

The Role of Omega-3 Fatty Acids in Heart Disease Prevention

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Abstract

- **Objective:** To discuss the benefits of fish oil in heart disease prevention and provide current recommendations for clinical use.
- **Methods:** Review of the literature.
- **Results:** Marine omega-3 fatty acids have an important role in reducing coronary artery disease (CAD) risk. This has been established by both epidemiologic and randomized intervention trials. While 4 g of omega-3 fatty acids per day are recommended to treat hypertriglyceridemia, the CAD-reducing effects occur with lower quantities and appear to be related to reducing the risk for sudden cardiac death. The American Heart Association currently recommends 1 g/day of omega-3 fatty acids for patients with CAD and for those without CAD the consumption of a variety of fish (preferably fatty fish) at least twice a week.
- **Conclusion:** Ongoing studies will continue to increase our understanding of the use of omega-3 fatty acids for reducing CAD risk.

Several decades of research now point to fish oil's beneficial effect in coronary artery disease (CAD). Early evidence for fish oil's cardioprotective effects came from studies of Greenland Eskimos in the 1970s that suggested ingestion of fat from marine sources could reduce CAD risk [1,2]. Subsequently, the benefits of fish consumption have been supported by most [3–10] but not all [11–14] epidemiologic studies. More recently, the ability of marine oils to reduce major cardiovascular events have been confirmed by large-scale intervention trials [15–18].

Despite the evidence indicating fish oil's benefit in CAD, physicians do not often advise their patients to increase their fish oil intake [19]. This article discusses the role of fish oil in reducing risk from CAD, proposed mechanisms for its effect, and provides recommendations for clinical use.

What Is Fish Oil?

Fish oils are a rich source of long-chain omega-3 fatty acids. A common misunderstanding is that fish themselves pro-

duce these fats. In reality, the oils are made by sea plants and accumulate in fish as they ascend the biologic food chain. Several systems of nomenclature are used to define polyunsaturated fatty acids. Currently the "omega" and the "n" classification systems are widely used and are interchangeable. In this paper, the omega terminology is used for consistency. The omega system names the terminal methyl carbon on the fatty acid chain as the omega carbon. The position of the first double bond along the chain from the "omega" carbon defines the "omega" position nomenclature. **Table 1** summarizes information on the 3 major families of polyunsaturated fatty acids, using the omega system of nomenclature. Fish oils are classified as belonging to the omega-3 family because their first double bond from the methyl end arises at the omega-3 carbon position. Sea sources are the primary contributors of the 2 biologically important dietary omega-3 fatty acids: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

Sources of Fish Oil

Table 2 lists some representative sources of natural and commercially available marine omega-3 fatty acids [20,21]. Deep sea fish typically have the greatest omega-3 fatty acid content. Shellfish have been historically erroneously labeled as being high in cholesterol because they have a high content of sea sterols such as brassicasterol. However, they do not contain significant amounts of cholesterol [22]. Although cod liver oil is a rich source of omega-3 fatty acids, it should not be consumed in excess due to the risk of hypervitaminosis A. There are a number of over-the-counter commercial fish oil capsules and 1 prescription fish oil, Lovaza (GlaxoSmithKline, Research Triangle Park, NC), which is approved for the treatment of high triglycerides (> 500 mg/dL).

Clinical Studies of Omega-3 Fatty Acids and CAD

Epidemiologic studies showing a cardioprotective effect of omega-3 fatty acids indicate this benefit can be accrued

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Table 1. The 3 Major Classes of Polyunsaturated Fatty Acids

Family	Source	Common Name	Chain Length	Double Bonds, <i>n</i>
Omega-9	Vegetable oils, animal fats	Oleic acid	18	1
Omega-6	Vegetable oils	Linoleic acid	18	2
Omega-3	Vegetable oils, marine oils	Alpha-linolenic acid	18	3
		Eicosapentaenoic acid (EPA)	20	5
		Docosahexaenoic acid (DHA)	22	6

by a diet consisting of omega-3 fatty acids consumption equivalent to 1 [8,10] or 2 [3,4] fish meals per week. In accord with population studies, the Diet and Reinfarction Trial (DART) [16] showed the cardioprotective effects derived from omega-3 fatty acid consumption occurred with 2 fish meals per week. In this study, 2033 men with CAD assigned to increase their consumption of seafood experienced a 29% reduction in total mortality over the subsequent 2 years compared with those assigned to either low-fat or increased-fiber diets.

