MAYO CLINIC

REVIEW

Sea Change for Marine Omega-3s: Randomized Trials Show Fish Oil Reduces Cardiovascular Events

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Abstract

Recently, 3 large randomized controlled trials (RCTs) have assessed the effects of supplementation with marine omega-3 fatty acids on the occurrence of cardiovascular disease (CVD) events. We reviewed this evidence and considered it in the context of the large and growing body of data on the CV health effects of marine omega-3s. One RCT examining 8179 patients, most with coronary heart disease (CHD), reported that 4 grams/day of a highly purified omega-3 product containing eicosapentaenoic acid (EPA) reduced the risk for major adverse CV events by 25% ($P<.001$). Two other recent RCTs in primary prevention populations showed that approximately 1 gram/day of purified fish oil containing 840 mg/day of EPA and docosahexaenoic acid (DHA) significantly reduced risks of CHD and CV death, especially in individuals who did not consume fish and seafood frequently. The American Heart Association (AHA) continues to emphasize the importance of marine omega-3s as a nutrient for potentially reducing risks of congestive heart failure, CHD, ischemic stroke, and sudden cardiac death. Marine omega-3s should be used in high doses for patients with CHD on statins who have elevated triglycerides and at about 1 gram/day for primary prevention for individuals who do not consume at least 1.5 fish or seafood meals per week.

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The family of marine omega-3 polyunsaturated fatty acids (PUFAs)—specifically, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)—ignited public interest after native Greenlandic Inuit populations sustaining themselves on a marine-based diet demonstrated a substantially lower incidence of cardiovascular disease (CVD) compared with their Western counterparts.[1] Because, in humans, the plant-derived omega-3 precursor alpha-linolenic acid is very poorly converted to EPA and DHA *in vivo*, consumption of these latter 2 fatty acids from the diet and/or supplementation is preferred. Typically, the modern Western diet lacks meaningful amounts of marine-based foods, and, accordingly, omega-3 fatty acid blood levels are low. Thus, the potential for improving long-term health—especially with respect to CV outcomes—through increasing intake of EPA and DHA is significant. Intervention studies over the past decade, however, have been inconsistent, with some studies reporting benefit and others finding none. Recently, large randomized controlled trials (RCTs) have helped clarify the role of omega-3 fatty acids in primary and secondary prevention of CVD.

Three large-scale RCTs were recently published in the *New England Journal of Medicine*: Reduction of Cardiovascular Events with Icosapent Ethyl—Intervention Trial (REDUCE-IT); A Study of Cardiovascular Events iN Diabetes (ASCEND); and VITamin D and OmegA-3 TriaL (VITAL). These landmark trials assessed the effects of omega-3 fatty acids on CV outcomes.[2-4] REDUCE-IT used a high dose (~4 grams/day) of icosapent ethyl (IPE) (Vascepa,

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ARTICLE HIGHLIGHTS

- High-dose EPA (4 grams/day) lowered adverse cardiovascular events in patients with coronary heart disease who are on statins, with baseline triglycerides > 150 mg/dL.
- Low-dose omega-3 (850 mg of EPA + DHA) reduced cardiovascular events for individuals who do not consume at least 1.5 fish/seafood meals per week.
- Low-dose omega-3 (850 mg of EPA + DHA) appears to reduce fatal cardiovascular events in both primary and secondary prevention.

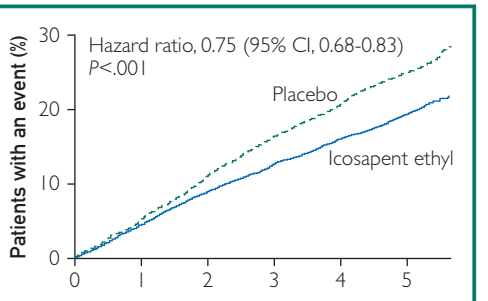

FIGURE 1. Cumulative incidence of cardiovascular events in REDUCE-IT. Kaplan–Meier event curves for the primary composite end point of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina in the icosapent ethyl (eicosapentaenoic acid ethyl esters) group vs the placebo group. Adapted from *New England Journal of Medicine*, with permission.[2]

