

Omega-3 Fatty Acids for Cardioprotection

JOHN H. LEE, MD; JAMES H. O'KEEFE, MD; CARL J. LAVIE, MD; ROBERTO MARCHIOLI, MD;
AND WILLIAM S. HARRIS, PhD

The most compelling evidence for the cardiovascular benefit provided by omega-3 fatty acids comes from 3 large controlled trials of 32,000 participants randomized to receive omega-3 fatty acid supplements containing docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) or to act as controls. These trials showed reductions in cardiovascular events of 19% to 45%. These findings suggest that intake of omega-3 fatty acids, whether from dietary sources or fish oil supplements, should be increased, especially in those with or at risk for coronary artery disease. Patients should consume both DHA and EPA. The target DHA and EPA consumption levels are about 1 g/d for those with known coronary artery disease and at least 500 mg/d for those without disease. Patients with hypertriglyceridemia benefit from treatment with 3 to 4 g/d of DHA and EPA, a dosage that lowers triglyceride levels by 20% to 50%. Although 2 meals of oily fish per week can provide 400 to 500 mg/d of DHA and EPA, secondary prevention patients and those with hypertriglyceridemia must use fish oil supplements if they are to reach 1 g/d and 3 to 4 g/d of DHA and EPA, respectively. Combination therapy with omega-3 fatty acids and a statin is a safe and effective way to improve lipid levels and cardiovascular prognosis beyond the benefits provided by statin therapy alone. Blood DHA and EPA levels could one day be used to identify patients with deficient levels and to individualize therapeutic recommendations.

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AA = arachidonic acid; AHA = American Heart Association; ALA = α -linolenic acid; CAD = coronary artery disease; CV = cardiovascular; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; FDA = Food and Drug Administration; GISSI = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; HDL = high-density lipoprotein; JELIS = Japan EPA Lipid Intervention Study; LDL = low-density lipoprotein; MI = myocardial infarction; SCD = sudden cardiac death

The American Heart Association (AHA) has endorsed the use of omega-3 fatty acids for secondary prevention of cardiovascular (CV) events in people with documented coronary artery disease (CAD). The recommendation calls for approximately 1 g/d of a mixture of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Although the AHA statement identifies oily fish as the ideal source, fish oil (in capsules or liquid form) is also an acceptable option.¹ This is the first time that the AHA has recommended a nutritional supplement for CAD prevention. The omega-3 fatty acid recommendation is based on an extensive and growing body of evidence supporting the CV benefits and triglyceride-lowering effects of omega-3 oils.

The Food and Drug Administration (FDA) has approved an omega-3 fatty acid ethyl ester formulation, at a dosage of 4.0 g/d, for the treatment of very high triglyceride levels. Nevertheless, many physicians and patients are confused

about the appropriate form, indications, and dosing of omega-3 fatty acids. This review briefly summarizes current scientific data on omega-3 fatty acids and CV health, specifically focusing on indications for use and recommended guidelines for administration and dosing. Throughout, the term *omega-3 fatty acids* is used to indicate DHA and EPA only; as discussed later, the evidence for a CV benefit from α -linolenic acid (ALA), a plant omega-3 fatty acid, is much weaker than it is for DHA and EPA.

EFFECTS ON CV HEALTH

BACKGROUND

During the past 3 decades, thousands of epidemiologic, observational, experimental, and randomized controlled studies have been published on the CV effects of omega-3 fatty acids. In the aggregate, these studies document clear CV protective effects.² The 2 specific omega-3 fatty acids that have been associated with CV benefit and triglyceride lowering are those from fish oils, DHA and EPA. In contrast, ALA, which is found in abundance in flaxseed and to a lesser extent in walnuts and other tree nuts, as well as in trace amounts in green leafy vegetables, is inadequate as the sole dietary source of omega-3 fatty acids because humans convert less than 5% of ALA to EPA (and less to DHA).³ In some but not all epidemiologic studies,² ALA intake has been inversely associated with CV events; however, because of the absence of convincing randomized trials with clinically relevant end

From the Mid America Heart Institute and University of Missouri-Kansas City (J.H.L., J.H.O.); Ochsner Medical Center, New Orleans, LA (C.J.L.); Laboratory of Clinical Epidemiology of Cardiovascular Disease, Italy (R.M.); and Nutrition and Metabolic Disease Research Center, Sanford Research/USD and Sanford School of Medicine of the University of South Dakota, Sioux Falls (W.S.H.).

Dr O'Keefe has received research grants from and is a consultant for CardioTabs. Dr Lavie has been a speaker and consultant for Reliant Pharmaceuticals. Dr Marchioli is a member of the steering committee of the Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-Heart Failure (GISSI-HF) trial sponsored by Astra-Zeneca and Società Prodotti Antibiotici (SPA), a member of the steering committee of the Rischio & Prevenzione trial sponsored by SPA, and a speaker for SPA, Sigma-Tau, Solvay Pharmaceuticals, and Pronova BioPharma. Dr Harris is a consultant for and has received research grants from both Reliant Pharmaceuticals and Monsanto and is a speaker for the former.

Individual reprints of this article are not available. Address correspondence to James H. O'Keefe, MD, 4330 Wornall Rd, Ste 2000, Kansas City, MO 64111 (jhokeefe@cc-pc.com).

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TABLE 1. Association Between Tissue Fatty Acids and Risk of CAD Events, Estimated by Effect Sizes in 25 Studies^a

Fatty acid	All studies			No. of studies
	g ^b	P value	95% CI	
EPA-DHA	-0.19	<.01	-0.06 to -0.33	19
DHA	-0.34	<.01	-0.12 to -0.59	19
EPA	-0.10	.08	0.01 to -0.21	15
ALA	-0.21	.03	-0.02 to -0.39	16

^a ALA = α -linolenic acid; CAD = coronary artery disease; CI = confidence interval; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid.

^b g: Hedges g (effect size), in which the case-control difference is expressed as a fraction of the pooled SD; negative values indicate that fatty acid values were lower in cases relative to controls.

Adapted from *Atherosclerosis*,⁴ with permission from Elsevier.

points, its role in cardioprotection is less clear than that of DHA and EPA.

CLINICAL TRIALS ON CORONARY ARTERY DISEASE

Harris et al⁴ reviewed 25 trials that evaluated risk of CAD events as a function of in vivo omega-3 fatty acid levels. The quantity of DHA in plasma and cellular phospholipids, which closely correlates with the quantity of DHA in the myocardium, was inversely related to the risk of events.^{4,5} Reduced risk appears to be more clearly linked to increased tissue levels of DHA than EPA (Table 1); however, it is difficult to separate completely the effects of these 2 omega-3 fatty acids that are almost always consumed together.

