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Additive Therapies for Cardiovascular Disease: Effectiveness and Value

Modeling Analysis Plan

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Institute for Clinical and Economic Review

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1. Approach

This analysis plan details the University of Colorado modeling approach and outcomes to be assessed for the economic evaluation of additive therapies for cardiovascular disease (CVD). Refer to the protocol for details on the systematic review of the clinical evidence on this topic.

The primary aim of this analysis will be to estimate the cost-effectiveness of rivaroxaban (Xarelto®, Janssen) and icosapent ethyl (Vascepa®, Amarin Pharma) as additive therapies to optimal medical management in patients with established CVD, and in the case of icosapent ethyl, patients without evidence of CVD but with diabetes and at least one additional risk factor, using a decision analytic model. In primary analyses, the cost-effectiveness of adding rivaroxaban to aspirin (ASA) therapy will be evaluated in comparison to aspirin alone. The cost-effectiveness of adding icosapent ethyl to optimal medical management (including statins) will be evaluated in comparison to optimal medical management (including statins) alone. The base-case analysis will take a health care sector perspective (i.e., focus on direct medical care costs only), and a lifetime horizon. Productivity losses and other indirect costs will be considered in a scenario analysis, if data allow. The model will be developed in Microsoft Excel 2016 (Redmond, WA).

