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LIPID ABNORMALITIES AND CARDIOVASCULAR PREVENTION (ED MICHOS, SECTION EDITOR)

A Fishy Topic: VITAL, REDUCE-IT, STRENGTH, and Beyond: Putting Omega-3 Fatty Acids into Practice in 2021

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Abstract

Purpose of Review To examine recently published data from clinical outcome and arteriographic studies that examined the addition of omega-3 fatty acids, eicosapentaenoic acid (EPA) ± docosahexanoic acid (DHA), to standard of care therapy on cardiovascular disease (CVD) risk.

Recent Findings Several trials that tested purified EPA (JELIS, REDUCE-IT, EVAPORATE) were associated with reduced CVD risk and regression of low attenuation coronary plaque volume, whereas studies that employed the combination EPA/DHA (VITAL, OMEMI, STRENGTH) failed to derive clinical benefit.

Summary Trials testing purified EPA consistently demonstrated reduction in atheromatous volume or CVD events beyond standard of care therapies, whereas the combination of EPA/DHA did not, despite producing similar reductions in triglycerides. Experimental and in vitro data suggest that compared to DHA, EPA exhibits antioxidant, anti-inflammatory, and membrane stabilizing properties that enhance vascular function and CVD risk. Consequently, purified EPA appears to be the treatment of choice for high-risk patients with hypertriglyceridemia.

Keywords Hypertriglyceridemia · Omega-3 fatty acids · Icosapent ethyl · REDUCE-IT trial · STRENGTH

Introduction

Atherosclerotic cardiovascular disease (CVD) remains a significant cause of morbidity and mortality globally [1]. Yet, despite optimization of statin therapy, persistent CVD risk remains problematic for a sizeable proportion of high-risk populations. As part of a comprehensive preventive medicine strategy, dietary omega-3 fatty acids have been evaluated in recent years to determine whether additional CVD reduction may be attained beyond statins and other standard-of-care (SOC) therapies.

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Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the two primary sources of dietary omega-3 fatty acids derived from marine oil. Both EPA and DHA have been shown to reduce triglyceride levels [2]. In 2019, the U.S. Food and Drug Administration (FDA) approved icosapent ethyl (IPE), a highly purified formulation of EPA, for adjunctive use to statins in patients with hypertriglyceridemia (HTG), defined as triglycerides greater than or equal to 150 mg per deciliter, and either established CVD OR diabetes mellitus with two or more additional CVD risk factors [3]. Previously, IPE had only been approved for triglyceride levels at or exceeding 500 mg/dL. The change in approval was based on results from the Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT), which demonstrated a 25% reduction in CVD events when IPE was added to SOC therapies [4••], thereby building upon a previous trial, the Japan EPA Lipid Intervention Study (JELIS), that found 1.8 g purified EPA to be associated with reduced CVD risk [5] (see below).

By contrast, the combination of EPA/DHA has not been shown to be cardioprotective. As will be described below, this review elaborates upon 4 recent clinical trials, OMEMI

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(Omega-3 fatty acids in Elderly with Myocardial Infarction), STRENGTH (STatin Residual Risk Reduction With EpaNova in HiGh CV Risk PatienTs

With Hypertriglyceridemia), ASCEND (A Study of Cardiovascular Events in Diabetes), and VITAL (The Vitamin D and Omega-3 Trial), and the potential reasons as to why these studies were negative compared to the positive results obtained in JELIS and REDUCE-IT.

Hypertriglyceridemia and CVD Risk

It is estimated that approximately 25% of adults in the USA have HTG, defined by levels greater than or equal to 150 mg/dL [6]. Hypertriglyceridemia is an independent CVD risk biomarker, especially in patients with type 2 diabetes mellitus (T2DM), metabolic syndrome, and obesity [6–21]. The mechanisms by which HTG contributes to CVD include upregulation of atherothrombotic signaling pathways that advance inflammation, endothelial dysfunction, and vascular impairment [11–14, 22].

Hypertriglyceridemia is also associated with elevation in atherogenic cholesterol-enriched remnant particles that deposit in the intimal layer of the vascular wall [6].

