

MAYO CLINIC
PROCEEDINGSOmega-3 Fatty Acid Therapy: The Tide
Turns for a Fish Story

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In the current issue of *Mayo Clinic Proceedings*, Alexander et al report on meta-analyses of data addressing the effects of eicosapentaenoic and docosahexaenoic (EPA+DHA) omega-3 fatty acids on the risk of coronary heart disease (CHD) events.¹ Their research employed data from 2 types of studies: (1) randomized controlled trials (RCTs) (approximately 93,000 patients) and (2) prospective cohort studies (approximately 732,000 patients). Their research is, to date, the most comprehensive analysis of its kind within the indexed biomedical literature. The meta-analysis of RCT data discovered that EPA+DHA supplementation produced a non-statistically significant 6% reduction of CHD (hazard ratio [HR], 0.94; 95% CI, 0.85-1.05). Further subgroup analysis found that EPA+DHA significantly reduced CHD risk by 16% (HR, 0.84; 95% CI, 0.72-0.98) among patients with elevated serum triglyceride (TG) levels (>150 mg/dL) and by 14% (HR, 0.86; 95% CI, 0.76-0.98) among patients with elevated low-density lipoprotein cholesterol (>130 mg/dL). In the subsequent meta-analysis of prospective cohort studies, Alexander et al discovered that EPA+DHA significantly reduced CHD risk by 18% (HR, 0.82; 95% CI, 0.74-0.92).

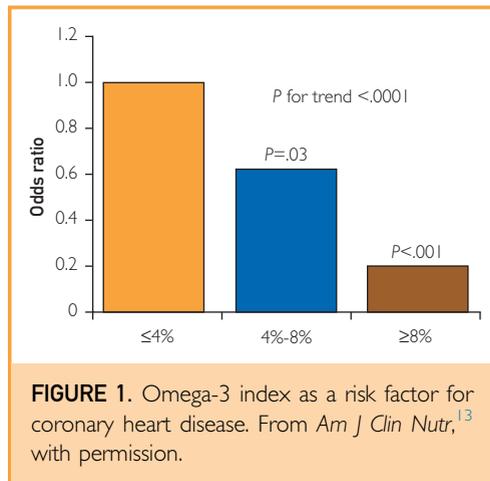
Although TG level is a significant independent risk factor for CHD,² several large RCTs have found that diet supplementation with niacin and fibrates, the pharmacological agents traditionally used to lower TG levels, generally do not improve outcomes. Niacin effectively lowers TG levels but does not lower the risk of CHD, and unfortunately, it increases the incidence of infection, bleeding, and diabetes mellitus.³ Fibrates effectively lower TG levels, but in RCTs, fibrates did not

significantly lower CHD events (except possibly in patients who have hypertriglyceridemia) and can actually increase the incidence of serious adverse effects when combined with statins.^{4,5}

Diet supplementation with omega-3 fatty acids or fish oils lower TG levels in a dose-dependent fashion; among patients who have hypertriglyceridemia, 3 to 4 g/d of EPA+DHA reduces TG levels by 20% to 50%.⁶ In contrast to niacin and fibrates, ingested omega-3 fatty acids are well tolerated and are largely free from serious adverse effects, liver toxicity, and drug-drug interactions. Furthermore, omega-3 fatty acids are safe even when used in combination with a high dose of one of the potent statins,⁷ and they are reported to provide additional reduction in risk of CHD events when added to statin therapy.⁸

The American Heart Association has previously recommended “omega-3 fatty acids from fish or fish oil capsules (1 g/d) for cardiovascular disease risk reduction.”⁹ However, most Americans do not consume sufficient quantities of omega-3 fats to acquire the unique cardiovascular disease protection conferred by this class of nutrient.¹⁰ Vitamin C bestows dramatic and lifesaving benefits to persons with scurvy but is no better than placebo for persons who are replete with vitamin C.¹¹ In a similar fashion, omega-3 fatty acid supplementation is most beneficial for those who consume inadequate amounts omega-3 and therefore are deficient in EPA+DHA.¹²

The omega-3 index—a quantitative measure of omega-3 content in red blood cell membranes—is a novel cardiovascular disease risk metric that is highly modifiable by increasing consumption of EPA+DHA (Figure 1).¹³ An



