Omega-3 Fatty Acids

MAGGIE B. COVINGTON, M.D., *University of Maryland School of Medicine, Baltimore, Maryland*

Omega-3 fatty acids have been shown to significantly reduce the risk for sudden death caused by cardiac arrhythmias and all-cause mortality in patients with known coronary heart disease. Fatty fish, such as salmon and tuna, and fish oil are rich sources of the omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid. Flaxseed, canola oil, and walnuts also are good dietary sources of omega-3 fatty acids. In addition to being antiarrhythmic, the omega-3 fatty acids are antithrombotic and anti-inflammatory. In contrast, omega-6 fatty acids, which are present in most seeds, vegetable oils, and meat, are prothrombotic and proinflammatory. Omega-3 fatty acids also are used to treat hyperlipidemia, hypertension, and rheumatoid arthritis. There are no significant drug interactions with omega-3 fatty acids. The American Heart Association recommends consumption of two servings of fish per week for persons with no history of coronary heart disease and at least one serving of fish daily for those with known coronary heart disease. Approximately 1 g per day of eicosapentaenoic acid plus docosahexaenoic acid is recommended for cardioprotection. Higher dosages of omega-3 fatty acids are required to reduce elevated triglyceride levels (2 to 4 g per day) and to reduce morning stiffness and the number of tender joints in patients with rheumatoid arthritis (at least 3 g per day). Modest decreases in blood pressure occur with significantly higher dosages of omega-3 fatty acids. (Am Fam Physician 2004;70:133-40. Copyright© 2004 American Academy of Family Physicians.)

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See page 13 for definitions of strength-of-recommendation labels.

Over the past 20 years, there has been a dramatic increase in the scientific scrutiny of and public interest in omega-3 and omega-6 fatty acids and their impact on personal health. Omega-3 fatty acids possess anti-inflammatory, antiarrhythmic, and antithrombotic properties; omega-6 fatty acids are proinflammatory and prothrombotic. Increased consumption of vegetable oils high in omega-6 fatty acids (such as corn, safflower, sunflower, and cottonseed oils) and meats from animals that were fed grains high in omega-6 fatty acids has drastically shifted the dietary ratio of omega-6 to omega-3 fatty acids from an estimated 1:1 in the early human diet to approximately 10:1 in the typical modern American diet.[1]

Fish and fish oil are rich sources of omega-3 fatty acids, specifically eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are present in fatty fish *(Table 1)*[2,3] and algae. Alpha-linolenic acid (ALA) is an omega-3 fatty acid present in seeds and oils *(Table 2)*, green leafy vegetables, and nuts and beans (such as walnuts and soybeans).[1] Linoleic acid, an omega-6 fatty acid, is present in grains, meats, and the seeds of most plants. While omega-3 fatty acids have been used for treatment of many conditions, this article discusses only the most common and well-researched treatment uses.

Pharmacology

Omega-3 and omega-6 fatty acids are essential because they are not synthesized by the body and must be obtained through diet or supplementation. Through an inefficient enzymatic process of desaturation (the rate of conversion is less than 1 percent), ALA produces EPA (20 carbons) and DHA (22 carbons), precursors to a group of eicosanoids (prostaglandins, thromboxanes, and leukotrienes) that are anti-inflammatory, antithrombotic, antiarrhythmic, and vasodilatory. The longer chain fatty acid derivative of linoleic acid is arachidonic acid (20 carbons), which is a precursor to a different group of eicosanoids that are proinflammatory and prothrombic. ALA and linoleic

TABLE 1
Approximate EPA Plus DHA Content in Fish and Amount of Fish Required to Provide 1 g of EPA plus DHA