Amarin Corporation, Bedminster, NJ), a concentrated omega-3 product that is an ethyl ester form of EPA, as an adjunctive therapy in combination with a high-intensity statin for persons with triglycerides (TGs) above 150 mg/dL. VITAL and ASCEND both used 840 mg/day of EPA + DHA ethyl esters for primary prevention of CVD.[3,4]

REDUCE-IT TRIAL

A total of 8179 patients on statin therapy at baseline were randomized in REDUCE-IT (71% for secondary prevention of CV events) and followed for a median of 4.9 years.[2] The active-treatment group received 4 grams/day of IPE, whereas the control group received a mineral oil placebo. IPE lowered the primary end point—composite of CV death, nonfatal myocardial infarction (MI), nonfatal stroke, coronary revascularization, or unstable angina—by 25% with a number needed to treat of 21 (Figure 1).[2] This regimen also significantly reduced the key secondary end point, major adverse CV events (MACE)—composite of CV death, nonfatal MI, or nonfatal stroke—by 26%, with an absolute risk reduction of 3.6 percentage points and a number needed to treat of 28.[2] These remarkable omega-3 benefits were observed against a background of statin use among virtually all patients (>99%). When considering risk reduction standards, REDUCE-IT improved MACE rates much more effectively than other add-on therapies to statin background tested in a large RCT (Table 1).[2,5-14]

Furthermore, in REDUCE-IT, IPE significantly reduced both CV death and sudden cardiac death by 20% and 31%, respectively (Figure 2).[2] Reduction in death from any cause, however, did not meet statistical significance in REDUCE-IT. Serious adverse events leading to discontinuation of the 4 capsules-per-day therapy were similar in the IPE and placebo groups. IPE compared with placebo was associated with a statistically significant increase in hospitalizations for atrial fibrillation (AFIB) (3.1% vs 2.1%, respectively, P=.004). Reassuringly, the IPE group experienced a significant 28% decrease in risk of stroke.[2] A meta-analysis of RCTs assessing the effects of omega-3 supplementation on occurrence of AFIB showed no statistically significant increase, although the trend was toward more, not less, AFIB in the omega-3 group (hazard ratio [HR]: 1.13, 95% CI, 0.96 to 1.33; P=.14).[15] None of these previous studies was done with pure EPA, nor did they test the high dose (4 grams/day) used in REDUCE-IT. Hence, the effects of high-dose omega-3 on AFIB should be investigated further in future trials.

TABLE 1. Add-on Drugs to Baseline Statin Therapy for Reducing MACE: RCT Results

Study	Drug tested	Change in absolute risk	HR	CI
REDUCE-IT[2]	IPE (omega-3)	−4.8%	0.75	0.68 to 0.83
FOURIER[10]	evolocumab	−1.5%	0.85	0.79 to 0.92
ODYSSEY[11]	alirocumab	−1.5%	0.85	0.78 to 0.93
IMPROVE-IT[6]	ezetimibe	−2.0%	0.93	0.89 to 0.99
HPS2-THRIVE[7]	niacin + laropiprant	−0.5%	0.96	0.90 to 1.03
AIM-HIGH[8]	niacin	+0.2%	1.02	0.87 to 1.21
ILLUMINATE[5]	torcetrapib	+1.2%	1.58	1.09 to 1.44
CANTOS[9]	canakinumab	−0.6%	0.85	0.74 to 0.98
REVEAL[14]	anacetrapib	−1.0%	0.91	0.85 to 0.97
EMPA-REG[13]	empagliflozin	−1.6%	0.86	0.74 to 0.99
LEADER[12]	liraglutide	−1.9%	0.87	0.78 to 0.97

CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiovascular events; RCT = randomized controlled trial.

Some investigators have argued that the differences in event rates in the REDUCE-IT trial may in part be due to the adverse lipid effects from the placebo rather than benefits from IPE. For the subjects enrolled in REDUCE-IT, the low-density lipoprotein cholesterol (LDL-C) was 75 mg/dL at baseline (on statins). In the active-intervention group, the LDL-C rose 2 mg/dL, whereas in the placebo (mineral oil) group it rose 7 mg/dL, for a net increase in LDL-C of 5 mg/dL in the latter. By extrapolating from previous RCTs (below), we can be confident that a net increase from 75 mg/dL to 80 mg/dL could not have caused the widely divergent MACE rates in REDUCE-IT.

