Add-On Therapies in Cardiovascular Disease: Reviewing ICER's Report and the Potential Effect on Payers

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COMMENTARY

Cardiovascular disease (CVD) accounted for over 17.6 million deaths in 2016 and is expected to exceed 23.6 million by 2030.^{1,2} Between 2014 and 2016, the direct and indirect costs associated with this burdensome disease reached \$351.2 billion. CVD is a disease of concern, given the associated clinical and financial hardships. In October 2019, the Institute for Clinical and Economic Review (ICER) released a final evidence report on the effectiveness and value of 2 additive therapies used to reduce the risk of major adverse cardiovascular events (MACE): rivaroxaban and icosapent ethyl. Rivaroxaban, a direct-acting oral anticoagulant, has been approved as adjunct to aspirin to reduce the risk of MACE in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD).³ These indications are supported by the COMPASS trial, which showed that the combination of rivaroxaban and aspirin reduced the rate of MACE compared with aspirin alone.⁴ Icosapent ethyl, an ethyl ester of eicosapentaenoic acid, was approved to reduce the risk of MACE among patients on statin therapy with elevated triglycerides and established CVD or at high risk for CVD.⁵ The indication is supported by the REDUCE-IT trial, which showed icosapent ethyl reduced composite outcomes (cardiovascular death, myocardial infarction (MI), stroke, coronary revascularization, or unstable angina) versus placebo.⁶

Rivaroxaban's COMPASS trial is representative of a Medicare population with CVD, with 75% of patients aged ≥ 65 years and taking multiple medications (e.g., angiotensin-converting enzyme inhibitors, beta blockers, and statins).⁴ The reduction in the primary outcome yielded a number needed to treat of 76. Conversely, COMPASS found a 1.2% absolute increased risk in major bleeding, and a number needed to harm of 83 was reported. However, there was no significant difference in the rate of severe bleeding events. ICER reports with high certainty that rivaroxaban and aspirin "provides a small-to-substantial net health benefit in patients with CAD, PAD, or both

conditions" (B+).¹ The significant reduction in MACE shown from the COMPASS trial is promising for Medicare patients; however, nearly 90% of major bleeds occurred in patients aged ≥ 65 years in the treatment arm.⁴ A subgroup analysis revealed a number needed to treat of 91 and a number needed to harm of 63 in the ≥ 65 years age group.⁷ Generalizability is limited because of the exclusion of patients at high risk for bleeding and patients intolerant or nonadherent to therapy. The benefit of this combination is offset by the significant increase in major bleeds. The study investigators suggested the early termination of the COMPASS trial because a significant difference in the primary efficacy measure may have "overestimated the treatment effect."

ICER estimates the maximum annual prices of rivaroxaban that correspond to willingness-to-pay (WTP) thresholds of \$50,000 per quality-adjusted life-year (QALY; \$2,849), \$100,000 per QALY (\$5,223), and \$150,000 per QALY (\$7,597).¹ According to ICER net pricing estimates, the average annual WAC of rivaroxaban is \$5,457, with an average discount of 59%, bringing the net price to \$2,215 per year. This estimated net price is below the price needed to achieve the \$50,000 per QALY threshold. Rivaroxaban is associated with approximately \$13,000 in discounted lifetime intervention costs compared with optimal medical management, yielding \$36,000 per QALY gained and \$120,000 per MACE avoided. Although this falls below the cost-effectiveness thresholds, the challenges of adherence and affordability remain in our real-world population.⁸ Adding another medication to a Medicare patient's already complex regimen increases risk of nonadherence, especially when factoring in costs of rivaroxaban. Many Medicare patients living on a fixed income who balance multiple medications may not see the benefit of rivaroxaban, given the associated costs and bleeding risks.

Icosapent ethyl's REDUCE-IT trial showed that icosapent ethyl significantly reduced cardiovascular events by 25% in patients with elevated triglycerides (135-499 mg/dL) and cardiovascular risk.⁶ Unlike alternative treatments (e.g., omega-3 fatty acids, niacin, and fibrates), adding icosapent ethyl to optimal medical management has demonstrated superiority to optimal medical management alone. In a subanalysis, total

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ischemic events were reduced by 30%.⁹ REDUCE-IT demonstrated consistent reductions in primary and secondary outcomes. The all-cause mortality had a 30% relative and 2.6% absolute risk reduction in U.S. patients randomized to icosapent ethyl versus placebo over a median follow-up of 4.9 years.¹⁰ With icosapent ethyl use, there were lower rates of revascularization and MI and higher rates of atrial fibrillation/flutter and bleeding.

The average annual WAC of icosapent ethyl is \$3,699, with an estimated discount of 56%, bringing the net price to \$1,625 per year.¹ While the average annual WAC is not below the \$50,000 WTP threshold, the estimated discount resulting in a net cost of \$1,625 per year is below the \$50,000 per QALY threshold of \$3,433. Although below the WTP threshold, icosapent ethyl remains a complementary treatment option and does not replace standard of care. Incorporating this medication into a patient's treatment regimen increases treatment complexity, patient disparities, and family burden. This is a concern for the Medicare population, which is likely to already have a complex medication regimen. The risk-benefit tradeoffs in lower risk patients are uncertain because the patients included in the trial were already considered high risk and compliant with statin therapy, which solidifies the importance of limiting therapy to the small proportion of patients who fit the trial population.

Previously, ICER determined that the annual budget threshold for any new molecular entity should not exceed \$819 million; otherwise, the entity is subject to an "access and affordability alert."¹ While the pricing of both products with expected discounts meet the \$50,000 threshold, the widespread indication and expected acceptance of the products could be too much for the market to bear. The projected annual spending for rivaroxaban and icosapent ethyl individually exceed this threshold. With approximately 6.7% of U.S. patients having CAD, the estimated size of the annual eligible population for rivaroxaban is 3.3 million. Clinical experts anticipate rivaroxaban use in approximately 30% of eligible patients, which means only 6% of eligible patients could receive rivaroxaban treatment without passing the ICER budget threshold.¹

Similarly, for icosapent ethyl, the estimated size of the annual population is 6.7 million individuals.¹ With double the eligible population for icosapent ethyl compared with rivaroxaban, only 4% of eligible patients could be treated with icosapent ethyl each year without crossing the ICER threshold. As such, ICER council members believe that the "majority of eligible patients would want to be on icosapent ethyl."¹ Although rivaroxaban and icosapent ethyl are below WTP thresholds, they are expensive in comparison with medications with similar cardiovascular indications. These pricing concerns will likely result in extensive prior authorization criteria for these products.

Payers are looked upon to determine how to ensure that treatments can be maximally utilized, without placing finan-

cial burden on the health care system. Unfortunately, CVD continues to be a driver of health care spend in this country, since it is a leading cause of mortality and morbidity. Our industry must continue to provide innovative therapies with affordable access to help decrease the burden of CVD on our patients and the health care system.

Despite positive outcomes from rivaroxaban and icosapent ethyl, the ICER report identifies significant financial hurdles to overcome. Because of the widespread nature of CVD, the incremental cost of adding one or both therapies can result in significant cost increases. Pricing concerns and the potential for broadly increased demand may result in extensive utilization management strategies for each of these products. The burden remains on the payer to carefully evaluate each option when managing this disease state.

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