Type of fish	*EPA plus DHA content, g per 3-oz serving of fish (edible portion)*	*Amount of fish (oz) required to provide approximately 1 g of EPA plus DHA per day**
Catfish		
Farmed	0.15	20.0
Wild	0.20	15.0
Crab, Alaskan King	0.35	8.5
Flounder/sole	0.42	7.0
Haddock	0.20	15.0
Halibut	0.40 to 1.00	3.0 to 7.5
Herring		
Atlantic	1.71	2.0
Pacific	1.81	1.5
Mackerel	0.34 to 1.57	2.0 to 8.5
Salmon		
Atlantic, farmed	1.09 to 1.83	1.5 to 2.5
Atlantic, wild	0.90 to 1.56	2.0 to 3.5
Chinook	1.48	2.0
Sockeye	0.68	4.5
Sardines	0.98 to 1.70	2.0 to 3.0
Shrimp, mixed species	0.27	11.0
Tuna		
Fresh	0.24 to 1.28	2.5 to 12.0
White, canned in water, drained	0.73	4.0

EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid.

**—The intakes of fish given are very rough estimates because oil content can vary markedly (more than 300 percent) with species, season, diet, and packaging and cooking methods.*

Adapted with permission from Kris-Etherton PM, Harris WS, Appel LJ; American Heart Association. Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Circulation 2002;106:2753, with information from reference 3.

acid use and compete for the same enzymes in the production of their longer chain fatty acids, EPA, and arachidonic acid. The ingestion of fish and fish oil provides EPA and DHA directly, therefore avoiding the competition for enzymes to convert ALA to EPA.

Uses and Efficacy

CARDIAC MORTALITY, SUDDEN DEATH, AND ALL-CAUSE MORTALITY

The Diet and Reinfarction Trial (DART)[4] was one of the first studies to investigate a relationship between dietary intake of omega-3 fatty acids and secondary prevention of myocardial infarction. In this study, 1,015 men were advised to eat at least two servings of fatty fish per week, and 1,018 men were not so advised. At the two-year follow-up, the men who had been advised to consume fish had a 29 percent reduction in all-cause mortality but no reduction in the incidence of myocardial infarction.[4]

Sudden death caused by sustained ventricular arrhythmias accounts for 50 to 60 percent of all deaths in persons with coronary heart disease (CHD).[5] To date, the largest, prospective, randomized controlled trial on the effects of omega-3 fatty acids

TABLE 2
Predominant Essential Fatty Acids in Common Oils

Omega-3 oils	Omega-6 oils
Canola oil	Borage oil
Fish oil	Corn oil
Flaxseed oil	Cottonseed oil
Soybean oil*	Grapeseed oil
Walnut oil	Peanut oil
	Primrose oil
	Safflower oil
	Sesame oil
	Soybean oil*
	Sunflower oil

**—Soybean oil is included in both categories because it is higher in omega-6 fatty acids than most omega-3 oils.*

is the GISSI-Prevenzione Trial.[6] This study included 11,324 patients with known CHD who were randomized to receive either 300 mg of vitamin E, 850 mg of omega-3 fatty acids, both, or neither. After three and one-half years, the group given omega-3 fatty acids alone had a 45 percent reduction in sudden death and a 20 percent reduction in all-cause mortality.[6]

A meta-analysis[7] of 11 randomized controlled trials conducted between 1966 and 1999 and including 7,951 patients with heart disease found that dietary and nondietary fatty acids reduced overall mortality, mortality caused by myocardial infarction, and sudden death. The number needed to treat in patients at low risk to prevent one premature death was 250 for one and one-half years, and 24 patients at high risk to prevent one death.[7]

The U.S. Physicians' Health Study[8] surveyed roughly 20,000 male physicians and found no apparent association between fish consumption or supplementation with omega-3 fatty acids and risk for myocardial infarction, nonsudden cardiac death, or total cardiovascular mortality. However, men who consumed fish at least once per week had a 50 percent reduction in the risk for sudden death and a significant reduction in all-cause mortality.[8]

A reanalysis[9] of the U.S. Physicians' Health Study found a significant inverse relationship between blood levels of omega-3 fatty acids and the risk of sudden death in men with no history of CHD. In another study,[10] consumption of 5.5 g of omega-3 fatty acids per month (equivalent to one weekly serving of a fatty fish) was associated with a 50 percent reduction in the risk of primary cardiac arrest. However, these findings were not supported by the EURAMIC (EURopean multicenter case-control study on Antioxidants, Myocardial Infarction and breast Cancer) study,[11] which concluded that fish consumption offered no protection against the risk of a first myocardial infarction.