A 2006 meta-analysis combining the results of randomized placebo-controlled intervention studies for primary and secondary prevention showed omega-3 fatty acids reduced total mortality risk by 17% (pooled relative risk, 0.83 [95% confidence interval, 0.68–1.00]) [19]. The largest trial included in this analysis is the Gruppo Italiano per la Sopravvivenza dell' Infarto Miocardico (GISSI) Prevenzione Study [17] conducted in 11,324 men who had suffered a myocardial infarction and were randomized to receive either vitamin E, omega-3 fatty acid ethyl esters (one 850-mg capsule/day), both, or usual care. After 3.5 years, those receiving the omega-3 supplements alone experienced a 20% reduction in total mortality and a 45% reduction in sudden cardiac death. Recently, the Japan EPA Lipid Intervention Study (JELIS) [18] randomized 18,645 men and women (14,981 without CAD and 3664 with CAD) treated with a low-dose statin (pravastatin 10 mg/day) to either 1.8 g/day of EPA or placebo. After 4.6 years, those receiving EPA experienced a 19% reduction in major CAD events compared with placebo, which was similar in both primary and secondary prevention groups (although it achieved statistical significance only in those with CAD).

Mechanisms of CAD Protection

There are several potential mechanisms by which omega-3 fatty acids can reduce CAD risk.

Antiarrhythmic Effects and Prevention of Sudden Cardiac Death

The major impact of omega-3 fatty acids on CAD risk reduction appears to be the result of its antiarrhythmic effect, which can reduce the risk for ventricular fibrillation and

subsequent sudden cardiac death [20,21]. Omega-3 fatty acids are incorporated into myocardial cell membranes [22] where they are a potent inhibitor of voltage-gated Na⁺/H⁺ channels in cardiac cardiomyocytes, preventing calcium overload by maintaining L-type calcium channels during periods of ischemic stress [15,23]. This effect increases the ventricular refractory period and the electrical threshold required to induce an action potential-depolarization, making the heart less vulnerable to ventricular arrhythmias as has been shown in canine models [15].

Findings from epidemiologic studies showing that the relative risk for sudden cardiac death is significantly reduced with increasing levels of blood [9] and red blood cell [7] fatty acid levels were later confirmed in the GISSI-Prevenzione Study [16]. More recent randomized placebo-controlled studies examining the effect of omega-3 fatty acid supplementation on high-risk patients with implantable cardioverter defibrillators (ICDs) have shown mixed results [24–26] and indicate omega-3 fatty acid-induced prevention of ICD-triggered events is greater among those with underlying myocardial ischemia.

Although the major public health benefit from omega-3 fatty acids appears to be its effects on suppressing ventricular arrhythmias, omega-3 fatty acids also reduce the risk for atrial fibrillation. Calo et al [27] randomized 160 patients who were waiting to undergo coronary artery bypass grafting to either 2 capsules, each containing 866 mg of EPA plus DHA ethyl esters, a day or placebo beginning 5 days before surgery and continuing during hospitalization. The primary endpoint was electrocardiogram-detected atrial fibrillation of greater than 5 minutes' duration or requiring intervention for angina or hemodynamic compromise. This study found that those receiving the fish oil supplements had reduced incidence (15% vs. 33%) and duration (16 hr vs. 24 hr) of atrial fibrillation compared with placebo recipients.

