CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will evaluate the benefit of dietary and supplemental omega-3 fatty acids

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What can we expect from omega-3 fatty acids?

ABSTRACT

Omega-3 fatty acids are abundant in fish oil. A high dietary intake of omega-3 fatty acids has been strongly linked to lower rates of cardiovascular disease in epidemiologic studies. Fish oil supplements lower triglyceride levels and may have other benefits such as preventing arrhythmias, reducing inflammation (although they have minimal impact on C-reactive protein), inhibiting platelet aggregation, and lowering blood pressure, all of which should reduce cardiovascular risk.

KEY POINTS

The American Heart Association recommends that healthy people consume fatty fish at least twice a week. The recommendation for people with coronary artery disease is 1 g of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) per day.

A formulation of EPA 465 mg plus DHA 375 mg is available by prescription and is approved for treating triglyceridemia in excess of 500 mg/dL. The dose is 2 to 4 capsules per day.

Experts generally believe that omega-3 fatty acids reduce arrhythmic events. Nevertheless, we lack clear evidence of their clinical effectiveness, and their use for such purposes is off-label.

Overall, omega-3 fatty acids have minimal side effects.

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Many patients are taking fish oil supplements, which contain omega-3 fatty acids, either on their own initiative or on their physician's advice. Driving this trend are accumulating data from observational and epidemiologic studies and clinical trials that these lipids actually reduce cardiovascular risk.

In the following article, we review available studies of omega-3 fatty acids in cardiovascular disease.

WHAT ARE OMEGA-3 FATTY ACIDS?

Omega-3 fatty acids are a class of polyunsaturated fatty acids. Their name means that they all have a double carbon-to-carbon bond in the third position from the omega (or methyl, or n) end of the fatty acid chain.

Most of the cardiovascular research on the omega-3 family has been on eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and alpha-linolenic acid (ALA). EPA and DHA are found primarily in fatty fish; ALA is abundant in flaxseed, walnuts, and soybeans.[1] The human body can convert small amounts of ALA into EPA and DHA: only about 5% of ALA is converted to EPA and less than 0.5% is converted to DHA. Currently, it is not known whether ALA is active itself or only via these metabolites. In this review, the term *omega-3 fatty acid* refers to EPA and DHA only.

GETTING ENOUGH FISH OIL

Healthy people should consume fish (preferably oily fish) at least twice a week, according to the American Heart Association.[1] However, not all fish contain the same amount of oil. Some, such as cod and catfish, contain only

TABLE 1

How much DHA and EPA do fish have?

FISH	EPA CONTENT (G/100 G)	DHA CONTENT (G/100 G)
Catfish (farmed)	0.049	0.128
Cod	0.004	0.154
Crab (Alaskan king)	0.295	0.118
Flounder	0.243	0.258
Halibut	0.091	0.374
Mackerel	0.504	0.699
Salmon (Atlantic)	0.690	1.457
Sea bass	0.206	0.556
Shrimp	0.171	0.144
Swordfish	0.138	0.681
Trout (rainbow)	0.334	0.820
Tuna (canned)	0.233	0.629
Tuna (fresh)	0.283	0.890

DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid

SOURCE: UNITED STATES DEPARTMENT OF AGRICULTURE. NUTRIENT DATA LABORATORY. WWW.NAL.USDA.GOV/FNIC/FOODCOMP/SEARCH.

Populations that consume diets rich in omega-3s have low rates of cardiovascular disease

0.2 g of EPA/DHA per 100-g serving; others, such as Atlantic salmon, contain about 10 times as much (TABLE 1).[2]

People with known coronary artery disease should take in 1 g of EPA/DHA per day, according to the American Heart Association.[1] This recommendation is based on clinical trials that found omega-3 fatty acids to have beneficial effects.

For most people with coronary artery disease, this means taking supplements. However, buyers need to carefully examine the label of over-the-counter fish oil supplements to see if they contain the recommended amounts of both DHA and EPA. Generic 1-g fish oil supplements may contain variable amounts of DHA and EPA, and some may have less than 300 mg.

