EDITORIAL

Effects of Omega-3 Fatty Acids on Major Adverse Cardiovascular Events
What Matters Most: the Drug, the Dose, or the Placebo?

Garima Sharma, MD; Seth S. Martin, MD, MHS; Roger S. Blumenthal, MD

Hypertriglyceridemia is associated with an increased risk of atherosclerotic cardiovascular disease (ASCVD), independent of low-density lipoprotein cholesterol (LDL-C) control.[1] Standard treatment strategies have included lifestyle modification, weight and diabetes management, and statin therapy. Previous triglyceride-lowering trials with niacin, fibrates, and mixed omega-3 fatty acids have not demonstrated consistent risk reduction of ASCVD.[1,2] However, strong evidence has recently emerged for the role of eicosapentaenoic acid (EPA), an omega-3 fatty acid, in its highly purified ethyl ester derivative, icosapent ethyl (IPE), in addition to statin treatment, for ASCVD risk reduction.[1,2]

Editor's Note page 2280

Related article page 2268

Omega-3 fatty acids can have a broad range of effects on inflammation, oxidation, stability of phospholipid membranes, and the composition and volume of atherosclerotic plaque.[3] These effects may differ between EPA and docosahexaenoic acid (DHA), another omega-3 fatty acid. EPA has stable extended conformation in cell membranes while DHA integrates in a disordered manner in vitro.[2,4]

The Japan EPA Lipid Intervention Study (JELIS), a randomized trial involving 18 645 Japanese patients, found a 19% relative risk reduction in ASCVD events among those treated with moderate-dose EPA (1.8 g/d) added to statin therapy compared with statin therapy alone, with absolute rates of ASCVD events of 2.8% vs 3.5%, respectively (hazard ratio [HR], 0.81 [95% CI, 0.69-0.95]; $P = .01$).[5] However, the trial was open-label and the apparent benefit was driven by less objective components of the composite end point, namely unstable angina and revascularization. Furthermore, the participants had high dietary fish consumption and background statin therapy was low in intensity.[5]

The Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) trial found that among 8179 patients already receiving statin therapy, 4 g/d of IPE compared with placebo led to a relative reduction in composite outcome of subsequent nonfatal myocardial infarction (MI), stroke, cardiovascular death, coronary revascularization, or hospitalizations for unstable angina by 25% for first events (absolute rates of ASCVD events of 17.2% vs 22%, respectively; HR, 0.75 [95% CI, 0.68-0.83]; $P < .001$) and 30% for key secondary events of cardiovascular death, nonfatal MI, and nonfatal stroke (absolute rates of ASCVD events of 11.2% vs 14.8%, respectively; HR, 0.74 [95% CI, 0.65-0.83]; $P < .001$) over the median 4.9 years of follow-up.[6] Rates of serious adverse bleeding events and atrial fibrillation (AF) were higher in the IPE group.[6]

The risk reduction observed in REDUCE-IT prompted further research into protective mechanistic changes of EPA on atherosclerotic coronary plaque.[7] The Effect of Vascepa on Improving Coronary Atherosclerosis in People With High Triglycerides Taking Statin Therapy (EVAPORATE) trial, which included 80 patients aged 30 through 85 years with known coronary atherosclerosis and taking stable statin therapy, found that 4 g/d of IPE in addition to maximally tolerated statin therapy led to a relative reduction of 17% (−0.3 ± 1.5 mm^3 in treatment group vs 0.9 ± 1.7 mm^3 in the statin-only group, $P = .006$) in low-attenuation plaque at 18 months in patients treated with IPE, compared with placebo.[7] Both trials used the same omega-3 fatty acid, EPA, and the same placebo, mineral oil.[7]

In a study in *JAMA*, Nicholls et al[8] present the results of the Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia (STRENGTH), investigating the effects of a carboxylic acid formulation of EPA and DHA (omega-3 CA) with enhanced bioavailability on ASCVD outcomes in patients with atherogenic dyslipidemia and at high cardiovascular risk.[8] In this double-blind, multicenter clinical trial, 13 708 patients were randomized to receive 4 g/d of omega-3 CA vs corn oil comparator. The primary efficacy measure was a composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization.

The STRENGTH trial was prematurely halted due to the low probability of demonstrating a clinical benefit of omega-3 CA over placebo. Participants had a median triglycerides level of 240 mg/dL at baseline and 70% of participants had diabetes. Patients in the omega-3 CA group had a greater reduction in triglycerides levels than those in the corn oil group (-19% vs -0.9%; $P < .001$) with modest changes in LDL-C, HDL-C, and non–HDL-C. Median baseline high-sensitivity C-reactive protein levels were 2.1 mg/L and significantly decreased with omega-3 CA use compared with corn oil (-20.0% vs -6.3%; $P < .001$). The primary end point occurred in 12.0% of the patients in the omega-3 CA group vs 12.2% in the corn oil group. Omega-3 CA was less well tolerated than corn oil, as evidenced by a greater intestinal adverse profile (24.7% vs 14.7%) leading to higher discontinuation (10.8% vs 8.0%) and dose reduction (12.0% vs 6.1%). Consistent with REDUCE-IT, higher rates of AF were observed with use of omega-3 CA than placebo (2.2% vs 1.3%; $P < .001$).

