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## Fish Oil: Getting to the Heart of It

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### Abstract and Introduction

#### Abstract

Over the past 30 years, both health professionals and the public have given much attention to the potential health benefits of omega-3 polyunsaturated fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from fish and fish oils. The purpose of this article is to examine the existing evidence linking the use of fish oil and to discuss dietary sources, safety, and recommendations for use.

#### Introduction

Over the past 30 years, both health professionals and the public have given much attention to the potential health benefits of omega-3 polyunsaturated fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from fish and fish oils. Interest in fish oils stems largely from a study done by Dyerberg et al<sup>[1]</sup> in the early 1970s, which found that Greenland Eskimos had a low rate of ischemic heart disease despite their high-fat diet consisting mainly of seal, caribou, and fish. Numerous studies done since then have linked fish intake with cardiovascular disease (CVD). The purpose of this article is to examine the existing evidence linking the use of fish oil and to discuss dietary sources, safety, and recommendations for use.

#### Polyunsaturated Fatty Acids

Polyunsaturated fatty acids (PUFAs) can be divided into two subcategories, the omega-3 and the omega-6 fatty acids. Both the omega-3 and the omega-6 fatty acids are considered "essential" because they cannot be synthesized by humans and thus must be obtained through diet or supplementation. Alpha-linolenic acid (ALA), classified as an omega-3 fatty acid, is found in certain plant oils, seeds, green leafy vegetables, beans, and nuts. Linoleic acid, classified as an omega-6 fatty acid, is found in grains, meats, and the seeds of most plants.

Through an enzymatic process of desaturation, ALA produces EPA and DHA. EPA and DHA are precursors to a group of eicosanoids (prostaglandins, thromboxanes, and leukotrienes) that have anti-inflammatory, antithrombotic, antiarrhythmic, and vasodilatory properties.<sup>[2]</sup> Arachidonic acid is a derivative of linoleic acid and a precursor to another group of eicosanoids responsible for proinflammatory and prothrombotic effects. ALA and linoleic acid use and compete for the same enzymes in the production of EPA and arachidonic acid. The ingestion of fish and fish oils provides both EPA and DHA directly, thereby avoiding the competition for enzymes for the conversion of ALA to EPA.

#### Evidence Linking Fish and Fish Oil to CVD Risk Reduction

A number of prospective epidemiologic studies show an inverse relation between fish consumption and death from coronary heart disease (CHD). More recent studies have shown that both consumption of fish and higher blood concentrations of omega-3 fatty acids favorably affect CHD mortality.

Marckmann and Granbaek<sup>[3]</sup> did a systematic review of 11 prospective cohort studies and examined the relation between fish intake and CHD mortality. Only 4 studies were considered high quality in terms of study design. Two of those studies evaluated populations at low risk for CHD and showed no cardioprotective effect from fish consumption. The other 2 studies evaluated populations at higher risk of CHD and found an inverse relation between fish consumption and CHD death, indicating 40 to 60 g fish consumed per day

could reduce the risk of death by 40% to 60%.

Randomized clinical trials provide the most reliable evidence that increased intake of omega-3 fatty acids provides a cardioprotective effect. All of the studies to date have been for secondary CHD prevention populations; no trial has investigated the role of fish intake in primary prevention of CHD.

The first clinical study was the Diet and Reinfarction Trial (DART)<sup>[2]</sup> in which 2033 men younger than age 70 with a previous history of myocardial infarction were randomly assigned to a control group or to groups receiving increased fish consumption either by diet or supplementation. In the groups that had an increased intake of fish oil, a 29% reduction in all cause mortality was observed, which was largely attributed to a reduction in CHD deaths.

The largest study was the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio Prevenzione (GISSI-Prevenzione) trial, which randomly assigned 11,324 patients with a history of a myocardial infarction into groups; each group was given approximately 850 mg omega-3 fatty acid, 300 mg vitamin E, both, or neither. The results showed a 45% reduction in sudden death and a 20% reduction in all-cause mortality in the group that was given the fatty acid alone. Although the GISSI-Prevenzione and DART studies point directly to EPA and DHA as the agents responsible for the cardiovascular health benefit, the mechanisms by which this occurs have not been shown with confidence.

### Cardioprotective Mechanisms

Potential cardioprotective mechanisms of action of omega-3 fatty acids include antiarrhythmic, antithrombotic, antiatherosclerotic, and anti-inflammatory properties as well as improving endothelial function and lowering both blood pressure and serum triglyceride levels.