People with hypertriglyceridemia. The US Food and Drug Administration (FDA) has approved Lovaza (formerly Omacor), which contains EPA/DHA in higher concentrations than over-the-counter preparations, for the treatment of hypertriglyceridemia in people with triglyceride levels higher than 500 mg/dL, along with a regimen of diet and regular exercise.[3] It is currently the only FDA-approved prescription form of omega-3 fatty acid ethyl esters. Each 1-g capsule contains 375 mg of DHA and 465 mg of EPA; the recommended dose is 2 to 4 g/day. To take in an equivalent amount of these substances with over-the counter-preparations, patients might have to take many capsules a day.

Safety of omega-3 fatty acids

Generally, omega-3 fatty acids are very well tolerated, and their adverse effects are limited to gastrointestinal complaints (discomfort, upset stomach) and a fishy odor. Common ways to prevent these effects are to freeze the capsules or take them at bedtime or with meals.

Mercury advisory on fish. Nursing or pregnant women should limit their consumption of certain fish, as some fish (but not fish oil) contain high levels of mercury. The highest levels of mercury are usually found in the larger, older predatory fish such as swordfish, tilefish, and mackerel, and the FDA advises women who are nursing or pregnant to avoid these fish completely. Tuna, red snapper, and orange roughy are lower in mercury, but nursing or pregnant women should still limit consumption of these fish to 12 oz per week.[4]

Theoretical risk of bleeding. In theory, high doses of omega-3 fatty acids may increase the bleeding time by inhibiting the arachidonic acid pathway. Clinically, this effect is minimal. In a trial in 511 patients undergoing coronary artery bypass grafting who were receiving aspirin or warfarin (Coumadin), the bleeding time and the number of bleeding episodes were no higher in those who were randomized to receive 4 g/day of omega-3 fatty acids daily than in a control group.[5]

Harris[6] reviewed 19 studies of omega-3 fatty acids in patients undergoing coronary artery bypass grafting, carotid endarterectomy, or femoral artery catheterization, and none of the studies found a significantly increased risk of bleeding.

HOW DO OMEGA-3 FATTY ACIDS REDUCE RISK?

After epidemiologic studies found that Greenland Eskimos (who consume diets rich in

omega-3 fatty acids) have low rates of cardiovascular disease,[7] omega-3 fatty acids were hypothesized to reduce cardiovascular risk. Over the past 3 decades, their potential benefit in lowering lipid levels, blood pressure, and the risk of death in patients with known heart disease has been widely researched.

Lower triglyceride levels

The growing problem of obesity in the United States has led to more patients presenting with hypertriglyceridemia, a risk factor for coronary heart disease.

In 2001, the National Cholesterol Education Program's third Adult Treatment Panel (ATP III)[8] redefined normal triglyceride levels as less than 150 mg/dL; previously, normal was defined as less than 200 mg/dL. For people with borderline-high triglyceride levels (150–200 mg/dL), the ATP III recommends focusing on lowering the level of low-density lipoprotein cholesterol (LDL-C). For those with high to very high triglyceride levels (> 500 mg/dL), the current treatment options are niacin, fibrates, and omega-3 fatty acids.

Hypertriglyceridemia is thought to increase the risk of coronary heart disease by two mechanisms. First, and more important, triglyceride-rich lipoproteins such as very-low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL) are thought to be atherogenic. Secondly, triglyceride-lipoprotein metabolism involves competition with high-density lipoprotein (HDL), leading to a decrease in HDL production and to denser LDL particles.[9]

How omega-3 fatty acids lower triglyceride levels has been inferred from preclinical studies. One mechanism, seen in animal studies, is by decreasing hepatic synthesis and secretion of VLDL particles by inhibiting various enzyme transcription factors. Another proposed mechanism is that EPA and DHA increase the activity of lipoprotein lipase, leading to an increase in chylomicron clearance.[10] This was validated by Khan et al,[11] who showed that lipoprotein lipase activity increased in patients who received omega-3 fatty acids 3 g/day for 6 weeks.

How much do they lower triglycerides? Data from the makers of Lovaza[3] indicate that in a patient population with a mean baseline triglyceride level of 816 mg/dL, 4 g/day of omega-3 fatty acids lowered triglyceride levels to 488 mg/dL, a 45% reduction ($P < .0001$). In addition, HDL cholesterol (HDL-C) levels increased by 9%.

