THE HEART-HEALTHY BENEFITS OF OMEGA-3 FATTY ACIDS

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ABSTRACT

In September 2004, the US Food and Drug Administration (FDA) approved a qualified health claim regarding cardiovascular risk reduction by foods containing the omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid. This approval signifies that the FDA has determined that evidence supports (although not conclusively) an association between consumption of foods rich in omega-3 fatty acids and a reduction in the risk of coronary heart disease. This paper reviews findings that led to the FDA's approval of the qualified health claim and considers potential mechanisms of omega-3 fatty acids in reducing the risk of coronary heart disease. Observational studies and randomized, controlled clinical trials generally support the benefits of omega-3 fatty acids in the primary and secondary prevention of coronary heart disease, although a minority of studies has not shown a benefit. Omega-3 fatty acids reduce triglycerides, platelet adhesion, blood pressure, and inflammation, among other cardioprotective effects. Any one or all of these effects may contribute to their cardiovascular risk-reducing properties. Further study is needed to define the optimum amount of omega-3 fatty acid intake for reducing cardiovascular risk, to elucidate the mechanisms of their cardioprotective effect, and to identify specific patient populations who will derive the most benefit from supplementation. Recently, Omacor (omega-3 acid ethyl esters) was approved by the US Food and Drug Administration, available solely by prescription, as an adjunct to diet for reduction of triglyceride levels in adults with hypertriglyceridemia (≥500 mg/dL). Supplement-derived omega-3 fatty acids may become an increasingly important component of cardiovascular risk-reduction strategies because toxins and other contaminants can be eliminated or reduced in supplements and higher daily doses can be administered than can feasibly be obtained in the diet.

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In September 2004, the US Food and Drug Administration (FDA) announced the availability of a qualified health claim regarding cardiovascular risk reduction by foods containing the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).[1] The regulatory approval of this qualified health claim signifies that the FDA has determined that evidence supports (although not conclusively) an association between consumption of foods rich in omega-3 fatty acids and a reduction in the risk of coronary heart disease. With the availability of a qualified health claim, food labels can include a statement regarding the supportive evidence for cardiovascular risk-reducing properties of EPA and DHA and can list the amount of omega-3 fatty acids contained in the food.[1] The label is intended to help consumers make informed choices about the foods they eat. In 2000, the FDA approved a similar qualified health claim for dietary supplements containing EPA and DHA.[1] What findings led to the FDA's approval of these qualified health claims? What are the potential mechanisms of omega-3 fatty acids in reducing coronary heart disease risk? This paper discusses the answers to these questions and considers areas for fur-

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ther research regarding the heart-healthy benefits of omega-3 fatty acids.

Sources of Omega-3 Fatty Acids

Omega-3 fatty acids can be derived from fish, as are EPA and DHA, or plants, as is α-linolenic acid (ALA). All fish contain EPA and DHA in amounts that vary by factors, including species, fish diet, and whether the fish are wild or farm-raised.[2] Primary dietary sources of EPA and DHA include fatty fish, such as salmon, herring, mackerel, sardines, and anchovies (Table 1).[2] EPA and DHA can also be obtained in dietary supplements in the form of fish oil capsules (Table 1).[2] Primary dietary sources of ALA include some oils (such as flaxseed and its oil, canola and soybean oils) and nuts (such as English walnuts; Table 2).[2] Both marine- and plant-derived omega-3 fatty acids are potentially beneficial in reducing cardiovascular risk, although the evidence is stronger for marine sources. Data for the cardioprotective benefits of ALA are emerging, but there is still a lack of clear benefit in randomized trials. Therefore, this review focuses on the findings on marine-derived omega-3 fatty acids.

