New Evidence for the Cardiovascular Benefits of Long Chain Omega-3 Fatty Acids

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The role of long chain omega-3 fatty acids (LC n-3 FAs) as cardioprotective agents has become even clearer with the recent publication of the Japan EPA Lipid Intervention Study. This was the largest randomized controlled trial in the field, and it demonstrated that even in a population with one of the highest LC n-3 FA intakes in the world, the addition of eicosapentaenoic acid could reduce cardiac events. A comprehensive analysis of the risks and benefits of fish consumption was likewise recently published that should quiet any remaining fears that there are substantial risks to consuming oily fish such as salmon. A new meta-analysis has now demonstrated that reduced tissue/blood levels of LC n-3 FAs provide a better indication of increased cardiovascular risk than the n-6:n-3 ratio. Finally, a supplementation study in cardiac surgery patients has demonstrated both the time course and extent of incorporation of LC n-3 FAs into the human heart.

Introduction

Long chain omega-3 fatty acids (LC n-3 FAs) have been reported to reduce risk for chronic disease conditions such as atherosclerosis, coronary heart disease (CHD), and metabolic syndrome [1–3]. They operate via a variety of mechanisms relating to lipid and eicosanoid metabolism [4,5] and inflammation [6], both of which are potentially mediated by changes in membrane properties [7]. The purpose of this review is to examine recent advances in n-3 research relevant to atherosclerosis and cardiovascular and metabolic disease states.

For decades, it has been recognized that the essential FAs, linoleic acid (LA) and α-linolenic acid (ALA), should provide at least 1% to 3% of dietary energy. They are essential because of their conversion to LC FAs of the n-6 and n-3 series, which serve a wide variety of metabolic functions. Because of the high intakes of n-6 FAs in the Western diet from vegetable oils, there is no lack of the LA metabolite arachidonic acid (AA), and because of this high intake, what little ALA that is present in the diet is sparingly converted to its long chain metabolites, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [8]. Accordingly, because these two LC n-3 FAs have been shown to have clinical benefits, direct consumption in the form of fish and fish oils has been promoted. There is no daily requirement for LC n-3 FAs established by the US Department of Agriculture, but the American Heart Association suggests that persons without known cardiovascular disease consume two, preferably oily, fish meals per week, which would result in intakes between 250 and 500 mg/d of EPA and DHA combined. In persons with documented CHD, about 1000 mg/d of EPA and DHA is recommended. Finally, for patients with elevated serum triglyceride levels, doses of 2 to 4 g of EPA and DHA are recommended (usually provided in the form of capsules under medical supervision) [9].

Cardiovascular Benefits of Adding EPA to Statin Therapy

The largest clinical trial yet conducted with an LC n-3 FA was recently reported from Japan [10••]. Yokoyama et al. [10••] tested the hypothesis that EPA (alone, without DHA) will reduce risk for major cardiac events when given to hypercholesterolemic patients on stable statin therapy. Conducting this study in Japan was particularly challenging because the baseline intake of LC n-3 FAs of people in Japan is about eight times higher than that of people in America [11•]. Hence, the challenge was to determine if additional benefit would accrue with the addition of supplemental LC n-3 FA in the context of an already high LC n-3 FA intake.

The Japan EPA Lipid Intervention Study (JELIS) [10••] assessed the effects of adding EPA (1800 mg/d, a dose previously standardized for treating hyperlipidemia

and peripheral artery disease) to a treatment regime for hypercholesterolemia. JELIS was conducted between 1996 and 2004 in 18,645 hypercholesterolemic Japanese men (31%) and postmenopausal women (69%) under the age of 75 years. Inclusion criteria required that study participants have high cholesterol levels (total cholesterol ≥ 6.5 mmol/L or 250 mg/dL), with or without coronary artery disease (defined as any previous myocardial infarction [MI], confirmed angina pectoris, or coronary interventions, including coronary artery bypass graft [CABG], angioplasty, or stenting). Excluded were those with cerebrovascular accidents, MI, or coronary interventions in the past 6 months, as well as persons with unstable angina pectoris, uncontrolled diabetes mellitus, severe renal, hepatic, or malignant diseases, and those with severe nonatherosclerotic heart disease (such as severe arrhythmias, heart failure, cardiomyopathy, or congenital and valvular disorders).