In a randomized trial performed almost 2 decades ago, omega-3 fatty acids, either in the form of oily fish or fish oil capsules, reduced 2-year all-cause mortality by 29% in post-myocardial infarction (MI) patients.⁶ More recently,

2 major randomized controlled trials examined the effects of supplemental omega-3 fatty acids on CAD risk. The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione study randomized 11,323 patients who had experienced an MI to omega-3 acid ethyl esters (1 capsule per day, providing 850 mg of DHA and EPA) or usual care. Treatment significantly reduced risk of death from any cause by 28%; after 4 months, risk of sudden cardiac death (SCD) was decreased by 45% (Figure 1).⁷ In another megatrial, the Japan EPA Lipid Intervention Study (JELIS),⁸ 18,645 patients with hypercholesterolemia (70% women; mean age, 61 years) were randomly assigned to either statin alone or statin and pure EPA (1.8 g/d). During the 5-year study, EPA reduced major adverse CV events by 19% (Figure 2). Omega-3 fatty acid supplementation lowered CV risk in both the GISSI-Prevenzione study and JELIS, despite aggressive therapy with standard pharmacotherapy (eg, statins, aspirin, β -blockers and angiotensin-converting enzyme inhibitors). Additionally, the JELIS trial established the safety and efficacy of combination therapy with EPA and a statin vs statin therapy alone for improving CV prognosis.⁸

MECHANISMS OF ACTION

Omega-3 fatty acids appear to confer CV benefits largely through DHA and EPA enrichment of membrane phospholipids.⁹ Via this mechanism, omega-3 fatty acids can ultimately increase arrhythmic thresholds,¹⁰ reduce blood pressure,^{11,12} improve arterial and endothelial function,¹³ reduce platelet aggregation,¹⁴ and favorably affect autonomic tone^{11,15} (Table 2). In a meta-regression analysis of 22

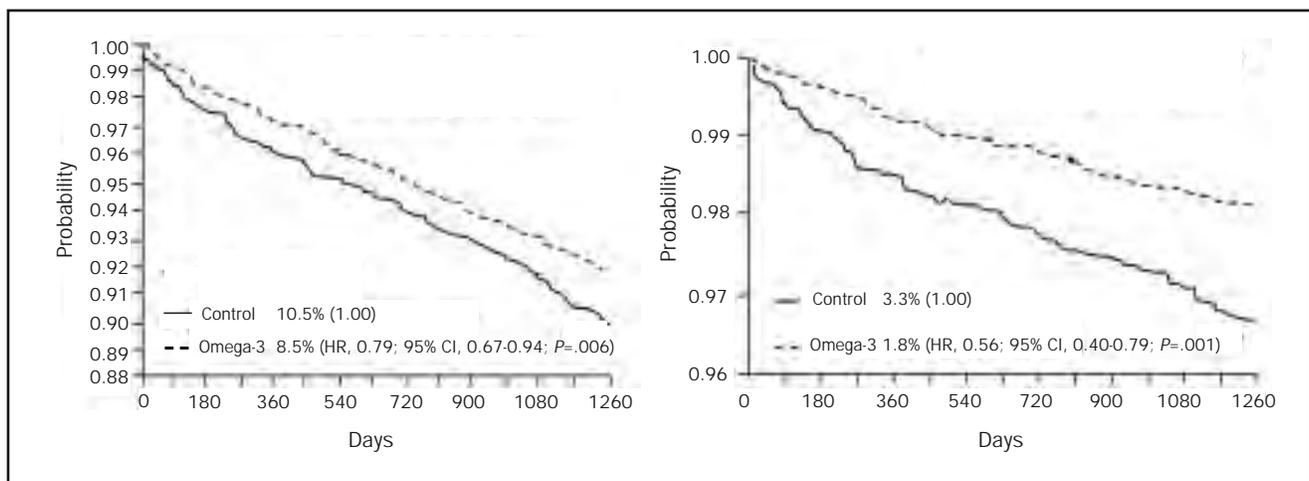


FIGURE 1. Time course of clinical events in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione study. Treatment with 850 mg/d of omega-3 acid ethyl esters reduced total mortality (left) by 21% and sudden cardiac death (right) by 45% at 3.5 years. CI = confidence interval; HR = hazard ratio. Data from reference 7.

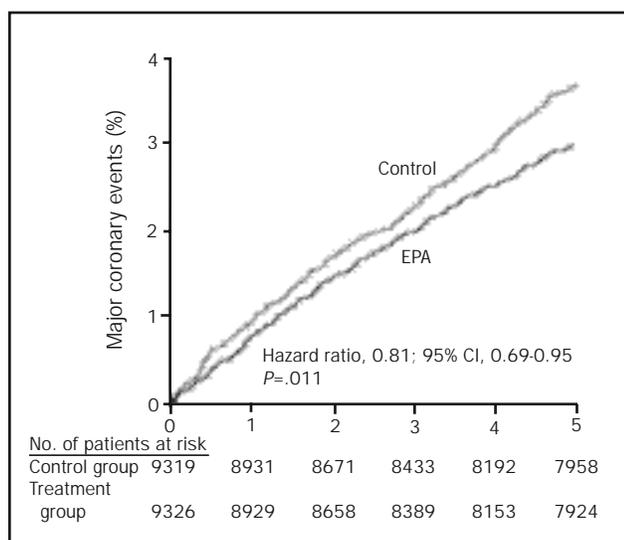


FIGURE 2. Eicosapentaenoic acid (EPA) (1.8 g/d) reduced the incidence of major adverse coronary events in the Japan EPA Lipid Intervention Study (JELIS) by 19%. CI = confidence interval. From *The Lancet*,⁹ with permission from Elsevier.

double-blind studies, Geleijnse et al¹⁶ reported that consumption of approximately 4.0 g/d of omega-3 fatty acid was associated with a significant 1.7- and 1.5-mm Hg reduction in systolic and diastolic blood pressures, respectively; these reductions were more pronounced in older patients and in those with higher blood pressures. Evidence suggests that lowering systolic blood pressure by as little as 2 mm Hg can yield reductions of 4% in mortality due to CAD.¹⁷