Triglyceride Lowering

Hypertriglyceridemia results from increased very low-density lipoprotein (VLDL) production, reduced VLDL clearance, or more commonly the dual effect of both [28]. Triglyceride-rich lipoprotein particles are produced by both endogenous and exogenous sources, but when clearance or

production of the particles becomes impaired, triglyceride levels become elevated. The liver (endogenous) produces triglyceride-rich VLDL particles that are secreted into the blood, which are then delivered to peripheral tissues where they are metabolized by lipoprotein lipases and used for energy by muscle tissue or stored in adipose tissue. Dietary fats (exogenous) are absorbed from the gastrointestinal tract and form triglyceride-rich chylomicron particles in the intestinal wall that are secreted into the blood and cleared by the liver. Both VLDL and chylomicron particles are cleared by a common pathway that involves tissue lipases [29]. When lipoprotein lipase activity is decreased, the clearance of both VLDL and chylomicron particles is impaired, resulting in an accumulation of triglyceride-rich lipoprotein particles in the blood (ie, underutilization). The fish oil related triglyceride-lowering mechanism(s) is related to both reducing VLDL production and VLDL clearance, although they remain to be more clearly defined [30].

Increasing evidence supports triglyceride concentration as an independent risk factor for CAD [31–34]; however, is not yet clear whether reducing triglyceride levels lowers CAD risk. The ATP III recommends treatment with a triglyceride-lowering drug (in addition to therapeutic lifestyle changes) [35] in patients with triglycerides greater than 500 mg/dL, but the primary goal in this setting is to prevent pancreatitis. Omega-3 fatty acids can reduce triglycerides on average 19% (range, 16%–45%) in a dose-dependent fashion with little effect on other lipid fractions [36,37]. Because the triglyceride-lowering effect is greatest among patients with severe hypertriglyceridemia, the impact of omega-3 fatty acids is the greatest in these patients, virtually cutting their triglyceride levels in half. Although plasma low-density lipoprotein (LDL) cholesterol levels are increased slightly in some studies, the LDL cholesterol-raising effect is not of great concern because LDL levels are typically low in hypertriglyceridemic patients, and any potential increased CAD risk is offset by the effects on VLDL (ie, triglyceride) lowering. Moreover, statins can be combined safely with fish oil with improved lipid outcomes [38]. **Table 3** shows changes in plasma lipids and lipoproteins in 254 patients taking open-label simvastatin 40 mg/day for 8 weeks with dietary counseling who were then randomized to Lovaza 4 g per day or placebo while continuing on simvastatin [39]. The study showed the combination resulted in substantial improvement in plasma lipoprotein profiles.

Thrombosis and Inflammation

EPA can reduce CAD risk by effecting processes that reduce both thrombosis and inflammation. As dietary EPA becomes incorporated into tissue membranes, it becomes a substitute for arachidonic acid (AA), an omega-6 fatty acid that is 20 carbons in length [22]. AA serves as a precursor structure

Table 2. Amount of Omega-3 Fatty Acids (EPA and DHA) in Selected Seafood and Commercial Products

	EPA (mg/100 g of food)	DHA (mg/100 g of food)
Anchovy	500	900
Bass, fresh water	100	200
Catfish, channel (wild)	100	200
Catfish, channel (farmed)	70	210
Haddock	100	100
Halibut, Pacific	700	900
Herring, Atlantic	700	900
Mackerel, Atlantic	900	1000
Perch	100	100
Salmon, Chinook	800	600
Salmon, pink (wild)	400	600
Salmon, pink (farmed)	400	800
Smelt	100	200
Sturgeon, Atlantic	1000	500
Trout, rainbow (wild)	100	400
Trout, rainbow (farmed)	260	670
Tuna, albacore	300	1000
Crab, dungeness	200	100
Lobster	100	100
Shrimp	200	200
Octopus	100	100
Oyster	200	200
Scallop	100	100
Fish oil capsules*		
GNC fish body oil	180	120
Natrol omega-3 complex	180	120
Twinlab omega-3	234	125
Mega Twin EPA	600	240
OmegaRx	400	200
Ultimate omega	350	250
Lovaza	465	375

DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid. (Adapted from Hepburn FN, Exler J, Weihrauch JL. Provisional tables on the content of omega-3 fatty acids and other fat components of selected foods. *J Am Diet Assoc* 1986;86:788–93 and Oh R. Practical applications of fish oil (omega-3 fatty acids) in primary care. *J Am Board Fam Pract* 2005;18:28–36.)