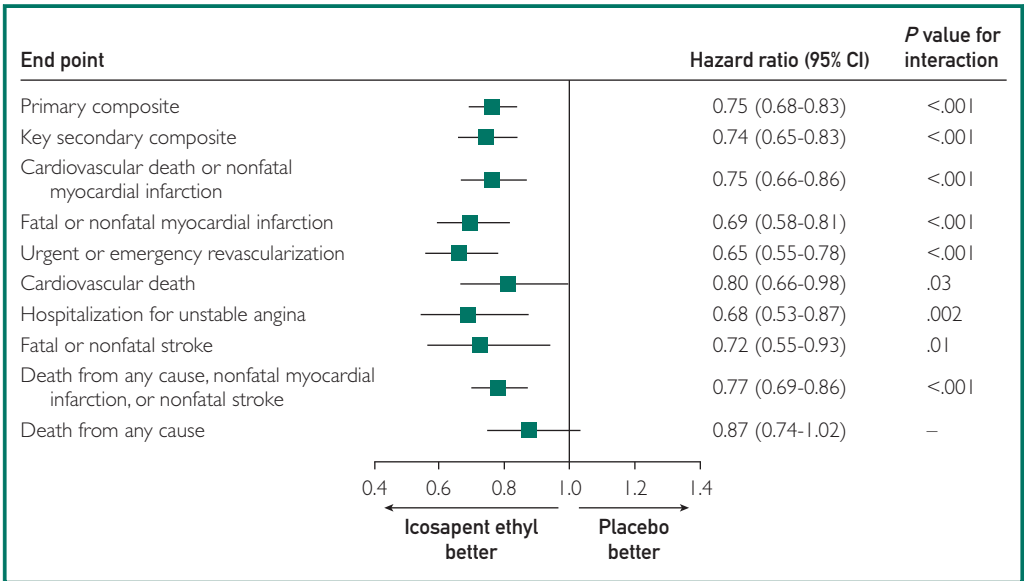

FIGURE 2. The prespecified end points in the REDUCE-IT trial. The rates of all end points, except death from any cause, were significantly lower in the icosapent ethyl (eicosapentaenoic acid ethyl esters) group than in the placebo group. Adapted from *New England Journal of Medicine*, with permission.[2]

For example, the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial[10] enrolled 27,500 patients with atherosclerotic CVD who, like the patients in REDUCE-IT, were all on statins at baseline. In FOURIER, evolocumab dramatically decreased LDL-C from 92 mg/dL at baseline down to a median of 26 mg/dL; this 66-mg/dL drop caused a 1.5% absolute risk reduction in the primary end point: a composite of CV death, MI, stroke, unstable angina, or coronary revascularization.[10] In contrast, a 5-mg/dL LDL-C difference in REDUCE-IT was associated with a remarkable 4.8% absolute risk difference in the same end point.[2] Clearly, the minimal LDL changes could not have been a major driver behind the extraordinary difference in risk of adverse CV events in REDUCE-IT.

Evidence supports TG levels as a significant independent risk factor for adverse CV events.[16] Disappointingly, niacin and fibrates—traditional TG-lowering agents—have recently failed to improve CV outcomes when added to statin therapy.[17-19] Although niacin significantly lowered TG levels by 21% in a large RCT, it did not lower the risk of CHD.[8] Unfortunately, niacin also potentially exacerbates risk for infection, serious bleeding, and diabetes.[7] Similarly, although fibrates effectively reduce TG levels, this class of agents confers no significant reduction in MACE when combined with a statin (except perhaps for patients with diabetes, metabolic syndrome, or atherogenic dyslipidemia).[20,21]