Omega-3 Fatty Acids and Risk of Coronary Heart Disease

Evidence germane to assessing the effect of omega-3 fatty acids on coronary heart disease risk comes from epidemiologic studies and clinical trials. Results of several epidemiologic studies show an inverse relationship between the amount of fish consumption and the mortality from coronary heart disease.[3-9] This relationship has been observed in men and women and in middle-aged and elderly individuals, regardless of whether omega-3 fatty acids were administered through diet, dietary supplements, or pharmacologic therapy.

Diet

In one of the most recently reported studies involving 16 years of data from 84 688 women ages 34 to 59 years, the frequency of fish consumption and omega-3 fatty acid intake were inversely related to the risk of nonfatal myocardial infarction and death related to coronary heart disease.[9] Compared to women who ate fish less frequently than once per month, those women

Table 1. EPA + DHA Content of Fish, Fish Oils, and Dietary Supplements

	EPA + DHA, g/3-oz serving fish or g/g oil
Fish	
Tuna	
Light, canned in water, drained	0.26
White, canned in water, drained	0.73
Fresh	0.24–1.28
Sardines	0.98–1.70
Salmon	
Chum	0.68
Sockeye	1.05
Pink	1.09
Chinook	1.48
Atlantic, farmed	1.09–1.83
Atlantic, wild	0.9–1.56
Mackerel	0.34–1.57
Herring	
Pacific	1.81
Atlantic	1.71
Rainbow trout	
Farmed	0.98
Wild	0.84
Halibut	0.4–1.0
Cod	
Pacific	0.24
Atlantic	0.13
Haddock	0.20
Catfish	
Farmed	0.15
Wild	0.20
Flounder/Sole	0.42
Oyster	
Pacific	1.17
Eastern	0.95
Farmed	0.37
Lobster	0.07–0.41
Crab, Alaskan King	0.35
Shrimp, mixed species	0.27
Clam	0.24
Scallop	0.17
Dietary Supplements	
Capsules	
Cod liver oil	0.19
Standard fish body oil	0.30
Omega-3 fatty acid concentrate	0.50
Omacor (omega-3 acid ethyl esters)	0.85

DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid.
Adapted from Kris-Etherton et al. *Circulation.* 2002;106:2747-2757.[2]

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consuming fish 1 to 3 times per month, once per week, 2 to 4 times per week, and at least 5 times per week were 21%, 29%, 31%, and 34% less likely, respectively, to have an adverse cardiac event during the 16-year follow-up period.

An association of fish consumption with reduced risk of mortality from coronary heart disease and other causes was observed across world regions in a study that used national fish-consumption data from the Food and Agriculture Organization and the World Health Organization.[7] During all of the time periods studied (ie, 1961–1963, 1979–1981, and 1989–1991), log fish consumption across 36 countries was inversely related to log all-cause mortality, ischemic heart disease, and stroke. This inverse relationship was observed when data from Iceland and Japan, countries with the highest amount of fish consumption and the lowest all-cause mortality rate, were excluded from analyses.

The bulk of the published observational data on omega-3 fatty acids obtained through diet supports a strong inverse relationship between fish consumption and the risk for coronary heart disease. However, other studies fail to verify this association or show a less robust association than those studies described earlier in this article.[10-13] The inconsistencies may arise from heterogeneity among studies in the means of defining and the methods of assessing for coronary heart disease, in the degree to which confounding variables were operating, in sample size, and in the means of quantifying fish consumption.[2]

Table 2. ALA Content of Oils, Nuts, and Seeds Rich in ALA

	ALA content, g/tbsp
Olive oil	0.1
English walnuts	0.7
Soybean oil	0.9
Canola oil	1.3
Walnut oil	1.4
Flaxseeds	2.2
Flaxseed (linseed) oil	8.5

ALA = α-linolenic acid.
Adapted from Kris-Etherton et al. *Circulation.* 2002;106:2747-2757.[2]

The observational data are complemented by randomized, controlled clinical trials of omega-3 fatty acids from diet. For example, in the Diet and Reinfarction Trial—the first of these trials to be published—a 29% reduction in all-cause mortality over 2 years was observed among male survivors of myocardial infarction (n = 2033) who were advised to consume 200 to 400 g of fish twice weekly, as compared to those men who were not given this advice.[14]