REDUCE-IT Trial

REDUCE-IT was a multi-center, randomized, double-blind, placebo-controlled trial consisting of 8179 patients; the median age at entry was 64 years; women comprised 28.8% of the study cohort [4••]. Study participants had established CVD or diabetes mellitus with at least one additional CVD risk factor, and baseline triglyceride levels ranged between 135 and 499 mg/dL (median 216 mg/dL). Participants were randomized to receive a daily dose of 4 g of IPE or placebo (mineral oil). The primary endpoint was a composite of CVD death, non-fatal myocardial infarction (MI), coronary revascularization, unstable angina, and non-fatal stroke. The secondary endpoint was a composite of CVD death, non-fatal MI, and non-fatal stroke. Over a median follow-up period of 4.9 years, the trial yielded a 25% reduction in the primary composite endpoint in patients assigned to IPE; for every twenty-one subjects treated with IPE over the study period, one event was prevented. In addition, there was a 26% reduction in the secondary endpoint with one CVD event prevented for every twenty-eight subjects treated with IPE.

The findings from this trial extended prior findings from the JELIS trial [5], a randomized, open-label trial conducted in Japan with 18,645 patients who had elevated total cholesterol (6.5 mmol/L or 250 mg/dL or greater). In addition to treatment with low dose statin (pravastatin or simvastatin), there was a 19% relative risk reduction in major CVD events among those assigned to 1.8 g of EPA daily over the 5-year study period. IPE has not only been shown to lower triglyceride levels, but also exhibits anti-inflammatory, plaque-stabilizing, antioxidant, and membrane stabilizing properties [23–26]. Consequently, IPE is now recommended for use in patients with clinical criteria akin to the REDUCE-IT trial [27].

OMEMI Trial

The omega-3 fatty acids in Elderly with Myocardial Infarction (OMEMI) trial was a Scandinavian multi-center, randomized, double blind, placebo-controlled clinical trial in elderly patients (aged 70–82 years old) following a recent (i.e., 2–8 weeks) MI. Patients were randomized to 1.8 g/day of omega-3 fatty acid (combination of 930 mg EPA and 660 mg DHA) vs placebo (corn oil) in addition to SOC therapy [28•]. A total of 1027 patients were randomized (follow-up data was available in 1014 patients); mean age was 75 $\pm$ 3.6 years in a non-HTG cohort (mean triglycerides, 111.4 $\pm$ 61.9 mg/dL), and nearly 30% were women. Over a 2-year follow-up period, there was no reduction in the primary endpoint (composite of non-fatal MI, unscheduled revascularization, stroke, all-cause mortality, and hospitalization for heart failure) in patients treated with the combination of EPA + DHA therapy as compared to placebo.

Differences between OMEMI and REDUCE-IT included a lower dose of EPA (930 mg versus 4 g) and use of a combination EPA-DHA omega-3 fatty acid versus the purified EPA formulation used in REDUCE-IT. Additionally, OMEMI tested a homogenous (predominantly Caucasian) population with lower baseline cholesterol and triglyceride levels than REDUCE-IT and higher fish consumption in both placebo and treated groups at baseline. Finally, the OMEMI trial was viewed as insufficiently powered and of too short duration compared to the more robustly designed REDUCE-IT trial.

STRENGTH Trial

The STRENGTH trial [29••] was a multicenter, double-blinded, placebo-controlled randomized clinical trial comprising 13,078 patients in 22 countries. Inclusion criteria consisted of increased CVD risk, HTG, low HDL cholesterol, on statin therapy, randomized to 4 g daily of a carboxylic formulation of EPA-DHA or placebo (corn oil). At baseline, mean age was 62.5 years,;35% were women with elevated triglycerides (median, 240 mg/dL), low HDL-C (median, 36 mg/dL) and treated LDL-C level (mean, 75 mg/dL). Primary endpoints were a composite of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, and unstable angina requiring hospitalization. Unfortunately, the trial was prematurely terminated after interim analysis demonstrated futility. Specifically, the primary endpoint was observed in 12% of patients treated with

EPA-DHA versus 12.2% in the placebo group (hazard ratio, 0.99 [95% CI, 0.90–1.09]; $p = 0.84$). As in REDUCE-IT, there was a small increased risk in atrial fibrillation. Post hoc analysis was negative for an association between EPA or DHA concentration (plasma or red blood cells) and subsequent CVD events.

Like OMEMI, a primary difference between STRENGTH and REDUCE-IT was the use of a combination EPA-DHA formulation rather than purified EPA. Not surprisingly, the administered content of EPA was lower in STRENGTH than REDUCE-IT, and this corresponded to lower circulating levels of EPA (89.6 vs 144 micrograms/mL).

