EDITORIALS

FISHing for the Miracle of Eicosapentaenoic Acid

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Bhatt et al. report in the *Journal* the results of the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT), in which 8179 high-risk patients who had elevated triglyceride levels and had been receiving statin therapy were randomly assigned to receive 2 g of icosapent ethyl twice daily or placebo containing mineral oil.[1] The patients were enrolled mostly on the basis of secondary prevention (71%), and almost 60% had diabetes. At baseline, low-density lipoprotein (LDL) cholesterol levels were well controlled among the patients (median value, 75.0 mg per deciliter [1.94 mmol per liter]), and triglyceride levels were slightly elevated (median value, 216.0 mg per deciliter [2.44 mmol per liter]). After a median follow-up of 4.9 years, the primary efficacy end point (a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina in a time-to-event analysis) was reported in 22.0% of the patients in the placebo group and in 17.2% of the patients in the icosapent ethyl group — an impressive 25% lower risk in the icosapent ethyl group. The risk of the prespecified key secondary end point (a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in a time-to-event analysis) was similarly lower in the icosapent ethyl group. Hierarchical statistical testing inferred consistent effects on all individual end points except death from any cause.

We welcome these results with surprise, speculation, and hope. Most surprising was the difference between the results of REDUCE-IT and those of many previous trials of n–3 fatty acids. A meta-analysis of 10 randomized trials involving 78,000 patients did not show that the groups that received n–3 fatty acids had a lower risk of major adverse cardiovascular events than those receiving placebo,[2] nor did ASCEND (A Study of Cardiovascular Events in Diabetes), which tested 1-g capsules containing 840 mg of marine n–3 fatty acids daily in patients with type 2 diabetes.[3] In addition, the results of the Vitamin D and Omega-3 Trial (VITAL), a primary-prevention trial involving more than 25,000 participants (also now reported in the *Journal*), did not show a lower incidence of the primary cardiovascular composite outcome of myocardial infarction, stroke, or cardiovascular death.[4] We find it reassuring that the results reported by Bhatt et al. are similar to those of the Japan EPA Lipid Intervention Study (JELIS), an open-label trial that reported that the risk of major adverse cardiovascular events was 19% lower with statin therapy plus 1.8 g of eicosapentaenoic acid daily than with statin therapy alone.[5] Arguments over whether there is something unique about icosapent ethyl or the high dose used can be postponed until after the results of the STRENGTH (Statin Residual Risk Reduction With Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia) trial of Epanova (AstraZeneca), another n–3 fatty acid (ClinicalTrials.gov number, NCT02104817), and other ongoing fish-oil studies become available.

Another surprise was that the cardiovascular benefits of icosapent ethyl were greater than would be predicted on the basis of the changes in triglyceride levels. The observed median reduction of 14 mg per deciliter (0.36 mmol per liter) in non–high-density lipoprotein (HDL) cholesterol level from baseline with icosapent ethyl would be expected to translate into a lower risk of cardiovascular events of only 6 to 8% — not the 25% observed in REDUCE-IT. Moreover, the results were similar regardless of whether a nor-

mal triglyceride level was attained. These findings argue against the theory that triglyceride lowering per se lowers cardiovascular risk, although one might speculate that a reduction in triglyceride level is a proxy for the metabolic effects of eicosapentaenoic acid; the separation of the Kaplan–Meier curves at 2 years is consistent with a lipoprotein-mediated mechanism and less so with an antithrombotic or an antiinflammatory mode of action.

Some aspects of the trial warrant attention. A total of 7% of patients withdrew consent, and 2% had incomplete final visits; however, these rates were balanced between groups. We have some apprehension about the use of mineral oil as placebo, because it may reduce the absorption of drugs and raise levels of atherogenic lipoproteins and C-reactive protein.[6,7] In REDUCE-IT, the levels of triglycerides, LDL cholesterol, and non-HDL cholesterol in the placebo group increased by 2.2%, 10.9%, and 10.4%, respectively, at 1 year, and the levels of apolipoprotein B and C-reactive protein increased by 7.8% and 32.3%, respectively, at 2 years. Thus, the true cardiovascular effects of icosapent ethyl might be less than that observed in this trial, although a post hoc analysis suggested a similar benefit with respect to major adverse cardiovascular events regardless of whether LDL cholesterol level increased in the placebo group. The mineral oil comparator also complicates the assessment of side effects; approximately one third of patients in both trial groups reported gastrointestinal symptoms.

Like the authors, we can only speculate about the mechanism of action. Fish oils are known to reduce levels of proinflammatory eicosanoids and increase production of antiinflammatory mediators,[8] and in REDUCE-IT, icosapent ethyl reduced C-reaction protein levels. Extrapolating from the results of the Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS),[9] we estimated that the observed reduction in C-reactive protein level (0.65 mg per liter) from baseline would be likely to account for only an additional 5% lower risk of ischemic events. Other potential mechanisms of action of icosapent ethyl include its effects on inflammation and on the development, progression, and rupture of arterial plaque, as well as an antiarrhythmic effect.[10] The observation of 30% fewer sudden cardiac deaths in the icosapent ethyl group in a tertiary analysis may provide support for the latter effect. However, these effects, even when combined, cannot fully explain the results of REDUCE-IT.

In conclusion, after a parade of failed cardiovascular outcome trials of fish oils, REDUCE-IT has shown a substantial benefit with respect to major adverse cardiovascular events. More data are needed to confirm these effects and to inform an understanding of the mechanism of action, the uniqueness of the compound tested, and the potential influence of mineral oil as the comparator. However, the finding that the risks of several cardiovascular outcomes were significantly and consistently lower with icosapent ethyl than with placebo make us hopeful that the use of icosapent ethyl can substantially improve cardiovascular health in patients with statin-controlled LDL cholesterol levels who have elevated triglyceride levels.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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