

Summary of Research on Use of Fish Oil Capsules to Reduce Death in Cardiac Patients

(Summary of the literature 10/19/2005)

Summary

“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. There are no significant drug interactions with omega-3 fatty acids.

- **Food sources** - 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.
- **Action** - In addition to being antiarrhythmic, the omega-3 fatty acids are antithrombotic and anti-inflammatory. Omega 6 and food sources **-In contrast**, omega-6 fatty acids, which are present in most seeds, vegetable oils, and meat, are prothrombotic and proinflammatory.”

Source: Am Fam Physician 2004;70:133-40. Copyright© 2004 American Academy of Family Physicians.

- **Omega 3 vs Omega 6** – “Two types of fatty acids that are essential for human health are omega-3 and omega-6. Studies suggest that decreasing the ratio of omega-6 (in vegetable oils) to omega-3 fatty acids (in fatty fish) is important to reduce risk of cancer and heart disease, inflammatory conditions, and depression. Most people consume too many omega-6 fatty acids and consume too little omega-3 fatty acids.”

Omega 6 oils - corn oil, sunflower, sesame, soybean oil and safflower oil

Omega 3 oil – canola, flax seed

Recommendations

The American Heart Association (AHA) published a 2002 scientific statement on fish and fish oils in cardiovascular disease. (Kris-Etherton PM, Harris WS, Appel LJ. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation* 2002;106(21):2747-2757.) They state that the data from epidemiological studies and prospective secondary prevention studies support the American Heart Association Dietary Guidelines to include at least two servings of fish per week, particularly fatty fish. The fish consumption recommendation must be balanced with concerns about environmental contaminants such as methylmercury. They recommend that patients with coronary heart disease consume approximately **1 gram of EPA+DHA per day**, preferably from oily fish such as salmon, tuna, sardines, etc. Supplements, they state, could be considered in consultation with the patient's physician. For patients who need to lower their triglyceride, the AHA statement suggests administering 2 to 4 grams of EPA+DHA per day provided as capsules under a physician's care. There are no significant drug interactions with omega-3 fatty acids.

Source: American Family Physician July 2004 (70:133-40) Maggie Covington UMD School of Medicine – Center for Integrative Medicine

On 9/8/ 04 FDA announced a “qualified health claim for the use of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) omega-3 fatty acids for conventional foods and dietary supplements”. On the same day the FDA “ announced the availability of a qualified health claim for reduced risk of coronary heart disease (CHD) on conventional foods that contain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) omega-3 fatty acids”.

Sources: FDA website Q & A <http://www.cfsan.fda.gov/~dms/labo3qa.html> and <http://www.fda.gov/bbs/topics/news/2004/NEW01115.html> 7/27/05

Researched and compiled by Ayn H. Crawley, Deer Run Consulting, Penns Park, PA and posted on the Peoples Law Library website (www.peoples-law.org) for general information purposes. This document is not medical advice. It can be used to inform consultations with the physicians of residents of assisted living facilities who have been diagnosed with coronary heart disease. 1

Dosage

“FDA recommends that consumers not exceed more than a total of 3 grams per day, with no more than 2 grams per day from a dietary supplement. Some scientific studies show that consumption levels well over 3 grams per day may lead to excessive bleeding. Therefore, FDA recommends that consumption not exceed 3 grams per day from all food sources.” *Ayn’s Note – FDA refers only to fish as a source and not capsules and not specifically deal with getting these levels from plant oil sources.*

Source: FDA website Q & A <http://www.cfsan.fda.gov/~dms/labo3qa.html> 7/27/05

“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.”

Source: American Family Physician July 2004 (70:133-40) Maggie Covington UMD School of Medicine – Center for Integrative Medicine

Evidence from prospective secondary prevention studies (*prevent second heart attack*) suggests that EPA+DHA supplementation ranging from 0.5 to 1.8 g/d (either as fatty fish or supplements) significantly reduces subsequent cardiac and all-cause mortality. For α -linolenic acid, total intakes of 1.5 to 3 g/d seem to be beneficial.