The study used a prospective, randomized, open-label, blinded endpoint design, and the two groups were followed for a mean duration of 4.6 years. Each group included equal proportions of primary and secondary prevention participants. All subjects (n = 18,645) were randomly assigned to receive either low-dose statin treatment alone (10 mg/d pravastatin or 5 mg/d simvastatin) or statin plus 1800 mg/d of purified EPA (Mochida Pharmaceuticals, Tokyo, Japan) dosed as 600 mg of EPA three times daily after meals. No other lipid-lowering therapies were allowed during the study. Although the medications and compliance were not blinded, all determinations of endpoints and adverse events were assessed by a blinded committee. Primary endpoints included sudden cardiac death, fatal MI, nonfatal MI, and nonfatal events (unstable angina pectoris, angioplasty, and CABG). Other factors monitored included lipid panels, annual plasma total fatty acid concentrations, blood glucose, and liver enzymes.

The secondary prevention subgroup (patients with documented coronary artery disease [n = 1050 with MI, n = 2903 with angina pectoris, n = 895 with CABG, angioplasty, or stenting; some patients had more than one]) included 3664 subjects. The primary prevention subgroup included 14,981 patients. After 5 years, 91% of subjects were still being followed. Statin compliance was equivalent in both groups (73% in the control group, 71% in the EPA group), and EPA compliance was 71%.

Adding 1.8 g/d of EPA to statin treatment significantly reduced the relative risk of major coronary events over 5 years by 19% (P = 0.011) when all subjects were considered (primary and secondary prevention subgroups) (Fig. 1). Patients in both the primary and secondary prevention cohorts had similar reductions in rates of major coronary events (19% and 18%, respectively), but the difference was statistically significant only for the secondary prevention cohort, in which 8.7% of EPA-treated individuals experienced major coronary events, relative to 10.7% of controls (P = 0.048). Despite the 18% relative risk reduction, the number of events was much lower in the primary prevention cohort (1.4% major coronary events in EPA-treated group vs 1.7% in controls), and was therefore not significant (P = 0.13). EPA treatment also lowered the overall rates of unstable angina pectoris and nonfatal coronary events, but there were no differences between the groups for sudden cardiac death (0.2% in both groups) or total mortality (2.8% for control vs 3.1% for EPA; P = 0.33). Low-density lipoprotein (LDL) cholesterol levels were not different between groups, whereas triglycerides were 5% lower in the EPA group (P < 0.0001).

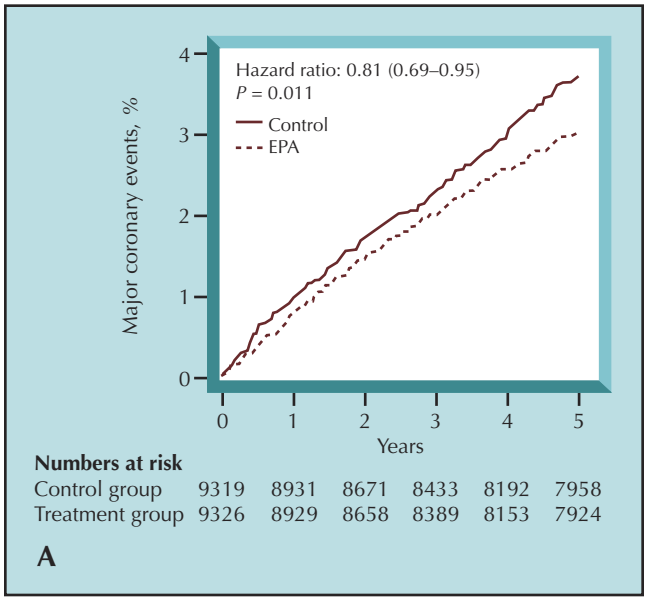
Total adverse events were somewhat higher in the EPA group (25%) than in controls (22%). Although this may have been drug related, it must be recalled that this was an open-label and not a placebo-controlled trial. Hence, reporting of adverse events could be influenced by the knowledge that a drug was being taken by one group and not by the other. Nevertheless, significant differences between the EPA and control groups were reported for gastrointestinal disturbances (3.8% vs 1.7%; P < 0.0001), skin abnormalities (1.7% vs 0.7%; P < 0.001), and hemorrhage (1.1% vs 0.6%; P < 0.001). There were no differences in the frequency of newly diagnosed cancers.

