort)<br>• Fasting triglyceride levels ≥135 mg/dL and <500 mg/dL<br>• LDL-C >40 mg/dL and ≤100 mg/dL<br>• On stable statin therapy (with or without ezetimibe) for ≥4 weeks<br>***Secondary Prevention Cohort*** (≥45 years with ≥1 of the following):<br>• Documented CAD (≥1 of the following):<br>  ○ Documented multivessel CAD (≥50% stenosis in ≥2 major arteries, with or without revascularization)<br>  ○ Documented prior MI<br>  ○ Hospitalization for high risk NSTE-ACS<br>• Documented cerebrovascular or carotid disease (≥1 of the following):<br>  ○ Prior ischemic stroke<br>  ○ Symptomatic carotid artery disease with ≥50% carotid arterial stenosis<br>  ○ Asymptomatic carotid artery disease with ≥70% carotid arterial stenosis<br>  ○ History of carotid revascularization<br>• Documented PAD (≥1 of the following):<br>  ○ Ankle-brachial index <0.9 with symptoms of intermittent claudication or<br>  ○ History of aortoiliac or peripheral arterial intervention<br>***Primary Prevention Cohort*** (≥50 years with diabetes mellitus and ≥1 of the following additional risk factors for CVD):<br>• Men ≥55 years and women ≥65 years<br>• Cigarette smoker within three months<br>• Hypertension (SBP ≥140 mm Hg OR DBP ≥90 mm Hg)<br>• HDL-C ≤40 mg/dL for men or ≤50 mg/dL for women<br>• hsCRP >3 mg/L<br>• Renal dysfunction<br>• Retinopathy<br>• Micro- or macroalbuminuria<br>• Ankle-brachial index <0.9 without symptoms of intermittent claudication |
| **Exclusion Criteria** | • Severe (class IV) heart failure<br>• Any life-threatening disease expected to result in death within the next two years (other than CVD)<br>• Active severe liver disease<br>• History of pancreatitis |

| | |
|---|---|
| | • HbA1c >10%<br>• Poorly controlled hypertension (SBP ≥200 mm Hg OR DBP ≥100 mm Hg) despite antihypertensive treatment<br>• Planned coronary intervention or any other major surgical procedure<br>• Known hypersensitivity to fish or shellfish, or ingredients of the study treatments<br>• Use of non-statin lipid-altering medications, dietary supplements, or foods (e.g., niacin, PCSK9 inhibitors, products containing omega-3 fatty acids) unless washout |
| **N** | 8,179 |
| **Interventions** | • Icosapent ethyl 4 g/day (n=4,089)<br>• Placebo (n=4,090) |
| **Follow-Up** | Median 4.9 years (maximum 6.2 years) |
| **Outcomes** | • ***Primary Endpoint:*** A composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina<br>• ***Key Secondary Endpoint:*** A composite of CV death, nonfatal MI, or nonfatal stroke<br>• ***Other Secondary Efficacy Endpoints:***<br>  ○ A composite of CV death or nonfatal MI<br>  ○ A composite of death from any cause, nonfatal MI, or nonfatal stroke<br>  ○ Death from any cause<br>  ○ CV death<br>  ○ Fatal or nonfatal MI<br>  ○ Fatal or nonfatal stroke<br>  ○ Urgent or emergency revascularization<br>  ○ Hospitalization for unstable angina<br>• ***Tertiary/Exploratory Efficacy Endpoints (selected):***<br>  ○ Total (first and subsequent) CV events<br>  ○ New coronary heart failure<br>  ○ Transient ischemic attack<br>  ○ Amputation for peripheral vascular disease<br>  ○ Carotid revascularization<br>  ○ New onset type 2 diabetes or hypertension<br>  ○ Cardiac arrhythmias requiring hospitalization ≥24 h<br>  ○ Cardiac arrest |

CAD: coronary artery disease, CVD: cardiovascular disease, DBP: diastolic blood pressure, HbA1c: glycated hemoglobin. HDL-C: high-density lipoprotein-cholesterol, hsCRP: high-sensitivity C-reactive protein, LDL-C: low-density lipoprotein- cholesterol; MI: myocardial infarction, NSTE-ACS: non–ST-segment elevation acute coronary syndrome, PAD: peripheral artery disease, SPB: systolic blood pressure