2. Methods

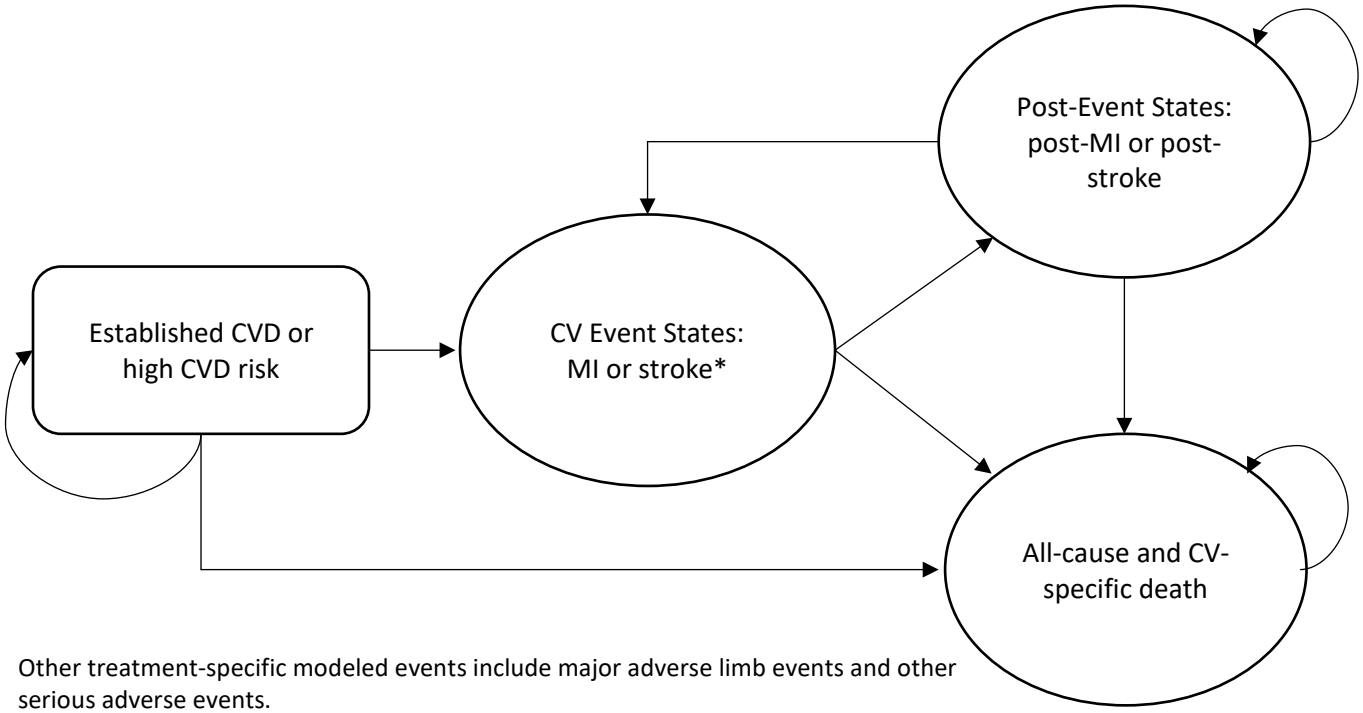
2.1 Overview and Model Structure

We will program a Markov cohort simulation model for this evaluation, based on key clinical trials, prior relevant economic models, the evidence review, and stakeholder input. Rivaroxaban and icosapent ethyl will be modeled separately sharing a similar overall model structure. The model structure will be informed by previously developed CVD models assessing the cost-effectiveness of other treatments to reduce the risk of cardiovascular events.[2-6] The model will focus 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 Markov model will include health states that define the pathways of cardiovascular disease and that have been used in previous modeling efforts. The base-case health states will include major cardiovascular (CV) events of myocardial infarction (MI) and stroke as well as post-event health states and death (from CV and other causes). A scenario analysis will include 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 (MALE), for rivaroxaban, and serious adverse events will be tracked in the model. For these additional consequences, we will assume event probabilities are equal for all living health states and therefore

will not require additional health states in the model structure. Specifically, the CVD cohort begins on treatment and may stay in that state, or pass into event states of MI or stroke (Figure 1) or death. Patients who experience a CV event move into post-event health states, where they may have higher likelihood for death as compared to the general CVD prevention population. Patients remain in the model until they die. All patients can transition to death from all-causes from any of the alive health states. Death may occur from all-cause or CV event/post-event related morality. As patients move through the model over the course of their lifetime, they collect costs and health utility weights related to management and treatment of specific CV conditions. The cumulative sum of costs and utility weights produces model outputs such as lifetime costs, life years gained, and quality-adjusted life years (QALYs).

Figure 1. Model Schematic



Other treatment-specific modeled events include major adverse limb events and other serious adverse events.
*Other CV events such as revascularization and unstable angina included in scenario analysis.

2.2 Key Model Choices and Assumptions

Model cycle length will be one year, based on what was observed in prior published economic models and clinical data. The base case analysis will assume a lifetime horizon, consistent with the ICER Value Framework. Given the limited duration of treatment in key clinical trial evidence, we will evaluate a shorter treatment time horizon (five years) in a scenario analysis. The base case analysis will take a health care sector perspective and thus focus on direct medical care costs only. Costs and outcomes will be discounted at 3% per year. Key model assumptions are described in Table 1.

Table 1. Key Model Assumptions

Assumption	Rationale
Individual hazard ratios (HRs) will be used for each subcomponent of composite endpoints observed in the clinical trials. Endpoint subcomponents include the common major adverse cardiovascular events: MI, stroke, and CV death. Other CV events (e.g., revascularization and unstable angina) will be evaluated in a scenario analysis.	Given differences across the severity of endpoints in terms of costs, disutility, or likelihood of CV death, endpoint subcomponents are tracked in the model. Relative reductions in other CV events such as revascularization and unstable angina are 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) will have 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 are statistical concerns regarding correlations between subsequent event types. However, the model will be 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. Scenario analyses will describe alternative approaches.
Patients can have more than one event in the same cycle. There will be additive costs and disutilities for multiple events.	By assuming that the costs and disutility of a stroke may be added to that of the costs and disutility of an MI, multiple events within a model cycle are allowed for this cohort-level model.
There is a higher risk of CV death for patients in a CV event or post-event health state.	Literature-based evidence.[7-12]
Model event rate will be consistent with control arm cumulative event (MI, stroke, and CV death) rates from clinical trials.	The trial evidence suggests high risk populations. Thus, the model will calibrate to the trial populations in terms of cumulative MI, stroke, and CV death events.
Patients continue on treatment after first event in the model.	Patients continuing on therapy after an event is consistent with the trial evidence.
Patients who discontinue treatment are not re-treated with the same initiating therapy. Discontinuation rates will mirror trial evidence and will be forecasted based on annualized discontinuation due to serious adverse events.	Patients discontinuing therapy did not re-initiate in the trials for both therapies. After the average trial duration, the model will assume an annualized discontinuation rate consistent with discontinuation due to serious adverse events from the trials.

2.3 Populations

The population of focus for this economic evaluation is adults with established CVD being treated with optimal medical management. The modeled populations will be consistent with those described in the pivotal trials cited in Tables 2 and 3. Note that for the assessment of icosapent ethyl, patients without known CVD but at high risk for cardiovascular (CV) events are also considered. Table 2 suggests that 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. Table 3 suggests that 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.