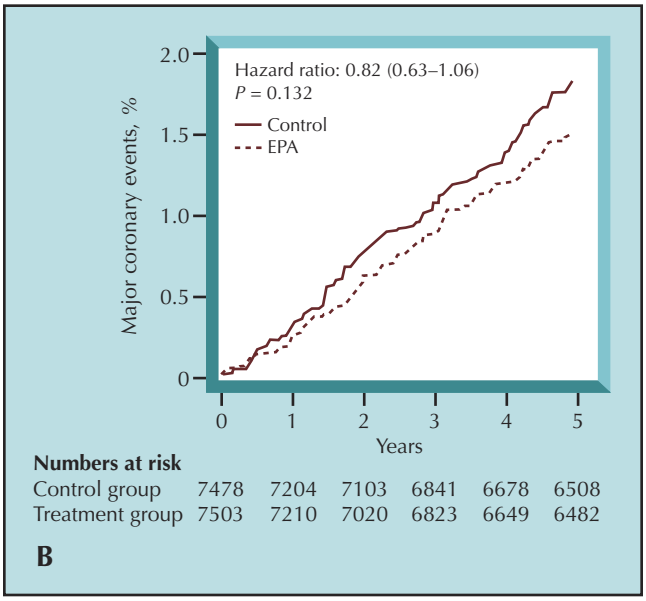
The JELIS study showed that with consumption of 1.8 g/d of EPA in addition to statins, in a population with a high baseline LC n-3 FA intake, the risk for major coronary events can be reduced. This finding applied regardless of sex, age (above or below 61 years), smoking status, diabetes, hypertension, or lipid profiles. Therefore, EPA operates independently of these classic risk factors. It now appears that, based on JELIS, the optimal intake of LC n-3 FAs for cardiovascular risk reduction remains undefined.

Fish Intake: Risk versus Benefits for Cardiovascular Health

One of the most informative and thoughtful analyses of the benefits and risks associated with LC n-3 FAs was published by Mozaffarian and Rimm [12••]. The purpose of the study was to first estimate the overall cardiovascular benefits to be expected from fish and/or LC n-3 FA consumption, and at the same time to estimate the potential health risks that are possible from consuming oily fish that may be contaminated with methyl mercury, dioxins, and polychlorinated biphenyls (PCBs).

The authors collected studies for their analysis of contamination or cardiovascular benefits of LC n-3 FA intake from MEDLINE searches. They first estimated the overall cardiovascular benefits derived from the intake of fish, fish oil, or EPA or DHA. Next, they compiled data on the most significant contaminants found in fish (and other foods), focusing on methyl mercury, dioxins, and PCBs. Table 1 summarizes concentrations of contaminants found per serving of various foods, along with information on the levels at which actions are advised by the US Food and Drug Administration (FDA).