**Table D12. Key Baseline Characteristics of REDUCE-IT[19,20]**

| Characteristic | Icosapent Ethyl 4 g/d (n=4089) | Placebo (n=4090) |
|---|---|---|
| ***Demographics and Cardiovascular Risk*** | | |
| Age, Median (IQR) | 64.0 (57.0-69.0) | 64.0 (57.0-69.0) |
| BMI, Median (IQR) | 30.8 (27.8-34.5) | 30.8 (27.9-34.7) |
| Secondary Prevention, No. (%) | 2892 (70.7) | 2893 (70.7) |
| Primary Prevention, No. (%) | 1197 (29.3) | 1197 (29.3) |
| Type 2 Diabetes, No. (%) | 2367 (57.9) | 2363 (57.8) |
| Prior MI, No. (%) | 1938 (47.4) | 1881 (46.0) |
| Prior Unstable Angina, No. (%) | 1017 (24.9) | 1015 (24.8) |
| Hypertension, No. (%) | 3541 (86.6) | 3543 (86.6) |
| ***Concomitant Medications*** | | |
| High Statin Intensity, No. (%) | 1290 (31.5) | 1226 (30.0) |
| Moderate Statin Intensity, No. (%) | 2533 (61.9) | 2575 (63.0) |
| Low Statin Intensity, No. (%) | 254 (6.2) | 267 (6.5) |
| Ezetimibe, No. (%) | 262 (6.4) | 262 (6.4) |
| Anti-Diabetic, No. (%) | 2190 (53.6) | 2196 (53.7) |
| Anti-Hypertensive, No. (%) | 3895 (95.3) | 3895 (95.2) |
| Anti-Platelet, No. (%) | 3257 (79.7) | 3236 (79.1) |
| ACE Inhibitor, No. (%) | 2112 (51.7) | 2131 (52.1) |
| ARB, No. (%) | 1108 (27.1) | 1096 (26.8) |
| Beta-Blocker, No. (%) | 2902 (71.0) | 2880 (70.4) |
| ***Laboratory Parameters*** | | |
| hsCRP, Median (IQR) | 2.2 (1.1-4.5) | 2.2 (1.1-4.5) |
| TG, Median (IQR) | 216.5 (176.5-272.0) | 216.0 (175.5-274.0) |
| HDL-C, Median (IQR) | 40.0 (34.5-46.0) | 40.0 (35.0-46.0) |
| LDL-C, Median (IQR) | 74.0 (61.5-88.0) | 76.0 (63.0-89.0) |
| EPA (µg/mL), Median (IQR) | 26.1 (17.1-40.1) | 26.1 (17.1-39.9) |

ARB: angiotensin II receptor blockers; BMI: body mass index, EPA: eicosapentaenoic acid, HDL-C: high-density lipoprotein- cholesterol, hsCRP: high-sensitivity c-reactive protein, IQR: interquartile range, LDL-C: low-density lipoprotein- cholesterol, No.: number of patients, TG: triglyceride

**Table D13. Key Efficacy Outcomes in REDUCE-IT[19] at a Median of 4.9 Years of Follow-Up**

| Outcome | Icosapent Ethyl 4 g/d (n=4089) | Placebo (n=4090) | HR (95% CI) | P-Value |
|---|---|---|---|---|
| ***Primary Outcome*** | | | | |
| CV Death, Nonfatal MI, Nonfatal Stroke, Revascularization, or Unstable Angina, No. (%) | 705 (17.2) | 901 (22.0) | 0.75 (0.68-0.83) | <0.001 |
| ***Individual Components of Primary Outcome*** | | | | |
| CV Death, No. (%) | 174 (4.3) | 213 (5.2) | 0.80 (0.66-0.98) | 0.03 |
| Nonfatal MI, No. (%) | 237 (5.8) | 332 (8.1) | 0.70 (0.59-0.82) | NR |
| Nonfatal Stroke, No. (%) | 85 (2.1) | 118 (2.9) | 0.71 (0.54-0.94) | NR |
| Revascularization, No. (%) | 376 (9.2) | 544 (13.3) | 0.66 (0.58-0.76) | NR |
| Hospitalization for Unstable Angina, No. (%) | 108 (2.6) | 157 (3.8) | 0.68 (0.53-0.87) | 0.002 |
| ***Key Secondary Outcome*** | | | | |
| CV Death, Nonfatal MI, or Nonfatal Stroke, No. (%) | 459 (11.2) | 606 (14.8) | 0.74 (0.65-0.83) | <0.001 |
| ***Other Secondary Outcomes*** | | | | |
| CV Death or Nonfatal MI, No. (%) | 392 (9.6) | 507 (12.4) | 0.75 (0.66-0.86) | <0.001 |
| Death from Any Cause, Nonfatal MI, or Nonfatal Stroke, No. (%) | 549 (13.4) | 690 (16.9) | 0.77 (0.69-0.86) | <0.001 |
| Death from Any Cause, No. (%) | 274 (6.7) | 310 (7.6) | 0.87 (0.74-1.02) | NS |
| Fatal or Nonfatal MI, No. (%) | 250 (6.1) | 355 (8.7) | 0.69 (0.58-0.81) | <0.001 |
| Fatal or Nonfatal Stroke , No. (%) | 98 (2.4) | 134 (3.3) | 0.72 (0.55-0.93) | 0.01 |
| Emergency or Urgent Revascularization, No. (%) | 216 (5.3) | 321 (7.8) | 0.65 (0.55-0.78) | <0.001 |