Table 2. Baseline Population Characteristics for Rivaroxaban Evaluation

Characteristic	Overall	Rivaroxaban + ASA (N=9152)	Aspirin Alone (N=9126)	Source
Age, yrs, Mean (SD)	68.2 (7.9)	68.3 (7.9)	68.2 (8.0)	13,14
Male (%)	78.0	77.5	78.2	
Total Cholesterol, mmol/liter	4.3 (3.5)	4.2 (1.1)	4.2 (1.1)	
Systolic Blood Pressure, mmHg	135.5 (17.57)	136.0 (17.0)	136.0 (17.0)	
Smoking (% Yes)	21.4	21.2	21.6	13
Diabetes (% Yes)	37.9	37.7	38.1	13,14
Prior Myocardial Infarction	62.1	61.8	62.7	
Prior Stroke	3.8	3.8	3.7	
Heart Failure	21.5	21.4	21.7	
Coronary Artery Disease	90.6	90.8	90.5	
Peripheral Artery Disease	27.3	27.2	27.4	
Angiotensin-Converting-Enzyme Inhibitor or Angiotensin II Receptor Blockers	--	70.7	70.8	
Calcium-Channel Blocker	--	26.4	27.2	
Diuretic	--	29.8	27.2	
Beta-Blocker	--	69.8	70.1	
Lipid-Lowering Agent	--	90.0	89.4	

Table 3. Baseline Population Characteristics for Icosapent Ethyl Evaluation

Characteristic	Overall	Icosapent Ethyl	Comparator/Placebo	Source
Age, yrs, Median (IQR)	64.0	64.0 (57.0-69.0)	64.0 (57.0-69.0)	15
Male (%)	71.2	71.6	70.8	
High-Density Lipoprotein, mg/dL, Median (IQR)	40.0	40.0 (34.5-46.0)	40.0 (35.0-46.0)	
Low-Density Lipoprotein, mg/dL, Median (IQR)	75.0	74.0 (61.5-88.0)	76.0 (63.0-89.0)	
Triglycerides, mg/dL, Median (IQR)	216	216.5 (176.5-272.0)	216.0 (175.5-274.0)	
Smoking (% Yes)	15.2	*	*	16
Diabetes – Type 2 (% yes)	57.8	57.9	57.8	15,16
Prior Cardiovascular Disease Events, % Yes	70.7	70.7	70.7	15

*Data not available in publicly disclosed sources.

2.4 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 + aspirin (ASA)
    - Patients are assumed to also be receiving optimal medical management, including ASA.
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.

Data permitting, rivaroxaban plus ASA will be compared to dual antiplatelet therapy (DAPT) with ticagrelor and/or clopidogrel, based on indirect comparisons performed as part of the synthesis of available evidence.

1. Rivaroxaban comparators:

- Optimal medical management including ASA without an additional antiplatelet agent
- Dual antiplatelet therapy (data permitting, scenario analysis only)

2. Icosapent ethyl comparator:
    - Optimal medical management including statin therapy

2.5 Input Parameters

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

Clinical Inputs

Key clinical inputs for the model include validated cardiovascular disease risk prediction models, baseline trial-based clinical markers (e.g., HDL-C, LCL-C, triglycerides), baseline comorbid conditions (e.g., diabetes), and other baseline factors (e.g., smoking, event history, etc.).

Transition Probabilities

As mentioned in Section 2.1, CV events included in the base-case model are: MI, stroke, and CV-related mortality. Validated CV risk calculators[17] will be used to estimate time-varying annualized event rates within the control arm (Table 4). The control arm's 10-year risk of CV events will be calibrated such that the model produces consistent cumulative CV events over the same period as observed within the trial. For risk of subsequent event, if the risk calculator[17] suggests lower likelihood of non-fatal CV events, we will assume the same likelihood as for the first future event. Once calibrated to the trial's control arm cumulative events, these same risk calculator parameters will be also used in the model's treatment arm in combination with the treatment- and event-specific hazard ratios.