The antiplatelet, anti-inflammatory, and triglyceride-lowering effects of omega-3 fatty acids require relatively higher doses of DHA and EPA (eg, 3.0-4.0 g/d), whereas the reduction in SCD risk can be achieved at lower intakes (0.5-1.0 g/d).^{4,7} Omega-3 fatty acids have been shown to suppress production of proinflammatory cytokines such as interleukin 6, interleukin 1β, and tissue necrosis factor α.¹⁸ Additionally, when administered to people who were obese, 1.8 g/d of EPA increased the level of adiponectin, which can reduce inflammation and improve insulin sensitivity.¹⁹ Very high doses of omega-3 fatty acids (ie, 8.0 g/d) have been shown to have anti-inflammatory effects and to improve body composition in patients with heart failure.²⁰ However, omega-3 fatty acids have not been shown consistently to lower C-reactive protein levels.²¹

TABLE 2. Possible Omega-3 Fatty Acid Benefits

Antiarrhythmic effects ^a	Decreased blood pressure
Modulation of autonomic function ^a	Anti-inflammatory effects
Decreased platelet aggregation	Plaque stabilization
Vasodilation	Decreased triglycerides

^a Conferred at lower doses of docosahexaenoic acid and eicosapentaenoic acid.

A “GISSI” dose of DHA and EPA (810 mg/d) given to stable CAD patients decreased resting heart rate, increased postexercise heart rate recovery, and increased beat-to-beat heart rate variability (in the high-frequency band).¹¹ These changes are consistent with augmented vagal tone, suggesting that omega-3 fatty acids could confer cardioprotection in part by improving autonomic sympathovagal balance.^{11,15} However, other studies in patients undergoing heart transplant suggest that omega-3 fatty acids can reduce heart rate independently of vagal activation.²²

To the extent that the omega-3 fatty acid cardioprotection is mediated by changes in cell membrane composition, the much higher levels of DHA than EPA in membrane phospholipids^{5,14} suggest that DHA is the more important of the 2 omega-3 fatty acids. However, data from JELIS demonstrated the efficacy of EPA, which is integrally involved in the antiplatelet and anti-inflammatory activities of omega-3 fatty acids. Although EPA can compete with arachidonic acid (AA) as a substrate for the production of cyclooxygenase- and lipoxygenase-derived eicosanoids, it is a much poorer substrate than AA.²³ Given that membranes typically contain 10 times as much AA as EPA, the beneficial effects of omega-3 fatty acids are not likely due to EPA-derived eicosanoids. As discussed earlier, the presence of both DHA and EPA in cellular membranes can alter the activity of membrane-bound proteins (receptors, ion channels, etc), and both omega-3 fatty acids can work synergistically to alter metabolism via this mechanism.

Some of the cardioprotective effects of omega-3 fatty acids, particularly at higher doses, could result from their favorable effects on the lipid profile. Davidson et al²⁴ recently reported that 3.4 g/d of omega-3 acid ethyl esters, when added to baseline simvastatin therapy, produced additional reductions of 29.5% in triglyceride levels and 9.0% in non-high-density lipoprotein (HDL) cholesterol levels, with a small but significant increase in HDL levels (Figure 3). Omega-3 fatty acids induce variable effects on low-density lipoprotein (LDL), depending on the baseline lipid profile. In JELIS, EPA reduced LDL by approximately 10%; however, omega-3 fatty acids can increase LDL by up to 10% when used in high doses to treat moderately elevated triglyceride levels,²⁵ and by 32% (from 79 to 104 mg/dL [to convert to millimoles per liter, multiply by 0.0113]) in patients with very high baseline triglyceride levels.²⁶

OPTIMAL OMEGA-3 FATTY ACID MIX: DHA VS EPA

Both DHA and EPA are present in all oily fish, although at variable ratios (Table 3).²⁷ Most commonly consumed fish,

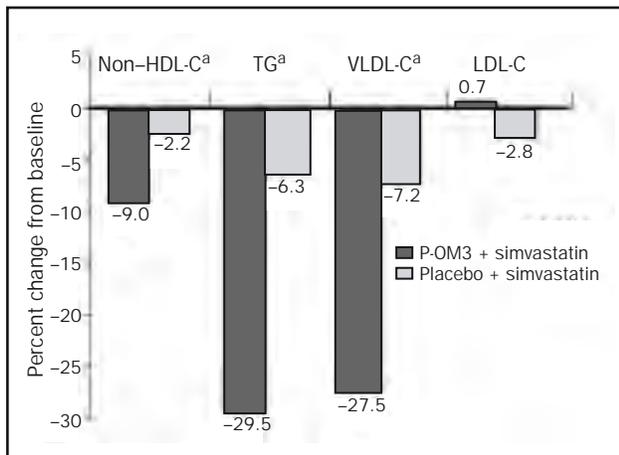


FIGURE 3. Effect of prescription omega-3 acid ethyl esters (P-OM3) (4.0 g/d) on lipid and lipoprotein levels in statin-treated patients with serum triglyceride (TG) levels of 200-499 mg/dL (2.26-5.64 mmol/L). Median percent changes are presented for non-high-density lipoprotein cholesterol (non-HDL-C), TGs, calculated very-low-density lipoprotein cholesterol (VLDL-C), and low-density lipoprotein cholesterol (LDL-C) from baseline to the end of treatment. ^a P < .05.

From *Clin Ther*,²⁴ with permission from Excerpta Medica, Inc.

such as salmon, contain DHA and EPA in a ratio of approximately 2:1, whereas standard fish oil (usually derived from menhaden, an oily fish of the herring family) contains DHA and EPA in a 2:3 ratio. To a small extent, DHA can

be retroconverted to EPA²⁸; however, EPA supplementation does not increase tissue or blood levels of DHA.²⁹ In vitro studies have shown both fatty acids to alter ion channel function.³⁰

A recent meta-analysis pooling the results of prospective clinical trials and epidemiologic studies suggests that most of the reduction in risk of CAD death is conferred with modest omega-3 fatty acid consumption (approximately 250-500 mg/d of DHA and EPA, corresponding to approximately 1-2 servings per week of oily fish) (Figure 4).³¹ Thus, the antiarrhythmic effects³² are apparent in studies in which the background intake of omega-3 fatty acids is already low and the risk of SCD is high. The reductions in SCD and fatal CAD in the GISSI-Prevenzione study appeared quickly, within weeks of initiating omega-3 fatty acid therapy. On the basis of the JELIS trial, the reduction in nonfatal CAD events could require higher doses (eg, 2000 mg/d of DHA and EPA) and a longer duration of treatment (3-5 years).