Why did the STRENGTH study find no effect of omega-3 CA yet REDUCE-IT found a positive effect of IPE? Comparisons between trials must be done with caution, but differences in the intervention and control warrant consideration.

As compared with REDUCE-IT, which tested a specific IPE formulation of EPA, STRENGTH evaluated a mixed EPA-DHA product. STRENGTH, which used a more potent dose than prior mixed EPA-DHA trials, provides the strongest evidence to date that a mixed omega-3 CA (EPA and DHA) approach to ASCVD prevention does not reduce ASCVD events. In prior trials, ASCVD outcomes were also similarly unaffected by combined omega-3 fatty acid therapy.[9-11] Adding STRENGTH to the list of null trials with a mixed omega-3 fatty acid is a reminder that the widespread use of over-the-counter mixed omega-3 products lacks evidence for clinical utility.

Blood EPA levels were tightly linked with ASCVD outcomes in the REDUCE-IT trial, whereas they were not in the STRENGTH study. It is unclear why this discordance exists. EPA levels were higher in REDUCE-IT (400% change vs 270% in STRENGTH). Nevertheless, the increase in EPA in STRENGTH appeared sufficient to improve ASCVD outcomes based on REDUCE-IT, but in STRENGTH even those in the top tertile of increase in EPA levels showed no signal of benefit.

It is possible that the specific formulation of EPA makes a difference in the way that EPA distributes and imparts downstream tissue effects. Such differences may not be adequately captured by measuring general plasma or serum concentrations of EPA. The findings also suggest the possibility of differences between EPA and DHA, prompting the question if DHA could have offset benefits of EPA? Although it seems unlikely that the more modest increase in DHA offset the much larger increase in EPA, there are no ASCVD outcome trials of DHA monotherapy to have confidence in its effect. There was a trend toward increased bleeding in REDUCE-IT, which was not observed in STRENGTH.

The choice of placebo is another consideration in understanding REDUCE-IT vs STRENGTH. There were concerns that the mineral oil placebo in REDUCE-IT might have affected the outcomes. For instance, high-sensitivity C-reactive protein increased from a median of 2.1 to 2.8 mg/L[6] in the mineral oil group as compared with a decrease of 2.2 to 1.8 mg/L in the treatment group, an effect that was not seen with corn oil in STRENGTH. However, a Food and Drug Administration advisory committee concluded that these increased levels likely had little effect on the end points.[12] Nevertheless, further data on inflammatory markers in people taking mineral oil could help clarify if the increase in high-sensitivity C-reactive protein with mineral oil is spurious or meaningful. In addition, there was an increase in LDL-C levels in the mineral oil control group in the REDUCE-IT trial. However, the change as measured by the Martin/Hopkins LDL-C equation was only modest (≈10 mg/dL), far below the approximately 40-mg/dL difference in LDL-C that would generally be considered to translate to a 22% difference in major cardiovascular outcomes.

IPE was an important breakthrough in the management of additional risk among patients already receiving statin therapy, with effects seeming to occur largely independently of the reduction in triglycerides. The JELIS, REDUCE-IT, and EVAPORATE studies provided further supportive information in favor of the benefits of IPE. Nevertheless, the mixed evidence with omega-3 fatty acid therapy is in contrast to LDL-C–lowering drugs for which numerous trials have shown the clear benefit in ASCVD prevention. Furthermore, the degree of risk reduction in REDUCE-IT may not have been as high if LDL-C–lowering therapy had been more aggressive to achieve levels well below 70 mg/dL. In REDUCE-IT, using the Martin/Hopkins equation, LDL-C decreased from 86 mg/dL at baseline to 84 mg/dL at the last visit for IPE as compared to an increase from 87 mg/dL at baseline to 92 mg/dL at the last visit in the mineral oil group. Thus, future clinical practice guidelines, which need to consistently examine the totality of evidence, may not give a class I endorsement (which means that there is strong evidence that a treatment has clear benefit) for IPE without additional trials. Future trials could assess the efficacy of IPE vs a placebo other than mineral oil to address the concerns regarding mineral oil. Alternatively, comparative effectiveness trials of IPE vs other new prevention therapies such as proprotein convertase subtilisin/kexin type 9 (PCSK9) serine protease inhibitors could be considered.

