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AHA Scientific Statement

Fish Consumption, Fish Oil, Omega-3 Fatty Acids, and Cardiovascular Disease

Penny M. Kris-Etherton, PhD, RD; William S. Harris, PhD; Lawrence J. Appel, MD, MPH; for the Nutrition Committee

Since the first AHA Science Advisory "Fish Consumption, Fish Oil, Lipids, and Coronary Heart Disease,"[1] important new findings, including evidence from randomized controlled trials (RCTs), have been reported about the beneficial effects of omega-3 (or n-3) fatty acids on cardiovascular disease (CVD) in patients with preexisting CVD as well as in healthy individuals.[2] New information about how omega-3 fatty acids affect cardiac function (including antiarrhythmic effects), hemodynamics (cardiac mechanics), and arterial endothelial function have helped clarify potential mechanisms of action. The present Statement will address distinctions between plant-derived (α-linolenic acid, C18:3n-3) and marine-derived (eicosapentaenoic acid, C20:5n-3 [EPA] and docosahexaenoic acid, C22:6n-3 [DHA]) omega-3 fatty acids. (Unless otherwise noted, the term *omega-3 fatty acids* will refer to the latter.) Evidence from epidemiological studies and RCTs will be reviewed, and recommendations reflecting the current state of knowledge will be made with regard to both fish consumption and omega-3 fatty acid (plant- and marine-derived) supplementation. This will be done in the context of recent guidance issued by the US Environmental Protection Agency and the Food and Drug Administration (FDA) about the presence of environmental contaminants in certain species of fish.

Epidemiological and Observational Studies

Coronary Heart Disease

As reviewed by Stone,[1] three prospective epidemiological studies within populations reported that men who ate at least some fish weekly had a lower coronary heart disease (CHD) mortality rate than that of men who ate none.[3–6] More recent evidence that fish consumption favorably affects CHD mortality, especially nonsudden death from myocardial infarction (MI), has been reported in a 30-year follow-up of the Chicago Western Electric Study.[7] Men who consumed 35 g or more of fish daily compared with those who consumed none had a relative risk of death from CHD of 0.62 and a relative risk of nonsudden death from MI of 0.33. In an ecological study conducted by Zhang et al,[8] fish consumption was associated with a reduced risk from all-cause, ischemic heart disease and stroke mortality across 36 countries. In addition, in a study of Japanese living in Japan or Brazil, Mizushima et al[9] reported a dose-response relationship between the frequency of weekly fish intake and reduced CVD risk factors (eg, obesity, hypertension, glycohemoglobin, ST-T segment change on the ECG). Until recently, little information was available about the effects of fish and omega-3 fatty acids and risk of CHD in women. A recent study conducted with women in the Nurses' Health Study[10] reported an inverse association between fish intake and omega-3 fatty acids and CHD death. Compared with women who rarely ate fish (less than once per month), the risk for CHD death was 21%, 29%, 31%, and 34% lower for fish consumption 1 to 3 times per month, once per week, 2 to 4 times per week, and >5 times per week, respectively (P for trend=0.001). Comparing the extreme quintiles of fish intake, the reduction in risk for CHD deaths seemed to be stronger for CHD death than for nonfatal MI (RR 0.55 versus 0.73).

Some studies have not reported a beneficial association of fish consumption and CHD mortality. In the Health Professionals' Follow-up Study,[11] no significant association was observed between fish intake (and omega-3 fatty acids) and risk of any CHD (ie, fatal coronary disease including sudden death, nonfatal MI, coronary artery bypass grafting, or angioplasty). Likewise, the US Physicians' Health Study did not show an association between fish consumption (or omega-3 fatty acid intake) and reduced risk of total MI, nonsudden cardiac death, or total cardiovascular mortality.[12] In contrast, however, fish consumption was related to a reduced risk of total mortality. The lack of an association between fish intake and CHD incidence and mortality also was reported from an analysis of the Seven Countries data and the EURAMIC (European Multicenter Case-Control Study on Antioxidants, Myocardial Infarction and Breast Cancer) Study.[13,14] In the

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Seven Countries Study, although an inverse association between fish consumption and 25-year mortality from CHD across several populations was observed,[13] when the confounding effects of saturated fatty acids, flavonoids, and smoking were considered, the association was not significant. In the EURAMIC Study, a large international case-control study, no evidence of a protective effect of adipose tissue DHA (a measure of long-term fish consumption) on the risk of developing MI was seen.[14]

Some investigators have speculated that the conflicting data from the epidemiological studies reflect differences in definitions of sudden death and the residual confounding of reference groups that had a less healthy lifestyle,[15] variability in the end points studied, experimental design or how fish intake was estimated, different study populations,[16] and the possible confounding effect of an increase in hemorrhagic stroke. Albert et al[12] proposed that their lack of an association may have been due to the small fraction of their study population (3.1%) reporting little to no fish consumption. Only studies including sizable non–fish-eating populations have reported an inverse association between fish consumption and coronary mortality. In the EURAMIC Study, only survivors of MI were evaluated, and it is conceivable that individuals who did not survive ate less fish. Another explanation, based on a rigorous analysis of 11 prospective cohort studies, is that the protective effect of fish consumption relates to the CHD risk status of the population studied[17]; this analysis concluded that fish consumption reduced CHD mortality (RR=0.4 to 0.6) in high-risk but not low-risk populations. Another consideration relates to the type of fish consumed (ie, fatty versus lean fish). Oomen et al[18] reported a lower CHD mortality (RR=0.66) in populations that consumed fatty fish but not lean fish.