In a recent review of the cumulative data, Anand et al¹⁰ showed significant benefits of DHA and EPA against atrial fibrillation,³³ as well as trends toward benefits in malignant ventricular arrhythmias.^{10,34-36} In a randomized trial of 160 patients with CAD, omega-3 fatty acid supplementation (1700 mg/d of DHA and EPA) reduced the occurrence of atrial fibrillation after coronary artery bypass surgery by 54% vs placebo.³³ Although omega-3 fatty acids are effective at reducing SCD in patients with CAD and reduced

TABLE 3. Fish Content of Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA)^a

Type	DHA (g/100 g)	EPA (g/100 g)	DHA and EPA (g/100 g)	Ratio DHA:EPA
Tuna				
Bluefin	1.141	0.363	1.504	3.1:1.0
Light, canned in water	0.223	0.047	0.270	4.8:1.0
Albacore, canned in water	0.629	0.233	0.862	2.7:1.0
Salmon				
Atlantic, farmed	1.457	0.690	2.147	2.1:1.0
Atlantic, wild	1.429	0.411	1.840	3.5:1.0
Chinook	0.727	1.010	1.737	1.0:1.4
Sockeye	0.700	0.530	1.230	1.3:1.0
Mackerel, Atlantic	0.699	0.504	1.203	1.4:1.0
Herring, Atlantic	1.105	0.909	2.014	1.2:1.0
Trout				
Rainbow, farmed	0.820	0.334	1.154	2.5:1.0
Rainbow, wild	0.520	0.468	0.988	1.1:1.0
Halibut	0.374	0.091	0.465	4.1:1.0
Cod	0.154	0.004	0.158	38.5:1.0
Haddock	0.162	0.076	0.238	2.1:1.0
Catfish				
Channel, farmed	0.128	0.049	0.177	2.6:1.0
Channel, wild	0.137	0.100	0.237	1.4:1.0
Swordfish	0.681	0.087	0.768	7.8:1.0
Grouper	0.213	0.035	0.248	6.1:1.0
Shrimp	0.144	0.171	0.315	1.0:1.2

^aData from reference 27.

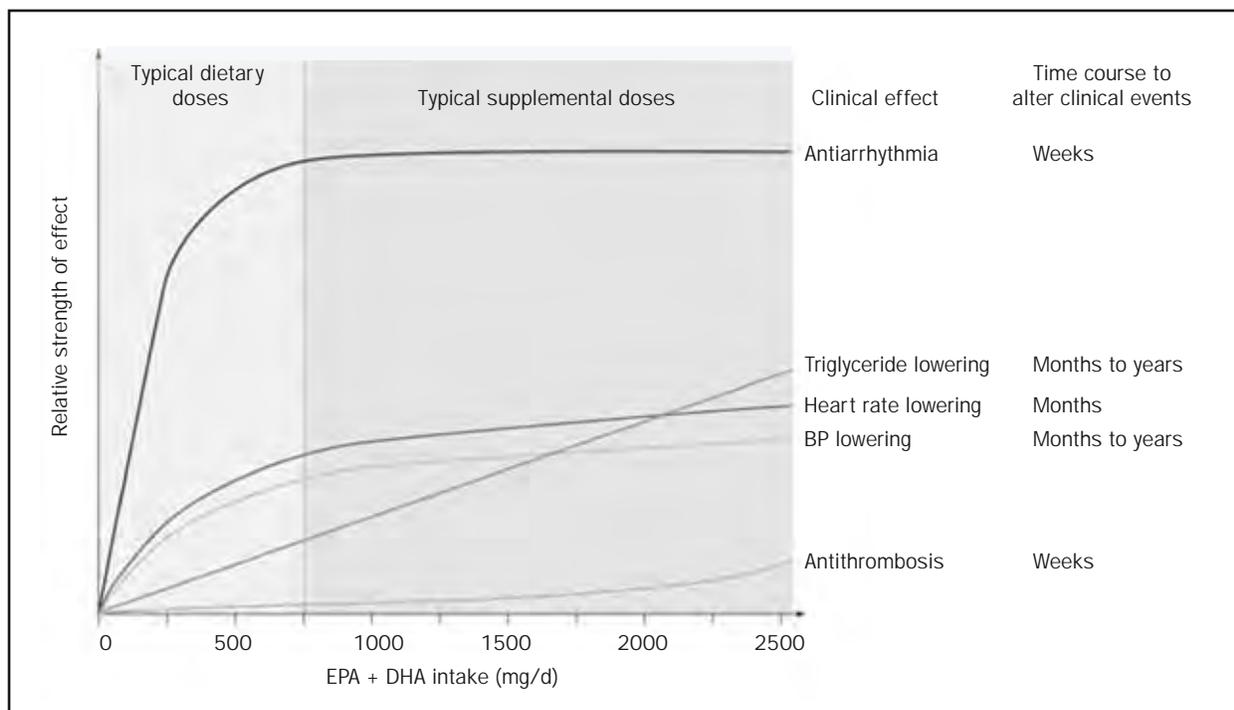


FIGURE 4. Schema of potential dose responses and time courses for altering clinical events of physiologic effects of fish or fish oil intake. BP = blood pressure; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid. From *JAMA*,³¹ Copyright © 2006, American Medical Association. All rights reserved.

left-ventricular systolic function,³⁷ mixed results were reported for 3 trials using omega-3 fatty acids in patients with implantable cardioverter-defibrillators.³⁴⁻³⁶ A large randomized trial of omega-3 fatty acids in 7000 patients with chronic heart failure is projected to be complete in 2008 and should help to clarify the effects of DHA and EPA on outcomes in patients with reduced left-ventricular function.³⁸