ASCEND and VITAL

ASCEND [30] was a randomized, placebo-controlled trial of 15,480 participants with diabetes mellitus but without evidence of atherosclerotic CVD that compared 1 g/day omega-3 fatty acid combination (EPA/DHA) versus olive oil capsule placebo in prevention of first serious CVD event (i.e., myocardial infarction, stroke/transient ischemic attack, or vascular death) over a mean follow-up period of 7.4 years. Secondary outcomes included major adverse cardiovascular event or revascularization, all-cause mortality, non-fatal myocardial infarction, and arrhythmias. Inclusion criteria was any patient 40 years or older with diabetes and no known cardiovascular disease. Average participant age was 63 years, and approximately 37% were female. This study did not demonstrate a benefit in daily omega-3 fatty acid supplementation in prevention of major cardiovascular events in diabetic patients without known CVD.

The Vitamin D and Omega-3 Trial (VITAL) [31] was a 5-year, randomized, placebo-controlled, 2 × 2 factorial trial of 25,871 participants investigating whether daily vitamin D3 (2000IU/day) or the omega-3 fatty acid combination, EPA/DHA (1 g/day), would reduce incident CVD (or cancer events) in middle-aged men (aged 50 or older) and women (aged 55 or older). Upon study entry, participants had no history of pre-existing CVD disease; approximately 14% had T2DM. Fifty-one percent of the participants were female, and 20% were African American. This study, like ASCEND, also did not demonstrate benefit in incident CVD events.

However, there were reductions in total MI (HR: 0.72 [95% CI, 0.59–0.90]) with the greatest benefit observed in African Americans (HR: 0.23 [95% CI, 0.11–0.47]). Additionally, reductions were observed in percutaneous coronary intervention (HR: 0.78 [95% CI, 0.63–0.95]) and fatal MI (HR: 0.50 [95% CI, 0.26–0.97]) among those assigned to omega-3 fatty acids with participants having the lowest fish intake at baseline exhibiting the most CVD benefit.

EPA vs DHA

EPA and DHA are both polyunsaturated omega-3 fatty acids (PUFAs). While both marine derived fatty acids reduce triglyceride levels to a similar magnitude, they differ in their effects on membrane structure and stabilization, lipid oxidation, inflammatory biomarkers, endothelial function, and tissue distribution. This may help to explain why the two EPA-only trials (JELIS and REDUCE-IT) exhibited cardiovascular benefit, whereas trials containing DHA did not [32•].

While both EPA and DHA incorporate into the phospholipid membrane bilayers, EPA exhibits antioxidant cell membrane stabilizing properties. In contrast, DHA has a membrane disordering effect and may promote cholesterol crystalline domain formation [25]. High-dose, purified EPA (2–4 g/d) reduces the ratio of circulating arachidonic acid to EPA, apolipoprotein C-III (ApoC-III), oxidized LDL, high sensitivity CRP, and cholesterol enriched remnant particles [4••, 23, 32•, 33–37]. EPA also enhances vascular function[26] [32•, 38–44], and has greater antioxidant activity than DHA [32•, 45]. The latter biological effects may in part be due to EPA's hydrocarbon length and double bonds, which allow it to scavenge reactive oxidative species by stabilizing unpaired electrons via EPA's conjugated double bonds (i.e., conjugative resonance stabilization) [23, 32•]. The capacity of DHA to act as an antioxidant is reduced because the longer hydrocarbon length of DHA (22 versus 20 carbons) is associated with conformational changes and reduction in free radical stabilizing properties compared to EPA [25, 26, 32•, 46] .

Studies have shown that low serum EPA levels and not DHA levels were predictive of all-cause and CVD mortality in patients with acute MI after 16 months follow-up or in-hospital mortality [24, 47]. The recently published EVAPORATE trial (Effect of Vascepa on Improving Coronary Atherosclerosis in People with High Triglycerides taking Statin Therapy) was a randomized, double-blind, placebo-controlled trial that akin to REDUCE-IT evaluated 4 g IPE daily versus placebo (mineral oil) in patients with coronary atherosclerosis [48]. The objective was to evaluate changes in plaque characteristics by measuring low attenuation plaque volume using computed tomography angiography. Compared to placebo, significant regression of low attenuation plaque volume was observed following 18 months of treatment. These findings are consistent with REDUCE-IT and support IPE as effective therapy in high-risk patients with HTG.

