



Additive Therapies for Cardiovascular Disease: Final Policy Recommendations

October 17, 2019

The following policy recommendations from the September 26, 2019 meeting reflect the main themes and points made during the Policy Roundtable discussion about how best to apply the evidence on rivaroxaban and icosapent ethyl to policy and practice associated with the treatment of cardiovascular disease (CVD). This conversation, which can be accessed here, [<https://www.youtube.com/watch?v=1FPdZEes7Ps&feature=youtu.be>], immediately followed the Midwest CEPAC voting portion of the meeting.

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. More information on Policy Roundtable participants, including biographical information and conflict of interest disclosures, can be found in ICER's Final Evidence Report [<https://icer-review.org/material/cvd-final-evidence-report/>] in Appendix G.

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.

Policy Recommendations

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 Food and Drug Administration (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 cardiovascular (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:

- a) 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 (CAD); 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.¹ 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.

9. 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 counterparts², and have rates of stroke that are twice as high.³ 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

10. 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 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

11. Researchers should develop explicit head-to-head evidence of the comparative benefits and risks of rivaroxaban + aspirin (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 a myocardial infarction(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.

12. 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.

REFERENCES

1. Graham D. BE, Zhang R., Liao J., Wernecke M., Reichman M.E., Hu M., Illoh O., Wei Y., Goulding M.R., Chillarige Y., Southworth M.R., MaCurdy T.E., Kelman J.A.. Comparative Stroke, Bleeding, and Mortality Risks in Older Medicare Patients Treated with Oral Anticoagulants for Nonvalvular Atrial Fibrillation. *The American Journal of Medicine*.