Although DHA is far more abundant than EPA in the myocardium,¹⁴ supplementation with DHA and EPA raises the levels of both.¹⁴ Risk of SCD has been reduced in studies that provide both DHA and EPA in roughly equivalent proportions. The discordance between the GISSI-Prevenzione study,⁷ in which DHA and EPA reduced SCD, and the JELIS study,⁸ in which EPA alone did not reduce SCD, might indicate that DHA is the more important omega-3 fatty acid for stabilizing the myocardial cell membranes and preventing dangerous rhythm abnormalities. However, the difference could also be a function of the high baseline intake of fish by the Japanese participants in the JELIS Trial (the typical Japanese person consumes 8 times more DHA and EPA than the typical American),³⁹ which would also explain the very low incidence of SCD in this trial. Only 35 of the 18,645 patients, split almost evenly between the control and

omega-3 fatty acid groups, experienced SCD during the 5 years of JELIS.⁸

ADVERSE EFFECTS

In prospective placebo-controlled trials, no adverse effects were observed to occur at a frequency of more than 5%, and no difference in frequency was noted between the placebo and omega-3 fatty acid groups.^{24,40} The most commonly observed adverse effects are nausea, gastrointestinal upset, and a “fishy burp.” Steps to reduce burping and improve adherence include taking the omega-3 fatty acid at bedtime or with meals, keeping the fish oil capsules in the freezer, or using enteric-coated products. The FDA made the recommendation that “consumers not exceed a total of 3 grams per day of DHA and EPA omega-3 fatty acids,” the equivalent of ten 1-gram capsules of standard fish oil (30% DHA and EPA). Early studies indicated that omega-3 fatty acids might prolong bleeding times (but not beyond the normal range), raising concerns that higher intakes could increase risk for hemorrhagic complications. However, a recent comprehensive report by Harris⁴¹ concluded that virtually no increased risk for clinically remarkable bleeding has been seen in patients with doses of omega-3 fatty acids up to 7

g/d of DHA and EPA, even when taken in combination with other antiplatelet medications.

One of the potential dangers of a diet high in fish (not fish oil) is the consumption of toxic contaminants, such as methyl mercury. For this reason, the FDA has advised that children and pregnant or nursing women specifically avoid king mackerel, shark, swordfish, and tile fish because they are particularly high in mercury.⁴² Interestingly, the Avon Longitudinal Study of Parents and Children (ALSPAC),⁴³ which followed 11,875 British women during their pregnancy and beyond, found that the children of women who ate fish in excess of US FDA/Environmental Protection Agency recommendations during pregnancy (ie, 3 fish meals/week) had better cognitive and behavioral development than offspring of women who consumed less fish during their pregnancies (Figure 5).⁴³ However, causality cannot be inferred in this retrospective study because of baseline differences in the groups that could have accounted in part for differences in neurocognitive development. Nevertheless, the ALSPAC study⁴³ and a meta-analysis by Mozaffarian and Rimm³¹ provide reassurance regarding the favorable risk-benefit ratio of fish consumption.

Most commonly consumed omega-3 fatty acid-rich fish and seafood, such as salmon, shrimp, sardines, trout, herring, and oysters, are very low in mercury. Farm-raised salmon and rainbow trout are safe because they have mercury levels similar to their wild counterparts and as much or more omega-3 fatty acids.⁴⁴ Fortunately, mercury is water soluble and protein bound and is therefore not extracted into fish oils. Thus, fish oil supplements contain negligible amounts of mercury.⁴⁵

PRIMARY AND SECONDARY PREVENTION OF CAD

To date, no randomized controlled trial has shown that omega-3 fatty acids reduce the risk of CV events and mortality in a primary prevention population. The evidence supporting a benefit in primary prevention comes instead from an observed 18% decrease in CV events in the 80% of patients in the JELIS trial without documented CAD ($P=.13$); this effect size was essentially the same as that observed in the secondary prevention cohort (19%, $P<.05$). In addition, prospective observational cohort studies have consistently found a significant inverse relationship between CAD risk and fish intake⁴⁶; in these primary prevention studies, 1 fish meal per week was associated with a 15% reduction in CAD risk, and 5 or more fish meals per week were associated with a 40% decrease in risk.⁴⁶ More importantly, blood EPA and DHA levels in the highest quartile were associated with a 90% reduction in risk of SCD compared with the lowest quartile in 2 observational

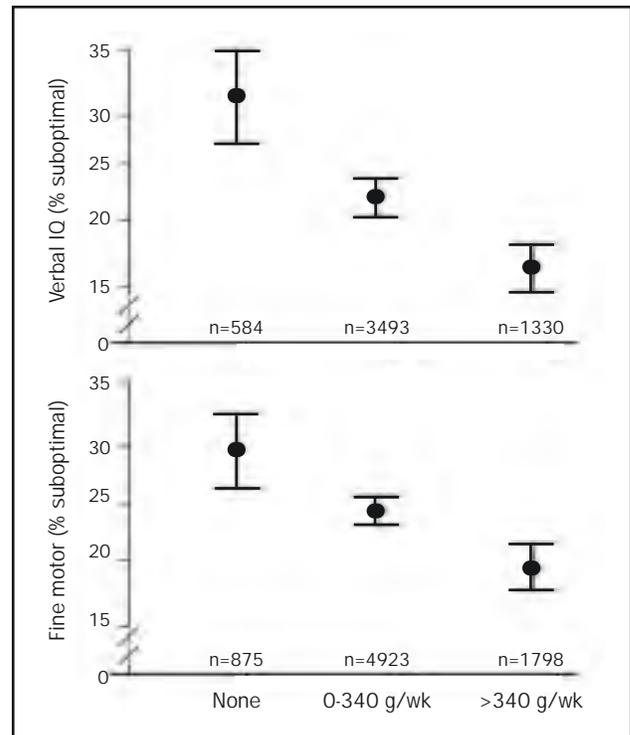


FIGURE 5. Outcomes in children according to tertiles of weekly seafood consumption by the mothers during pregnancy: the Avon Longitudinal Study of Parents and Children (ALSPAC). IQ = intelligence quotient. From *The Lancet*,⁴³ with permission from Elsevier.

studies.^{47,48} Currently, a large prospective study of 12,500 patients is under way to investigate omega-3 fatty acid supplementation in high-risk patients.

The Diet and Reinfarction Trial (DART),⁶ the GISSI study,⁷ and JELIS⁸ (the subset of patients with CAD), all large well-designed trials, showed significant benefits for omega-3 fatty acids in patients with established CAD. However, other studies have not reported positive outcomes. The randomized trial reported by Ness et al⁴⁹ and Burr et al⁵⁰ and that by Nilsen et al⁵¹ are cases in point. In the former,^{49,50} patients with angina who were given fish oil capsules seemed to have higher rates of SCD than untreated controls. This trial was described as “well designed” but suboptimally “conducted or reported” in a review by von Schacky and Harris,⁵² and thus its results are questionable. The Nilsen et al study⁵¹ might not have shown a significant benefit to omega-3 fatty acid supplementation in post-MI patients because of the high background intake of fish oils in the Norwegian study participants, which could have masked the treatment effects. Despite the results of these studies, many international bodies including the AHA, American College of Cardiology, and the European Society of Cardiology have found the overall evi-

dence for benefit sufficiently strong to make public recommendations for increased omega-3 fatty acid intake for both primary and secondary prevention.⁵³

RECOMMENDATIONS FOR ADMINISTRATION

The correct dosage of any fish oil product can be calculated simply by adding up the amount of DHA and EPA per capsule and dividing this number into the target daily doses for triglyceride lowering or primary or secondary prevention. For example, the standard fish oil concentrate contains 120 mg of DHA and 180 mg of EPA per 1-g capsule. Thus, 1 to 2 capsules of standard over-the-counter fish oil per day (300-600 mg of DHA and EPA) would meet the recommendations for primary prevention; 3 to 4 capsules per day (900-1200 mg of DHA and EPA), for secondary prevention; and 5 to 7 capsules twice daily (3000-4200 mg of DHA and EPA), for triglyceride lowering.