*Amount of EPA and DHA shown is mg per 1000-mg capsule.

that can be converted into prostacyclines [40] and leukotrienes [41] via enzymes cyclooxygenase and lipoxygenase, respectively. The metabolites produced by these 2 main metabolic pathways affect a number of important body metabolic processes including platelet function and inflammation [22]. Prostaglandins derived from AA are of the A 2-series and include thromboxane A2. Thromboxane A2 promotes platelet

Table 3. Change in Plasma Lipid and Lipoprotein Levels in Hypertriglyceridemic Patients Receiving Simvastatin*

	Triglycerides	LDL	Non-HDL	HDL
Lovaza (n = 122)	-29.5%	0.7%	-9%	3.4%
Placebo (n = 132)	-6.3%	-2.8%	-2.2%	-1.2%

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

*Patients received Lovaza 4 g/day or placebo following 8 weeks of treatment with simvastatin 40 mg/day [39].

aggregation and vasoconstriction, thus creating a thrombotic milieu. Conversely, EPA prostaglandin derivatives are of the A 3-series (ie, thromboxane A₃), which are less vasoconstrictive and produce less platelet aggregation [42]. Likewise, the series of 5 lipoxygenase metabolites (ie, leukotrienes) derived from EPA have a lower atherogenic potential than those derived from AA precursors because they have lesser proinflammatory effects.

Blood Pressure Lowering

A meta-analysis of randomized trials showed that a median dose of 3.7 g/day of omega-3 fatty acids reduces systolic (by 2.1 mm Hg) and diastolic (by 1.6 mm Hg) blood pressure [43]. This effect is likely the result of increased systemic arterial compliance [44] and improved endothelial function [45].

Toxicity and Potential Side Effects

Some concerns exist regarding potential side effects from seafood consumption. The issue of toxicity from mercury, dioxins, and polychlorinated biphenyls among those who consume large quantities of contaminated seafood has been raised [46,47]. The U.S. Food and Drug Administration (FDA) and Environmental Protection Agency (EPA) jointly released a consumer advisory regarding fish intake addressing these issues [48]. However, a recent in-depth review concludes that the overall benefit of marine omega-3 polyunsaturated fatty acids outweighs potential risks [20]. Those reviewers also noted that while low-level methylmercury may adversely affect early neurodevelopment, DHA appears to be beneficial in this regard. Those authors suggest women of childbearing age and nursing mothers avoid consuming large amounts of marine products. These conclusions are consistent with the joint FDA/EPA recommendations that women of childbearing age not eliminate fish from their diet but rather eat 2 fish meals per week (up to 12 oz) of low-risk fish for its potential benefits in cardiovascular health and childhood growth and development [48].

Concerns have also been raised regarding high levels of methylmercury contamination in fish oil supplements [46].

Yet a study by Foran et al [49] that analyzed the amount of mercury in commonly used fish oil supplements found levels of mercury in the supplements ranged from nondetectable to negligible. These authors suggested one explanation is that mercury may be removed during the process of manufacturing purified fish oil and ironically concluded that fish oil supplements "may be a safer alternative to fish consumption."

Increased bleeding risk from omega-3 fatty acids is a potential concern, especially when daily consumption is greater than 3 g. However, this is not borne out in clinical trials employing lower quantities of omega-3 fatty acids. Randomized studies comparing the effects of standard dose systemic anticoagulation with and without omega-3 fatty acid supplementation showed no increased bleeding risk among those receiving combination therapy in patients undergoing coronary artery bypass grafting [50] and percutaneous transluminal angioplasty [51] procedures. Patients treated with high doses of omega-3 fatty acids (such as those treated for hypertriglyceridemia) can be monitored for clinical bleeding. The major side effect noted for Lovaza is increased eructation. This can be reduced by using divided daily doses.

Recommendations and Conclusions

Based on these findings, the American Heart Association (AHA) currently recommends 1 g/day of omega-3 fatty acids under the supervision of a physician for patients with CAD. For those without CAD, the AHA recommends the consumption of a variety of fatty fish at least twice a week [15]. In addition the AHA recommends 2 to 4 g/day of omega-3 fatty acids to treat hypertriglyceridemia under a physician's care. Ongoing studies will continue to increase our understanding of the use of omega-3 fatty acids for reducing CAD risk.

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