**Arrhythmias.** EPA and DHA may reduce the susceptibility of the myocardium to fatal arrhythmias. Results from epidemiologic and randomized clinical trials suggest that omega-3 fatty acids decrease the risk of sudden cardiac death by reducing the myocardium's susceptibility to malignant arrhythmias. Leaf et al<sup>[5]</sup> hypothesized that omega-3 fatty acids stabilize the electrical activity of cardiac myocytes by inhibiting L-type calcium channels, thereby preventing triggered arrhythmia after potential discharges caused by excessive cytosolic calcium fluctuations. This results in a prolongation of the relative refractory period, reducing the risk of developing ventricular fibrillation. Although most of the antiarrhythmic data has been primarily from animal and cell culture studies, evidence does suggest the acute antiarrhythmic effects of omega-3 fatty acids in human beings,<sup>[6]</sup> although this study is limited by the lack of a placebo group and small sample size.

**Hyperlipidemia.** Omega-3 fatty acids lower serum triglycerides, in a dose-dependent manner particularly in persons with hypertriglyceridemia by inhibiting the synthesis of very-low-density lipoprotein (VLDL) cholesterol and triglycerides in the liver.<sup>[7]</sup> Only a small reduction in triglycerides occurred at the lower doses used in the GISSI-Prevenzione trial (about 1 g/day).<sup>[4]</sup>

A review of human studies conducted in 1997 concluded that about 4 g omega-3 fatty acid/day decreased serum triglyceride concentrations by 25% to 30%, increased serum low-density lipoprotein (LDL) cholesterol levels by 5% to 10%, and increased high-density lipoprotein (HDL) cholesterol levels by 1% to 3%.<sup>[8]</sup>

A prescription formulation of omega-3 fatty acids, Omacor, was approved November 2004 by the Food and Drug Administration (FDA) as an adjunct to diet in reducing triglyceride levels greater than 500 mg/dL in adults. Durrington et al<sup>[9]</sup> compared 2 groups of patients with persistent hypertriglyceridemia. One group received 10 to 40 mg simvastatin/day plus 4 g Omacor/day, which contains 90% omega-3 fatty acid (840 mg EPA and DHA per capsule), whereas those in the second group received the same dosage of simvastatin and a placebo. A 20% to 30% decrease was observed in serum triglyceride levels and a 30% to 40% decrease in VLDL cholesterol levels in the simvastatin plus Omacor group compared with those receiving simvastatin and a placebo.

**Blood Pressure.** Fish oil may produce dose-response effects in blood pressure in hypertensive patients. A meta-analysis study found a modest systolic blood pressure reduction of 5.5 mm Hg and diastolic blood pressure reduction of 3.5 mm Hg using at least 3 g fish oil/day.<sup>[10]</sup> A more recent meta-analysis of 36 randomized trials found a reduction in systolic blood pressure of 2.1 mm Hg and a reduction in diastolic blood pressure of 1.6 mm Hg using a dose of 3.7 g fish oil/day.<sup>[11]</sup> Although these analyses show only small changes in blood pressure with the use of fish oil, it must not be ignored that all changes in blood pressure have marked changes in mortality rates from CHD and stroke. For every 20 mm Hg systolic or 10 mm Hg diastolic increase in blood pressure, a doubling of mortality occurs from both ischemic heart disease and stroke.<sup>[12]</sup> The relation between blood pressure and risk of CVD events is continuous, consistent, and independent of other risk factors.

**Thrombosis.** EPA was shown to inhibit the synthesis of thromboxanes A<sub>2</sub>, a prostaglandin that causes platelet aggregation and vasoconstriction,<sup>[13]</sup> but the dose-related effects of omega-3 fatty acids on platelet function and thrombosis remain unclear. There seem to be inconsistent effects on fibrinolysis and little effect on blood coagulability.<sup>[5]</sup> Overall, omega-3 fatty acids have an antithrombotic effect, but the clinical relevance, especially with lower doses, remains uncertain. Little evidence suggests that an intake less than 3 g omega-3 fatty acid/day would cause clinically significant bleeding.<sup>[14]</sup>

**Atherosclerosis.** Omega-3 fatty acids may influence the atherosclerotic process by reducing lipids and inflammation. Also fatty acids may decrease platelet-derived growth factor production which is a key chemoattractant and mitogen for smooth muscle cells and macrophages which are key to the development of atherosclerotic plaque formation.