CV: cardiovascular, CI: confidence interval, HR: hazard ratio, No. number of patients, NS: not significant, MI: myocardial infarction

**Table D14. Key Safety Events in REDUCE-IT[19] at a Median of 4.9 Years of Follow-Up**

| Event | Icosapent Ethyl 4 g/d (n=4089) | Placebo (n=4090) | P-Value |
|---|---|---|---|
| Any TEAE, No. (%) | 3343 (81.8) | 3326 (81.3) | 0.63 |
| Serious TEAE, No. (%) | 1252 (30.6) | 1254 (30.7) | 0.98 |
| TEAE Leading to Withdrawal of Study Drug, No. (%) | 321 (7.9) | 335 (8.2) | 0.60 |
| Serious TEAE Leading to Withdrawal of Study Drug, No. (%) | 88 (2.2) | 88 (2.2) | 1.00 |
| Serious TEAE Leading to Death, No. (%) | 94 (2.3) | 102 (2.5) | 0.61 |
| *Bleeding TEAEs* | | | |
| Any Bleeding-Related Disorder , No. (%) | 111 (2.7) | 85 (2.1) | 0.06 |
| GI Bleeding, No. (%) | 62 (1.5) | 47 (1.1) | 0.15 |
| Central Nervous System Bleeding, No. (%) | 14 (0.3) | 10 (0.2) | 0.42 |
| Other Bleeding, No. (%) | 41 (1.0) | 30 (0.7) | 0.19 |
| *AEs occurring ≥5%* | | | |
| Peripheral Edema, No. (%) | 267 (6.5) | 203 (5.0) | 0.002 |
| Atrial Fibrillation, No. (%) | 215 (5.3) | 159 (3.9) | 0.003 |
| Constipation, No. (%) | 221 (5.4 ) | 149 (3.6) | <0.001 |
| Diarrhea, No. (%) | 367 (9.0) | 453 (11.1) | 0.002 |
| Anemia, No. (%) | 191 (4.7) | 236 (5.8) | 0.03 |
| Back Pain, No. (%) | 335 (8.2) | 309 (7.6) | 0.29 |
| Hypertension, No. (%) | 320 (7.8) | 344 (8.4) | 0.35 |
| Nasopharyngitis, No. (%) | 314 (7.7) | 300 (7.3) | 0.56 |
| Arthralgia, No. (%) | 313 (7.7) | 310 (7.6) | 0.9 |
| Upper Respiratory Tract Infection, No. (%) | 312 (7.6) | 320 (7.8) | 0.77 |
| Bronchitis, No. (%) | 306 (7.5) | 300 (7.3) | 0.8 |
| Chest pain, No. (%) | 273 (6.7) | 290 (7.1) | 0.48 |
| Pneumonia, No. (%) | 263 (6.4) | 277 (6.8) | 0.56 |
| Influenza, No. (%) | 263 (6.4) | 271 (6.6) | 0.75 |
| Dyspnea, No. (%) | 254 (6.2) | 240 (5.9) | 0.52 |
| Urinary Tract Infection, No. (%) | 253 (6.2) | 261 (6.4) | 0.75 |
| Cough, No. (%) | 241 (5.9) | 241 (5.9) | 1.00 |
| Osteoarthritis, No. (%) | 241 (5.9) | 218 (5.3) | 0.27 |
| Dizziness, No. (%) | 235 (5.7) | 246 (6.0) | 0.64 |
| Pain in Extremity, No. (%) | 235 (5.7) | 241 (5.9) | 0.81 |
| Cataract, No. (%) | 233 (5.7) | 208 (5.1) | 0.22 |
| Fatigue, No. (%) | 228 (5.6) | 196 (4.8) | 0.11 |