The higher the dose and the higher the baseline triglyceride level, the greater the effect. Balk et al[12] performed a meta-analysis of 25 randomized trials and calculated that each 1-g increase in fish oil dose per day lowered the triglyceride level by about 8 mg/dL. However, patients with high baseline triglyceride levels had more dramatic reduction of triglycerides with fish oil. The average reduction in triglyceride levels was 27 mg/dL, accompanied by an increase in HDL-C of 1.6 mg/dL, an increase in LDL-C of 6 mg/dL, and no change in total cholesterol levels.

Pownall et al[13] report that, in 19 patients with hypertriglyceridemia (median baseline level 801 mg/dL), omega-3 fatty acids 4 g/day reduced triglyceride levels to 512 mg/dL, a 38.9% change ($P = .001$). In 21 patients receiving placebo, triglyceride levels decreased by 7.8% ($P = .001$ compared with active therapy). The effect on HDL-C was minimal, but the median LDL-C level increased by 16.7% (from 43 to 53 mg/dL, $P = .007$) with fish oil therapy.

The ATP III guidelines redefined a normal triglyceride level as < 150 mg/dL

Fish oil plus a statin may have advantages

Most patients seen in clinical practice present with mixed dyslipidemias. The current ATP III guidelines aim for stricter triglyceride and LDL-C targets than in the past, which monotherapy alone may not be able to achieve.

Statin therapy by itself effectively lowers LDL-C but has modest effects on triglycerides. Omega-3 fatty acids effectively reduce triglycerides but have been known to increase LDL-C levels. This net LDL-C increase averaged around 10 mg/dL as reported in a review by Harris et al,[14] and 6 mg/dL as reported by Balk et al.[12] However, despite the net effect of an increase in LDL-C, it is hypothesized that the larger LDL particles produced by omega-3 fatty acid treatment may be less atherogenic.[15]

The effectiveness of combined therapy in reducing triglycerides has been widely studied.

Chan et al,[16] in a randomized, placebo-controlled trial, looked at the effectiveness of atorvastatin (Lipitor) and EPA/DHA. Fifty-

TABLE 2

Does adding fish oil to a statin reduce coronary events? The Japan EPA Lipid Intervention Study (JELIS)

EVENT	STATIN-ONLY GROUP (N = 9,319)	EPA/STATIN GROUP (N = 9,326)	P VALUE
Major coronary events	324 (3.5%)	262 (2.8%)	.011
Sudden cardiac death	17 (0.2%)	18 (0.2%)	.854
Fatal myocardial infarction	14 (0.2%)	11 (0.1%)	.557
Nonfatal myocardial infarction	83 (0.9%)	62 (0.7%)	.086
Unstable angina	193 (2.1%)	147 (1.6%)	.014
Coronary artery bypass grafting/ percutaneous coronary intervention	222 (2.4%)	191 (2.1%)	.135
Death from any cause	265 (2.8%)	286 (3.1%)	.333

ADAPTED FROM YOKOYAMA M, ORIGASA H, MATSUZAKI M, ET AL; JAPAN EPA LIPID INTERVENTION STUDY (JELIS) INVESTIGATORS. EFFECTS OF EICOSAPENTAENOIC ACID ON MAJOR CORONARY EVENTS IN HYPERCHOLESTEROLAEMIC PATIENTS (JELIS): A RANDOMISED OPEN-LABEL, BLINDED ENDPOINT ANALYSIS. LANCET 2007; 369:1090–1098, WITH PERMISSION FROM ELSEVIER, WWW.ELSEVIER.COM.

two obese men were randomized to receive atorvastatin 40 mg/day, EPA/DHA 4 g/day, both in combination, or placebo. After 6 weeks, triglyceride levels had decreased by 26% from baseline in the atorvastatin group, 25% in the EPA/DHA group, and 40% in the combination therapy group ($P = .002$). LDL-C levels decreased to a similar degree with either atorvastatin monotherapy or combination therapy. Similar studies show similar results.

Combination therapy may also lower the rate of major coronary events (see below).