Source: Circulation 2002 (106:2747) “Fish Consumption, Fish Oil, Omega-3 Fatty Acids, and Cardiovascular Disease” © 2002 American Heart Association

A dose of 1 g/day as used in the GISSI-Prevenzione study is probably adequate. *Source Pharmacists online 3/15/03*

What is the daily recommended intake of omega-3 fatty acids? There are currently no established guidelines regarding optimal omega-3 intake. According to the Institute of Medicine, the Adequate Intake (AI) is 1.1g daily for women and 1.6 g daily for men. Although some experts believe that these recommendations might be too low to obtain the health benefits associated with omega-3s. Research shows benefits associated with higher intake of 2-3 g per day.

Source for IOM assertion: the Macronutrients Table for n-3 polyunsaturated fatty acids (linolenic acid) under Institute of Medicine Dietary Reference Intakes Tables published September 2002 (no updates as of 8/05)

Which brands?

Beneficial Effects of Fish and Fish Oils in Cardiovascular Diseases

Source: US Pharmacist 2/15/03

Table 4: Fish Oil Products Containing at Least 500 mg of EPA+DHA per Capsule				
Product	Distributor	EPA (mg)	DHA (mg)	Total of EPA + DHA
Carlson Super Omega-3 Fish Oils	J.R. Carlson Laboratories Inc.	330	220	550
TwinEPA Extra Strength Fish Oil Concentrate	Twin Lab	600	240	840
Pure Encapsulations EPA/DHA Essentials	Pure Encapsulations Inc.	300	200	500
Solgar Omega-3 "700" EPA & DHA from Cold Water Fish	Solgar Vitamin and Herb	360	240	600
Super EPA 2000	Advanced Nutritional	563	312	875
Super EPA 1200	Advanced Nutritional	360	240	600
Marine Lipid Concentrated Softgels	Vitaline Formulas	360	240	600
Sea Omega 50 Softgels	Watson	300	200	500

Also see the GISSI study recommendation of 2:1 ratio of DHA to EPA

AC NOTE: Also see New Zealand manufacturer's claim for Xtend Life "One capsule provides 1,000 mgs of Fish Oil Esters, which contains: 440 mgs of Omega 3 Fatty Acids, 250 mgs of DHA, 110 mgs of EPA, 1.5 IU's of Vitamin E" (ratio and purity claims – total omega 3 query?)

Also see comparative table from University of Wisconsin Preventive Cardiology Program available online with specific brand recommendations.

Food Sources: Omega 3 from Fish

Source: *American Family Physician July 1, 2004*

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

Source: *University of Michigan Center for Integrative Medicine website July 2005*

Finfish High in Omega-3s (2.0 g and above)	Grams of omega-3 fatty acids per 6 ounce portion
Anchovy, European, canned in oil	3.4 g
Salmon, Atlantic, wild	3.2 g
Mackerel, Pacific and Jack	3.2 g
Sable Fish	3.0 g
Whitefish	3.0 g
Sardine, Pacific	2.8 g
Tuna, bluefin	2.8 g
Herring, Atlantic	2.4 g
Mackerel, Atlantic	2.0 g
Trout, rainbow	2.0 g

Researched and compiled by Ayn H. Crawley, Deer Run Consulting, Penns Park, PA and posted on the Peoples Law Library website (www.peoples-law.org) for general information purposes. This document is not medical advice. It can be used to inform consultations with the physicians of residents of assisted living facilities who have been diagnosed with coronary heart disease. 4

**Selected Fish Sources with Moderate-Low
Omega-3 Fatty Acid Content**

Common Finfish	Grams of Omega-3's per 6 oz. portion (less than 2.0 g per serving)
Tuna, white albacore, canned in water	1.4 g
Halibut	0.8 g
Pollock	0.8 g
Perch, Ocean	0.4 g
Tuna, light, canned in water	0.4 g
Tuna, yellowfin	0.4 g
Cod	0.2 g

Note: While the fish above do contain some omega-3s, other fish are richer sources (see High Omega-3 table above)

Selected Seafood Sources with Moderate-Low Omega-3 Fatty Acid Content

Seafood			
Portion size: 4-6 oz	Grams of Omega-3s per 6 oz. portion (less than 2.0 g per serving)	Portion size: 4-6 oz	Grams of Omega-3s per 6 oz. portion (less than 2.0 g per serving)
<i>Mollusks</i>		<i>Shellfish</i>	
Mussel	1.4 g	Crab, Alaska king	0.8 g
Oyster, Eastern, wild	1.0 g	Crab, blue	0.8 g
Oyster, Eastern, farmed	0.8 g	Shrimp	0.6 g
Scallop	0.6 g	Lobster	0.2 g
Clam	0.4 g	Crayfish	0.2 g