AE: adverse event, GI: gastrointestinal, No.: number of patients, TEAE: treatment-emergent adverse event

**Table D15. Key Safety Events in MARINE[66] and ANCHOR[67] at 12 Weeks**

| | MARINE | | ANCHOR | |
|---|---|---|---|---|
| | Icosapent Ethyl 4 g/d (n=77) | Placebo (n=76) | Icosapent Ethyl 4 g/d (n=233) | Placebo (n=233) |
| Any TEAE, No. (%) | 27 (35.1) | 28 (36.8) | 106 (45.5) | 112 (48.1) |
| Serious Adverse Event, No. (%) | 1 (1.3) | 0 | 7 (3.0) | 5 (2.1) |
| TEAE Leading to Withdrawal of Study Drug, No. (%) | 0 | 3 (3.9) | 5 (2.1) | 12 (5.2) |
| Musculoskeletal and Connective Tissue Disorders, No. (%) | NR | NR | 18 (7.7) | 10 (4.3) |
| Arthralgia, No. (%) | NR | NR | 4 (1.7) | 1 (0.4) |
| GI Disorders, No. (%) | NR | NR | 27 (11.6) | 40 (17.2) |
| Diarrhea, No. (%) | 1 (1.3) | 5 (6.6) | 8 (3.4) | 10 (4.3) |
| Nausea, No. (%) | 1 (1.3) | 4 (5.3) | 5 (2.1) | 7 (3.0) |
| Eructation, No. (%) | 0 | 3 (3.9) | 2 (0.9) | 4 (1.7) |
| Infections and Infestations, No. (%) | NR | NR | 31 (13.3) | 38 (16.3) |
| Nasopharyngitis, No. (%) | NR | NR | 1 (0.4) | 7 (3.0) |

GI: gastrointestinal, No.: number of patients, TEAE: treatment-emergent adverse event

# Appendix E. Comparative Value Supplemental Information

**Table E1. Impact Inventory**

| Sector | Type of Impact (Add Additional Domains, as Relevant) | Included in This Analysis from… Perspective? | | Notes on Sources (if Quantified), Likely Magnitude & Impact (if Not) |
|---|---|---|---|---|
| | | Health Care Sector | Societal | |
| **Formal Health Care Sector** | | | | |
| **Health Outcomes** | Longevity effects | X | X | |
| | Health-related quality of life effects | X | X | |
| | Adverse events | X | X | |
| **Medical Costs** | Paid by third-party payers | X | X | |
| | Paid by patients out-of-pocket | ☐ | ☐ | |
| | Future related medical costs | ☐ | ☐ | |
| | Future unrelated medical costs | ☐ | ☐ | |
| **Informal Health Care Sector** | | | | |
| **Health-Related Costs** | Patient time costs | NA | ☐ | |
| | Unpaid caregiver time costs | NA | ☐ | |
| | Transportation costs | NA | ☐ | |
| **Non-Health Care Sectors** | | | | |
| **Productivity** | Labor market earnings lost | NA | X | |
| | Cost of unpaid lost productivity due to illness | NA | X | |
| | Cost of uncompensated household production | NA | ☐ | |
| **Consumption** | Future consumption unrelated to health | NA | ☐ | |
| **Social Services** | Cost of social services as part of intervention | NA | ☐ | |
| **Legal/Criminal Justice** | Number of crimes related to intervention | NA | ☐ | |
| | Cost of crimes related to intervention | NA | ☐ | |
| **Education** | Impact of intervention on educational achievement of population | NA | ☐ | |
| **Housing** | Cost of home improvements, remediation | NA | ☐ | |
| **Environment** | Production of toxic waste pollution by intervention | NA | ☐ | |
| **Other** | Other impacts (if relevant) | NA | ☐ | |

NA: not applicable

Adapted from Sanders et al.[117]

**Description of the evLYG Calculations**

The cost per evLYG considers any extension of life at the same "weight" no matter what treatment is being evaluated. Below are the stepwise calculations used to derive the evLYG.

i) First, we attribute a utility of 0.851, the age- and gender-adjusted utility of the general population in the U.S. that are considered healthy.[118]

ii) For each cycle (cycle i) in the model where using the intervention results in additional years of life gained, we multiply this general population utility with the additional life years gained (ΔLYG).