Dietary Supplements

Omega-3 fatty acids given as dietary supplements also reduce cardiovascular risk, as shown by the results of the Indian Experiment of Infarct Survival-4,[15] a randomized, placebo-controlled, 1-year assessment of the effects of treatment with fish oil (EPA 1.08 g/day) or mustard oil (ALA 2.9 g/day) in patients with suspected acute myocardial infarction. After 1 year of treatment, significantly fewer patients treated with fish oil or mustard oil had a cardiac event compared to placebo (24.5% and 28% vs 34.7%). Nonfatal infarctions were also significantly less frequent in the patients treated with fish oil or mustard oil groups compared to placebo (13.0% and 15.0% vs 25.4%). Patients treated with fish oil, but not those patients treated with mustard oil, were significantly less likely to die of a cardiac event than patients treated with placebo (11.4% vs 22.0%).

Pharmacologic Omega-3 Fatty Acids

Omega-3 fatty acids administered as pharmacotherapy also reduce cardiovascular risk as shown in the GISSI Prevention Study,[16] which to date is the largest prospective, randomized trial of omega-3 fatty acids for secondary prevention of coronary events. In the GISSI Prevention Study that was conducted in Italy, 11 324 patients (85% male) who suffered a recent myocardial infarction were randomly assigned to receive 850 mg of purified and concentrated EPA and DHA as ethyl esters (Omacor), 300 mg of vitamin E, EPA + DHA and vitamin E, or neither EPA + DHA nor vitamin E (control group).[16] After 3.5 years, the group receiving EPA + DHA alone experienced a 15% reduction in nonfatal myocardial infarction and stroke (P <.02 vs control group), a 20% reduction in risk of all-cause mortality (P <.01 vs control group), and a 45% reduction in sudden death (P <.001 vs control group). Omega-3 fatty acid treatment was also associated with reductions in triglyceride levels by 4% and

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an increase in low-density lipoprotein (LDL) cholesterol levels by 2.5% at the end of 6 months of treatment. Addition of vitamin E to the EPA + DHA regimen did not confer additional benefit. These data on the lack of benefit of vitamin E is congruent with clinical trial data from the HOPE study and the MRC/BHF Heart Protection Study.[17,18]

The cardiovascular risk-reducing benefits of supplemental DHA + EPA were not confirmed in a study conducted in Norway.[19] In this study, cardiac events in patients who were post-myocardial infarction were assessed after 1.5 years of treatment with supplemental DHA + EPA at a dose of 3.5 g/day. All of the patients were randomly assigned to receive 2 gelatin capsules of Omacor (omega-3 acid ethyl esters) or corn oil twice a day. Each capsule contained 850 to 882 mg EPA and DHA as ethyl esters in the average ratio of EPA to DHA of 1:2 or the same amount of corn oil. Alpha-tocopherol (4 mg) was added to all capsules. Between-study differences that may explain the discrepant findings include a much smaller sample size in the Norwegian study and the possibility that the typical diet in Scandinavian populations is higher in fatty marine fish than the Italian diet—a difference that may have obscured between-group differences in outcomes in the Norwegian study.

Omega-3 Fatty Acids and Angiographic Measures

The potential influence of omega-3 fatty acids on the angiographic measures of the progression of coronary artery disease has also been assessed in several studies.[20-25] Results are mixed, with approximately 50% showing less progression and 50% not showing an effect of omega-3 fatty acids. In one of the more promising studies, 188 adults awaiting elective carotid endarterectomy were randomly assigned to receive fish oil, safflower oil, or a control oil.[26] The total dose of EPA + DHA was 1.4 g/day in the fish-oil group. After a median of 42 days of therapy, the patients underwent carotid endarterectomy, and the excised plaques were examined histologically. Plaques from patients receiving the fish-oil treatment had higher EPA and DHA content, in addition to fewer macrophages and a thicker fibrous cap, as compared to those patients from the other 2 groups. These data suggest that this level of fish-oil supplementation readily penetrates existing atherosclerotic plaques and seems to stabilize them.