Omega-3 fatty acid supplements can be taken at any time, in full or divided doses, without raising concerns for interactions with any medications. For people who need larger doses of omega-3 fatty acids, liquid tasteless products are available that provide 1300 mg of DHA and EPA per teaspoon, and 3900 mg of DHA and EPA per tablespoon. One tablespoon of standard liquid fish oil taken twice weekly provides approximately the same amount of omega-3 fatty acids as 6 oz of salmon twice weekly (500 mg/d of DHA and EPA). Omega-3 fatty acids persist in cell membranes for weeks after consumption, and thus intermittent bolus dosing, ie, twice weekly intake of fish or fish oil, provides the same benefits as daily consumption of lower doses.⁵⁴

The triglyceride-lowering dose is 3 to 4 g/d of DHA and EPA. This dose typically lowers triglyceride levels by 30% to 50%²⁵ and has been shown to reduce severely elevated (>500 mg/dL) triglyceride levels by 45%.²⁶ When added to baseline statin therapy in patients with triglyceride levels between 200 and 499 mg/dL, this dosage lowers triglycerides by an additional 23% to 29%.^{24,55} Fish oil can only be prescribed in a capsular form, which contains omega-3 acid ethyl esters. Although typically more expensive than dietary supplements, the capsular form is a standardized preparation with FDA-approved safety and efficacy data and is the most concentrated source of DHA and EPA available.⁵⁶

The AHA currently recommends that patients with CAD consume "about 1 gram" of a DHA and EPA combination per day.¹ This recommendation is based largely on the results of the GISSI-Prevenzione study, in which a dose of 850 mg/d was used. For people without known CAD or hypertriglyceridemia, the AHA recommends the con-

sumption of approximately 2 servings per week of an oily fish such as salmon (ie, approximately 500 mg/d of DHA and EPA), which can raise red blood cell DHA and EPA levels by at least 50%.⁵⁴ Even half this intake has been suggested as a cardioprotective target in the general population.³¹ For patients with clinically relevant hypertriglyceridemia, the AHA recommends 2.0 to 4.0 g/d of DHA and EPA. However, the lower end of this dose range is ineffective in most patients, and thus clinicians should target between 3.0 and 4.0 g/d to achieve meaningful triglyceride lowering.

Because no trials comparing DHA and EPA with CAD as an end point have been conducted, neither of these omega-3 fatty acids can be conclusively said to be more cardioprotective than the other. Evidence does show that DHA (4 g/d) can affect some surrogate risk markers (eg, blood pressure) more than an equivalent dose of EPA.⁵⁷ However, EPA was shown in the JELIS study to reduce CAD events even in a population with very high intakes of omega-3 fatty acids. Accordingly, it is currently recommended that both DHA and EPA (from either fish or supplements) be consumed in roughly equal amounts. Most patients with CAD find it difficult to consume enough fish to provide 1 g/d of DHA and EPA, much less the amount required to reach therapeutic levels for hypertriglyceridemia (3.0-4.0 g/d of DHA and EPA). Even patients who eat several fish meals per week often consume fish that are low in omega-3 fatty acids, such as cod, fried fish sandwiches, and catfish; as a result, these patients require a fish oil supplement to achieve optimal omega-3 fatty acid levels. Omega-3 fatty acid supplements should be given in conjunction with healthy lifestyle changes.

Target blood levels of DHA and EPA have been suggested as markers of cardioprotection.⁹ For example, red blood cell membrane levels of greater than 8% appear to be associated with the lowest risk of CAD death^{9,58} and with reduced risk of acute coronary syndromes.⁵⁹ In contrast, those with less than 4% DHA and EPA are associated with a higher risk of CV events.⁵⁹ Low blood omega-3 fatty acid levels are associated with increased risk of SCD⁴⁷ (Figure 6). Optimal membrane levels of omega-3 fatty acids usually are achieved with consumption of 1.0 to 1.5 g/d of DHA and EPA,⁵⁸ an intake similar to that in Japan.

CONCLUSION

Current data suggest that patients with known CAD should consume at least 1.0 g/d of long-chain omega-3 fatty acids; people without disease, at least 250 to 500 mg/d. Both DHA and EPA should be consumed. Regardless of statin

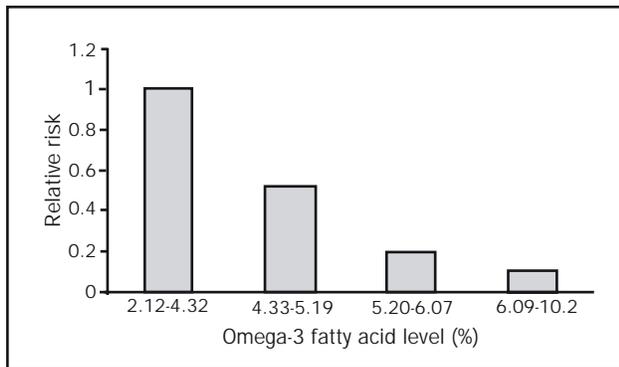


FIGURE 6. Relative risk of sudden cardiac death according to baseline blood levels of omega-3 fatty acids as percentage of total fatty acids. Data from reference 47.

use, patients with hypertriglyceridemia benefit from treatment with 3.0 to 4.0 g/d of DHA and EPA.