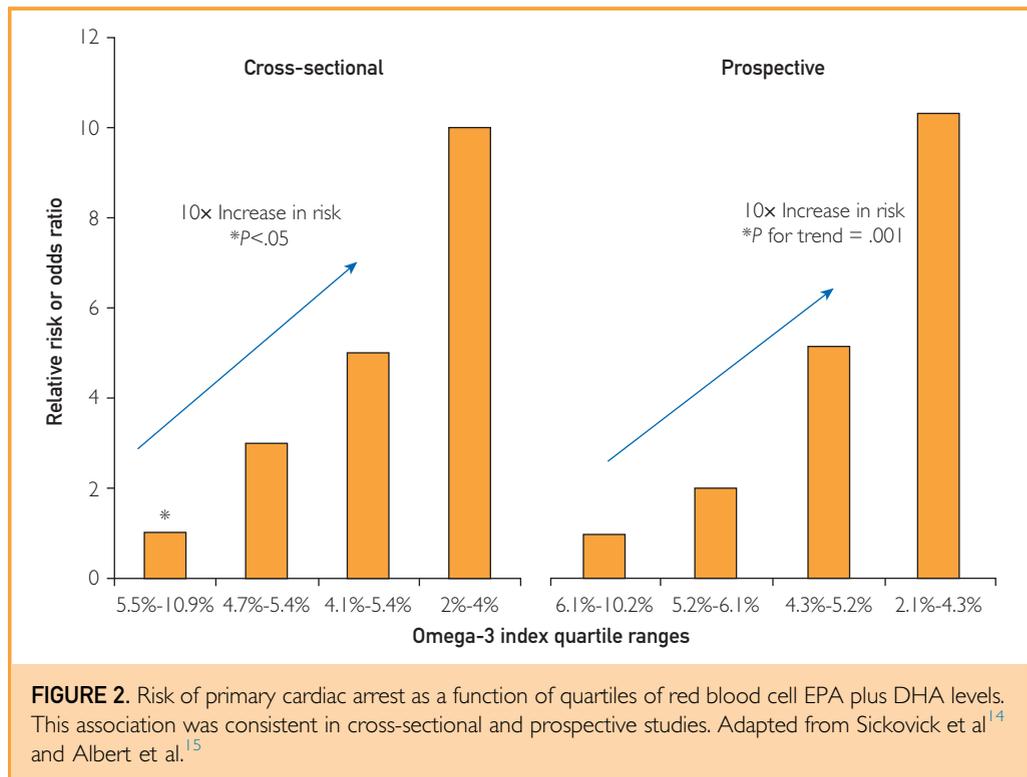
omega-3 index of less than 4% is associated with increased CHD risk, particularly for sudden cardiac death. In contrast, an omega-3 index of more than 8% is associated with low CHD risk, whereas the range between 4% and 8% is considered intermediate risk (Figure 2).^{14,15}

The recently published OMEGA-REMODEL (Omega-3 Acid Ethyl Esters on Left Ventricular Remodeling After Acute Myocardial Infarction) study was an RCT

involving 360 patients who had survived a myocardial infarction and were receiving current guideline-based background CHD therapies.¹⁶ Within the first 30 days following the acute myocardial infarction, the patients were randomized to either 3.6 grams of EPA+DHA or placebo for 6 months. The omega-3 therapy resulted in a 5.8% ($P=.017$) reduction in left ventricular end-systolic volume index and a 5.6% ($P=.026$) reduction in fibrosis in the nondamaged heart muscle. Additionally, the omega-3 significantly lowered the serum levels of biomarkers of systemic and vascular inflammation and myocardial fibrosis.

Studies also indicate that omega-3 intake and omega-3 levels are inversely associated with blood pressure (BP). Their antihypertensive effects are modest but statistically significant—3 g/d of EPA+DHA is associated with BP reductions of 4 mm/Hg systolic and 2 mm/Hg diastolic.¹⁷ Of these 2 omega-3 fats, DHA appears to be more potent in its BP-lowering effects.

To summarize, the meta-analyses of Alexander et al¹ suggest that omega-3 fatty acid intake may reduce the risk of adverse CHD events, especially among patients with elevated levels of TGs or low-density



lipoprotein cholesterol. Several large RCTs are currently under way that should help to clarify the issues surrounding the dosing and indications for omega-3 fatty acids. In the meantime, omega-3 fatty acid intake of at least 1 gram of EPA+DHA per day, either from seafood or supplementation (as recommended by the American Heart Association), continues to be a reasonable strategy.

Nearly 30 years ago, Rogans wrote in the *New England Journal of Medicine* that “fish oil is a whale of a story that not surprisingly gets bigger with each telling.”¹⁸ The current article by Alexander et al adds oil to this engine.

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Potential Competing Interests: Dr O’Keefe is Chief Medical Officer and founder of CardioTabs, a nutraceutical company, and has a major ownership interest in the company, which sells products that contain omega-3. Dr Lavie is a speaker for Amarin Corp on Vascepa, has consulted for DSM Nutritional Products, and 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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