One study[12] showed increased regression and decreased progression of coronary lesions in patients taking 1.5 g of fish oil per day for two years, as assessed by angiography. Evidence for the protective effects of fish and ALA in women comes from the U.S. Nurses' Health Study,[13] which analyzed the diets of 84,688 female nurses and found that higher consumption levels of fish and ALA were associated with a decreased risk of CHD and CHD-related deaths.

HYPERLIPIDEMIA

Omega-3 fatty acids lower plasma triglyceride levels, particularly in persons with hypertriglyceridemia,[14] by inhibiting the synthesis of very-low-density lipoprotein (VLDL) cholesterol and triglycerides in the liver. A review[15] of human studies concluded that approximately 4 g per day of omega-3 fatty acids reduced serum triglyceride concentrations by 25 to 30 percent, increased serum low-density lipoprotein (LDL) cholesterol levels by 5 to 10 percent, and increased high-density lipoprotein (HDL) cholesterol levels by 1 to 3 percent. Total cholesterol was not significantly affected.[15]

A randomized controlled trial[16] compared two groups of patients with persistent hypertriglyceridemia. One group received simvastatin in a dosage of 10 to 40 mg per day plus 4 g per day of Omacor (which contains 90 percent omega-3 fatty acid; 840 mg EPA plus DHA per capsule), while those in the second group received the same dosage of simvas-

TABLE 3
EPA and FDA Recommendations for Fish and Shellfish Consumption by Women* and Young Children

Do not eat shark, swordfish, king mackerel, or tilefish, because they contain high levels of mercury.
Eat up to 12 oz (two average meals) a week of a variety of fish and shellfish that are lower in mercury.
Five of the most commonly eaten fish that are low in mercury are shrimp, canned light tuna, salmon, pollock, and catfish.
Another commonly eaten fish, albacore ("white") tuna has more mercury than canned light tuna. Albacore tuna should be limited to no more than 6 oz (one average meal) per week.
Check local advisories about the safety of fish caught by family and friends in your local lakes, rivers, and coastal areas. If no advice is available, eat up to 6 oz (one average meal) per week of fish you catch from local waters but don't consume any other fish during that week.
Follow these same recommendations when feeding fish and shellfish to children, but serve smaller portions.

EPA = Environmental Protection Agency; FDA = U.S. Food and Drug Administration.

**—Recommendations apply to women who might become pregnant, women who are pregnant, and breastfeeding mothers.*

Information from U.S. Food and Drug Administration. What you need to know about mercury in fish and shellfish. FDA/CFSAN Consumer Advisory. EPA-823-R-04-005. March 2004. Acccessed online April 20, 2004, at: http://www.cfsan.fda.gov/~dms/admehg3.html.

tatin and a placebo. Patients who received simvastatin plus Omacor had 20 to 30 percent decreases in serum triglyceride concentrations and 30 to 40 percent decreases in VLDL cholesterol levels compared with those receiving simvastatin and placebo.[16] No increases in LDL cholesterol levels were observed. Overall, results have shown variable effects of omega-3 fatty acids on total cholesterol, LDL, and HDL cholesterol levels.[14-17]

HYPERTENSION

Omega-3 fatty acids appear to have a dose-response hypotensive effect in patients with hypertension and have little to no effect in normotensive patients.[18] A meta-analysis[19] of 31 trials and a total of 1,356 patients found that 5.6 g per day of fish oil reduced blood pressure by 3.4/2.0 mm Hg. Similarly, another study[20] found modest blood pressure reductions of 5.5/3.5 mm Hg in trials in which patients received at least 3 g per day of fish oil. A meta-analysis[21] of 36 trials found that a median dosage of 3.7 g per day of fish oil reduced systolic blood pressure by only 2.1/1.6 mm Hg.