iii) We sum the product of the life years and average utility (cumulative LYs/cumulative QALYs) for cycle i in the comparator arm with the value derived in step 2 to derive the equal value of life years (evLY) for that cycle.

iv) If no life years were gained using the intervention versus the comparator, we use the conventional utility estimate for that cycle i.

v) The total evLY is then calculated as the cumulative sum of QALYs gained using the above calculations for each arm.

vi) We use the same calculations in the comparator arm to derive its evLY.

vii) Finally, the evLYG is the incremental difference in evLY between the intervention and the comparator arms.

**Table E2. Model Cohort Characteristics for DAPT Scenario Analysis**

| Characteristic | Clopidogrel + ASA | ASA Alone | Source |
|---|---|---|---|
| Age, Yrs., Median | 64 | 64 | [18] |
| Male (%) | 72.7 | 73.1 | |
| Smoking (% Yes) | 21.6 | 22.2 | |
| Diabetes (% Yes) | 30.8 | 31.3 | |
| Prior MI | 40.2 | 41.0 | |
| Prior Ischemic Stroke | 34.5 | 34.0 | |
| Congestive Heart Failure | 6.3 | 6.5 | |
| Atrial Fibrillation | 3.6 | 3.4 | |
| PAD | 32.3 | 32.3 | |
| Hypertension | 68.3 | 69.9 | |
| Hypercholesterolemia | 69.8 | 70.5 | |
| Angiotensin II Receptor Blockers | 21.9 | 22.1 | |
| Calcium-Channel Blocker | 33.8 | 34.7 | |
| Diuretic | 44.4 | 44.0 | |
| Beta-Blocker | 55.7 | 56.8 | |

From CHARISMA post-hoc analysis in patients with prior MI, documented prior ischemic stroke, or symptomatic PAD.

**Table E3. Clinical Inputs and Costs for DAPT Scenario Analysis**

| Input | Rivaroxaban + ASA vs. ASA | Clopidogrel + ASA vs. ASA | Rivaroxaban + ASA vs. Clopidogrel + ASA |
|---|---|---|---|
| Estimated HR for Composite Primary Endpoint* | 0.70 (0.48-1.02) | 0.77 (0.61-0.98) | 0.91 (0.58-1.40) |
| | WAC per Dose | Price per Year | |
| Clopidogrel* | $0.18 per 75mg tablet | $65.70 | |

*A network meta-analysis was conducted as part of the clinical review to estimate the comparative risk of a composite endpoint of cardiovascular death, stroke, or MI between each of the regimens of focus.
†Dosage 75mg/day. Wholesale acquisition cost (WAC) per Redbook®.[33]

**Table E4. Efficacy Estimates for DAPT Scenario Analysis**

| Parameter | Clopidogrel + ASA n (%) | ASA Alone n (%) | HR (95% CI) | *P*-Value | Source |
|---|---|---|---|---|---|
| Composite Primary Endpoint: Stroke, CV Death, MI | 347 (7.3) | 416 (8.8) | 0.829 (0.719-0.956) | 0.010 | [18] |
| Stroke* | 144 (3.0) | 179 (3.8) | 0.802 (0.644–0.998) | 0.048 | |
| Ischemic Stroke* | 126 (2.7) | 152 (3.2) | 0.828 (0.654-1.048) | 0.115 | |
| CV Death | 142 (3.0) | 163 (3.4) | 0.870 (0.695-1.090) | 0.224 | |
| MI* | 117 (2.5) | 145 (3.1) | 0.805 (0.631-1.027) | 0.080 | |
| Severe Bleeding | 79 (1.7) | 71 (1.5) | 1.114 (0.808-1.535) | 0.509 | |

*Fatal plus nonfatal events.

The CHARISMA trial had a median follow-up of 28 months.

