The Fish Oil Story Remains Fishy

Robert H. Eckel, MD

There is substantial evidence, mostly observational, that diets that include fish reduce the risk of coronary heart disease.1–4 Yet, a major question remains as to whether this benefit is due entirely to the omega-3, or long-chain, n-3 fatty acids such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) and/or other nutrient contents in fish. An alternative explanation is that people who consume more fish are already consuming a heart-healthy diet. Although an effect of omega-3 fatty acids on cardiac sudden death has been suggested,5–7 minimal evidence exists to support their use in the setting of an acute myocardial infarction (AMI).

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The Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico (GISSI)–Prevenzione was a trial in patients surviving a recent (<3 months earlier) AMI.3 In that trial, 11,323 patients were randomly assigned to 1-g supplements of n-3 polyunsaturated fatty acids, vitamin E (300 mg/d), both, or no treatment on top of the optimal pharmacological treatment and lifestyle advice at the time. Survival curves for n-3 polyunsaturated fatty acid treatment diverged early after randomization, and total mortality was significantly lowered after 3 months of treatment (risk reduction, 0.59; 95% confidence interval, 0.36 to 0.97; {P=0.037}, and the reduction in risk of sudden death was particularly relevant and statistically significant at 4 months (risk reduction, 0.47; 95% confidence interval, 0.219 to 0.995; {P=0.048}). Although this study was implemented 10 years ago, it set the stage for the OMEGA Trial, a double-blind, randomized, placebo-controlled trial of earlier administration of omega-3 fatty acids in patients with AMI who were receiving more recent and aggressive state-of-the-art and guidelines-based therapy.

The OMEGA Trial8 set out to evaluate the effect of highly purified omega-3-acid ethyl esters (DHA, 380 mg; EPA, 460 mg) versus placebo administered 3 to 14 days after an AMI (ST-elevation or non-ST-elevation MI) on the rate of sudden cardiac death within 1 year after the infarct. Sudden death was defined as death within 1 hour of the first symptoms or an un witnessed event occurring overnight. Also included was sudden cardiac arrest with initially successful resuscitation and subsequent death during the hospital stay. The secondary end points tested included all-cause mortality, nonfatal cardiovascular events, rhythm abnormalities, and depression score. On the basis of the GISSI-Prevenzione Trial,4 a 45% projected reduction in the number of total deaths resulting from sudden death by omega-3 fatty acids was expected. Importantly, because the event rate was less than expected, from April 2005 on, 75% of the subjects enrolled had 1 or more of the following characteristics: no early revascularization, an ejection fraction of <40%, diabetes mellitus, and age >70 years. This lower event rate should be of no surprise, acknowledging that substantial progress has been made in modifying cardiovascular disease risk after AMI in the last several decades.9,10

Overall, the 3804 patients randomized to omega-3 fatty acids versus placebo were well matched in all categories except diuretics use at discharge, which was more common in the omega-3 group; compliance to the medication and placebo was >93% in both groups. Although the dose of omega-3 fatty acids was far from being in the nutraceutical range of 3 to 4 g daily,11,12 there was still a slight reduction in the level of plasma triglycerides in the omega-3 group, 1.37 versus 1.43 mmol/L (P<0.01). The only other biomarker reported was low-density lipoprotein cholesterol, and no difference between groups was observed. Overall, there were only 28 and 29 sudden cardiac deaths in the omega-3 and control groups, respectively; obviously, an absolute risk reduction in the omega-2 group was nonexistent at −0.1% (95% confidence interval, −0.9 and 0.7). Moreover, the risk reduction for all-cause mortality was 0.9 (95% confidence interval, −0.4 to 2.1) and for major adverse cerebrovascular or cardiovascular events was 1.6 (95% confidence interval, −0.3 to 3.6). Of interest, after the AMI, fish consumption increased significantly in both groups. Yet, although the number of subjects who consumed fish several times a week increased from 30% to 45% during the study interval, the projected increase in omega-3 fatty acids by ~1 g weekly would be an unlikely explanation as to why the omega-3 group failed to benefit from the intervention.

Clearly, the OMEGA Trial was underpowered in the age of more aggressive risk factor management in which we live. In the GISSI-Prevenzione Trial, the baseline and 42-month use of pharmacological therapy was 91% and 83% for antiplatelet agents, 47% and 39% for angiotensin-converting enzyme inhibitors, 44% and 38% for β-blockers, and 47% and 46% for cholesterol-lowering drugs. In Omega, at the time of hospital discharge, antiplatelet agents (aspirin and/or clopidogrel) were prescribed in 96%, angiotensin-converting enzyme inhibitors or AT1 receptor blockers in 90%, β-blockers in 95%, and statins in 95%. Particularly in the setting of aggressive and interventions that have been proven efficacious in secondary prevention, the dose of omega-3 fatty acid

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supplementation was quite modest and would not be expected to favorably modify the many biomarkers known to be altered by higher doses of fish oils such as hypertriglyceridemia, platelet function, vascular dysfunction, and inflammation (the Table). What may be needed is a more highly powered study with higher doses of omega-3 fatty acids. Of course, then adverse effects, not experienced in the OMEGA Trial, need to be carefully considered, particularly in the setting of AMI.

A direct antiarrhythmic effect of omega-3 fatty acids has frequently been reported. This benefit could be related to alterations in autonomic tone, including relative bradycardia, reductions in heart rate variability, ischemia preconditioning, and/or reductions in reperfusion-induced arrhythmias. However, the benefit of omega-3 fatty acid interventions to satisfy this hypothesis has been inconsistent. And if such a mechanism of omega-3 fatty acids exists, perhaps an earlier intervention when life-threatening arrhythmias ensue would be best. Despite evidence that links n-3 fatty acid consumption before hospitalization to a reduced risk of ventricular arrhythmias among AMI patients, evidence to document a benefit of omega-3 supplementation within the first several days after an infarct is lacking.

Of note, the recently published Alpha Omega Alpha trial approached the use of omega-3 fatty acids after AMI in a different manner. In Alpha Omega Alpha, patients who had experienced an AMI sometime within the past 10 years and, like the OMEGA Trial, who received state-of-the-art antihypertensive, antithrombotic, and lipid-modifying therapy were randomized to receive 40 months of 1 of 4 margarines: a margarine supplemented with a less potent EPA plus DHA (with a targeted additional daily intake of 400 mg of DHA), 1.9 g ALA, or both in those randomized to placebo and EPA plus DHA alone, with a rate of major cardiovascular events that approached statistical significance with placebo and EPA plus DHA alone, with a rate of major cardiovascular events.

The Table. DHA+EPA Dose Needed to Modify Cardiovascular Risk

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<th>DHA+EPA daily dose needed, g</th>
<th>To Decrease Triglycerides</th>
<th>To Decrease Inflammation</th>
<th>To Decrease Platelet Function</th>
<th>To Increase Vascular Reactivity</th>
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Table. DHA+EPA Dose Needed to Modify Cardiovascular Risk

have no need for additional studies of low-dose omega-3 fatty acid therapy in the first few weeks to months after an AMI. If the safety of a higher-dose intervention, eg, 2 to 4 g DHA plus EPA can be demonstrated, such a trial could be informative. Until then, let us continue with the evidence-based risk management strategies on discharge such as statins, an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, aspirin with or without a second antiplatelet drug if indicated, and β-blocker.

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References


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