The higher the dose and the higher the baseline triglyceride level, the greater the effect

The Japan EPA Lipid Intervention Study (JELIS)[17] randomized more than 18,000 patients to receive either a statin alone or a statin plus EPA 1,800 mg daily, in an open-label fashion. The statins used were pravastatin (Pravachol) 10 mg daily or simvastatin (Zocor) 5 mg daily; if hypercholesterolemia remained uncontrolled, these doses were doubled. The patients were 5,859 men and 12,786 postmenopausal women (mean age 61) with or without coronary artery disease who had total cholesterol levels of 251 mg/dL or greater. The mean baseline LDL-C level was 180 mg/dL. People who had had an acute myocardial infarction in the past 6 months or unstable angina were excluded. The primary end point examined was any major coronary event, defined as sudden death, fatal or nonfatal myocardial infarction, unstable angina, angioplasty, or coronary artery bypass grafting.

After 5 years, patients with a history of coronary artery disease had a 19% lower rate of major coronary events in the EPA group than in the control group ($P = .011$). There was no significant difference between the two groups in the rates of sudden cardiac death, fatal myocardial infarction, nonfatal myocardial infarction, coronary artery bypass grafting, or percutaneous coronary interventions (TABLE 2).

The JELIS trial showed that combination therapy may reduce the risk of coronary events, the aim of treating dyslipidemia. It was the largest randomized trial to date comparing statin use alone and in combination with omega-3 fatty acids. However, it was performed in Japan, where people already have a high intake of fatty fish, and the results may not be applicable to other countries.

May prevent arrhythmias

The *Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Prevenzione* (GISSI-Prevention) trial[18] was the largest randomized trial to date of fish oil therapy as secondary prevention. In this trial, 11,323 patients who had had a myocardial infarction less than 3 months before enrollment were randomized to receive either EPA/DHA 850 mg daily, vitamin E, both, or no treatment. The primary end points were death from

TABLE 3

Does fish oil prevent ventricular arrhythmias in patients with an implanted cardioverter-defibrillator?

STUDY	STUDY SIZE AND FOLLOW-UP	DOSE	EVENT RATE (FISH OIL GROUP)	EVENT RATE (CONTROL GROUP)	P VALUE
Raitt et al[21]	200 patients, 24 months	1.8 g/day	65%	59%	.19
Leaf et al[22]	402 patients, 12 months	4 g/day	28%	39%	.057
Brouwer et al[23]	500 patients, 12 months	2 g/day	30%	33%	.33

any cause, nonfatal myocardial infarction, and nonfatal stroke.

At 3 months, 63 (1.1%) of the patients in the EPA/DHA group had died, compared with 88 (1.6%) of those in the no-treatment group, for a relative risk of 0.59 (P = .037), and the benefit persisted for the duration of the study. However, the difference between the groups in the rates of nonfatal myocardial infarction did not reach statistical significance. Vitamin E seemed to have no effect.

EPA/DHA is thought to have prevented deaths in this study, not by reversing atherosclerosis, but rather by suppressing arrhythmias and inflammation. In support of this theory, Getz and Reardon[19] noted that in GISSI the treatment showed its maximal benefit on the incidence of sudden death by 9 months, whereas statin treatment takes 1 to 2 years to reach its maximal effect. This point suggests that the role of omega-3 fatty acids in secondary prevention will be different from that of statins.

Extensive clinical studies have looked at the possibility of using omega-3 fatty acids as part of the treatment for reducing arrhythmic events. Several animal and human studies have shown that these drugs reduce the incidence of sudden death and ventricular fibrillation.[20]

Omega-3 fatty acids are thought to prevent arrhythmias by stabilizing the myocardial membrane through interaction with voltage-gated sodium and L-type calcium channels. During an ischemic event, the affected heart cells allow potassium ions to escape. Since potassium ions carry a positive charge, the resting membrane potential (ie, the difference in electrical charge between the inside and outside of the cell) is increased, lowering the threshold for initiating an action potential through sodium channels and increasing the risk of fatal arrhythmias. It is hypothesized that omega-3 fatty acids inhibit sodium channels by being incorporated into the membrane phospholipid bilayer, increasing its fluidity and thereby affecting the sodium channel. This reduces membrane excitability and arrhythmic potential.[20]

Omega-3s lower triglycerides but may raise LDL-C by 10%

This premise was examined in three large randomized clinical trials specifically looking at ventricular arrhythmias in patients with an implanted cardioverter-defibrillator (ICD).[21–23] The results were mixed.