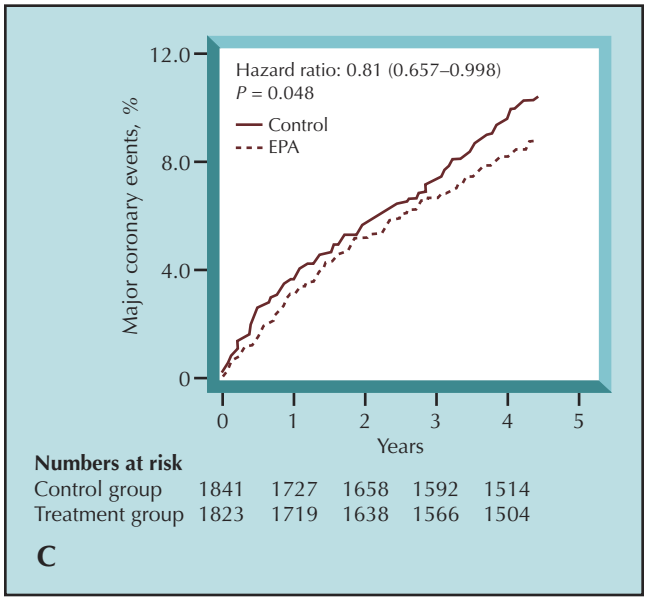


Figure 1. Major coronary event rates in the Japan EPA Lipid Intervention Study (JELIS). Hypercholesterolemic patients on statin therapy were randomized to usual care with or without 1.8 g/d of EPA and followed for a mean of 4.6 years. Kaplan-Meier estimates for the control and EPA groups are shown for all 18,645 patients (**A**), for 14,981 patients without documented cardiovascular disease at baseline (**B**), and for 3664 patients with documented disease (**C**). EPA—eicosapentaenoic acid. (*From* Yokoyama et al. [10••]; with permission.)

Methyl mercury is an environmental contaminant that crosses the placental barrier and can cause serious neurologic disorders in the developing infant. In adults, mercury toxicity can cause paresthesias, ataxia, and sensory abnormalities. Whether there are adverse cardiovascular effects of mercury remains controversial [13,14], and even the impact of fish-derived mercury on human development is not clear [15]. Dioxins are the byproducts of polyvinyl chloride plastic production, waste incineration, paper bleaching, and pesticide production. PCBs are man-made organochloride compounds that were originally used in agriculture, industry, and commercial processes. Although PCBs were banned in the United States in 1977, they nevertheless persist in the environment. The major dietary sources of both PCBs and dioxins are beef, chicken, and pork (34%); dairy products (30%); vegetables (22%); fish and shellfish (9%); and eggs (5%). The potential health risks of PCBs and dioxins are related to their impact on gene expression, which can increase risk for cancer in humans and experimental animals.

In their synthesis of the literature, Mozaffarian and Rimm [12••] found that even a modest intake (250 mg/d of EPA and DHA) appeared to lower risk for death from cardiovascular disease by 36% ($P < 0.001$) and for total mortality by 17% ($P < 0.05$). Higher intakes did not seem to confer greater benefits. The dose of LC n-3 FAs associated with various clinical benefits varies widely. For instance, for triglyceride lowering, at least 3 g/d of EPA and DHA is needed to achieve clinically meaningful benefits. However, the antiarrhythmic benefits and reduction in heart rate appear to require around 500 mg/d, whereas antithrombotic effects seem to require 2 to 3 g/d.

To avoid the risks associated with industrial and agricultural pollutants in edible fish, the FDA recommends

Table 1. Levels of EPA plus DHA and contaminants in selected foods

100-g portions	EPA + DHA*, *mg/100 g*	Mercury, μ*g/g*	PCBs, *ng/g*	Dioxins†, *pg/g*
US FDA action level		1	2000	None
Anchovy	1449	< 0.05	–	0.35
Catfish, farmed	177	0.05	0.5	0.51–2.09
Cod, Atlantic	158	0.1	–	0.05–0.15
Fish burger	–	< 0.05	8	0.01–0.11
Fish sticks, frozen	402	0.17	–	–
Clams	–	0.05	2–3	0.05–0.10
Crab	474	0.09	6	0.55–1.05
Halibut	465	0.25	–	1
Herring, Atlantic	2079	< 0.05	–	0.97
Herring, pickled	1389	–	–	–
Lobster	104	0.31	–	0.12–0.69
Mackerel, Atlantic	1203	0.05	–	0.32–0.87
Mackerel, King	401	0.73	–	–
Mahi-mahi‡	532	0.15	–	–
Mussels	389	0.15	0.8–7	0.07–0.45
Oysters, eastern	1120	0.15	0.8–17	0.19–0.46
Pollock, Atlantic	542	< 0.05	–	0.01–0.24
Salmon, farmed	2147	< 0.05	15–51 (with skin)	0.33–0.87
Salmon, wild	1840	< 0.05	0.5–5 (with skin)	0.03–0.34
Sardines	982	< 0.05	22–57	0.18–0.60
Scallops	365	< 0.05	–	0.16
Shark	689	0.99	–	–
Shrimp	315	0.05	0.2–2	0.06–0.19
Snapper	321	0.19	–	–
Swordfish	819	0.98	–	–
Tilefish (golden bass)	905	0.14–1.45	–	–
Tuna, light/skipjack	270	0.12	45	0.02
Tuna, albacore	862	0.35	100	0.23
Beef	0	0	22	0.13–0.27
Bologna	0	0	–	0.16–0.29
Butter	0	0	70	0.22–0.66
Cheese	0	0	–	0.25–0.77
Chicken	9	0	32	0.02–0.20
Egg (1 egg)	41	0	19	0.05–0.52
Milk, whole	0	0	–	0.01–0.13
Pork	0	0	18	0.10–0.23

