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**INVITED COMMENTARY**

# Omega-3 Fatty Acids and Secondary Prevention of Cardiovascular Disease—Is It Just a Fish Tale?

Omega-3 fatty acids are among the most extensively studied nutrients for their potential cardiovascular benefits. There are 2 major classes of omega-3 fatty acids. The first is α-linolenic acid, an essential fatty acid derived from plant sources, such as flaxseed, walnut, soybean, and canola oils. The second class includes long-chain omega-3 fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), which are derived primarily from fatty fish. α-Linolenic acid can be converted to EPA and DHA in the human body, although the efficiency of such conversions seems to be low.[1] A large body of evidence from experimental, clinical, and epidemiologic research has demon-

strated the potential benefits of EPA-rich and DHA-rich fish oil on cardiovascular health.[2] In addition, consistent findings from prospective observational cohort investigations indicate that regular consumption of fatty fish (≥2 times per week) is associated with a significantly lower risk of cardiovascular death.[3]

Several randomized clinical trials (RCTs) have examined the effects of fish oil supplementation on cardiovascular disease (CVD) morbidity and mortality, and almost all RCTs were conducted in secondary prevention settings. However, the findings from these trials have been inconsistent. Two earlier open-label trials (the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico [GISSI]–Prevenzione trial[4] and the Japan EPA Lipid Intervention Study[5]) found significant benefits of fish oil supplementation on CVD outcomes, but more recent trials (Alpha Omega,[6] OMEGA,[7] and SU.FOL.OM3[8]) did not find such benefits. The GISSI–Heart Failure trial,[9] the RCT with the largest number of CVD end points conducted to date, found that fish oil supplementation reduced fatal CVD by 10% (95% CI, 1%-19%) among patients with chronic congestive heart failure.

The inconsistent results from secondary prevention trials set the stage for the meta-analysis by the Korean Meta-analysis Study Group[10] reported in this issue of the *Archives*. The meta-analysis included 14 RCTs among a total of 20 485 patients with a history of CVD. In these trials, the daily dose of EPA or DHA ranged from 0.4 to 4.8 g/d (mean [SD], 1.7 [1.2] g/d), and the follow-up period ranged from 1.0 to 4.7 years (mean [SD], 2.0 [1.2] years). Supplementation with omega-3 fatty acids did not reduce the risk of overall cardiovascular events, all-cause mortality, or sudden cardiac death. Based on these data, the authors concluded that omega-3 supplements were not beneficial for secondary prevention of CVD.

Several aspects of this meta-analysis need to be carefully considered. Among 14 RCTs included in the meta-analysis, most were very small short-term studies and were not designed to evaluate CVD end points. By using random-effects models in the primary analysis, disproportionally greater weights were given to these small studies. In addition, the authors excluded the 2 large open-label trials (the GISSI-Prevenzione trial[4] and the Japan EPA Lipid Intervention Study[5]) that found beneficial effects of omega-3 supplementation in the primary analysis. When these trials were included in a secondary analysis, the pooled estimate for omega-3 supplementation on overall CVD events was changed to the protective direction, although it remained nonsignificant in the random-effects model. One can argue that because these 2 large trials with rigorous outcome ascertainment have made important contributions to the totality of the evidence, the data should not be simply ignored in evaluating overall evidence.

One question that has been raised is why more recent trials (Alpha Omega,[6] OMEGA,[7] and SU.FOL.OM3[8]) have not replicated significant effects of fish oil supplementation on secondary prevention of CVD that were found in earlier trials. Differences in study designs, population characteristics, and types and dosages of omega-3 fatty acids are possible explanations. Most important, the newer trials were each substantially underpowered and unable to detect significant small to modest benefits on CVD outcomes because of their small sample sizes and much lower-than-expected event rates. Of note, the absolute risk for fatal CVD and sudden cardiac deaths in the Alpha Omega trial[6] was only half of that observed in the GISSI-Prevenzione trial.[4] Mozaffarian and Wu[2] estimated that the OMEGA[7] and SU.FOL.OM3[8] trials, with 57 and 40 coronary heart disease deaths, respectively, provided less than 20% power to detect a 25% risk reduction. The power to detect a more modest effect (eg, 10% risk reduction) by these trials would be close to zero.

Another explanation could be that the patients in the more recent trials received much better treatment with statins and antithrombotic and antihypertensive medications than those in earlier trials. The prevalences of statin use were 29% in GISSI-Prevenzione,[4] 23% in GISSI–Heart Failure,[9] 85% in Alpha Omega,[6] 94% in OMEGA,[7] and 87% in SU.FOL.OM3.[8] The additional benefits of fish oil supplementation or any other therapy on top of statins, β-blockers, angiotensin-converting enzyme inhibitors, and other cardiovascular medications are likely to be small; therefore, a much larger sample size is critical to achieve sufficient power.

Another important question is whether fish oil has different effects in primary and secondary prevention of CVD. The trials included in the meta-analysis by the Korean Meta-analysis Study Group[10] were conducted among patients with existing CVD. The Japan EPA Lipid Intervention Study,[5] which was not included in the meta-analysis, enrolled a mixed primary and secondary population. The ongoing Vitamin D and Omega-3 Trial[11] is enrolling men older than 50 years and women older than 55 years, for a total of 20 000 participants. In this double-blind placebo-controlled primary prevention trial, the participants will be randomized to receive vitamin D (2000 IU/d), marine omega-3 fatty acids (1 g/d, with 840 mg EPA and DHA), both supplements, or neither (double placebo). The trial is powered to examine major cardiovascular events, as well as coronary heart disease and stroke individually.

While waiting for more definitive results, what should physicians tell their patients? To date, there is no conclusive evidence to recommend fish oil supplementation for primary or secondary prevention of CVD. However, a diet high in fatty fish (≥2 servings of marine fish per week) should continue to be recommended for the general population and for patients with existing CVD because fish not only provides omega-3 fatty acids but also may replace less healthy protein sources, such as red meat. Individuals who are unable or unwilling to eat fish or related products should consider increasing their consumption of plant-derived omega-3 fatty acid (α-linolenic acid). For primary or secondary prevention, omega-3 supplementation cannot supersede an overall healthy diet,

but a cardioprotective diet needs to be rich in omega-3 fatty acids.

*Frank B. Hu, MD, PhD*
*JoAnn E. Manson, MD, DrPH*

**Published Online:** April 9, 2012. doi: 10.1001/archinternmed.2012.463
**Author Affiliations:** Departments of Nutrition (Dr Hu) and Epidemiology (Drs Hu and Manson), Harvard School of Public Health, and Channing Laboratory (Dr Hu) and Division of Preventive Medicine (Dr Manson), Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.
**Correspondence:** Dr Manson, Division of Preventive Medicine, Brigham and Women's Hospital, 900 Commonwealth Ave, Third Floor, Boston, MA 02215 (jmanson@rics.bwh.harvard.edu).
**Financial Disclosure:** None reported.
**Funding/Support:** Dr Manson receives funding from the National Institutes of Health to conduct the Vitamin D and Omega-3 Trial, a large-scale randomized trial of vitamin D and omega-3s in the prevention of cancer and cardiovascular disease.

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