**Table E5. Weighted Average Stroke Utility Estimate using COMPASS Control Arm**

| Stroke Severity, Modified Ranking Scale (mRS) | mRS Score Description | Stroke Utility* | Control Arm (n) | Control Arm Weight | Source |
|---|---|---|---|---|---|
| **mRS score 0** | No symptoms at all | 0.92 | 29 | 0.2057 | [14,95] |
| **mRS score 1** | No significant disability despite symptoms; able to carry out all usual duties and activities | 0.85 | 32 | 0.2270 | |
| **mRS score 2** | Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance | 0.77 | 27 | 0.1915 | |
| **mRS score 3** | Moderate disability; requiring some help, but able to walk without assistance | 0.64 | 16 | 0.1135 | |
| **mRS score 4** | Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance | 0.41 | 18 | 0.1277 | |
| **mRS score 5** | Severe disability; bedridden, incontinent, and requiring constant nursing care and attention | 0.14 | 7 | 0.0496 | |
| **mRS score 6** | Dead | | 12 | 0.0851 | |
| ***Weighted Stroke Utility Value*** | 0.6615 | | | | |

*These utility values were elicited from the general US population using the time trade-off method and EQ-5D-3L.

**Table E6. Model Comparison Results**

| Model | Cumulative Incidence of Total Events at 36 Months‡ | Incremental Cost (Discounted) | Incremental QALYs | ICER (per QALY) |
|---|---|---|---|---|
| Model with Fonarow et al. Inputs† | 14.6% | $120,307 | 0.28 | $435,169 |
| Fonarow et al. Model Findings* | 14.9% | $139,817 | 0.34 | $413,579 |

*Table 3, FOURIER trial participants, full annual list price of $14,500.[107]

†Inputs changed include baseline risk to FOURIER trial participants, health state costs, intervention effects, baseline demographics and lipid panels, discontinuation. Indirect costs were not included, and health state utility input calculations differed between models.

‡Sabatine et al. Figure 2A.[119]

**Table E7. Rivaroxaban Model Calibration**

| Model | Sum of First MI, First Stroke, and CV Death | First MI | First Stroke | CV Death* |
|---|---|---|---|---|
| Model Estimate at 2 Years (3 Cycles in the Model for Death; 2 Cycles for MI, Stroke) | 6% | 2.2% | 1.5% | 2.2% |
| Trial-Based Findings at 23 Months | 6% | 2.2% | 1.6% | 2.2% |

*From Eikelboom *NEJM* 2017.[11]

**Table E8. Icosapent Ethyl Model Calibration**

| Model | Sum of First MI, First Stroke, and CV Death* | First MI | First Stroke | CV Death* |
|---|---|---|---|---|
| Model Estimate at 5 Years (6 Cycles in the Model for Death; 5 Cycles for MI, Stroke) | 16.1% | 8.2% | 2.7% | 5.2% |
| Trial-Based Cumulative Incidence Sum of Composite Endpoints at 5 Years | 16.2% | 8.1% | 2.9% | 5.2% |

*From Bhatt *NEJM* 2019 (approximate).[92]

†Bhatt *NEJM* 2019 Supplementary Figure 3.[92]

# Appendix F. Public Comment

*This section includes summaries of the public comments prepared for the Midwest CEPAC Public Meeting on September 26, 2019 in St. Louis, MO. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery.*

*A video recording of all comments can be found here, beginning at minute 01:28:55. Conflict of interest disclosures are included at the bottom of each statement for each speaker who is not employed by a pharmaceutical manufacturer.*

**Alina Kolomeyer, Pharm.D.**
**Associate Director, Corporate Alliances at Amarin**

On behalf of my colleagues at Amarin Pharma, Inc, thank you for the opportunity to submit comments for the record following the September 26, 2019 Midwest Comparative Effectiveness Public Advisory Council (CEPAC) Institute for Clinical and Economic Review's (ICER) Public Meeting on additive therapies for cardiovascular (CV) disease. We thank ICER and the Midwest CEPAC for the opportunity to meet with experts in the field, the public, and fellow manufacturers, and to share Amarin's position on ICER's Draft Evidence Report.

Amarin takes very seriously its mission of developing innovative, life-saving, and quality-of-life enhancing medicines for patients and in conducting rigorous, high-quality science to clearly evaluate their benefits.

While statin use and optimal medical management have reduced cardiovascular risk and improved patient health outcomes over the last few decades, substantial residual cardiovascular risk remains. This residual risk represents an important unmet medical need for patients and accounts for significant health care and economic burden.

With regard to ICER's economic analysis, Amarin believes that it's essential to use all of the evidence from REDUCE-IT in the economic analysis, including (1) using all five components of the prespecified primary endpoint in the Markov model base-case analysis and (2) using total event data. We believe it is beneficial to use a patient-level, microsimulation approach to modeling as well as incorporating more recent US national cost data for cardiovascular events.