Safety of Omega-3 Fatty Acids

Ingestion of omega-3 fatty acids is rarely associated with side effects at daily intakes of up to 3 g/day, an amount that the FDA has designated as "generally recognized as safe."[2] Some patients experience gastrointestinal upset and a fishy aftertaste. Intakes exceeding 3 g/day may be associated with worsening glycemia in patients with impaired glucose tolerance and diabetes and with increases in LDL cholesterol levels in patients with hypertriglyceridemia (Table 3).[2]

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Table 3. Risk of Side Effects from Ingestion of Omega-3 Fatty Acids

	Intake of Omega-3 Fatty Acids		
	<1 g/day	1–3 g/day	>3 g/day
Fishy aftertaste	Low	Moderate	High
Gastrointestinal upset	Very low	Moderate	Moderate
Worsening glycemia (mostly in patients with impaired glucose tolerance and diabetes)	Very low	Low	Low
Increase in LDL (mostly in patients with hypertriglyceridemia)	Very low	Moderate	Likely
Clinical bleeding	Very low	Very low	Low

LDL = low-density lipoprotein.
Adapted from Kris-Etherton et al. *Circulation.* 2002;106:2747-2757.[2]

Table 4. Potential Mechanisms of the Cardiovascular Risk-Reducing Properties of Omega-3 Fatty Acids

- Reduce triglycerides
- Reduce blood pressure
- Decrease platelet aggregation
- Promote nitric oxide-induced endothelial relaxation
- Stabilize the myocardium (to reduce susceptibility to ventricular arrhythmia)

Data from Kris-Etherton et al. *Circulation.* 2002;106:2747-2757.[2]

Fish contain toxins including mercury, polychlorinated biphenyls (PCBs), and organochlorine pesticides.[27] These toxins may pose a safety risk because their generally long half-lives allow them to accumulate, particularly in those individuals who frequently consume contaminated fish.[2] The amount of toxins varies by fish source (ie, farm-raised, wild) and species, but no fish is toxin-free. The use of supplements may be a viable alternative to the frequent consumption of fish when toxins in fish are a safety concern. Fish-oil supplements appear to have much lower levels of toxins than fish. In a study of 5 over-the-counter fish-oil preparations, levels of PCBs and organochlorines were below the detectable limit in all of the supplements.[27] Omega-3 fatty acids can be manufactured to eliminate toxins by using a process known as molecular distillation.

Hypothesized Mechanisms of the Cardiovascular Risk-Modulating Properties of Omega-3 Fatty Acids

The mechanisms underlying the cardiovascular risk-reducing properties of omega-3 fatty acids are not known. Omega-3 fatty acids reduce triglyceride levels, platelet adhesion, blood pressure levels, and inflammation, among other cardioprotective effects (Table 4).[2] Any one or all of these effects may contribute to their cardiovascular risk-reducing properties.

Among these mechanisms, the ability of omega-3 fatty acids to reduce triglycerides is best documented. On average, fish oils in the dose range of 3 to 9 g/day reduce fasting serum triglyceride levels by 20% to 30%. The effect of omega-3 fatty acids is dose-dependent and observed with fasting and postprandial triglyceride levels.[2] The triglyceride-reducing effects of omega-3 fatty acids are illustrated by the results of a double-blind, placebo-controlled study with Omacor (omega-3 acid ethyl esters; containing 44% EPA and 36% DHA; 2 g twice daily) administered for 24 weeks to patients with coronary heart disease and hypertriglyceridemia despite treatment with simvastatin.[28] The double-blind phase of the study was followed by an optional open-label extension during which patients could continue on Omacor for an additional 24 weeks. Serum triglyceride levels were reduced by 20% to 30% versus baseline in the group receiving Omacor at 3, 6, and 12 months. The decreases in triglyceride levels with Omacor during the double-blind phase of the study were significantly larger than those with a placebo.