A recent study randomly assigned patients awaiting carotid endarterectomy to fish oil capsules, sunflower oil capsules, or placebo.<sup>[15]</sup> Structural characteristics of the plaque were assessed. Omega-3 fatty acids were incorporated into the atherosclerotic plaques in the fish oil group, making these plaques more likely to have thick fibrous caps and less inflammatory infiltrate. This implies the plaque has increased stability and is less vulnerable to rupture.

**Inflammation.** Omega-6 fatty acids are converted into arachidonic acid and then metabolized to omega-6 eicosanoids that act in a proinflammatory manner by enhancing platelet aggregation. Ingestion of omega-3 fatty acids increases EPA in the cell membrane, which competes with arachidonic acid for enzymatic conversion into its own metabolites, the omega-3-derived eicosanoids, which are anti-inflammatory in nature. These anti-inflammatory actions may have beneficial cardiac effects, but their potential effect on CHD has yet to be determined.

## Dietary Sources of Omega-3 Fatty Acids

Currently, the average US intake of total omega-3 fatty acids is about 1.6 g/day, which accounts for approximately 0.7% of energy intake.<sup>[16]</sup> The suggested dose from a US panel of nutrition scientists of total omega-3 fatty acid intake is 2.85 g/day.<sup>[3]</sup> The primary sources of omega-3 PUFAs in the US diet are vegetable oils and fish. Omega-3 fatty acid-enriched eggs are now available throughout the United States. These eggs may provide an alternative source of omega-3 fatty acids in place of fish as well as meeting the recommendation of the American Heart Association (AHA) of one egg per day.

The AHA nutrition committee recommends oily fish as the preferred source of omega-3 fatty acids and, for persons who cannot eat enough fish to meet recommended doses, an EPA and DHA supplement could be considered in consultation with their health care provider. Approximate levels of omega-3 oil present in various fish and seafood are shown in [Table 1](#).<sup>[17,18]</sup>

Fish preparation must also be considered. A study by Mozaffarian et al<sup>[19]</sup> noted an inverse association between broiled and baked fish but not fried fish sandwiches and the risk of ischemic heart disease.

## Safety

In 1997, the FDA indicated that the consumption of up to 3 g EPA + DHA/day from all sources would be considered safe for American adults.<sup>[20]</sup> No significant drug interactions were found with fish oil supplements, and they are generally well tolerated. Side effects are uncommon but may include a fishy aftertaste and gastrointestinal disturbances such as nausea, bloating, and belching. The fishy aftertaste can be lessened or eliminated by simply keeping the supplements in the freezer.

Dosing of approximately 3 to 4 EPA and DHA daily has resulted in moderate increase in bleeding times that are generally lower than those seen with aspirin therapy.<sup>[21]</sup> One source recommended the discontinuation of fish oil supplements at least 14 days before dental or surgical procedures,<sup>[22]</sup> but little evidence has shown this to be common practice. The effects of fish oil on hemostatic factors with concomitant anticoagulation therapy need to be further examined. Concerns about prolonged bleeding time are unlikely to be dominant given the apparent cardiac benefits, but clinicians starting patients on anticoagulation therapy with warfarin need to educate them on the possible drug-herb interactions.

Systematic reviews noted no significant difference in fasting glucose levels or glycemic control in patients with diabetes who received fish oil supplements.<sup>[23]</sup> Currently, no FDA-regulated manufacturing practices are available for over-the-counter preparations. An independent analysis by Consumers' Union of fish oil capsules from 16 different vendors sold in the United States found no significant contamination with either metals or chlorinated hydrocarbons.<sup>[15]</sup> Omacor, the only FDA-approved fish oil preparation, has a patented refining process that eliminates toxins such as mercury and other environmental contaminants. Omacor also contains 90% PUFAs compared with 60% in some commercially prepared products, lending support to claims that Omacor has better efficacy because of less variability dose to dose. One caution for Omacor is that it looks like and sounds like Amicar. Care should be taken to match the patient's diagnosis with the drug indication to minimize confusion.

Significant levels of methylmercury, polychlorinated biphenyls, dioxins, and other environmental contaminants can be found in species of fish that are at the top of the food chain. This has prompted the FDA to issue an advisory about mackerel, shark, swordfish, and tile fish (also known as golden bass or golden snapper). This advisory is directed at pregnant women, women wanting to become pregnant, and nursing mothers. Pregnant or lactating women and children may be at increased risk of mercury intoxication; therefore, avoiding intake of these potentially contaminated fish is a higher priority for this group.