*EPA plus DHA values are from the US Department of Agriculture [25].
†Expressed as toxic equivalents.
‡Also known as dolphin fish.
DHA—docosahexaenoic acid; EPA—eicosapentaenoic acid; FDA—Food and Drug Administration; PCB—polychlorinated biphenyl.
(*Adapted from* Mozaffarian and Rimm [12••].)

that pregnant and nursing women consume 12 oz of oily fish (including salmon, sardines, mackerel, and herring) weekly, but they are advised to avoid the four most contaminated species of fish. These fish include shark (0.99 parts per million [ppm] of mercury), tilefish (golden bass, 1.45 ppm), King mackerel (0.73 ppm), and swordfish (0.98 ppm). Albacore tuna (with intermediate levels of mercury, 0.35 ppm) should be limited to 6 oz per week. These FDA suggestions exceed the American Heart Association recommendations for all adults to consume at least two oily fish meals (4–5 oz servings) per week. It should be emphasized that these recommendations to restrict certain types of fish are not for the general population but for women who are pregnant or lactating. There are no formal warnings by the US government regarding fish based on mercury content for other adults, but state-based advisories regarding sport-caught fish should always be heeded.

In assessing the overall risk-to-benefit ratio of consuming potentially contaminated fish while attempting to ingest adequate quantities of EPA and DHA, Mozaffarian and Rimm [12••] concluded that even if one consumed, on a daily basis for 70 years, enough farmed salmon to provide about 1000 mg/d of EPA and DHA (four 6-oz servings per week), the theoretical increase in cancer deaths per 100,000 people would be 24. This number was based on extrapolations from animal experiments, limited high-dose studies in humans, and a 10-fold safety factor. On the other hand, there would be approximately 7125 fewer CHD deaths, and this estimate is based on large, prospective cohort and intervention studies in humans; therefore, the benefits outweigh risks by about 300-fold. The authors also estimated that the cost to consume 250 mg of LC n-3 FAs from oily fish, whether from fillets or canned products, was $0.50 per day or less. Overall, this paper provided an extensive review and analysis of the benefits, risks, and costs associated with increasing LC n-3 FA intakes and concluded with this statement: "Avoidance of modest fish consumption due to confusion regarding risks and benefits could result in thousands of excess CHD deaths annually and suboptimal neurodevelopment in children."

Absolute Amount of LC n-3 FAs in Tissues Is More Important than the n-6:n-3 Ratio

There continues to be controversy regarding the relative merits of absolute intakes or tissue levels of n-3 FAs versus considering them as a ratio to n-6 FAs. Harris et al. [16••] reviewed case control studies over the past four decades to determine the relations between blood/serum/tissue content of n-3 and n-6 FAs and risk for cardiovascular disease events. They hypothesized that tissue LC n-3 FA levels would be lower, and that LC n-6 FAs (specifically AA) would be higher in CHD cases than controls. If this were true, then measures of the AA:EPA or the n-6:n-3 ratio in tissues may be more reflective of risk for CHD than n-3 or n-6 tissue levels alone.

Articles were included in their meta-analysis if they reported specific tissue FA composition data in relation to risk or incidence of CHD events (not CHD risk factors, the presence of CHD, or other forms of vascular disease). Studies were conducted with prospective cohort, or nested or cross-sectional case-control designs. Blood or tissue samples had to be drawn either prior to or very soon after the cardiac event. Tissues examined were grouped into two major categories for a subanalysis: triglyceride-rich (ie, adipose) and phospholipid (PL)-rich (ie, whole serum, serum, plasma PL, platelet PL, erythrocytes, coronary arteries, or whole blood). Studies were conducted worldwide, in populations with diverse diets, but cases and controls were always handled identically within each study.