The mechanisms underlying the potent CV risk reduction in REDUCE-IT remain speculative, although the 22% TG reduction with IPE (217 to 170 mg/dL) probably played a role. Subgroup analysis of REDUCE-IT revealed that IPE reduced rates of MACE significantly better in patients with high TG and low HDL levels at baseline, with relative risk reductions of 38% for those with TG $\geq$ 200 mg/dL and HDL $\leq$ 35 mg/dL, vs 21% for those with TG $<$ 200 mg/dL and/or HDL $>$ 35 mg/dL (both decreases were significant, P=.04 for the interaction).[2]

Previous studies have shown that omega-3 fatty acids reduce TG levels in a dose-dependent manner, with TG reductions of 15% to 45%, when using 2 to 6 grams/day of EPA + DHA.[22] Omega-3 is more effective for lowering TG when used in combination with a high-intensity statin and/or with a weight-loss diet.[23,24] Thus, with the publication of REDUCE-IT, omega-3 (IPE in this case) is now the only TG-lowering agent that has been shown to lower MACE on top of statin therapy. Whether its capacity to lower TGs was the actual cause for the benefits IPE will require further study, as EPA has other potentially cardioprotective properties such as reducing inflammation and LDL oxidation and improving endothelial function.[2,22,25] The omega-3 in REDUCE-IT significantly lowered the high-sensitivity C-reactive protein (hsCRP) levels. In that trial, a log scale was used to adjust for skewness in the data; this analysis showed reduction in hsCRP of 23% and 4% in the EPA and mineral oil (placebo) arms, respectively (P<.0001).

Theoretically, omega-3 could increase bleeding risk by its effects on the arachidonic acid pathway, yielding decreased production of prothrombotic metabolites such as thromboxane A2 and plasminogen activator inhibitor-1 (PAI-1).[26,27] Although REDUCE-IT saw no increase in fatal bleeding, hemorrhagic stroke, serious central nervous system or gastrointestinal bleeding, the rates of serious adverse bleeding events trended higher in the omega-3–treated group: 2.7% and 2.1% in the IPE group and placebo arms, respectively (P=.06). Although clinicians often assume that fish oil increases the risk of bleeding, omega-3 supplementation (1.7 grams/day of EPA + DHA) in the perioperative period did not increase the risk bleeding after open-heart surgery.[26] Surprisingly, this recent placebo-controlled RCT of 1600 patients undergoing CV surgery found that the higher the blood level of EPA + DHA level on the morning of the surgery, the lower the need for blood transfusion.[26]

VITAL TRIAL

VITAL was a RCT funded by the National Institutes of Health that was composed of 25,871 Americans above 50 years of age, with no previous history of cancer or CVD.[3] Participants in the active arm took 1-gram daily concentrated fish oil capsules containing 460 mg of EPA and 380 mg of DHA (Lovaza, GlaxoSmithKline, Philadelphia, PA). During a median follow-up of 5.3 years, the primary end point—the reduction in risk of MACE (a composite of MI, stroke, or death from CV causes)—failed to meet statistical significance in the omega-3 group (HR, 0.92; 95% confidence interval [CI]), 0.80 to 1.06 (P=.24). However, in VITAL, this combined daily dose of 840 mg of EPA + DHA produced statistically significant reductions in several key secondary CV end points including MI −28%, and CHD death, −17% (Figure 3).[3]

The patients in the VITAL trial, consuming less than the median amount of fish and seafood (1.5 fish meals per week), had particularly robust reductions in CV events. In this cohort with low fish consumption, the omega-3 product significantly reduced risk of MACE by 19% and risk of MI by 40%.[3]

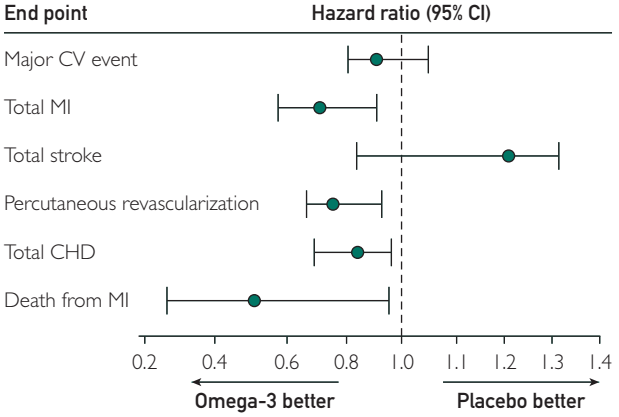

FIGURE 3. HR and 95% CI for prespecified end points in the VITAL trial.[3] CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction.