In REDUCE-IT, 16 hospitalizations for unstable angina and 76 coronary revascularization procedures were prevented per 1000 patients treated over a five-year period. Despite ICER's analysis reaching favorable conclusions based on select events, these data represent clinically meaningful and statistically significant benefits for patients, as well as cost offsets for payers,

and should be included in the base-case cost-effectiveness and budget impact analyses due to the high quality of this scientific evidence.

We also believe that recurrent long-term, downstream cardiovascular events after the first cardiovascular event involve real costs to patients, payers, and society, and need to be included in the model. Each component of the primary endpoint was reduced by icosapent ethyl therapy in a statistically significant, clinically meaningful, and economically relevant manner.

On behalf of Amarin, we again thank ICER and the Midwest CEPAC for the opportunity to submit comments and to be part of an open dialogue around the clinical and economic benefits of icosapent ethyl to patients, payers, and society. Amarin is dedicated to working with relevant stakeholders to ensure access for eligible and appropriate patients to innovative, life-saving, and quality-of-life-enhancing therapies such as icosapent ethyl.

**Marie Warshauer, M. Ed.**
**Former Program Director of WomenHeart: the National Coalition for Women with Heart Disease**

Why am I here? Eighteen years ago my life changed. In my early 40's I was busy raising three boys, exercising, eating healthy, just living a busy life, however my heart had other ideas. After several trips to my GP, complaining of being exhausted, having numbness in my left arm and feeling short of breath, I was diagnosed with Coronary Artery Disease. I had 99% blockage in my LAD. Angioplasty was preformed unexpectedly the day of my stress test. Five months later stents had closed, bypass surgery followed by several months of rehab all while adding on to our home. My life, my family's life had changed.

Why am I here? As one of the first women to participate in WomenHeart's Science and Leadership Symposium, I learned about the science of my disease as well as understanding that it was also a disease that touches your confidence, emotional balance, and depth of understanding for what I am now living with. Understanding that I would forever be on medications that might cause side effects, cause damage to other organs, make a difference in so many ways other than how it helps my heart was just the start. Through WomenHeart I learned the value of participating in drug trials and research studies. With patient help, the research might be of value to so many and not just me.

Why am I here? In 2005 just as we are getting ourselves settled after my diagnosis, my husband is diagnosed with a meningioma. His easy surgery was anything but. After a month in the hospital and weeks in a rehab center learning to walk, swallow, and talk again, our home became a full time health care center. I was no longer the patient I had become the caregiver. The navigation of the medical world was truly an eye opening experience. My husband endured 10 years of medical chaos and disconnected care. We quickly learned the ropes and had the where with all to be able to seek additional advice. Our nonstop research and inquiring about treatments or to try new drugs and explore how we could keep David with us longer kept us going. We sought out holistic treatments, acupuncture, therapeutic massages, exercise and meditation all in the name of trying to make a difference.

Why am I here? Because I have experienced first hand the side effects and challenges of taking various drugs. Emotional impact of taking medicines include being afraid to change drugs or brands of

drugs, dose adjustments, lack of sleep or being constantly tired. Stomach problems, headaches, and weight gain, long-term effects. The drugs caused emotional ups and down's. Remembering to take them at the right time. The expense.

The effects of the variety of drugs my husband was given changed his personality, made him grumpy, made a difference on what he could and wanted to eat. In so many ways it controlled his life. Every time he went to the doctor there were new prescriptions. What do we do with the old medicine we have hardly used? How does someone who is ill keep track of when they are to take what drug? How do patients know if drug A or B causing the side effect? How does a drug interact with other meds? How will it help me?

I am here today to make a small contribution to something I would hope helps others navigate the world of medical diagnosis and the drugs we take to make us feel better.

*Marie Warshauer has no conflicts of interest to disclose.*

**Taylor Kelly**
**Law Clerk at DCBA Law & Policy, Policy Advisor at Aimed Alliance**

Aimed Alliance is pleased that the Institute for Clinical and Economic Review (ICER) has deemed rivaroxaban and icosapent ethyl to be cost effective. Yet, we remain concerned that its analysis and recommendations will impact patient access by encouraging the use of restrictive policies on plan formularies, such as prior authorization and step therapy, to control costs. Such policies can be unethical and inconsistent with standards of care, interfere with the patient-practitioner relationship, and result in significant delays to prescribed treatments.