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REFERENCES

- Kris-Etherton PM, Harris WS, Appel LJ, American Heart Association Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease [published correction appears in *Circulation*. 2003;107(3):512]. *Circulation*. 2002;106(21):2747-2757.
- Wang C, Harris WS, Chung M, et al. n-3 Fatty acid from fish or fish-oil supplements, but not α -linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. *Am J Clin Nutr*. 2006;84(1):5-17.
- Plourde M, Cunnane SC. Extremely limited synthesis of long chain polyunsaturates in adults: implications for their dietary essentiality and use as supplements. *Appl Physiol Nutr Metab*. 2007;32(4):619-634.
- Harris WS, Poston WC, Haddock CK. Tissue n-3 and n-6 fatty acids and risk for coronary heart disease events. *Atherosclerosis*. 2007 Jul;193(1):1-10. Epub 2007 May 15.
- Metcalfe RG, James MJ, Gibson RA, et al. Effects of fish-oil supplementation on myocardial fatty acids in humans. *Am J Clin Nutr*. 2007;85(5):1222-1228.
- Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet*. 1989;2(8666):757-761.
- Marchioli R, Barzi F, Bomba E, et al, GISSI-Prevenzione Investigators. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. *Circulation*. 2002;105(16):1897-1903.
- Yokoyama M, Origasa H, Matsuzaki M, et al, Japan EPA lipid intervention study (JELIS) Investigators. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomized open-label, blinded endpoint analysis [published correction appears in *Lancet*. 2007;370(9584):220]. *Lancet*. 2007;369(9567):1090-1098.
- Harris WS. Omega-3 fatty acids and cardiovascular disease: a case for omega-3 index as a new risk factor. *Pharmacol Res*. 2007 Mar;55(3):217-223. Epub 2007 Jan 25.
- Anand RG, Alkadiri M, Lavie CJ, Milani RV. The role of fish oil in arrhythmia prevention. *J Cardiopulm Rehabil Prev*. 2008;28:2-8.
- O'Keefe JH Jr, Abuiasa H, Sastre A, Steinhilb DM, Harris WS. Effects of omega-3 fatty acids on resting heart rate, heart rate recovery after exercise, and heart rate variability in men with healed myocardial infarctions and depressed ejection fractions. *Am J Cardiol*. 2006 Apr 15;97:1127-1130. Epub 2006 Mar 3.
- Ventura HO, Milani RV, Lavie CJ, et al. Cyclosporine-induced hypertension: efficacy of omega-3 fatty acids in patients after cardiac transplantation. *Circulation*. 1993;88(5, pt 2):II281-II285.
- Thies F, Garry JM, Yaqoob P, et al. Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomised controlled trial. *Lancet*. 2003;361(9356):477-485.
- Din JN, Harding SA, Valerio CJ, et al. Dietary intervention with oil rich fish reduces platelet-monocyte aggregation in man [published online ahead of print April 27, 2007]. *Atherosclerosis*. doi:10.1016/j.atherosclerosis.2007.04.047.
- Abuissa A, O'Keefe JH Jr, Harris WS, Lavie CJ. Autonomic function, omega-3, and cardiovascular risk [editorial]. *Chest*. 2005;127(4):1088-1091.
- Geleijnse JM, Giltay EJ, Grobbee DE, Donders AR, Kok FJ. Blood pressure response to fish oil supplementation: metaregression analysis of randomized trials. *J Hypertens*. 2002;20(8):1493-1499.
- Ueshima H, Stamler J, Elliott P, et al, INTERMAP Research Group. Food omega-3 fatty acid intake of individuals (total, linolenic acid, long-chain) and their blood pressure: INTERMAP study. *Hypertension*. 2007 Aug;50(2):313-319. Epub 2007 Jun 4.
- Zhao G, Etherton TD, Martin KR, Gilles PJ, West SG, Kris-Etherton PM. Dietary α -linolenic acid inhibits proinflammatory cytokine production by peripheral blood mononuclear cells in hypercholesterolemic subjects. *Am J Clin Nutr*. 2007;85(2):385-391.
- Itoh M, Suganami T, Satoh N, et al. Increased adiponectin secretion by highly purified eicosapentaenoic acid in rodent models of obesity and human obese subjects. *Arterioscler Thromb Vasc Biol*. 2007 Sep;27(9):1918-1925. Epub 2007 Jan 14.
- Mehra MR, Lavie CJ, Ventura HO, Milani RV. Fish oils produce anti-inflammatory effects and improve body weight in severe heart failure. *J Heart Lung Transplant*. 2006 Jul;25(7):834-838. Epub 2006 May 24.
- Madsen T, Schmidt EB, Christensen JH. The effect of n-3 fatty acids on C-reactive protein levels in patients with chronic renal failure. *J Ren Nutr*. 2007;17(4):258-263.
- Harris WS, Gonzales M, Laney N, Sastre A, Borkon AM. Effects of omega-3 fatty acids on heart rate in cardiac transplant recipients. *Am J Cardiol*. 2006 Nov 15;98(10):1393-1395. Epub 2006 Oct 2.
- Wada M, Delong CJ, Hong YH, et al. Enzymes and receptors of prostaglandin pathways with arachidonic acid-derived versus eicosapentaenoic acid-derived substrates and products. *J Biol Chem*. 2007 Aug 3;282(31):22254-22266. Epub 2007 May 22.
- Davidson MH, Stein EA, Bayes HE, et al, COMBination of prescription Omega-3 with Simvastatin (COMBOS) Investigators. Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study. *Clin Ther*. 2007;29(7):1354-1367.
- Harris WS. n-3 fatty acids and serum lipoproteins: human studies. *Am J Clin Nutr*. 1997;65(5)(suppl):1645s-1654s.
- Harris WS, Ginsberg HN, Arunakul N, et al. Safety and efficacy of Omacor in severe hypertriglyceridemia. *J Cardiovasc Risk*. 1997;4(5-6):385-391.
- USDA Agricultural Research Service. Nutrient Data Laboratory. <http://www.ars.usda.gov/nutrientdata>. Accessed January 23, 2008.
- Conquer JA, Holub BJ. Dietary docosahexaenoic acid as a source of eicosapentaenoic acid in vegetarians and omnivores. *Lipids*. 1997;32(3):341-345.
- Park Y, Harris WS. Omega-3 fatty acid supplementation accelerates chylomicron triglyceride clearance. *J Lipid Res*. 2003 Mar;44(3):455-463. Epub 2002 Dec 1.
- Harris WS. Omega-3 fatty acids and cardiovascular disease: a case for omega-3 index as a new risk factor. *Pharmacol Res*. 2007 Mar;55(3):217-223. Epub 2007 Jan 25.
- Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health: evaluating the risks and the benefits [published correction appears in *JAMA*. 2007 Feb 14;297(6):590]. *JAMA*. 2006;296(15):1885-1899.
- Reiffel JA, McDonald A. Antiarrhythmic effects of omega-3 fatty acids. *Am J Cardiol*. 2006 Aug 21;98(4A):50i-60i. Epub 2006 May 26.
- Calo L, Bianconi L, Colivicchi F, et al. N-3 fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a randomized, controlled trial. *J Am Coll Cardiol*. 2005;45(10):1723-1728.
- Raitt MH, Connor WE, Morris C, et al. Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implant