In order to perform a meta-analysis, the results from disparate analytical techniques and tissue samples needed to be normalized. Hence, the effect size for each FA of interest was calculated in each study using Hedge's *g* statistic. This statistic is the difference in FA levels between cases and controls divided by the pooled SD for both. A *g* of -0.5, for instance, meant that cases had FA levels that were 50% of 1 SD lower than controls. Given the multiple assumptions made in this analysis, a conservative *P* value of 0.01 was required for statistical significance.

Twenty-five studies were included. In the overall analysis, tissue proportions of DHA (alone or when combined with EPA) were significantly reduced in the cases. In addition, the greatest effect sizes were seen with DHA (-0.34). Both LA and ALA tended to be depressed in cases ($P = 0.02$). Four subanalyses were conducted. To determine the cardiovascular risk associated with FA content measured before a CHD event relative to associations with FA content assessed after the CHD event, results from prospective studies were compared with those from cross-sectional study designs. The nine nested case-control studies (seven studies) and prospective cohorts (two studies) showed a significant effect size only for DHA (-0.77; $P < 0.01$), whereas no fatty acids were significantly related to CHD events in cross-sectional, postcoronary event studies (16 studies included). AA had the second largest effect size in prospective studies at -0.25 ($P = 0.05$), but this did not reach the level for statistical significance.

When studies were stratified by fatal versus nonfatal outcomes, only LA content of tissues was associated with a protective effect on cardiovascular risk, with an effect size of -0.22. DHA had a similar effect size but did not achieve statistical significance. However, DHA was, again, the best FA marker at distinguishing cases from controls, with an effect size of -0.66. AA was not associated with either outcome.

The fourth subanalysis compared triglyceride-rich versus PL-rich tissues, because the n-3 and n-6 FA compositions involved were so diverse. Triglyceride-rich adipose tissue of cases had significantly lower DHA and higher AA concentrations than controls, whereas in PL-rich tissues, cases had reduced EPA plus DHA, and ALA, relative to controls.

Low DHA or DHA plus EPA levels were consistently predictive of major CHD events. Prospective studies showed significantly reduced LC n-3 FAs in cases, suggesting that tissue content of EPA and DHA does have prognostic value. This conclusion supports the view that metrics like the Omega-3 Index (erythrocyte membrane EPA plus DHA) may serve in the future as a new risk factor for CHD [17]. Alternatively, no FA examined in this meta-analysis was significantly linked to overall risk of CHD events in traditional case-control designs, although the effect sizes for EPA and DHA were similar to those seen in the prospective trials. The exact role of LC n-3 FAs in nonfatal CHD remains unclear.

In summary, tissue DHA (alone or in combination with EPA) was the best predictor of cardiovascular risk and demonstrated the strongest association between cardiac events and FA content in both triglyceride-rich and PL-rich tissues. DHA or DHA plus EPA were consistently reduced in cases relative to controls in all studies combined, in the prospective studies, in the studies with fatal endpoints, and in both tissue types. In contrast, short chain n-3 FA ALA composition was only associated with CHD risk in one setting: cases contained less ALA than controls in PL-rich tissues, whereas no associations could be made with ALA levels overall, in analyses of fatal/nonfatal events, or in prospective versus traditional study designs. Based on this analysis, the FAs of most relevance for distinguishing CHD cases versus controls were the LC n-3 FAs. Ratios provided no additional information. The authors contend that the ratio only obscured the risk signal provided by the n-3 FA alone, and elevated tissue PL AA or LA content was not associated with increased CHD risk. Others have come to the same conclusion [18–20].

Effects of Fish Oil or Flaxseed Oil on Myocardial FA Composition

As the cardioprotective effects of LC n-3 FAs appear to derive from their presence in myocardial cell membranes [21], the question of the rate and extent of incorporation of these FAs into the heart is of considerable interest. Harris et al. [22] reported that 6 months of supplementation with about 1 g/d of EPA and DHA approximately doubled both the erythrocyte and myocardial levels of these two FAs, but they did not examine the time course of incorporation or study the effects of ALA on myocardial enrichment with LC n-3 FAs. A recent study by Metcalf et al. [23••] at the Royal Adelaide Hospital fills this gap. These investigators used a novel and challenging study design to determine the effects of short-term oral supplementation with short chain (ie, ALA) and LC n-3 FAs on the FA composition of cardiac tissue.