Moreover, ICER's analysis does not appear to incorporate several important considerations into its potential budget impact analysis and value-based benchmark prices, such as data that represents the patient perspective; data from two of the REDUCE-IT trial's primary endpoints – coronary revascularization and hospitalization; and adequate data about the risk of subsequent adverse events. We believe that the exclusion of such pertinent data does not adequately capture the full value that these therapies provide to patients.

Finally, Aimed Alliance reiterates its long-standing opposition to the use of QALYs. QALYs can result in inappropriate health care rationing and discrimination based on age and health status, unfairly favoring younger and healthier populations. QALYs put a price tag on the value of a human life that merely reflects the individual's diagnosis and deems those with chronic, debilitating, and rare conditions, such as cardiovascular disease, as being worth less than the rest of us.

*Taylor Kelly is an employee of DCBA Law & Policy, a law firm whose practice is focused on corporate, drug and device, and health law. The majority of DCBA's clients are health care companies, health care professionals, biopharmaceutical companies, and not-for-profit organizations, and it consequently receives more than 25% of its funding from these organizations and individuals. Aimed Alliance is a client of DCBA.*

# Appendix G. Conflict of Interest Disclosures

Tables G1 through G3 contain conflict of interest (COI) disclosures for all participants at the September 26, 2019 Public meeting of the Midwest CEPAC.

**Table G1. ICER Staff and Consultant COI Disclosures**

| Name | Organization | Disclosures |
|---|---|---|
| **Ellie Adair, MPA** | Institute for Clinical and Economic Review | * |
| **Daniel A. Ollendorf, PhD** | Tufts Medical Center | Received funding from ICER for this evaluation and report |
| **Jonathan Campbell, PhD** | University of Colorado | * |
| **Katherine Fazioli** | Institute for Clinical and Economic Review | * |
| **Serina Herron-Smith** | Institute for Clinical and Economic Review | * |
| **R. Brett McQueen** | University of Colorado | * |
| **Steve Pearson, MD, MSc** | Institute for Clinical and Economic Review | * |
| **Michelle Poulin** | Institute for Clinical and Economic Review | * |
| **David Rind, MD, MSc** | Institute for Clinical and Economic Review | * |
| **Patty Synnott, MALD, MS** | Institute for Clinical and Economic Review | * |

**Table G2. Midwest CEPAC Panel Member COI Disclosures**

| Name | Organization | Disclosures |
|---|---|---|
| **Eric Armbrecht, PhD** | Saint Louis University Center for Health Outcomes Research, School of Medicine and College for Public Health & Social Justice | * |
| **Bijan Borah, PhD** | Mayo Clinic College of Medicine and Science | * |
| **Aaron Carroll, MD, MS** | Indiana University School of Medicine | * |
| **Donald Casey, MD, MPH, MBA** | Medicision | * |
| **Gregory Curfman, MD** | JAMA | * |
| **Jill Johnson, PharmD** | University of Arkansas for Medical Sciences | * |
| **Timothy McBride, PhD** | Center for Health Economics and Policy, Washington University in St. Louis | * |
| **Rachel Sachs, JD, MPH** | Washington University in St. Louis | |
| **Kurt Vanden Bosch, PharmD** | St. Luke's Health System | * |
| **Timothy Wilt, MD, MPH** | Minnesota Evidence-Based Synthesis Program, Minneapolis VA Center for Chronic Disease Outcomes Research | * |
| **Stuart Winston** | Integrated Health Associates, St Joseph Mercy Health System | * |

* No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

**Table G3. Policy Roundtable Participant COI Disclosures**

| Name | Organization | Disclosures |
|---|---|---|
| **Andrea Baer, MS, MCPA** | Mended Hearts | Mended Hearts has received more than $5,000 in funding from Janssen and AstraZeneca |
| **Chester B. Good, MD, MPH** | UPMC Health Plan | Full-time employee of UMPC Health Plan. |
| **Craig Granowitz** | Amarin Corporation | Full-time employee of Amarin Corporation |
| **Kayla Lesser** | IngenioRx | Full-time employee of IngenioRx. |
| **Jeremy Sussman, MD, MS** | University of Michigan Medical School | * |
| **Marie Warshauer** | WomenHeart, The National Coalition for Women with Heart Disease | * |
| **Jason Wasfy, MD, MPhil** | Harvard Medical School<br>Quality and Outcomes Research<br>Massachusetts General Hospital | Received speaking fees (<$5,000) for participation at the iHEAR conference sponsored by Biotronik |

* No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.