Note: While seafood does contain some omega-3s, THERE are richer sources (see High Omega-3 table above)

Research Summary and Sources

- **The 1999 GISSI-Prevenzione study** examined the effect of dietary fish oil and vitamin E supplementation on mortality and morbidity in **over 11,000 subjects** who had suffered a myocardial infarction within three months of entering the trial. The subjects (85% men, 51% younger than 60) were randomly assigned to one of four groups. One group, consisting of 2,836 subjects, received 1 gram of fish oil daily containing 850 to 882 milligrams of EPA and DHA in the form of the ethyl esters and in a ratio of EPA to DHA of 1 to 2. A second group, consisting of 2,830 subjects, received 300 milligrams of vitamin E in the form of synthetic D alpha-tocopherol. A third group of 2,830 subjects received both the fish oils and vitamin E, while the fourth group of 2,828 acted as the control. The trial lasted for 42 months.

The primary combined endpoint was death, non-fatal myocardial infarction and stroke. Treatment with fish oil, but not vitamin E, significantly lowered the risk of the primary endpoint. The effect of the combined treatment was similar to that of fish oil alone. Although vitamin E did show a trend toward a reduction in mortality, the trend did not show significance. No adverse effects

Researched and compiled by Ayn H. Crawley, Deer Run Consulting, Penns Park, PA and posted on the Peoples Law Library website (www.peoples-law.org) for general information purposes. This document is not medical advice. It can be used to inform consultations with the physicians of residents of assisted living facilities who have been diagnosed with coronary heart disease. 5

were reported except for some mild gastrointestinal symptoms. The dose of fish oil used in the trial lowered serum triglycerides by 3.4%.

The most significant result of this trial was the reduction in risk for overall and sudden cardiac death. It is believed that the reduction of sudden cardiac death was due to the anti-arrhythmic effect of the LCPUFAs. The study suggests that up to 20 lives per 1,000 post-MI patients could be saved by consuming daily doses of less than 1 gram of EPA and DHA.

Source: GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet*. 1999; 354:447-455.

- **Note on 1999, GISSI study report** - This was the first large scale trial that showed supplementation of essential fatty acids significantly lowered the risk of death. **This trial used a supplement with a ratio of DHA to EPA of approximately 2:1.** This is important to note, as most fish oil products contain more EPA than DHA. In this Italian study, researchers found that simply adding 1,000 mg of fish oil per day to a healthy diet resulted in a 20% reduction in deaths. Note also this was not a double-blind study but see studies below.
- **Followup to GISSI Study** - The GISSI-Prevenzione and epidemiological studies mentioned are not the only evidence that mortality is reduced in those groups who consume fish or fish oil capsules. In fact, a criticism of the GISSI-Prevenzione study was that it was not a double-blind trial, i.e., physicians and patients were not blinded as to which treatment was received. However, there have been several randomized, double-blind, placebo-controlled clinical trials where fish oil was administered to patients who survived a myocardial infarction. In two of these trials,^{17,18} fish oil was administered in the hope of preventing a second infarction or death (termed secondary prevention) and the other was investigating the effects on heart rate variability.¹⁹ **TABLE 2** lists the results of these randomized, double-blind trials.

The lack of an effect in the trial of Nilsen et al. may well be attributed to the fact that the participants resided in a coastal area and already received a diet rich in fish products.¹⁹ Another possible confounding factor is that mercury from eating contaminated fish seems to increase the probability of dying and offsets some of the beneficial effects of fish consumption.²⁰ The trial by Christensen, *et al.* was designed to see if fish oil supplementation could increase heart rate variability, which would make the heart less susceptible to ventricular fibrillation and be consistent with a protective effect from fish oil.¹⁹ The lowered mortality risk is not statistically significant since the study was small in size and carried out for only three months, though they did show a statistically significant increase in heart rate variability.