Conclusions and Future Directions

As elaborated upon above, clinical trials that have tested purified EPA (e.g., JELIS, REDUCE-IT, CHERRY [38], EVAPORATE) have consistently demonstrated reduction in

atheromatous volume or CVD events beyond statin and other SOC therapies, whereas the combination of EPA/DHA have not been shown to yield clinical benefit (see Fig. 1). Some have suggested that the pharmaceutical grade of mineral oil used as placebo in REDUCE-IT (and in EVAPORATE) may have exaggerated clinical differences between the groups due to mild elevations in LDL-C observed with mineral oil. This has been hypothesized to be due to relative inhibition of statin absorption. However, no differences in CVD outcomes were observed in mineral oil-treated patients in REDUCE-IT, irrespective of whether on treatment LDL-C levels rose. Rather, mineral oil placebo is believed to exhibit "cardio-neutral" properties as demonstrated by Lakshmanan et al. in EVAPORATE where coronary artery plaque progression (total and non-calcified) volumes were not significantly different between mineral oil and non-mineral oil placebo groups [49].

Finally, in view of the modest amount of mineral oil used in REDUCE-IT (1 teaspoon/day) compared to the considerably larger doses used medicinally to treat constipation (1–3 tablespoons/day), a recent review found mineral oil to exert minimal systemic effects, and therefore, could not account for the clinical benefits observed [50•]. Moreover, in studies where mineral oil was not used (e.g., JELIS), significant improvement in CVD events were still observed with highly purified EPA. By contrast, it has also been suggested that the corn oil placebo used in STRENGTH and OMEMI may have beneficial effects. As a representative PUFA, atherogenic lipoprotein particles are reduced when compared to monounsaturated fatty acids (MIFAs) such as extra virgin olive oil [51, 52]. Nonetheless, because corn oil was not universally used as the placebo comparator in all of the failed EPA/DHA trials, it is unlikely that placebo in of itself was the primary basis for the negative results obtained. Taken together, purified EPA rather than EPA/DHA has been shown to be cardioprotective in multiple, independently conducted clinical trials. Thus, based upon the aforementioned differences between EPA and DHA vis-à-vis membrane stabilization, inflammatory and oxidative stress potential, and endothelial function, EPA but not DHA appears to be cardioprotective. As such, purified EPA formulations (e.g., IPE) are a treatment of choice for patients with HTG and other CVD co-morbidities.

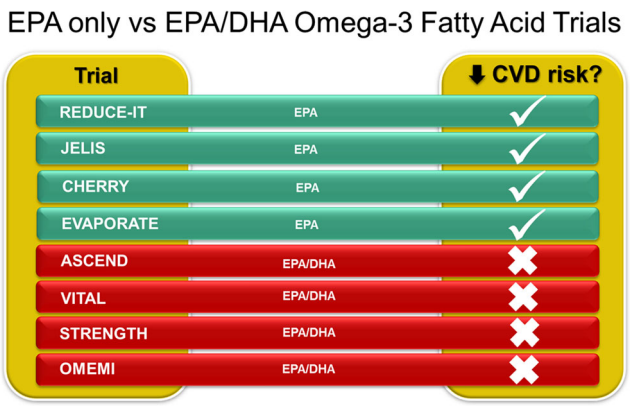

Fig. 1 Differences between EPA only vs EPA/DHA omega-3 fatty acid studies. EPA only studies consistently demonstrate reduction in atheromatous volume or CVD events beyond statin and other SOC therapies, whereas the combination of EPA?DHA have not shown to yield clinical benefits