Table 4. Sources for Baseline Risk Equations for First Future Events, Subsequent Events, and Mortality

Baseline Risk Equations	Values	Source
First Future Event (Myocardial Infarction or Stroke)	Varies by age and risk factors	[17]
Subsequent Future Events (Myocardial Infarction or Stroke)	Varies by age and risk factors	[17]
Event-Specific Mortality	Increased mortality relative risk of 2.5	Multiple sources[7-12]
Mortality Post-Myocardial Infarction or Stroke	Increased mortality relative risk of 2.5	Multiple sources[7-12]
Mortality, All-Cause	Varies by age	U.S. Life Tables[18]

The treatment- and event-specific hazard ratios for endpoints from the treatment-specific clinical trials will be applied to baseline risk estimates to model the transition from the established CVD to the CV event health states at the end of each model cycle (each year). Efficacy estimates for each intervention are detailed in Tables 5 and 6. The base case will assume efficacy estimates from time to first event. Alternatives such as the relative risk of total events and the inclusion of other CV events (revascularization and unstable angina) will be evaluated in a scenario analysis.

Table 5. Efficacy Estimates for Rivaroxaban

Parameter	Rivaroxaban + ASA n (%)	ASA Alone n (%)	HR (95% CI)	*P*-Value	Source
Composite Primary Outcome: Stroke, CV Death, Myocardial Infarction*	379 (4.1)	496 (5.4)	0.76 (0.66-0.86)	<0.001	[14]
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	
Myocardial Infarction†	178 (1.9)	205 (2.2)	0.86 (0.70-1.05)	0.14	
Major Adverse Limb Events	30 (1)	56 (2)	0.54 (0.35-0.84)	0.0054	

*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.

Table 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 Myocardial Infarction	459 (11.2)	606 (14.8)	0.74 (0.65-0.83)	<0.001	[15]
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 Myocardial Infarction	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	[19]

Discontinuation

Treatment discontinuation rates will be 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).[14]

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.[19]

Beyond two years duration in the model for rivaroxaban and five years duration for icosapent ethyl, we will assume an annualized discontinuation based on serious adverse event-related discontinuation of 2.7% for rivaroxaban and 2.2% for icosapent ethyl. The observed trial-based hazard ratios will be assigned for all patients in the first two or five years of the model (no matter the discontinuation status, i.e., consistent with 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 will be assigned the observed trial-based hazard ratios whereas the proportion who discontinue treatment will be assigned the costs and outcomes consistent with optimal medical management.

Adverse Events

The model will include all reported treatment-related serious adverse events (SAEs) and bleeding events for each of the two comparisons. Each SAE will have an associated cost and disutility (if available) that will be applied for each occurrence of the event. Inputs related to SAEs for each intervention are detailed in Tables 7 and 8.

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% versus 1.9%).[14] SAEs were reported in 7.9% of patients assigned to rivaroxaban + ASA and 7.3% of patients assigned to ASA alone.[14]

Table 7. Adverse Event and Bleeding Event Parameters 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	[14]
Transfusion within 48 h after Bleeding	87 (1.0)	44 (0.5)	1.97 (1.37-2.83)	<0.001	
SAEs	721 (7.9)	662 (7.3)			[14]

*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. However, there was an observed trend toward increased serious bleeding in the icosapent ethyl arm. This did not include significant increases in serious central nervous system bleeding, gastrointestinal bleeding, or adjudicated hemorrhagic stroke. There was a small, statistically significant increase in hospitalization for atrial fibrillation or flutter endpoints.[19]

Table 8. Adverse Event Parameters for Icosapent Ethyl Evaluation

Parameter	Icosapent Ethyl	Comparator/Placebo	*P*-value	Source
Serious TEAE (%)	30.6	30.7	0.98	[19]
Hospitalization for Atrial Fibrillation or Flutter (%)	3.1	2.1	0.004	[19]
Bleeding-Related Disorders (%)	2.7	2.1	0.06	[19]

TEAE: treatment-emergent AE

Health State Utilities

Health state utilities will be derived from publicly available literature and applied to health states. Utility values are primarily from a study on preference-based EQ-5D index scores for chronic conditions in the US.[20] We will use consistent health state utility values across both comparisons. Disutilities for adverse events will be applied to the proportion with an event within each cycle.

Table 9. Health State Utilities and Disutilities

Parameter	Value	Source
Treated Population without Observed Events	0.854*	21,22
Post-Event MI (Disutility Applied to State)	-0.150	20
Post-Event Stroke (Disutility Applied to State)	-0.204	20
Event Cycle MI (Disutilities Applied to Event)	-0.0409 + -0.150	20
Event Cycle Stroke (Disutilities Applied to Event)	-0.0524 + -0.204	20
Major Bleeding (Disutility Applied to Event)	-0.181	23
Acute Non-Fatal Major Adverse Limb Event (Disutility Applied to Event)	-0.220	3

*Based on average utilities of coronary heart disease patients who had undergone coronary artery bypass grafting (CABG) and percutaneous coronary interventions (PCI) and later stabilized. (CABG=0.847, PCI=0.861).
SSR Health. US Brand Rx Net Price. Access-restricted document. 2019.