Sixty individuals were recruited for participation who had low baseline fish intake (≤ 1 fish meal per week) and were not taking fish oil or flaxseed oil supplements. All were undergoing either CABG or valve repair or replacement (or both) and had never had cardiac surgery previously. Volunteers were randomly assigned to one of six groups. The 7-day, 14-day, and 21-day fish oil groups were given 6 g/d of EPA plus DHA for at least the corresponding number of days before surgery. Controls included one group receiving no supplements, and an olive oil group and a flaxseed oil group whose participants received 10 mL/d of these oils for at least 21 days. The flaxseed oil group thus ingested about 5.5 g/d of ALA. Blood samples were collected at enrollment and at surgery, and right atrial appendage tissue was collected during surgery.

The erythrocyte membrane PL FA composition of all participants was similar at enrollment and reflected a low baseline intake of dietary n-3 FA (erythrocyte EPA and DHA < 6% of total FA). Blood loss during cardiac surgery was not significantly different between the groups (yet another indication that LC n-3 FAs do not increase risk for clinically significant bleeding [24•]). Olive oil did not affect the FA composition of either blood or atrial tissue, whereas flaxseed oil increased the proportion of ALA in erythrocytes and atrial tissue (from about 0.1% to 0.3% of total FAs). Neither EPA nor DHA levels increased in either tissue with flaxseed oil supplementation.

Short-term fish oil supplementation, however, significantly increased the EPA plus DHA composition of both erythrocyte and atrial tissue in a dose-dependent fashion, with DHA deposition being more pronounced than EPA. The erythrocyte EPA plus DHA (the Omega-3 Index [17]) tracked with the rise in atrial EPA plus DHA content, confirming the results of previous studies [22].

Because some patients had to wait up to 60 days for their surgery, the investigators were able to follow the incorporation curves out for about 2 months. Although neither cardiac nor erythrocyte EPA plus DHA levels had reached a new steady state, incorporation did appear to be nearly complete after 2 months. Finally, as EPA and DHA levels rose from about 5% to 12% of total FAs in myocardial tissue, AA proportions decreased from about 21% to 16% of total FAs. Hence, the LC n-3 FAs primarily replaced the LC n-6 FAs.

There is now unequivocal evidence that dietary n-3 FAs are directly incorporated into cardiac tissue in a dose-dependent fashion. Because flaxseed oil did not alter LC n-3 FA levels in human myocardium, they are unlikely to provide the same level of cardioprotection as EPA and DHA provide.

Conclusions

With the publication of the JELIS study, the field of n-3 FAs continues to mature, with new evidence regarding the effects of high tissue n-3 FA levels on cardiovascular health. Based on the risk-to-benefit analysis conducted by Mozaffarian and Rimm [12••], it is clear that by avoiding just a few types of fish, even women of childbearing age can safely consume n-3 FA–rich fish. A meta-analysis now

confirms that the most relevant FAs to use as biomarkers for CHD are the LC n-3 FAs, especially DHA. A low level of this FA, not an elevated or an increased n-6:n-3 ratio, predicts cardiac events prospectively and cross-sectionally. Lastly, the analysis by Metcalf et al. [23••] of human heart tissue after LC n-3 FA supplementation confirms a dose-response effect and shows that a shorter chain n-3 FA (ALA) does not materially increase heart or blood levels of EPA or DHA.

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- •• Of major importance

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This is the largest and longest study of LC n-3 FAs for the prevention of CHD. EPA (1.8 g/d over 4.6 years) reduced risk for major CHD events by 19% in Japanese patients taking statins. This effect was seen in the face of very high baseline intakes of DHA and EPA in this population.

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This study reported the association between the intake of fish and LC n-3 FA and risk for CHD events in over 45,000 Japanese adults. Higher intakes were shown, even in this fish-consuming population, to still afford CHD benefit.

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In this short review of the risk for clinically significant bleeding associated with LC n-3 FA intake, no increased risk was found in 15 studies, even when patients were also taking anticoagulant agents. This supports the safety of high-dose LC n-3 FAs (3–4 g/d) in combination with drugs like aspirin.

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