The doses of EPA + DHA used in the trials were 1.8 g/day in the study by Singh *et al.*, 4 g/day in the study by Nilsen *et al.*, and 4.8 g/day in the study by Christensen *et al.*

Finally, there are dietary intervention studies--the Diet and Reinfarction Trial (DART) and the Lyon Diet Heart Study.²¹⁻²³ These studies are summarized in **TABLE 3**, and both demonstrated a statistically significant risk reduction. As can be seen from **TABLES 2** and **3**, the effects of the omega-3 fatty acids seem consistent and safe. **It should be noted that participants in the DART trial who could not tolerate fish were given fish oil capsules equivalent to about 540 mg EPA daily.**

Table 2: Overall Mortality in Studies of Fish Oil Administration to Survivors of a Myocardial Infarction

Study (Reference)	Fish Oil Mortality	# of Subjects	Placebo Mortality	# of Subjects	Time Interval (months)
Singh, <i>et al.</i> ^{(a)16}	14	122	26	118	12
Nilsen, <i>et al.</i> ¹⁷	11	150	11	150	18
Christensen, <i>et al.</i> ¹⁸	0	28	1	27	3

(a) = statistically significant risk reduction

Table 3: Overall Mortality in Dietary Intervention Studies of Survivors of a Myocardial Infarction

Study (Reference)	Fish Oil Mortality	# of Subjects	Placebo Mortality	# of Subjects	Time Interval (months)
DART, <i>et al.</i> ¹⁶	94	1,015	130	1,018	24
Lyon, <i>et al.</i> ¹⁷	8	302	20	303	27
Lyon, <i>et al.</i> ¹⁸	14	302	24	303	46

Source: On-line Journal “US Pharmacist” 2/15/03 – “Beneficial Effects of Fish and Fish Oils in Cardiovascular Disease” Brian Chatel, MLT(ASCP), Pharm.D. (Candidate), Robert Belloto, , R.Ph., Ph.D., CGP, FASCP , Tina Esposito, B.S. Biol., Pharm.D. (Candidate)

- **RCTs have demonstrated that omega-3 fatty acid supplements can reduce cardiac events** (eg, death, nonfatal MI, nonfatal stroke) and decrease progression of atherosclerosis in coronary patients. However, additional studies are needed to confirm and further define the health benefits of omega-3 fatty acid supplements for both primary and secondary prevention. For example, placebo-controlled, double-blind RCTs are needed to document both the safety and efficacy of omega-3 fatty acid supplements in both high-risk patients (eg, patients with type 2 diabetes, dyslipidemia, and hypertension, and smokers) and coronary patients on drug therapy. Mechanistic studies on their apparent effects on sudden death are also needed.

A dietary (ie, food-based) approach to increasing omega-3 fatty acid intake is preferable.

Still, for patients with coronary artery disease, the dose of omega-3 (≈1 g/d) may be greater than what can readily be achieved through diet alone (Table 5). These individuals, in consultation with their physician, could consider supplements for CHD risk reduction. Supplements also could be a component of the medical management of hypertriglyceridemia, a setting in which even larger doses (2 to 4 g/d) are required (Table 5). The availability of high-quality omega-3 fatty acid supplements, free of contaminants, is an important prerequisite to their extensive use.

Dosage - Depending on the preparation, up to three 1-g fish oil capsules per day will be necessary to provide ≈1 g/d of omega-3 fatty acids. The most common fish oil capsules in the United States today provide 180 mg of EPA and 120 mg DHA per capsule. It is important that consumers read the nutrition label to determine EPA and DHA levels in the fish oil capsule.

Omega-3 fatty acids have been shown in epidemiological and clinical trials to reduce the incidence of CVD. Large-scale epidemiological studies suggest that individuals at risk for CHD benefit from the consumption of plant- and marine-derived omega-3 fatty acids, although the ideal intakes presently are unclear. **Evidence from prospective secondary prevention studies suggests that EPA+DHA supplementation ranging from 0.5 to 1.8 g/d (either as fatty fish or supplements) significantly reduces subsequent cardiac and all-cause mortality. For α -linolenic acid, total intakes of 1.5 to 3 g/d seem to be beneficial.**

Collectively, these data are supportive of the recommendation made by the AHA Dietary Guidelines to include at least two servings of fish per week (particularly fatty fish). In addition, the data support **inclusion of vegetable oils (eg, soybean, canola, walnut, flaxseed)** and food sources (eg, walnuts, flaxseeds) high in α -linolenic acid in a healthy diet for the general population ([Table 5](#)). The fish recommendation must be balanced with concerns about environmental pollutants, in particular PCB and methylmercury, described in state and federal advisories. Consumption of a variety of fish is recommended to minimize any potentially adverse effects due to environmental pollutants and, at the same time, achieve desired CVD health outcomes.