Compliance with Ethical Standards

Conflict of Interest Dr. Miller is a scientific advisor for Amarin, Inc. and Steering Committee Member for the REDUCE-IT trial. Dr. Iqbal declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. WHO. "Cardiovascular diseases." (n.d.). Retrieved from https://blog.apastyle.org/apastyle/2010/11/how-to-cite-something-you-found-on-a-websitein-apa-style.html.
2. Mori TA, Burke V, Puddey IB, Watts GF, O'Neal DN, Best JD, et al. Purified eicosapentaenoic and docosahexaenoic acids have differential effects on serum lipids and lipoproteins, LDL particle size, glucose, and insulin in mildly hyperlipidemic men. Am J Clin Nutr. 2000;71:1085–94.
3. FDA. "FDA approves use of drug to reduce risk of cardiovascular events in certain adult patient groups." (2019). Retrieved from https://www.fda.gov/news-events/press-announcements/fda-approves-use-drug-reduce-risk-cardiovascular-events-certain-adult-patient-groups. Accessed 15 Jan 2021.
4.•• Bhatt DL, Steg PG, Miller M, et al. REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med. 2019;380:11–22 **Landmark study demonstrating that 4 grams of IPE daily reduced the primary CVD endpoint (cardiovascular death, non-fatal myocardial infarction, stroke, coronary revascularization and unstable angina by 25% in patients with hypertriglyceridemia and pre-existing cardiovascular disease or diabetic patients with at least one cardiovascular risk factor**.
5. Yokoyama M, Origasa H, Matsuzaki M, et al. Japan EPA lipid intervention study (JELIS) Investigators. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet. 2007;369:1090–8.
6. Toth PP. Triglyceride-rich lipoproteins as a causal factor for cardiovascular disease. Vasc Health Risk Manag. 2016;12:171–83.
7. Ference BA, Kastelein JJP, Ray KK, Ginsberg HN, Chapman MJ, Packard CJ, et al. Association of triglyceride-Lowering LPL variants and LDL-C–lowering LDLR variants with risk of coronary heart disease. JAMA. 2019;321:364–73.