ASCEND TRIAL

Another recent large omega-3 study also deserves consideration. ASCEND was a 7-year randomized trial of 15,480 patients with diabetes without known CVD who received daily 1- gram capsules of Lovaza (Omacor [Reliant Pharmaceuticals, Inc., Liberty Corner, NJ], the same product used in VITAL).[4] The placebo was a 1-gram capsule of olive oil. ASCEND was considered a negative trial because the primary end point—risk of MI, stroke or vascular death—was only 3% lower in the omega-3 group, and this did not meet statistical significance.

However, the low-dose omega-3 product used in ASCEND did produce a statistically significant 18% relative risk reduction in vascular death, defined as death from coronary disease, stroke, or other vascular causes (Figure 4).[4] This important benefit was largely dismissed by investigators, who wrote that their findings did "not support the current recommendations for routine dietary supplementation with omega-3 fatty acids to prevent vascular events."[4] We take exception to this conclusion, as the omega-3s clearly provided an important benefit. Just because omega-3s at relatively low doses did not reduce risk for MI or stroke in ASCEND (the 2 other components of the composite primary end point) does not mean that the significant reduction in total vascular deaths (the third component) can simply be dismissed as a non-event. In fact, a reduced risk of CV death tends to be the common denominator among many—but not all—large studies of omega-3 supplementation (Table 2).[2-4,28-34]

IMPORTANCE OF ACHIEVING OPTIMAL OMEGA-3 LEVELS

A large meta-analysis of global studies using biomarkers of omega-3 levels in 45,637 participants without prevalent CHD revealed that higher omega-3 levels—as measured in the red blood cell (RBC) membranes, plasma, or adipose tissue—are strongly correlated with lower incidence of fatal CHD (Figure 5).[35] Experimental studies in humans and animals indicate that omega-3s may have membrane-stabilizing antiarrhythmic effects that protect against ischemia-induced ventricular fibrillation.[36,37]

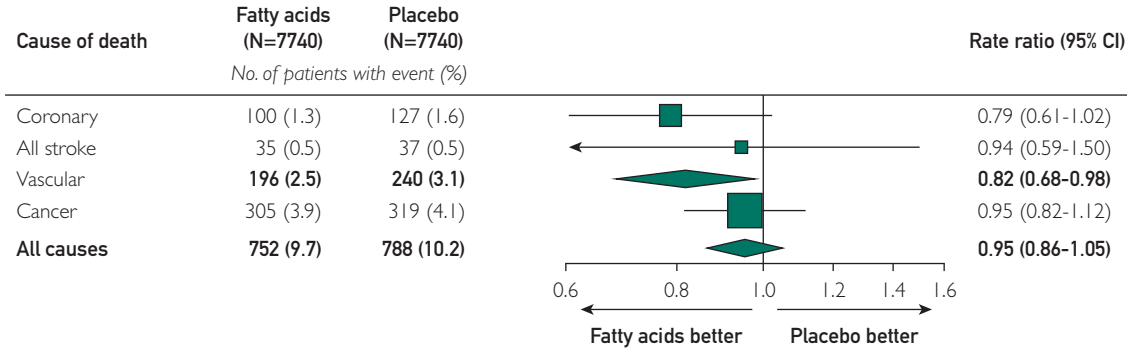

FIGURE 4. ASCEND trial risk of death, according to cause, in the omega-3 group vs the placebo group. Vascular death is the combined end point, which includes death from coronary disease, stroke, and other vascular causes of death. The **diamonds** represent the death-rate ratio and its corresponding 95% confidence interval for each of the causes. Adapted from *New England Journal of Medicine*, with permission.[4]

