Summary

WHAT IS CARDIOVASCULAR DISEASE?

Cardiovascular disease (CVD) is a set of conditions that result primarily from the build-up of plaque in the blood vessels. Depending on where there is build-up, patients can have chest pain ("angina"), muscle pain with walking ("claudication") and an increased risk of heart attack, stroke, and death. In total, CVD is estimated to affect one-half of adults in the US and is the leading cause of death across all races and ethnicities, with approximately 850,000 deaths annually.

TREATMENT OPTIONS

Standard management of CVD may include lifestyle adjustment (e.g., diet and exercise), medical therapy to control blood pressure, lower cholesterol, and prevent blood clots, and sometimes procedures to restore blood flow.

Rivaroxaban (**Xarelto**®, Janssen Pharmaceuticals, Inc.), is an approved anticoagulant used in combination with aspirin for the prevention of cardiovascular death, stroke, and heart attack in patients with CVD affecting the blood vessels to the heart.

Icosapent ethyl (**Vascepa**®, Amarin Pharma, Inc.), is an omega-3 fatty acid derived from fish oil. Icosapent ethyl was first approved to treat very elevated triglycerides (hypertriglyceridemia). It is now being evaluated by the FDA for an expanded indication for patients with CVD or at high risk of cardiovascular events; a decision is expected in December 2019.

KEY REPORT FINDINGS

- Tremendous health gains have been achieved with now inexpensive treatments such as aspirin and statins, but high-risk patients have substantial rates of cardiovascular events even on these treatments.
- This evidence review suggests that treatments like rivaroxaban and icosapent ethyl can provide additional benefits for such patients.
- For both therapies, clinical experts suggested there are a large number of eligible patients who will likely receive treatment. As such, ICER is issuing an Access and Affordability Alert for both rivaroxaban and icosapent ethyl.

KEY POLICY RECOMMENDATIONS

- Payers should not consider dual antiplatelet therapy (DAPT) an appropriate candidate in a step therapy protocol as a first step prior to receiving coverage for rivaroxaban. Clinical experts do not view these two treatment options as interchangeable, given their different mechanisms of action and risk profiles.
- Clinical and specialty societies should develop a decision algorithm and/or tool for clinicians to use in determining the most appropriate additive therapies to consider for a given patient.
- Regulators and the research community should align on a common, single definition for key outcomes (such as major bleeding), so clinicians and patients have the information they need to make informed decisions.

Clinical Analyses

ICER EVIDENCE RATINGS

How strong is the evidence that rivaroxaban or icosapent ethyl improves outcomes in patients with CVD who are already receiving optimal medical management?

Rivaroxaban + aspirin:

- Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit compared with aspirin alone.
- Insufficient evidence to compare rivaroxaban + aspirin to DAPT with aspirin and a $P2Y_{12}$ inhibitor (e.g., clopidogrel or ticagrelor).

Icosapent ethyl:

- When used with statins, moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit compared with statins alone.

KEY CLINICAL BENEFITS AND HARMS STUDIED IN CLINICAL TRIALS

How effective are these therapies?

Compared to treatment with aspirin alone, rivaroxaban plus aspirin reduced the risk of a combined outcome of cardiovascular death, stroke, or heart attack in patients with stable CVD compared to aspirin alone. Looking at outcomes individually, adding rivaroxaban to aspirin reduced the risk of stroke, cardiovascular death, CHD death, and death from any cause. Strokes due to bleeding in the brain ("hemorrhagic" strokes) were increased with rivaroxaban, but the results were not statistically significant.

Compared to optimal medical management (including statins) alone, adding icosapent ethyl reduced the risk of a combined outcome of cardiovascular death, stroke, heart attack, bypass surgery or other procedures to improve blood flow, or unstable angina or discomfort in patients with established CVD or with diabetes and additional risk factors. Looking at outcomes individually, icosapent ethyl reduced the risk of cardiovascular death, hospitalization for unstable angina, heart attack, stroke, and bypass surgery or other procedures to improve blood flow. Death from any cause was also reduced, but the results were not statistically significant.

Clinical Analyses (continued)

HARMS

Rivaroxaban + aspirin increases the risk of major bleeding (i.e., bleeding that requires a visit to an acute care facility). Most major bleeding events have occurred in the gastrointestinal tract.

In the randomized trial, patients treated with icosapent ethyl had more episodes of atrial fibrillation.

SOURCES OF UNCERTAINTY

Generalizability of the clinical trials: Treatment with rivaroxaban decreased cardiovascular events but increased bleeding. Patients in the clinical trial of rivaroxaban may have been at lower risk for bleeding than most patients with high cardiovascular risk. For icosapent ethyl, it is unclear whether the therapy would be effective in patients not treated with statins.

Comparison between rivaroxaban + aspirin and DAPT: More robust data are needed to determine how rivaroxaban + aspirin compares to DAPT, particularly with regard to bleeding risks.

Potentially active "placebo" for icosapent ethyl: The mineral oil placebo used in the trial may not have been biologically inert; LDL-C ("bad") cholesterol and a measure of inflammation increased in patients receiving placebo. If the placebo actually caused harm, the trial could have overestimated the benefit of icosapent ethyl.

Inconsistent results: Many prior studies of omega-3 preparations that showed little to no cardiovascular benefit. The trial of icosapent ethyl studied a different preparation at a higher dose, but the prior negative results have led some to worry that these new results could be wrong by chance.