Drug Utilization

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

- Duration of treatment
- Schedule of doses for each drug

Table 10. Treatment Regimens

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

Cost Inputs

Drug Costs

For both drugs, we obtained net pricing estimates from SSR Health, LLC,[24] 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 arrive at a mean discount

from WAC for the drug. Finally, we applied this average discount to the most recent available WAC (January 1, 2019) to arrive at an estimated net price per unit.

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

Vascepa WAC for 1-month supply of 4g/day is $303.65 (each bottle contains 120 each of 1g capsules) (Source: Amarin), or $2.53 per 1 g capsule. The average discount from WAC is 56.04% for Vascepa, leading to an estimated net price of $1.11 per dose.

Table 11. Drug Costs

Drug	WAC per Dose	Net Price per Dose	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

Wholesale acquisition cost (WAC) per Redbook®; net pricing estimates from SSR Health.[24,25]

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

Non-Drug Costs

Health state costs will be derived from literature-based estimates. Indirect costs will not be included in the base-case analysis, but may be included in additional scenarios. All costs were inflated to 2019 levels using the health care component of the personal consumption expenditure index,[26] in accordance with the ICER Reference Case.[27]

Table 12. Non-Drug Cost Inputs

Input	2019 USD Mean Value*	Source
MI Treatment and Event Year Cost	$51,104	[28] and supporting references
Stroke Treatment and Event Year Cost	$58,932	[28] and supporting references
Post-MI Annual Cost (Assumed the Same as Subsequent Years of Coronary Heart Disease)	$2,728	[28] and supporting references
Post-Stroke Annual Cost	$5,742	[28] and supporting references
Cardiovascular Death Cost	$18,341	[29]
Major Bleeding (Cost Applied to Event Year)	$3,367	[3]
Acute Non-Fatal Major Adverse Limb Event (Cost Applied to Event)	$17,979	[3]

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

2.6 Model Outcomes

Model outcomes will include life years (LYs) gained, QALYs gained, and total costs for each intervention over a lifetime time horizon. Costs and QALYs will also be reported by the health state to understand the contribution of different cost elements. All the costs and QALYs will be reported as discounted values, using a discount rate of 3% per annum.

2.7 Model Analysis

Cost-effectiveness will be estimated using the incremental cost-effectiveness ratios, with incremental analyses comparing: 1) rivaroxaban plus aspirin therapy to aspirin alone, and 2) icosapent ethyl to standard secondary prevention treatment, from a health care sector perspective in the base case analyses.

Sensitivity Analyses

We will conduct one-way sensitivity analyses to identify the impact of parameter uncertainty and key drivers of model outcomes. Probabilistic sensitivity analyses will also be 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. We will also perform threshold analyses for drug costs across a range of incremental cost-effectiveness ratios (from $50,000 to $150,000 per QALY).

Scenario Analyses

If data allow, we will consider conducting scenario analyses that include:

1) Modified/restricted societal perspective that includes components such as productivity losses, criminal justice and incarceration, or other indirect costs and effects as applicable.
2) The addition of other CV events such as revascularization and unstable angina will be included in the CV event health state within the model.
3) Using the composite primary endpoints instead of individual primary endpoints from the intervention-specific trials.
4) For rivaroxaban, if comparative clinical evidence is available versus dual antiplatelet therapy, then a cost-effectiveness scenario will be conducted.
5) Finally, assuming the same baseline cardiovascular risk by averaging the baseline risk across the two interventions' trial populations but assuming the same intervention-specific hazard ratios, we will estimate the potential cost-effectiveness of the interventions versus their respective optimal medical management comparator.

Model Validation

We will use several approaches to validate the model. First, we will provide preliminary methods and results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we will refine data inputs used in the model, as needed. Second, we will vary model input parameters to evaluate face validity of changes in results. We will perform 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 the manufacturers for external verification around the time of publishing the draft report for this review. Finally, we will compare results to other cost-effectiveness models in this therapy area, and the outputs from the model will be validated against the trial/study data of the interventions.

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