The results of REDUCE IT, in particular, suggest that optimal omega-3 benefits require a high-enough dose. It is an axiom in medicine that if the dose of any agent is too low, the agent will be ineffective. Why would the same not be true for omega-3 fatty acids? Hence, the goal in future omega-3 RCTs should be to achieve a target blood/tissue level of EPA and DHA, regardless of what dose is required to accomplish this. The Omega-3 Index is a quantitative measurement of EPA + DHA content of RBC membranes that was proposed in 2004 to be a risk factor for CVD death.[30,37] This metric is highly correlated with omega-3 levels of human cardiac tissue[38,39] and is preferred to more volatile plasma-based measurements of omega-3. Hence, just as hemoglobin A1C is the clinical standard for assessing glycemic status, the Omega-3 Index is the superior method for evaluating long-term omega-3 status.

A large meta-analysis recently reported that a 1 standard deviation (SD) increase (2.1%) in the Omega-3 Index, above the mean, was associated with a 15% relative risk reduction for fatal CHD.[31] Thus, compared with an Omega-3 Index of 4%,

TABLE 2. Omega-3 Effects on Risk of Cardiovascular Death in Major Studies[a]

Study	End point	HR	CI
ASCEND[4]	Vascular death[b]	0.82	0.68 to 0.98
REDUCE-IT[2]	CV death	0.75	0.68 to 0.83
VITAL[3]	Death from MI	0.50	0.26 to 0.97
DART[30]	CV death	0.71	0.54 to 0.92
GISSI Prevenzione[40]	Total mortality	0.80	0.67 to 0.95
GISSI-HF[31]	Total mortality	0.91	0.83 to 0.99
Meta-analysis of omega-3 levels (RBC/plasma/adipose)[30]	CHD death[c]	0.70	0.60 to 0.81
Meta-analysis of RCTs[28]	CHD death	0.81	0.65 to 1.00
Meta-analysis of prospective cohort studies[28]	Total mortality	0.77	0.66 to 0.90

[a]CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; RBC = red blood cell; RCT = randomized controlled trials.
[b]Vascular death defined as cumulative deaths due to coronary disease, stroke, and other cardiovascular causes.
[c]Risk reduction from increasing Omega-3 Index from 4% (average for US adult) to 8% (average Japanese adult).

which is the current American approximate mean, an Omega-3 Index of approximately 8% would translate into predicted risk reduction in fatal CHD by approximately 35%.[31]

A dose-response study indicates that to raise the Omega-3 Index from 4% to 8% would require an increased consumption of approximately 1.5 g/day of EPA + DHA.[41] This would equate to a daily intake of 3 ounces of salmon, 5 standard 1-gram fish oil capsules, or 2 highly concentrated 1-gram omega-3 capsules.[40] Trials of combined EPA/DHA using these doses or higher are needed to assess the effects in primary and secondary prevention studies.

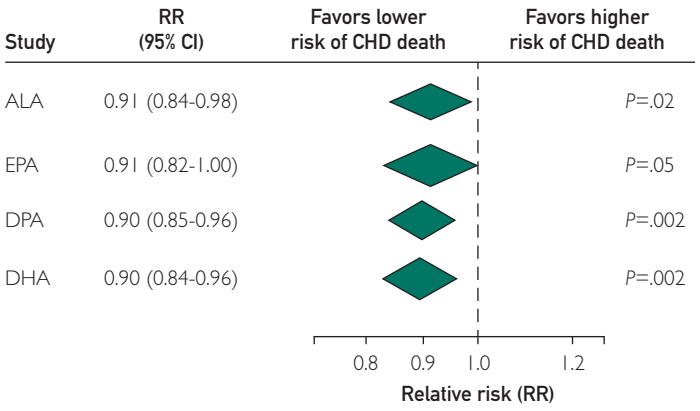

FIGURE 5. RR of fatal CHD per 1-SD increase in the blood/tissue/cell membrane levels for 4 different omega-3 fatty acids: ALA, EPA, DPA, and DHA. Estimates were pooled using random effects meta-analysis. The **diamonds** represent the RR for fatal CHD and its corresponding 95% CI for each of the omega-3 fatty acids. Original figure with information obtained from *JAMA Internal Medicine*.[34] ALA = α-linolenic acid; CHD = coronary heart disease; CI = confidence interval; DHA = docosahexaenoic acid; DPA = docosapentaenoic acid; EPA = eicosapentaenoic acid; RR = relative risk.