## Recommendations

A food-based approach to increasing intake of omega-3 fatty acids is preferable. However, for those with known CHD, the increased

dose required to lower triglycerides could be as much as 4 g/day. Consuming fish 2.5 to 3 times a week would provide a combined intake of about 500 mg EPA and DHA/day.<sup>[21]</sup> It is unrealistic to think that these high daily doses could be achieved through diet alone, resulting in a requirement for supplementation.

For persons without known CHD, the AHA recommends eating fish at least twice a week or supplementing with about 500 mg EPA and DHA/day.<sup>[20]</sup> For persons with known CHD, 1 g EPA and DHA daily is sufficient. For persons with known hypertriglyceridemia, 2 to 4 g EPA and DHA/day with fish oil supplementation may be taken under a health professional's care. At doses greater than 3 g EPA and DHA/day, monitoring for bleeding side effects, elevated LDL cholesterol, and glycemic responses is recommended. Women who are pregnant or of childbearing age should consume 2 fatty fish meals a week (up to 12 ounces), being careful to avoid shark, tile fish, king mackerel, and swordfish and to limit albacore tuna to 6 ounces/week.

## Conclusion

Currently, the favorable effect of omega-3 fatty acids on cardiovascular health is most consistently related to the use of fish oil. Fish and fish oil supplements should be recognized as a potential treatment choice in persons with known cardiovascular disease. Clients without known CVD should be advised to consume a variety of fish at least 1 to 2 times a week, avoiding deep-fried fish or fast-food fish.

More studies are needed to determine the preventative effects of fish oil as well as the concomitant use with other antiplatelet medications. Serum hemostatic factors need to be monitored closely in patients on higher doses of EPA and DHA who are also receiving other anticoagulation and thrombogenic medications. The informed clinician will be able to recommend fish oil by way of diet or supplementation as an attractive alternative or as complementary treatment with CVD and particularly with hypertriglyceridemia. Health professionals need to educate themselves about benefits, side effects, dose, duration, and drug-drug interactions to maximize therapy and to extract the maximum benefit from fish oil.

## Table 1. Omega-3 Oil Levels in Various Fish and Seafood

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Type of Fish	Omega-3 oil per 3-ounce serving, g	Equivalent of 1 g EPA and DHA, ounces/day	
<b>Tuna</b>			
Light, canned in water, drained	0.26	12	
White, canned in water, drained	0.73	4	
Fresh	0.24-1.28	2.25-12	
<b>Sardines</b>			
	0.98-1.70	2-3	
<b>Salmon</b>			
Sockeye	1.05	2.5	
Chinook	1.48	2	
Coho, farmed	1.09	3	
Coho, wild	0.91	3	
Atlantic, farmed	1.09-1.83	1.5-2.5	
Atlantic, wild	0.9-1.56	2-3.5	
<b>Mackerel</b>			
	0.34-1.57	2-8.5	
<b>Herring</b>			
Pacific	1.81	1.5	
Atlantic	1.71	2	
<b>Trout, rainbow</b>			
Farmed	0.98	3	
Wild	0.84	3.5	
<b>Cod</b>			
Atlantic	0.13	23	
Pacific	0.24	12.5	
<b>Catfish</b>			
Farmed	0.15	20	
Wild	0.2	15	
<b>Flounder or sole</b>			
	0.42	7	
<b>Oyster</b>			
Pacific	1.17	2.5	
Eastern	0.95	3	
<b>Lobster</b>			
	0.07-0.41	7.5-42.5	
<b>Crab, Alaskan king</b>			
	0.35	8.5	
<b>Shrimp, mixed species</b>			
	0.27	11	
<b>Clam</b>			
	0.24	12.5	
<b>Scallop</b>			
	0.17	17.5	

*Omega-3 fatty acid content varies widely depending on the season, the fish's diet and age, and the storage and preparation methods.*

Sources: adapted from American Heart Association. Fish, Levels of Mercury and Omega-3 Fatty Acids. Available at: [www.americanheart.org](http://www.americanheart.org). Accessed February 26, 2006.

US Department of Agriculture Nutrient Data Laboratory. Available at <http://www.nalusda.gov/fnic/foodcomp/>. Accessed May 12, 2005.

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