On the basis of these and other data, the FDA approved Omacor as an adjunct to diet for reduction of triglyceride levels in adults with hypertriglyceridemia (≥500 mg/dL). Omacor is available solely by prescription. It is the only patented omega-3–derived pharmaceutical product approved by the FDA based on clinical studies demonstrating safety and efficacy in patients and the only product FDA approved to treat severe hypertriglyceridemia. Omacor reduced triglycerides by a median of 45% in patients with very high levels in controlled clinical trials.[29] The proprietary manufacturing process for Omacor yields very high concentrations of the active patented pharmaceutical ingredients for the treatment of hypertriglyceridemia and eliminates heavy metals and other environmental pollutants that can be found in other omega-3 products. Omacor provides clinicians with a prescription option for lowering triglycerides.

Recommendations for Omega-3 Fatty Acid Consumption

The American Heart Association and the third Adult Treatment Panel (ATP III) report of the National Cholesterol Education Program have considered recommendations for omega-3 fatty acid intake.[2,30] The American Heart Association recommends the consumption of at least 2 servings of fish weekly for primary prevention of coronary heart disease and the intake of approximately 1 g of EPA + DHA daily—the daily equivalent of approximately two to three 3-ounce servings of fish or several capsules of fish oils—for secondary prevention.[2] Because consumption of this amount of fish in secondary prevention is difficult for most individuals, dietary supplementation is generally needed and should be recommended. The dose in secondary prevention should be at least 875 mg of EPA + DHA per day. This dose can generally be obtained by taking 2 capsules of concentrated fish oils (at least 50% EPA + DHA) per day. For example, such a preparation would contain 500 mg of EPA + DHA per each 1000-mg fish-oil capsule. To minimize gastrointestinal symptoms, these capsules should be taken with food. Clinicians can review a list of independently

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tested supplements at ConsumerLab.com's Web site (www.consumerlab.com), which has tested dozens of commonly used fish oils for verification of fatty acid content and the presence of contaminants.

The ATP III guidelines, citing the need for additional studies on the effects of omega-3 fatty acids and the risk for coronary heart disease, do not currently recommend the consumption of omega-3 fatty acids as a cardiovascular risk-reduction strategy.[30] Recommendations for the intake of omega-3 fatty acids through dietary fish should be considered in the context of potential safety risks of toxins in fish. In view of the potential for exposure to toxins, the US Environmental Protection Agency recommends that pregnant women, nursing mothers, and women who may become pregnant limit the consumption of sport-caught fish to a 6-ounce serving per week; the FDA recommends that pregnant or nursing women and young children eliminate shark, swordfish, king mackerel, and tilefish from their diets and consume no more than 12 ounces per week of other fish.[2] More research is warranted to study the benefits and risks of fish consumption as a means of increasing omega-3 fatty acid intake in children and pregnant women.

CONCLUSIONS

Observational studies and randomized, controlled clinical trials generally support the benefits of omega-3 fatty acids in the primary and secondary prevention of coronary heart disease, although some studies have not shown a benefit. Further study is needed to define the optimum amount of omega-3 fatty acid intake for reducing cardiovascular risk and to elucidate the mechanisms of their cardioprotective effect. Future trials should also test whether fish-oil supplementation can reduce events in noncoronary heart disease populations, especially diabetics. Finally, clinical trials are needed to assess whether plant-based omega-3 fatty acids derived from flaxseed have similar cardioprotective effects. Supplement-derived omega-3 fatty acids may become an increasingly important component of cardiovascular risk-reduction strategies because toxins and other contaminants can be reduced or eliminated in supplements and higher daily doses can be administered than can feasibly be obtained in the diet.

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