The STRENGTH trial[8] reported in *JAMA* is an important and informative clinical trial with neutral results. The findings may invigorate further investigation regarding IPE, generate additional constructive debate around the optimal placebo control, and should prompt reconsideration of over-the-counter mixed omega-3 fatty acid products for ASCVD prevention. This latter point is especially important given the lack of evidence for benefit, and the potential for harm due to increased AF.

The reasons the findings from the REDUCE-IT trial were positive and the STRENGTH trial were not, and that EPA levels correlated with outcomes in REDUCE-IT but did not in STRENGTH, remain uncertain. The importance of the specific omega-3 formulation in achieving ASCVD risk reduction and the degree to which the placebo (ie, mineral oil vs corn oil) may have affected outcomes remain unresolved. As these 2 trials indicate, science can be cloudy before it becomes clear. Continued scientific discovery and rigorous research will be necessary to get closer to the truth and provide the evidence to best inform clinicians and patients about the effects of omega-3 fatty acids on major adverse cardiovascular events.

ARTICLE INFORMATION

Author Affiliations: Ciccarone Center for the Prevention of Cardiovascular Disease, Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, Maryland.

Corresponding Author: Roger S. Blumenthal, MD, Ciccarone Center for the Prevention of Cardiovascular Disease, Johns Hopkins University School of Medicine, Halsted 560, 600 N Wolfe St, Baltimore, MD 21287 (rblument@jhmi.edu).

Published Online: November 15, 2020. doi:10.1001/jama.2020.22387

Conflict of Interest Disclosures: Dr Martin reports receiving consulting fees from AstraZeneca, Amgen, Esperion, REGENXBIO, and 89bio outside the submitted work; in addition, Dr Martin has a patent pending for a system of LDL-C estimation filed by Johns Hopkins University. No other disclosures were reported.

REFERENCES

1. Ganda OP, Bhatt DL, Mason RP, Miller M, Boden WE. Unmet need for adjunctive dyslipidemia therapy in hypertriglyceridemia management. *J Am Coll Cardiol*. 2018;72(3):330-343. doi:10.1016/j.jacc.2018.04.061

2. Boden WE, Baum S, Toth PP, Fazio S, Bhatt DL. Impact of expanded FDA indication for icosapent ethyl on enhanced cardiovascular residual risk

reduction. *Future Cardiol*. Published online September 22, 2020. doi:10.2217/fca-2020-0106

3. Nelson JR, True WS, Le V, Mason RP. Can pleiotropic effects of eicosapentaenoic acid (EPA) impact residual cardiovascular risk? *Postgrad Med*. 2017;129(8):822-827. doi:10.1080/00325481.2017.1385365

4. Allaire J, Couture P, Leclerc M, et al. A randomized, crossover, head-to-head comparison of eicosapentaenoic acid and docosahexaenoic acid supplementation to reduce inflammation markers in men and women: the Comparing EPA to DHA (ComparED) Study. *Am J Clin Nutr*. 2016;104(2):280-287. doi:10.3945/ajcn.116.131896

5. Saito Y, Yokoyama M, Origasa H, et al; JELIS Investigators, Japan. Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS). *Atherosclerosis*. 2008;200(1):135-140. doi:10.1016/j.atherosclerosis.2008.06.003

6. Bhatt DL, Steg PG, Miller M, et al; REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2019;380(1):11-22. doi:10.1056/NEJMoa1812792

7. Budoff MJ, Bhatt DL, Kinninger A, et al. Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: final results of the EVAPORATE trial. *Eur Heart J*. 2020;ehaa652. doi:10.1093/eurheartj/ehaa652

8. Nicholls SJ, Lincoff AM, Garcia M, et al. Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: the STRENGTH randomized clinical trial. *JAMA*. Published online November 15, 2020 doi:10.1001/jama.2020.22258

9. Bowman L, Mafham M, Wallendszus K, et al; ASCEND Study Collaborative Group. Effects of n-3 fatty acid supplements in diabetes mellitus. *N Engl J Med*. 2018;379(16):1540-1550. doi:10.1056/NEJMoa1804989

10. Manson JE, Cook NR, Lee IM, et al; VITAL Research Group. Marine n-3 fatty acids and prevention of cardiovascular disease and cancer. *N Engl J Med*. 2019;380(1):23-32. doi:10.1056/NEJMoa1811403

11. Bosch J, Gerstein HC, Dagenais GR, et al; ORIGIN Trial Investigators. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. *N Engl J Med*. 2012;367(4):309-318. doi:10.1056/NEJMoa1203859

12. November 14, 2019: Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee meeting announcement. Posted November 14, 2019. Accessed October 10, 2020. https://www.fda.gov/advisory-committees/november-14-2019-meeting-endocrinologic-and-metabolic-drugs-advisory-committee-meeting-announcement