OTHER OMEGA-3 BENEFITS

An accumulating body of data shows that omega-3 fatty acids from fish and seafood lower TG levels, decrease risk for CVD mortality, inhibit atherosclerotic plaque growth, improve endothelial function, reduce resting heart rate, improve heart rate variability, and possibly lower risk of sudden cardiac death.[37,42,43] OMEGA-REMODEL was a recent RCT composed of 358 patients with acute MI who were randomized to either omega-3 (3.36 grams/day of EPA + DHA) or placebo for the first 6 months post-MI.

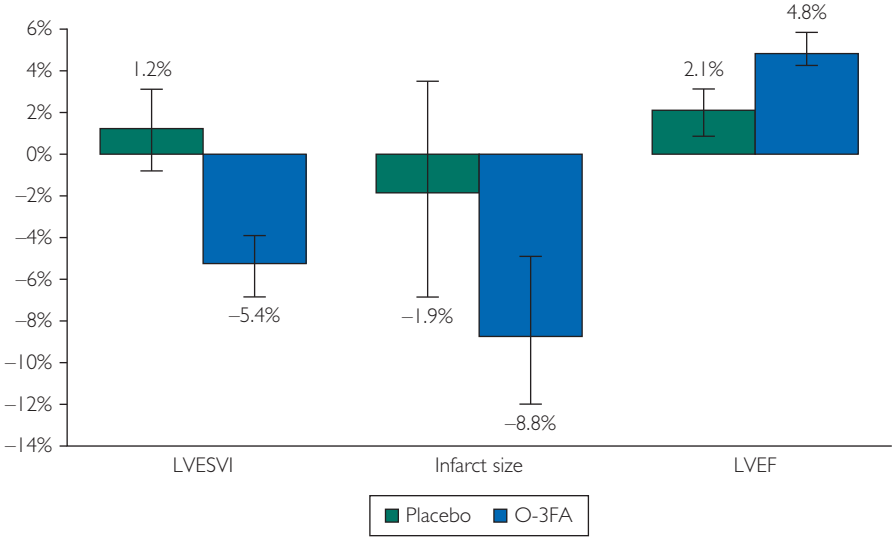

FIGURE 6. Primary and secondary end points in REMODEL. Omega-3 group (**blue bars**) and placebo arm (**green bars**). Changes from baseline to 6 months post-MI. Measurements derived from MRI indicates LVEF; LVESVI; and omega-3 fatty acids from fish oil. Adapted from *Circulation*, with permission.[43] LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; MI = myocardial infarction; MRI = magnetic resonance imaging.

Omega-3s significantly improved left ventricular ejection fraction (LVEF) $P=.07$ and LV end systolic volume ($P=.007$), and nonsignificantly reduced infarct size ($P=.27$) (Figure 6), and these benefits showed a dose-response relationship with the rise of the Omega Index values.

Studies consistently report that marine omega-3s are helpful for reducing risks of preterm birth, low birth-weight babies, and perinatal morbidity.[44] Omega-3s may also be helpful to decrease abdominal obesity, preserve muscle mass, ameliorate muscle pain after exercise, reduce cerebral atrophy, boost mood, and dampen systemic inflammation.[33,36,45,46]

The benefits of marine long chain fatty acids may turn out to be greater in specific subsets of patients, such as those with systolic dysfunction,[32,47,48] low levels of omega-3 fatty acids in the cell membranes, and African Americans, although this will need to be clarified in future RCTs.

OMEGA-3 RECOMMENDATIONS

Unfortunately, approximately 90% of Americans do not consume the recommended amount of fish and/or omega-3.[31,33] Fish rich in omega-3s include salmon, herring, trout, sardines, and albacore tuna; cod, catfish, tilapia, scallops, lobster, mussels, and shrimp contain omega-3s, but only in small amounts. There are 4 types of fish—shark, swordfish, tilefish, and king mackerel—that often contain elevated levels of mercury, which potentially could be neurotoxic, particularly for infants and adults who consume very large amounts of fish and seafood. On the other hand, methylmercury (the type of mercury in marine life) is water soluble and mostly in the muscle of the fish; thus, it is not present in meaningful amounts in the oils of fish, particularly in refined and concentrated omega-3 products.