Unclear mechanism of action: Icosapent ethyl was studied in patients with high triglyceride levels, but the results suggested that it might work to reduce cardiovascular events in patients with normal triglyceride levels.

Economic Analyses

LONG-TERM COST-EFFECTIVENESS

Do these treatments meet established thresholds for long-term cost-effectiveness?

Both rivaroxaban and icosapent ethyl fall within commonly cited thresholds for cost-effectiveness.

VALUE BASED PRICE BENCHMARKS

What is a fair price for rivaroxaban and icosapent ethyl based on its value to patients and the health care system?

	Rivaroxaban + Aspirin
Annual List Price	$5,457
Net Price	$2,215
Annual Price to Achieve $100,000-$150,000/QALY Threshold	$5,223-$7,597
Cost-effective?	Yes

Rivaroxaban's annual list price of $5,457 falls within ICER's value-based price benchmark range of $5,200-$7,600 per year. Further, rivaroxaban's estimated net price of $2,215 per year is significantly lower than ICER's value-based price benchmark.

To reach alternative thresholds of between $100,000 and $150,000 per Equal Value of Life Year Gained (evLYG), rivaroxaban could be priced between $5,400-$7,800 per year.

Economic Analyses (continued)

	Icosapent Ethyl
Annual List Price	$3,699
Net Price	$1,625
Annual Price to Achieve $100,000-$150,000/QALY Threshold	$6,282-$9,204
Cost-effective?	Yes

Icosapent ethyl's annual list price of $3,699 and estimated net price of $1,625 are both significantly lower than ICER's value-based price benchmark range of $6,300-$9,200 per year.

To reach alternative thresholds of between $100,000 and $150,000 per Equal Value of Life Year Gained (evLYG), icosapent ethyl could be priced between $6,500-$9,400 per year.

POTENTIAL SHORT-TERM BUDGET IMPACT

How many patients can be treated before crossing ICER's $819 million budget impact threshold?

Rivaroxaban plus aspirin: At the current net price for rivaroxaban, only approximately 6% of eligible patients could be treated in a given year without crossing the potential ICER annual budget impact threshold of $819 million. Clinical experts suggested that around one-third of eligible patients should likely receive rivaroxaban. As such, ICER is issuing an Access and Affordability Alert for rivaroxaban.

Icosapent ethyl: At the current net price for icosapent ethyl, only approximately 4% of eligible patients could be treated in a given year without crossing the potential ICER budget impact threshold of $819 million. Clinical experts suggested that the majority of eligible patients should likely receive icosapent ethyl. As such, ICER is issuing an Access and Affordability Alert for icosapent ethyl.

The purpose of an ICER Access and Affordability 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, if these issues are not appropriately planned for, there is a risk to sustainable access to high-value care for all patients.

Voting Results

The Midwest CEPAC deliberated on key questions raised by ICER's report at a public meeting on September 26, 2019. The results of the votes are presented below. More detail on the voting results is provided in the full report.

CLINICAL EVIDENCE

- A majority of panelists did find adequate evidence to demonstrate that the net health benefit of rivaroxaban plus aspirin is superior to that provided by aspirin alone.
- A majority of the panelists did find adequate evidence 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 alone.
- The panel did not find adequate evidence to demonstrate that the net health benefit of rivaroxaban plus aspirin is superior to that provided by DAPT with an oral $P2Y_{12}$ inhibitor.

LONG-TERM VALUE FOR MONEY

- In accordance with ICER's Value Assessment Framework, both therapies were deemed to be high long-term value for money by default (without a vote from the panel) based on their cost-effectiveness ranges.

OTHER BENEFITS AND CONTEXTUAL CONSIDERATIONS

- A majority of the panel found that both therapies treat conditions of high severity and high lifetime burden of illness.
- A majority of panelists found that both therapies offer a new approach that will allow successful treatment of many patients for whom other therapies have failed.
- The panel also found that both therapies pose significant uncertainty related to their longterm benefit and risks, including the risk of serious side effects for rivaroxaban.

Policy Recommendations

For Payers

- There is a lack of clinical trial evidence in comparing rivaroxaban to DAPT plus aspirin due to limited head-to-head-trials and differing outcome measures.
- Clinical experts do not view rivaroxaban versus DAPT treatment as interchangeable options given their different mechanisms of action and risk profiles, so DAPT should not be considered an appropriate candidate in a step therapy protocol as a first step prior to receiving coverage for rivaroxaban.

For Providers and Clinical / Specialty Societies

- Clinical and specialty societies should develop a decision algorithm and/or tool for clinicians to use in determining the most appropriate additive therapies to consider for a given patient.
- Clinicians should individualize decisions about adding treatments that decrease cardiovascular risk but increase risk of bleeding based on patients' individual risks for these events.
- Providers should weigh the apparent benefit of rivaroxaban plus aspirin with the fact that patients with a high risk of bleeding were excluded from the clinical trials.

For Manufacturers and Clinical Researchers

- Researchers should develop explicit head-to-head evidence of the comparative benefits and risks of rivaroxaban plus aspirin versus DAPT in patients who have completed an initial course of DAPT (12-30 months).
- Manufacturers should also conduct additional studies of icosapent ethyl in patients not on statin therapy. Some patients, if not strictly statin-intolerant, are unwilling to take statins, and such a requirement might prevent some patients from receiving what could be a promising intervention.

For Regulators

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

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care.

For more information about ICER, please visit ICER's website (www.icer-review.org).