- able defibrillators: a randomized controlled trial. *JAMA*. 2005;293(23):2884-2891.
35. Brouwer IA, Zock PL, Camm AJ, et al, SOFA Study Group. Effect of fish oil on ventricular tachyarrhythmia and death in patients with implantable cardioverter defibrillators. *JAMA*. 2006;295(22):2613-2619.
36. Leaf A, Albert CM, Josephson M, et al, Fatty Acid Antiarrhythmia Trial Investigators. Prevention of fatal arrhythmias in high-risk subjects by fish oil n-3 fatty acid intake. *Circulation*. 2005;112(18):2762-2768.
37. Macchia A, Levantesi G, Franzosi MG, et al, GISSI-Prevenzione Investigators. Left ventricular systolic dysfunction, total mortality, and sudden death in patients with myocardial infarction treated with n-3 polyunsaturated fatty acids. *Eur J Heart Fail*. 2005;7(5):904-909.
38. Tavazzi L, Tognoni G, Franzosi MG, et al, GISSI-HF Investigators. Rationale and design of the GISSI heart failure trial: a large trial to access the effects of n-3 polyunsaturated fatty acids and rosuvastatin in symptomatic congestive heart failure. *Eur J Heart Fail*. 2004;6(5):635-641.
39. Iso H, Kobayashi M, Ishihara J, et al, JPHC Study Group. Intake of fish and n3 fatty acids and risk of coronary heart disease among Japanese: the Japan Public Health Center-Based (JPHC) Study Cohort I. *Circulation*. 2006 Jan 17;113(2):195-202. Epub 2006 Jan 9.
40. Reliant Pharmaceuticals, Inc. Patient Information: Lovaza. Liberty Corner, NJ. http://www.lovaza.com/downloads/LOVAZA_Patient_Info.pdf. 2007. Accessed January 24, 2008.
41. Harris WS. Expert opinion: omega-3 fatty acids and bleeding—cause for concern? *Am J Cardiol*. 2007 Mar 19;99(6A):44C-46C. Epub 2006 Nov 29.
42. US Food and Drug Administration, Department of Health and Human Services. Backgrounder for the 2004 FDA/EPA Consumer Advisory: What You Need to Know About Mercury in Fish and Shellfish. <http://www.fda.gov/oc/opacom/hottopics/mercury/backgrounder.html>. Accessed January 24, 2008.
43. Hibbeln JR, Davis JM, Steer C, et al. Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. *Lancet*. 2007;369(9561):578-585.
44. Foran JA, Hites RA, Carpenter DO, Hamilton MC, Mathews-Amos A, Schwager SJ. A survey of metals in tissues of farmed Atlantic and wild Pacific salmon. *Environ Toxicol Chem*. 2004;23(9):2108-2110.
45. Foran SE, Flood JG, Lewandrowski KB. Measurement of mercury levels in concentrated over-the-counter fish oil preparations: is fish oil healthier than fish? *Arch Pathol Lab Med*. 2003;127(12):1603-1605.
46. He K, Song Y, Daviglius ML, et al. Accumulated evidence on fish consumption and coronary heart disease mortality: a meta-analysis of cohort studies. *Circulation*. 2004;109(22):2705-2711.
47. Albert CM, Campos H, Stampfer MJ, et al. Blood levels of long-chain n-3 fatty acids and the risk of sudden death. *N Engl J Med*. 2002;346(15):1113-1118.
48. Siscovick DS, Raghunathan TE, King I, et al. Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. *JAMA*. 1995;274(17):1363-1367.
49. Ness AR, Hughes J, Elwood PC, Whitley E, Smith GD, Burr ML. The long-term effect of dietary advice in men with coronary disease: follow-up of the Diet and Reinfarction trial (DART). *Eur J Clin Nutr*. 2002;56(6):512-518.
50. Burr ML, Ashfield-Watt PA, Dunstan FD, et al. Lack of benefit of dietary advice to men with angina: results of a controlled trial. *Eur J Clin Nutr*. 2003;57(2):193-200.
51. Nilsen DW, Albrektsen G, Landmark K, Moen S, Aarsland T, Woie L. Effects of a high-dose concentrate of n-3 fatty acids or corn oil introduced early after an acute myocardial infarction on serum triacylglycerol and HDL cholesterol. *Am J Clin Nutr*. 2001;74(1):50-56.
52. von Schacky C, Harris WS. Cardiovascular benefits of omega-3 fatty acids. *Cardiovasc Res*. 2007 Jan 15;73(2):310-315. Epub 2006 Sep 1.
53. Harris WS. International recommendations for consumption of long-chain omega-3 fatty acids. *J Cardiovasc Med (Hagerstown)*. 2007;8(suppl 1):S50-S52.
54. Harris WS, Pottala JV, Sands SA, Jones PG. Comparison of the impact of fish and fish oil capsules on the n-3 fatty acid content of blood cells and plasma phospholipids. *Am J Clin Nutr*. In press.
55. Shalwitz RA, Maki KC, Doyle RT, Ballantyne CM. Lipoprotein subfraction responses differentially predict changes in lipoprotein-associated phospholipase A2 (Lp-PLA2) during prescription omega-3 therapy [abstract P383]. Presented at: Arteriosclerosis, Thrombosis and Vascular Biology Annual Conference; April 19-21, 2007; Chicago, IL.
56. Brunton S, Collins N. Differentiating prescription omega-3-acid ethyl esters (P-OM3) from dietary-supplement omega-3 fatty acids. *Curr Med Res Opin*. 2007;23(5):1139-1145.
57. Mori TA, Woodman RJ. The independent effects of eicosapentaenoic acid and docosahexaenoic acid on cardiovascular risk factors in humans. *Curr Opin Clin Nutr Metab Care*. 2006;9(2):95-104.
58. Harris WS, von Schacky C. The omega-3 index: a new risk factor for death from coronary heart disease? *Prev Med*. 2004;39(1):212-220.
59. Block RC, Harris WS, Reid KJ, Sands SA, Spertus JA. EPA and DHA in blood cell membranes from acute coronary syndrome patients and controls [published online ahead of print September 15, 2007]. *Atherosclerosis*. doi:10.1016/j.atherosclerosis.2007.07.042.