In May 2018, the AHA released an updated Scientific Advisory on the benefits of consuming marine omega-3s, preferably by eating 1 to 2 seafood meals per week.[45] The initial AHA advisory[49] on this topic (released 16 years ago and was co-authored by Harris, a co-author of this review) emphasized the benefit of at least 2 servings per week of fish high in omega-3. The AHA continues to endorse omega-3 as a nutrient that reduces risk of heart failure, CHD, ischemic stroke, and sudden cardiac death.[45] The 2010 Dietary Guidelines for Americans recommend adults consume fish and/or seafood at least twice per week, totaling 8 to 10 ounces or more of fish plus seafood per week, preferably in place of other protein foods such as meat, poultry, or eggs.[50]

The omega-3 products used in REDUCE-IT, VITAL, and ASCEND were FDA-approved pharmaceuticals. Whether taking EPA + DHA in similar doses from fish-oil supplements would have produced similar effects is unclear, as these products have rarely been used in major RCTs. Nevertheless, when given at similar doses, pharmaceutical and dietary-supplement omega-3 products affect the Omega-3 Index equivalently,[51] and oily fish intake has clearly been linked with reduced risk of CVD.[45] So even though there can be significant differences among encapsulated omega-3 formulations,[52] it is not unreasonable to assume that equivalent doses of EPA + DHA—from whatever source—should have similar effects on risk of CVD.[53]

CONCLUSION

In recent years, many people ceased omega-3 supplementation after a run of publicity suggested no benefit for fish oil. It now appears that these studies were either too small or studied populations already consuming high levels of omega-3 in their diets or did not provide a high-enough dose of EPA/DHA to achieve cardioprotective omega-3 levels. With REDUCE-IT, ASCEND, and VITAL, we now have a clearer picture of the potential long-term benefits that can accrue from taking EPA alone or combined EPA/DHA. For people who do not routinely consume at least 2 fish meals per week, an omega-3 product is a reasonable option. Taking an omega-3 product that supplies between 500 to 4000 mg per day of EPA + DHA appears to be an effective, safe, and affordable strategy for improving long-term CV health, particularly for high-risk persons

who have elevated TG levels and for people who do not consume fish regularly.

Abbreviations and Acronyms: **AFIB** = atrial fibrillation; **AHA** = American Heart Association; **ALA** = α-linolenic acid; **CHD** = coronary heart disease; **CV** = cardiovascular; **CVD** = cardiovascular disease; **DHA** = docosahexaenoic acid; **DPA** = docosapentaenoic acid; **EPA** = eicosapentaenoic acid; **hsCRP** = high-sensitivity C-reactive protein; **HR** = hazard ratio; **IPE** = icosapent ethyl; **LDL-C** = low-density lipoprotein cholesterol; **LV** = left ventricle; **LVESVI** = left ventricular end-systolic volume index; **LVEF** = ventricular eject faction; **MRI** = magnetic resonance imaging; **MACE** = major adverse CV events; **MI** = myocardial infarction; **O-3FA** = omega-3 fatty acids; **PUFA** = polyunsaturated fatty acid; **RBC** = red blood cell; **RCT** = randomized controlled trial; **TG** = triglyceride

Potential Competing Interests: Dr Harris is the owner of OmegaQuant, LLC, a laboratory that offers the Omega-3 Index test; Dr James O'Keefe has a major ownership interest in CardioTabs, a nutraceutical company that sells dietary supplements, including omega-3 products; Dr DiNicolantonio is author of *The Salt Fix* and *Superfuel*; Dr Lavie is a speaker for Amarin Corporation on Vascepa, has consulted for DSM Nutritional Products, and has made an omega-3 educational video at the American Heart Association meeting on November 14, 2016, for the Global Organization for EPA and DHA Omega-3s.

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