RHEUMATOID ARTHRITIS

Several small studies[21-24] have found that fish oil at dosages of at least 3 g per day (one study[22] used 18 g per day) significantly reduced morning stiffness and the number of tender, swollen joints in patients with rheumatoid arthritis. These beneficial effects were more common in patients receiving higher dosages of fish oil and were not apparent until fish oil had been consumed for at least 12 weeks.[22,24]

It has been reported that reducing dietary intake of omega-6 fatty acids while increasing consumption of omega-3 fatty acids reduces the inflammatory mediators of

The Author

MAGGIE B. COVINGTON, M.D., is clinical assistant professor of family medicine with the Center for Integrative Medicine at the University of Maryland School of Medicine, Baltimore. She also has a private practice in integrative medicine in Bethesda, Md. Dr. Covington received her medical degree from Howard University College of Medicine, Washington, D.C., and completed residency training at the University of Maryland School of Medicine. She also completed postgraduate training in acupuncture through the Helms Medical Institute and the University of California, Los Angeles, School of Medicine.

Address correspondence to Maggie B. Covington, M.D., University of Maryland School of Medicine, Center for Integrative Medicine, 2200 Kernan Dr., Baltimore, MD 21207 (e-mail: mcovington@compmed.umm.edu) Reprints are not available from the author.

rheumatoid arthritis and, consequently, allows some patients to reduce or discontinue use of nonsteroidal anti-inflammatory drugs.[24-26] One study[27] showed no improvements in symptoms of rheumatoid arthritis after three months of supplementation with ALA in the form of flaxseed oil.

Interactions and Adverse Effects

Omega-3 fatty acids exert a dose-related effect on bleeding time; however, there are no documented cases of abnormal bleeding as a result of fish oil supplementation, even at high dosages and in combination with other anticoagulant medications.[28] High dosages of fish oil may increase LDL cholesterol levels, but the clinical relevance of this finding remains unclear.[14,15] Other potential side effects of omega-3 fatty acids include a fishy aftertaste and gastrointestinal disturbances, all of which appear to be dose-dependent.[2]

Significant amounts of methylmercury, polychlorinated biphenyls, dioxins, and other environmental contaminants may be concentrated in certain species of fish, such as shark, swordfish, king mackerel, and tilefish (also known as golden bass or golden snapper).[29] In March 2004, the U.S. Food and Drug Administration (FDA) and the Environmental Protection Agency issued a new statement[29] advising women who may become pregnant, women who are pregnant, breastfeeding mothers, and young children to avoid eating some types of fish and to eat fish and shellfish that are lower in mercury. These recommendations[29] are summarized in *Table 3*. According to a recent survey,[30] farmed salmon have significantly higher levels of polychlorinated biphenyls and other organochlorine contaminants than wild salmon. There is disagreement among researchers, however, about the amount of farmed salmon that is safe to eat. High-quality fish oil supplements usually do not contain these contaminants.

Although there is conflicting evidence for the effect of fish oil on glucose control,[17,31] most evidence shows that fish oil does not significantly elevate glucose or hemoglobin A1C levels.[32,33]

Dosage

The American Heart Association's recommendations for intake of omega-3 fatty acids *(Table 4)*[2] state that patients without documented CHD should eat at least two servings of fatty fish per week along with other foods rich in omega-3 fatty acids. Persons with CHD are encouraged to eat at least one daily meal that includes a fatty fish or take a daily fish oil supplement to achieve a recommended level of 0.9 g per day of EPA.[2]

Most commercial fish oil capsules (1 g) contain 180 mg of EPA and 120 mg of DHA. Therefore, three 1-g capsules per day in divided doses provides the recommended dosage of 0.9 g of omega-3 fatty acids. Fish oil is also available in a more highly concentrated liquid form that provides 1 to 3 g of omega-3 fatty acids per teaspoon, depending on the product and manufacturer. The effective dosage for treating hypertriglyceridemia is 2 to 4 g per day,[2] which is significantly higher than the dosage recommended for cardiovascular protection. The FDA has concluded that dietary dosages of up to 3 g per day of omega-3 fatty acids from marine sources are "Generally Recognized as Safe."[34] For persons who are vegetarians or nonfish eaters, a total daily intake of 1.5 to 3 g per day of ALA seems to be beneficial.[2]