8. Musunuru K, Kathiresan S. Surprises from genetic analyses of lipid risk factors for atherosclerosis. Circ Res. 2016;118:579–85.
9. Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, et al. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. Circulation. 2007;115:450–8.
10. Ganda OP, Bhatt DL, Mason RP, Miller M, Boden WE. Unmet need for adjunctive dyslipidemia therapy in hypertriglyceridemia management. J Am Coll Cardiol. 2018;72:330–43.
11. Kim JY, Park JH, Jeong SW, Schellingerhout D, Park JE, Lee DK, et al. High levels of remnant lipoprotein cholesterol is a risk factor for large artery atherosclerotic stroke. J Clin Neurol. 2011;7:203–9.
12. Miller M, Cannon CP, Murphy SA, Qin J, Ray KK. Braunwald E; PROVE IT-TIMI 22 investigators. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. J Am Coll Cardiol. 2008;51:724–30.
13. Imke C, Rodriguez BL, Grove JS, McNamara JR, Waslien C, Katz AR, et al. Are remnant-like particles independent predictors of coronary heart disease incidence? The Honolulu heart study. Arterioscler Thromb Vasc Biol. 2005;25:1718–22.
14. Saeed A, Feofanova EV, Yu B, Sun W, Virani SS, Nambi V, et al. Remnant-like particle cholesterol, low-density lipoprotein triglycerides, and incident cardiovascular disease. J Am Coll Cardiol. 2018;72:156–69.
15. Freiberg JJ, Tybjaerg-Hansen A, Jensen JS, Nordestgaard BG. Nonfasting triglycerides and risk of ischemic stroke in the general population. JAMA. 2008;300:2142–52.
16. Bansal S, Buring JE, Rifai N, Mora S, Sacks FM, Ridker PM. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. JAMA. 2007;298:309–16.
17. Nichols GA, Philip S, Reynolds K, Granowitz CB, Fazio S. Increased residual cardiovascular risk in patients with diabetes and high versus normal triglycerides despite statin-controlled LDL cholesterol. Diabetes Obes Metab. 2019;21:366–71.
18. Kasai T, Miyauchi K, Yanagisawa N, Kajimoto K, Kubota N, Ogita M, et al. Mortality risk of triglyceride levels in patients with coronary artery disease. Heart. 2013;99:22–9. https://doi.org/10.1136/heartjnl-2012-302689.
19. Libby P. Triglycerides on the rise: should we swap seats on the seesaw? Eur Heart J. 2015;36:774–6.
20. Klempfner R, Erez A, Sagit BZ, Goldenberg I, Fisman E, Kopel E, et al. Elevated triglyceride level is independently associated with increased all-cause mortality in patients with established coronary heart disease: twenty-two-year follow-up of the bezafibrate infarction prevention study and registry. Circ Cardiovasc Qual Outcomes. 2016;9:100–8.
21. Toth PP, Philip S, Hull M, Granowitz C. Association of elevated triglycerides with increased cardiovascular risk and direct costs in statin-treated patients. Mayo Clin Proc. 2019;94:1670–80.
22. Miller M, Stone NJ, Ballantyne C, Bittner V, Criqui MH, Ginsberg HN, et al. American Heart Association clinical Lipidology, Thrombosis, and Prevention Committee of the Council on nutrition, physical activity, and metabolism; council on arteriosclerosis, thrombosis and vascular biology; council on cardiovascular nursing; council on the kidney in cardiovascular disease. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2011;123:2292–333.
23. Bays HE, Ballantyne CM, Braeckman RA, Stirtan WG, Soni PN. Icosapent ethyl, a pure ethyl ester of eicosapentaenoic acid: effects on circulating markers of inflammation from the MARINE and ANCHOR studies. Am J Cardiovasc Drugs. 2013;13:37–46.
24. Nelson JR, Wani O, May HT, Budoff M. Potential benefits of eicosapentaenoic acid on atherosclerotic plaques. Vasc Pharmacol. 2017;91:1–9.
25. Mason RP, Jacob RF, Shrivastava S, Sherratt SCR, Chattopadhyay A. Eicosapentaenoic acid reduces membrane fluidity, inhibits cholesterol domain formation, and normalizes bilayer width in atherosclerotic-like model membranes. Biochem Biophys Acta. 1858;2016:3131–40.
26. Sherratt SCR, Mason RP. Eicosapentaenoic acid and docosahexaenoic acid have distinct membrane locations and lipid interactions as determined by X-ray diffraction. Chem Phys Lipids. 2018;212:73–9.
27. Bazarbashi N, Miller M. Icosapent ethyl: niche drug or for the masses? Curr Cardiol Rep. 2020;22:104.
28.• Kalstad AA, Myhre PL, Laake K, et al. OMEMI investigators. Effects of n-3 fatty acid supplements in elderly patients after myocardial infarction: a randomized controlled trial. Circulation. 2020. https://doi.org/10.1161/CIRCULATIONAHA.120.052209 **Randomized clinical trial in elderly men and women that did show clinical benefit after treatment with 1.8 grams daily of EPA/DHA on cardiovascular events over a 2-year follow-up period**.
29.•• 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. 2020;324:e2022258. https://doi.org/10.1001/jama.2020.22258 **Large, randomized clinical outcomes study that found no cardiovascular benefit following the combination of 4 grams daily EPA/DHA carboxylic acids in patients with hypertriglyceridemia and pre-existing cardiovascular disease or at increased cardiovascular risk.**
30. ASCEND Study Collaborative Group, Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, et al. Effects of n-3 fatty acid supplements in diabetes mellitus. N Engl J Med. 2018;379(16):1540–50. https://doi.org/10.1056/NEJMoa1804989.
31. Manson JE, Bassuk SS, Cook NR, Lee IM, Mora S, Albert CM, et al. Vitamin D, marine n-3 fatty acids, and primary prevention of cardiovascular disease current evidence. Circ Res. 2020;126:112–28.
32.• Mason RP, Libby P, Bhatt DL. Emerging mechanisms of cardiovascular protection for the omega-3 fatty acid eicosapentaenoic acid. Arterioscler Thromb Vasc Biol. 2020;40:1135–47 **Review of potential mechanisms subserving the cardiovascular benefit observed with REDUCE-IT and the differences between EPA and DHA that may explain discrepancy in results obtained in recent clinical trials.**
33. Braeckman RA, Manku MS, Bays HE, Stirtan WG, Soni PN. Icosapent ethyl, a pure EPA omega-3 fatty acid: effects on plasma and red blood cell fatty acids in patients with very high triglyceride levels (results from the MARINE study). Prostaglandins Leukot Essent Fat Acids. 2013;108:682–90.
34. Satoh N, Shimatsu A, Kotani K, Sakane N, Yamada K, Suganami T, et al. Purified eicosapentaenoic acid reduces small dense LDL, remnant lipoprotein particles, and C-reactive protein in metabolic syndrome. Diabetes Care. 2007;30:144–6.
35. Satoh-Asahara N, Shimatsu A, Sasaki Y, et al. Highly purified eicosapentaenoic acidincreases interleukin-10 levels of peripheral blood monocytes in obese patients withdyslipidemia. Diabetes Care. 2012;35:2631–9.
36. Ballantyne CM, Bays HE, Philip S, Doyle RT Jr, Braeckman RA, Stirtan WB, et al. Icosapent ethyl (eicosapentaenoic acid ethyl ester): effects on plasmaapolipoprotein C-III levels in patients from the marine and anchor studies. J Clin Lipidol. 2016;10:635–645.e1.
37. Ballantyne CM, Bays HE, Philip S, Doyle RT Jr, Braeckman RA, Stirtan WB, et al. Icosapent ethyl (eicosapentaenoic acid ethyl ester): effects onremnant-like2526particle cholesterol from the MARINE and ANCHOR studies. Atherosclerosis. 2016;253:81–272887.
38. Watanabe T, Ando K, Daidoji H, et al. A randomized controlled trial of eicosapentaenoic acid in patients with coronary heart disease on statins. J Cardiol. 2017;70:537–44.

