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Prescription ω-3 Therapy to Reduce Triglyceride Levels—A New Horizon for Cost-effective Therapy

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Fifty years ago in 1971, Bang et al[1] published their landmark article on the Inuit population of Greenland, finding low plasma cholesterol levels and little coronary heart disease despite a high intake of dietary fats and leading to their seminal identification of 2 unusual ω-3 fats, eicosapentaenoic acid and docosahexaenoic acid, as likely responsible for these benefits. During the past 5 decades, our knowledge of ω-3 fats has greatly expanded and continues to evolve.[2]

Weintraub and colleagues[3] estimate the cost-effectiveness of using icosapent ethyl (IPE), a purified eicosapentaenoic acid drug, to reduce high triglyceride levels and cardiovascular disease (CVD) events in high-risk patients with existing CVD or diabetes and another risk factor. The investigators used findings from the REDUCE-IT (Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention) trial, including 8179 patients with baseline triglyceride levels between 135 and 499 mg/dL (to convert to millimoles per liter, multiply by 0.0113) who were randomly assigned to receive IPE or a mineral oil placebo (4 g/d). All patients were stable at baseline and receiving statin therapy, a recognized cost-effective intervention for high-risk patients. The estimated health gains were based on the in-trial observed 30% relative risk reduction in CVD events, comparing IPE with mineral oil. The analysis included estimated costs of acute and long-term cardiovascular care, medications, and background health costs. Icosapent ethyl drug costs were estimated at either $4.16 per day (cost after discounts and rebates) or $9.28 per day (wholesale acquisition cost).

During the trial (median follow-up, 4.9 years), IPE treatment was estimated to gain a mean of 0.07 quality-adjusted life-years (QALYs) per patient, at an incremental net cost of approximately $22 000 (rebate cost) or $107 000 (wholesale cost) per QALY gained. These values can be compared with common willingness-to-pay thresholds of less than $50 000 per QALY (considered high value), $50 000 to $150 000 per QALY (intermediate value), and more than $150 000 per QALY (low value).[4]

The investigators also projected to lifetime estimates, extrapolating follow-up by a mean of approximately 10 years beyond the end of the trial. During a lifetime, the model projected IPE treatment to be either cost saving (rebate cost) or high value (wholesale cost, approximately $24 000 per QALY). Such lifetime analyses of drugs should be interpreted with great caution, given the low likelihood of most patients continuing to take a drug for a lifetime, particularly those patients who are sicker and who might otherwise experience the most benefits (and therefore cost-effectiveness).

What are the implications of these findings? Based on the most data-driven "in-trial" estimates, IPE appears to be a cost-effective treatment for patients who have hypertriglyceridemia and either existing CVD or diabetes and another risk factor. A few caveats should be considered. First, cost-effectiveness was based on patient-level data across 473 sites in 11 countries (with only 38.5% of patients from the US), and provision of clinical care, especially for hospitalizations and procedures, could vary across countries. However, the main results in the US subset appear similar to the overall trial,[5] making use of all global data less likely to appreciably alter the findings. Second, estimated costs of IPE did not include the incremental physician visits, screening for eligibility, or initial and follow-up laboratory testing of triglyceride levels that would be associated with IPE treatment in practice. This omission is surprising because such costs would not be trivial. The investigators may have assumed that these costs would be identical to usual background efforts and costs of seeing

such patients, but that is a liberal assumption; starting a new medication is often associated with additional screening, follow-up visits, and laboratory testing. Based on the additional costs of a few extra clinic visits and blood tests over a 4.9-year period, the cost-effectiveness of IPE treatment is likely overestimated.

A third caveat is the lingering concern about the mineral oil placebo in REDUCE-IT, which could overestimate benefits of IPE, with implications for the current cost-effectiveness analysis. During the trial, levels of low-density lipoprotein cholesterol, apolipoprotein B, and C-reactive protein significantly worsened in the placebo group—highly unusual findings not seen in other, similar trials using different placebos. A modeling study of the REDUCE-IT trial, based on observed changes in risk factors from baseline, estimated that approximately one-fourth of the observed relative risk reduction in the IPE group may have been attributable to increased risk during the trial in the placebo group.[6] Thus, if clinical benefits are overestimated from the trial, cost-effectiveness would be accordingly overestimated.

Nonetheless, even with these caveats, the principal finding of high value (<$50 000 per QALY) at the lower drug cost (after existing discounts and rebates) is unlikely to be altered. However, incorporating the costs of additional medical screening, follow-up visits, and laboratory testing, as well as potentially modestly reduced effectiveness, could alter conclusions when IPE is priced at its wholesale cost, resulting in a final incremental cost that may exceed a conventional willingness-to-pay threshold of $150 000 per QALY. This possibility suggests that containing the drug cost of IPE at or below $4 per day is critical to maintain its cost-effectiveness as a treatment. At a time when Congress is actively debating the need for payers to have greater ability to negotiate prescription drug prices, this sensitivity of cost-effectiveness to drug price has particular salience, especially when pharmaceutical spending per capita in the US is already 2- to 3-fold higher than in other high-income countries.[7]

During the past 50 years, US health care spending has increased from 7% to 18% of the gross domestic product and from 5% to nearly 33% of the federal budget.[8] Treatments for preventable chronic diseases, particularly type 2 diabetes and CVD, are the top factors associated with this spending. Today, 1 in 2 US adults has diabetes or prediabetes, 3 in 4 have overweight or obesity, and only 1 in 8 has optimal metabolic health.[8] Continued development of cost-effective medical treatments such as IPE is important. At the same time, nations will not achieve better health, more health equity, or lower health care spending until they equally emphasize and invest in public health and prevention policy to reduce lifestyle-related chronic diseases.

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