Additive Therapies for Cardiovascular Disease: Effectiveness and Value

Draft Background and Scope

March 18, 2019

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 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, or stroke, among other problems. In total, CVD is estimated to affect one-half of adults in the US, and is the leading cause of death, with approximately 850,000 deaths annually.[1] CVD also imposes a substantial financial burden, with annual direct and indirect costs estimated to total $1.1 trillion.[1]

The management of patients with CVD has commonly consisted of behavior modification (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, antiplatelet therapy, and when necessary, 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 for cardiovascular events. Therefore, there is clinical interest in exploring other types of medical management in addition to the strategies described above.

The cardioprotective effects of two such agents, rivaroxaban (Xarelto®, Janssen) and icosapent ethyl (Vascepa®, Amarin Pharma) were recently investigated as add-on therapy in patients with established CVD. Rivaroxaban is a direct inhibitor of factor Xa in the blood coagulation pathway. It was 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, and received an indication for the prevention of major cardiovascular events in patients with CAD or PAD in the fall of 2018. It is the latest in a line of antithrombotic regimens that have been tested as alternatives or additions to aspirin, including vitamin K antagonists, antiplatelet therapies, and thrombin receptor antagonists.[2]

Icosapent ethyl (Vascepa®, Amarin Pharma) 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). After a randomized trial showed lower CVD event risk in patients treated with icosapent ethyl,[3] the manufacturer announced its plan to file for an expanded indication at the end of the first quarter of 2019. The mechanism of action in cardioprotection is not fully known, but reduction in triglycerides, antithrombotic effects, and stabilization and regression of coronary plaque have been hypothesized.[3]

Stakeholder Input

This draft scoping document was developed with input from clinicians. A final scoping document will be posted following a three-week public comment period, which will include additional input from clinicians, from patients and their families, researchers, and manufacturers of the agents of focus in this review. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of additive therapies.

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. We also heard that medication adherence might also 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.

Report Aim

This project will evaluate the health and economic outcomes of rivaroxaban and icosapent ethyl as additive therapies to existing medical management in patients with established cardiovascular disease. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

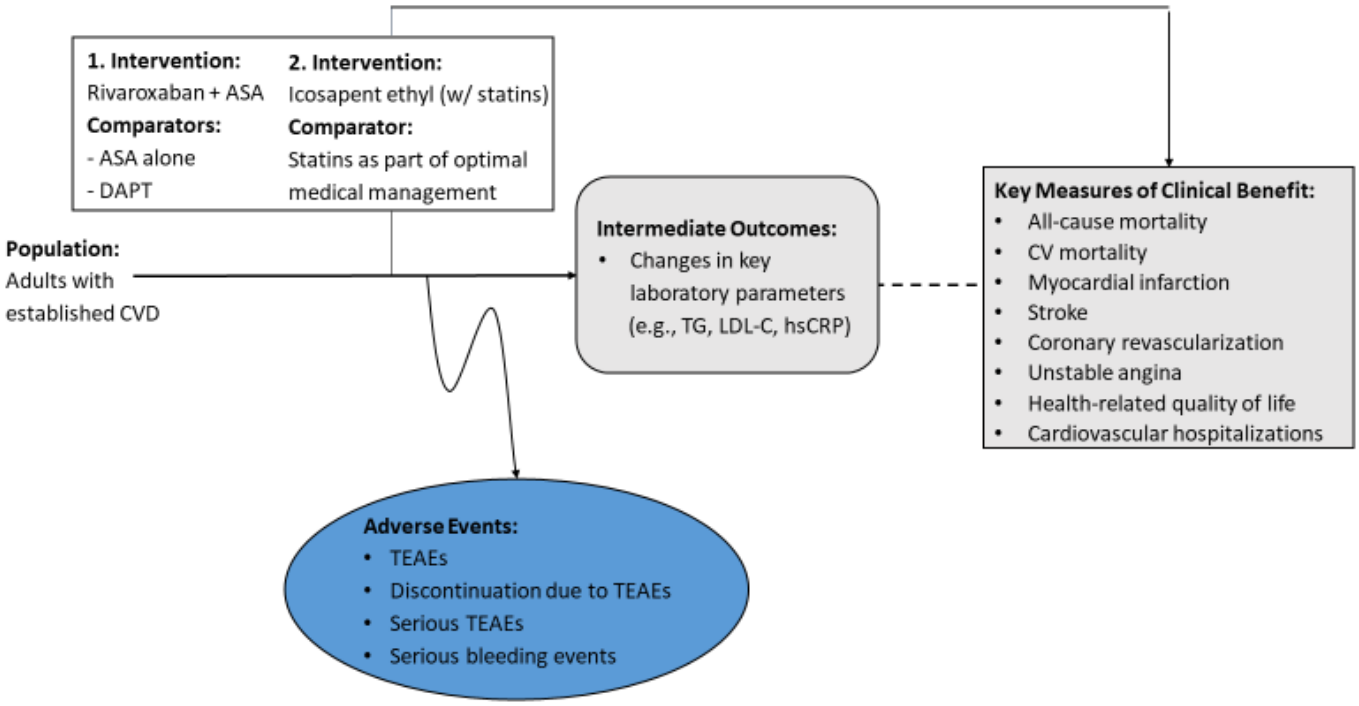
The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the finalized scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Analytic Framework

The general analytic framework for assessment of additive therapies for CVD is depicted in Figure 1.1. Comparators to the interventions of interest include those studied in the key clinical trials of rivaroxaban and icosapent ethyl as well as alternative therapies mentioned during scoping conversations with clinical experts.