Raitt and associates[21] found that patients who recently received an ICD had higher rates of ventricular tachycardia and fibrillation if they received EPA/DHA than if they received placebo, 65% vs 59% (P = .07). In contrast, Leaf et al[22] reported a lower rate of ventricular arrhythmias with EPA/DHA than with placebo, 28% vs 39%. Brouwer et al[23] reported similar results, with rates of 30% vs 33% (**TABLE 3**). The difference in the results of these studies could be explained by differences in baseline fish consumption, the underlying causes of ventricular arrhythmia, and the programming thresholds of the ICDs in these studies.[24]

In another study, Calo and colleagues[25] randomized 160 patients to receive omega-3 fatty

acids 2 g per day or placebo starting at least 5 days before elective coronary artery bypass surgery and continuing until discharge. The primary end point measured was the development of atrial fibrillation after surgery. The incidence of atrial fibrillation in the omega-3 fatty acid group was 15.2%, compared with 33% in the control group ($P = .013$).

Despite the differences in the results of these studies, experts generally believe that these agents reduce arrhythmic events. Nevertheless, we lack clear evidence of their clinical effectiveness, and their use for such purposes is off-label.

May reduce inflammation and platelet aggregation

Arachidonic acid is an omega-6 fatty acid that is metabolized into prostaglandins, leukotrienes, and thromboxanes, which are important for cell function. Many of these by-products (eg, leukotriene B4) have inflammatory effects, and others (eg, prostaglandin I2 E2) promote arrhythmias. EPA and DHA competitively inhibit the arachidonic acid cascade, leading to different by-products that promote vasodilation and inhibit platelet aggregation, among other effects.[26] The impact of this effect in clinical practice is still unclear.

In the GISSI-Prevention trial, EPA/DHA lowered the risk of death after MI

The evidence still conflicts as to whether omega-3 fatty acids reduce markers of inflammation such as C-reactive protein (CRP). Balk et al,[12] in their meta-analysis, looked for studies that examined the effect of these agents on CRP and cardiovascular disease (either known risk factors or coronary artery disease). They excluded studies that were less than 4 weeks in duration, did not specify the dose of fish oil, or used doses higher than 6 g/day. Four trials were found that met their criteria, with dosages of omega-3 fatty acids ranging from 1.6 g/day to 5.9 g/day and from 12 to 20 patients in each study. Although baseline CRP levels in these studies varied, the net change in CRP was minimal, ranging from –0.15 to +1.7 mg/L.

May stabilize plaque

Thies et al[27] randomized 188 patients to receive fish oil supplements before carotid endarterectomy. They found that the carotid plaque of patients who received the supplements had higher levels of EPA and DHA and had thicker fibrous caps and fewer signs of inflammation (eg, macrophages) compared with a control group and a group that received sunflower oil.

These findings show that omega-3 fatty acids are readily incorporated into atheromatous plaque and can help stabilize it. An inference from this study is that fish oil could also play a role in stabilizing coronary artery plaque.

No effect on restenosis

These agents, however, have no effect on restenosis rates after coronary angioplasty, as restenosis is mediated less by plaque formation than by intimal hyperplasia and negative remodeling within the endothelium. Even at high doses of 5 mg/day before angioplasty, omega-3 fatty acids failed to reduce the incidence of restenosis at 6 months.[28]

Modest effect on blood pressure

Omega-3 fatty acids are incorporated into the phospholipid bilayer of the endothelial membrane, increasing its fluidity and promoting vasodilation via an increase in nitric oxide production. These effects suggest they could be used to help control blood pressure, but studies have shown this effect to be minimal.

In a meta-analysis of 36 trials, Geleijnse et al[29] estimated the reduction in blood pressure to be 2.1 mm Hg systolic and 1.6 mm Hg diastolic. The median intake of fish oil was 3.7 g/day. The largest reductions were in patients with known hypertension and those over age 45.

These findings seem consistent with the hypothesis that omega-3 fatty acids affect the endothelium, given that the arterial wall tends to become stiffer with age. Overall, however, the results of a number of studies show that fish oil supplementation is of limited clinical use in lowering blood pressure.

Confounding factors among studies

The variability in the results of different studies may be due to confounding factors such as the patients' baseline diet, the doses of EPA and DHA given, the duration of treatment, and patient compliance. These factors must be considered when examining evidence supporting the use of omega-3 fatty acids. ■

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