Source: Circulation 2002 (106:2747) “Fish Consumption, Fish Oil, Omega-3 Fatty Acids, and Cardiovascular Disease” © 2002 American Heart Association

- A 16-year study of almost 85,000 women found that those who ate fish two to four times weekly cut their risk of heart disease by 30 percent, compared with women who rarely ate fish. Women who ate fish five or more times weekly reduced their risk 34 percent. Past studies showed similar benefits for men.

Source: April, 2001, Journal of the American Medical Association.

- **Mortality reduction** - In a, 11,000 patients were randomly assigned to receive either 1 gram daily of DHA/EPA, 300 units vitamin E, both essential fatty acids and vitamin E with a fourth group receiving no treatment. After only three months of treatment, those individuals receiving the essential fatty acids had a significant reduction in the total mortality by over 40%. The reduction in risk of sudden death at four months had increased to 53%. It was concluded that low dose (1 gm daily) of omega 3 DHA and EPA on total mortality and sudden death supported the hypothesis that this nutrient had an anti-arrhythmic effect.

Source: study published in the journal Circulation in April 2002

- **DHA/EPA more important than total cholesterol** -“In the most recent edition of the American Journal of Clinical Nutrition, researchers conducted an extensive case control study of cardiovascular disease in adults over the age of 65. Researchers measured plasma phospholipid concentrations of omega 3 polyunsaturated fatty acids in the blood of over 5,000 men and women. Over the next few years, 54 of these individuals experienced fatal myocardial infarction (heart attack) or sudden death from a cardiac cause. This group was then matched against a control group who did not have fatal heart attacks. It was found that a higher concentration of combined DHA and EPA omega 3 EFA reduced the risk of fatal heart disease by approximately 70% compared to the control group. What was even more amazing is the total cholesterol levels between the two groups was the lowest in the group with the fatal heart attacks. This proves that total cholesterol levels should not be relied upon alone to determine the health of your heart.”

Unknown secondary source

- **Critical to reduce Omega-6 consumption** – “This study also indicates those with the highest levels of omega-6 consumption (primarily from corn oil, sunflower, sesame, soybean oil and safflower oil in the American diet) had a 800% higher risk of death compared to the group with the highest omega-3 consumption. Please read the labels of foods you buy, almost all snack

foods, baked foods, boxed foods, use these harmful oils. Even worse many are partially hydrogenated. Also it is important to realize that the fast food industry fries its food in these harmful oils.”

Unknown secondary source

- **Omega 3 not recommended** except in persistent high cholesterol cases

Source: Circulation 1996 article

- **Premature to recommend** – “When considering cardiovascular health, it seems premature to recommend general usage until compelling evidence for the beneficial action of fish oil supplements is at hand. Although doses of 3 to 8 g of n-3 PUFA per day in those with CHD were not associated with significant adverse effects in recent clinical trials,^{8 34} evidence for beneficial effects in CHD patients is either lacking or needs additional study. Currently, fish oil capsules can only be recommended for the infrequent patients with severe, treatment-resistant hypertriglyceridemia who are at increased risk for pancreatitis. A nested case-control study was conducted among the 14 916 participants in the Physicians' Health Study.³³ Each participant with MI was matched by smoking status and age with a randomly chosen control participant who had not developed CHD. Fish oil intake was estimated by measuring plasma levels in cholesterol esters and phospholipids. No association was found between fish oil levels and the incidence of MI even when results were adjusted for major cardiovascular risk factors. Although early trials suggested that fish oil held some promise if ingested early before angioplasty, a clinical trial large enough to find a significant effect did not, despite a dose of 8 g/d of n-3 PUFA.³⁴ This trial did document the safety of fish oil supplementation without any evidence of excess bleeding in the patients who all took aspirin. Moreover, a clinical trial with angiographic end points showed that among normo-cholesterolemic men with CHD, fish oil treatment (6 g n-3 PUFA for 2 years) did not produce significant changes in the diameter of the coronary arteries.”

Source: Fish Consumption, Fish Oil, Lipids, and Coronary Heart Disease by Neil J. Stone, MD – Circulation. 1996;94:2337-2340.) © 1996 American Heart Association, Inc