TABLE 4
Summary of AHA Recommendations for Omega-3 Fatty Acid Intake

Patient population	*Recommendation*
No documented history of CHD	Eat a variety of fish (preferably oily) at least twice per week. Include oils and foods rich in alpha-linolenic acid (flaxseed, canola, and soybean oils; flaxseeds and walnuts).
Documented history of CHD	Consume approximately 1 g of EPA plus DHA daily, preferably from oily fish. EPA plus DHA capsule supplements may be used in consultation with a physician.
Needs to lower triglyceride level	Consume 2 to 4 g of EPA plus DHA daily in capsules in consultation with a physician.

AHA = American Heart Association; CHD = coronary heart disease; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid.

Adapted with permission from Kris-Etherton PM, Harris WS, Appel LJ; American Heart Association. Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Circulation 2002;106:2755.

Final Comment

Therapy with low-dose omega-3 fatty acids (approximately 1 g per day of EPA plus DHA) significantly reduces the incidence of sudden death caused by cardiac arrhythmias and all-cause mortality in patients with known CHD. More studies are needed to confirm the benefits of omega-3 fatty acids in the primary and secondary prevention of CHD. Although higher dosages of omega-3 fatty acids (2 to 4 g per day) are effective in lowering triglyceride levels in patients with hypertriglyceridemia, the clinical significance of elevations in LDL cholesterol resulting from high-dose fish oil therapy remains unclear.

While consumption of omega-3 fatty acids may benefit patients with rheumatoid arthritis and hypertension, the higher dosage requirement of at least 3 g per day may limit its usefulness in the medical management of these disorders. *Table 5* outlines the efficacy, safety, tolerability, dosage, and cost of fish oil supplements.

TABLE 5
Key Points About Fish Oil Supplements

Efficacy	Reduces risk for sudden death Reduces all-cause mortality Lowers serum triglyceride levels* Modest effect on lowering blood pressure in patients with hypertension* Reduces morning stiffness and number of tender, swollen joints in patients with rheumatoid arthritis*
Adverse effects	Generally well tolerated. Side effects may include fishy aftertaste, gastrointestinal disturbances (e.g., nausea, bloating, belching), prolonged bleeding time, elevations in LDL-C, and exposure to environmental contaminants with certain fish species.
Interactions	No significant drug interactions
Dosage	Capsules: 1 g generally contains 180 mg of EPA and 120 mg of DHA. Liquid concentrate: 1 tsp contains approximately 1 to 3 g of EPA plus DHA. For cardiac health, approximately 1 g of EPA plus DHA daily For lowering triglycerides, 2 to 4 g of EPA plus DHA daily For rheumatoid arthritis, ≥3 g of EPA plus DHA daily
Types of fish oil supplements	Cod liver oil† Standard fish body oil (e.g., herring, salmon) Omega-3 fatty acid concentrate
Cost	Capsules: $0.13 to $0.42 per capsule‡ Liquid: $0.95 to $9.77 per oz‡
Bottom line	Safe complementary medication; reduces risk for sudden death caused by cardiac arrhythmias and all-cause mortality in patients with known coronary heart disease. Higher dosages may be effective in hypertriglyceridemia, hypertension, and rheumatoid arthritis, but data are limited.

LDL-C = low-density lipoprotein cholesterol; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid.

**—Higher doses required.*
†—Also provides vitamins A and D.
‡—Prices vary according to brand and manufacturer.

Strength of Recommendation (SOR) Labels

Key clinical recommendation	SOR labels	Reference
Omega-3 fatty acids appear to have a dose-response hypotensive effect in patients with hypertension and have little to no effect in normotensive patients.	A	18
In March 2004, the U.S. Food and Drug Administration and the Environmental Protection Agency issued a new statement advising women who may become pregnant, women who are pregnant, breastfeeding mothers, and young children to avoid eating some types of fish and to eat fish and shellfish that are lower in mercury.	C	29
The American Heart Association recommends that patients without documented congestive heart disease eat at least two servings of fatty fish per week along with other foods rich in omega-3 fatty acids.	C	2

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