39. Borow KM, Nelson JR, Mason RP. Biologic plausibility, cellular effects, and molecular mechanisms of eicosapentaenoic acid (EPA) in atherosclerosis. Atherosclerosis. 2015;242:357–66.
40. Mason RP, Dawoud H, Jacob RF, Sherratt SCR, Malinski T. Eicosapentaenoic acidimproves endothelial function and nitric oxide bioavailability in a manner that is enhanced in combination with a statin. Biomed Pharmacother. 2018;103:1231–7.
41. Sasaki J, Miwa T, Odawara M. Administration of highly purified eicosapentaenoic acid to statin-treated diabetic patients further improves vascular function. Endocr J. 2012;59:297–304.
42. Cawood AL, Ding R, Napper FL, et al. Eicosapentaenoic acid (EPA) from highly concentrated n-3 fatty acid ethyl esters is incorporated into advanced atherosclerotic plaques and higher plaque EPA is associated with decreased plaque inflammation and increased stability. Atherosclerosis. 2010;212:252–9.
43. Nishio R, Shinke T, Otake H, et al. Stabilizing effect of combined eicosapentaenoic acid and statin therapy on coronary thin-cap fibroatheroma. Atherosclerosis. 2014;234:114–9.
44. Nosaka K, Miyoshi T, Iwamoto M, et al. Early initiation of eicosapentaenoic acid and statin treatment is associated with better clinical outcomes than statin alone in patients with acute coronary syndromes: 1-year outcomes of a randomized controlled study. Int J Cardiol. 2017;228:173–9.
45. Sherratt SCR, Mason RP. Eicosapentaenoic acid inhibits oxidation of high density lipoprotein particles in a manner distinct from docosahexaenoic acid. Biochem Biophys Res Commun. 2018;496:335–8.
46. Mason RP, Sherratt SC, Jacob RF. Eicosapentaenoic acid inhibits oxidation of ApoB-containing lipoprotein particles of different size in vitro when administered alone or in combination with atorvastatin active metabolite compared with other triglyceride-lowering agents. J Cardiovasc Pharmacol. 2016;68:33–40.
47. Lee SH, Shin MJ, Kim JS, et al. Blood eicosapentaenoic acid and docosahexaenoic acid as predictors of all-cause mortality in patients with acute myocardial infarction–data from Infarction Prognosis Study (IPS) registry. Circ J. 2009;73:2250–7.
48. 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;41:3925–32.
49. Lakshmanan S, Shekar C, Kinninger A, et al. Comparison of mineral oil and non-mineral oil placebo on coronary plaque progression by coronary computed tomography angiography. Cardiovasc Res. 2020;116:479–82.
50.• Olshansky B, Chung MK, Budoff MJ, et al. Mineral oil: safety and use as placebo in REDUCE-IT and other clinical studies. Eur Heart J Suppl. 2020;22(Suppl J):J34–48 **Review of studies examining the use and safety of mineral oil as placebo in cardiovascular and non-cardiovascular clinical trials.**
51. Maki KC, Lawless AL, Kelley KM, Kaden VN, Geiger CJ, Dicklin MR. Corn oil improves the plasma lipoprotein lipid profile compared with extra-virgin olive oil consumption in men and women with elevated cholesterol: results from a randomized controlled feeding trial. J Clin Lipidol. 2015;9:49–57.
52. Maki KC, Lawless AL, Kelley KM, Kaden VN, Geiger CJ, Palacios OM, et al. Corn oil intake favorably impacts lipoprotein cholesterol, apolipoprotein and lipoprotein particle levels compared with extra-virgin olive oil. Eur J Clin Nutr. 2017;71:33–8.