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



ASA: acetylsalicylic acid; CV: cardiovascular; CVD: cardiovascular disease; DAPT: dual antiplatelet therapy; hsCRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; TEAE: treatment-emergent adverse event; TG: triglyceride

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 health outcomes. Outcomes are listed in the shaded boxes; those within the rounded boxes are intermediate outcomes (e.g., changes in laboratory parameters), and those within the squared-off boxes are key measures of benefit (e.g., CV mortality). The key measures of 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 adverse events of treatment which are listed within the blue ellipse.[4]

Populations

The population of focus for the review is adults with established CVD being treated with optimal medical management. While the Phase III trial of icosapent ethyl included a primary prevention cohort (i.e., patients with risk factors for CVD), input from clinical experts suggested that patients with *established* CVD are more likely to be candidates for the additive therapies of interest for this review.

Data permitting, we also plan to examine evidence for key subgroups suggested by clinical experts, including (but not necessarily limited to) the following:

1. Diagnosis of diabetes mellitus
2. Diagnosis of PAD versus CAD
3. Levels of high-sensitivity C-reactive protein (hsCRP) at baseline (i.e., ≤2 mg/l or >2 mg/l)

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 (Xarelto®, Janssen Pharmaceuticals) + ASA
2. Icosapent ethyl (Vascepa®, Amarin Pharma)

Comparators

1. In patients treated with optimal medical management, we intend to compare rivaroxaban + ASA to:
    - ASA alone
    - Dual antiplatelet therapy with an oral $P2Y_{12}$ inhibitor (e.g., clopidogrel) and ASA
2. In patients treated with optimal medical management that includes statins, we intend to compare icosapent ethyl to:
    - Statins as part of optimal medical management

Outcomes

The outcomes of interest are described in the table below.

Table 1.1. Outcomes and Harms

Outcomes	Key Harms
All-cause mortality	Treatment-emergent adverse events (TEAEs)
Cardiovascular mortality	Discontinuation due to TEAEs
Myocardial infarction	Serious TEAEs
Stroke	Serious bleeding events
Coronary revascularization	
Unstable angina	
Heart failure	
Venous thromboembolism	
Health-related quality of life	
Cardiovascular hospitalization	

Timing

Evidence on intervention effectiveness will be 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 will be considered, with a focus on outpatient management in the United States.

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.

Table 1.2. Potential Other Benefits and Contextual Considerations

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 "the comparator," there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to "the comparator," 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.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop a de novo decision analytic model to assess the cost-effectiveness of each intervention included in the clinical evidence review (rivaroxaban and icosapent ethyl). The cost-effectiveness of adding rivaroxaban to aspirin therapy will be evaluated in comparison to aspirin alone as well as (data permitting) dual antiplatelet therapy. The cost-effectiveness of adding icosapent ethyl to standard secondary prevention treatment will be evaluated in comparison to no additional therapy. To assess the incremental costs per outcome achieved, we will conduct a cost-effectiveness analysis from the health care system perspective. A Markov model will track CVD-related outcomes and costs in a representative established CVD population for each of the interventions over a lifetime horizon.

A detailed economic model analysis plan with proposed methodology, model structure, parameters, and assumptions are forthcoming. The model structure will be informed by previously developed established CVD models assessing the cost-effectiveness of other treatments to reduce the risk of cardiovascular events.[5-9] The structure of the model includes health states that define the pathway of cardiovascular disease and that have been used in previous modeling efforts. The health states for the Markov model include events such as myocardial infarction (MI), stroke, and other CVD events, as well as post-event time. Specifically, the established CVD cohort begins on treatment and may stay in that state, or pass into event states such as subsequent MI, stroke, or other CVD events. Patients who experience an event move into post-event health states where they may have a higher likelihood for additional events or death as compared to the general established CVD prevention population. Death may occur from all-cause or event/post-event related mortality. Key clinical inputs for the model, informed by the evidence review, will include validated cardiovascular disease risk prediction models,[10-12] baseline trial-based clinical markers (e.g., HDL-C, LDL-C, triglycerides), baseline comorbid conditions (e.g., diabetes), and other baseline factors (e.g., smoking, event history, and baseline 10-year risk of CVD events). Hazard ratios on major endpoints (e.g., reduction in MI, stroke, or other events) from intervention-specific Phase III trials will be applied to baseline risk estimates in the model.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of events averted, life years gained and quality-adjusted life years gained (QALY). Quality of life weights will be applied to each health state, including potential quality of life decrements for serious adverse events (e.g., bleeding events). The model will include direct medical costs, including but not limited to costs related to the interventions and their administration, condition-related care including treatment of CVD-related events, and serious adverse events. The primary model outcome will be expressed in terms of the incremental cost per event averted, cost per QALY gained, and cost per life-year gained. Costs and outcomes will be discounted at 3% per year.

A number of other scenario analyses will be conducted. First, a separate measure of cost-effectiveness—the cost per equal value of life years gained (evLYG)—will be calculated to allow for equal weighting of gains in life expectancy across populations and conditions. In addition, patient and caregiver time and productivity losses will be included in a separate societal analysis if available data allow. Further, if data permit, we will evaluate the cost-effectiveness of the intervention(s) versus other evidence-based comparators and/or in sub-group populations.

In separate analyses, we will explore the potential health system budgetary impact of rivaroxaban and icosapent ethyl over a five-year time horizon, utilizing published or otherwise publicly available information on the potential population eligible for treatment and results from the simulation model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact and will allow assessment of any need for managing the cost of the intervention.

More information on ICER's methods for estimating potential budget impact can be found at: http://icer-review.org/wp-content/uploads/2018/05/ICER-value-framework-v1-21-18.pdf.

Identification of Low-Value Services

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/material/final-vaf-2017-2019/). These services are ones that would not be directly affected by additive therapy for CVD (e.g., hospitalization, required cardiovascular procedures), 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. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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