Finally, another explanation for the discordant results of epidemiological studies pertains to the hypothesized adverse effects of methylmercury, an environmental contaminant found in certain fish that may diminish the health benefits of omega-3 fatty acids.[19] Recent studies have produced conflicting results with regard to the effects of methylmercury on CHD risk.[20,21] Thus, the extent to which methylmercury in fish may mask the beneficial effects of omega-3 fatty acids requires further study.

Fish consumption has been shown to be related to reduced sudden cardiac death. In a population-based, nested, case-control study, a strong negative relationship was reported between fish intake and risk for sudden death (ie, 5.5 g of omega-3 fatty acids per month, equivalent to two fatty fish meals per week, was associated with a 50% reduced risk of primary cardiac arrest).[22] In the US Physicians' Health Study, men who consumed fish at least once weekly had a relative risk of sudden death of 0.48 (P=0.04) versus men who consumed fish less than once per month.[12] A recent report from the Physicians' Health Study[23] reported an inverse relationship between blood levels of long-chain omega-3 fatty acids and risk of sudden death in men without a history of CVD. The relative risk of sudden death was significantly lower among men with levels in the third quartile (RR=0.28) and the fourth quartile (RR=0.19) compared with men whose blood levels were in the first quartile.

Further evidence for a protective effect of omega-3 fatty acids comes from two recent studies by Landmark et al[24,25] who reported that chronic intake of fish or fish oil was associated with a reduction in infarct size as estimated by the frequency of Q-wave infarcts and by peak creatine kinase and lactate dehydrogenase activities after MI. In contrast to all the studies demonstrating a beneficial association, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study found that estimated omega-3 fatty acid intake from fish was associated with a trend toward increased relative risk of coronary death after adjustment for trans, saturated, and cis-monounsaturated fatty acids.[26]

A growing body of evidence from recent epidemiological studies indicates that α-linolenic acid is associated with a lower risk of MI and fatal ischemic heart disease in women and in men. In the EURAMIC Study, Guallar et al[14] compared the highest quintile of adipose tissue α-linolenic acid to the lowest and found a relative risk for MI of 0.42 (P for trend=0.02). This became nonsignificant after adjusting for classic risk factors (primarily smoking). Using a food-frequency questionnaire from a 10-year follow-up of the Nurses' Health Study, and after controlling for standard coronary risk factors, Hu et al[27] reported a dose-response relationship between α-linolenic acid intake and relative risk of fatal ischemic heart disease, which was reduced by 45% in the highest quintile (P for trend=0.01). Similar findings were reported with the same methodology in the all-male Health Professionals' Study, in which a 1% increase in α-linolenic acid intake was associated with a 0.41 relative risk for acute MI (P for trend=0.01).[28] Lowest-quintile intakes of α-linolenic acid in these latter two trials were 0.7 to 0.8 g/d, and highest quintile intakes, 1.4 to 1.5 g/d. In the National Heart, Lung, and Blood Institute Family Heart Study, a cross-sectional study with 4584 participants, α-linolenic acid was inversely related to coronary artery disease.[29] The prevalence odds ratio of coronary artery disease was reduced ≈40% for men in the top three quintiles of α-linolenic acid intake and ≈50% to 70% for women. In contrast, in the Zutphen Elderly Study, a prospective epidemiological study with 667 men, ages 64 to 84 years, there was no beneficial effect of α-linolenic acid intake on risk of 10-year coronary artery disease incidence.[30] In the latter study, however, these negative results have been explained by the association between α-linolenic acid and trans-fatty acid intake,[30] as well as by limitations in the collection of the dietary data.[31] Despite this latter study, a growing epidemiological database demonstrates a protective effect of α-linolenic acid on coronary disease. Nonetheless, intervention studies are needed to establish a causal relationship between α-linolenic acid intake and coronary disease.

Stroke

Compared with the literature describing the effects of omega-3 fatty acids on CHD, relatively little information about the association of omega-3 fatty acids and cerebral infarctions (stroke) is available. Several epidemiological studies have examined the relationship between fish intake and stroke incidence. In the Zutphen Study, the unadjusted hazard ratio of men who consumed an average of 20 g/d of

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fish was 0.49 ($P<0.05$) compared with those who consumed less.[32] Likewise, in the National Health and Nutrition Examination Survey (NHANES) Epidemiologic Follow-up Study, white females who consumed fish more than once per week had an age-adjusted stroke incidence that was only half that of women who reported not consuming fish.[33] A similar protective effect was seen in both black women and men but not in white men. A trend ($P=0.06$) toward reduced risk for stroke with increasing reported fish consumption was also reported in the Nurses' Health Study.[34] In contrast, both the Chicago Western Electric Study[35] and the Physicians' Health Study[36] failed to find any relationship between reported fish intake and reduced stroke risk.

According to the serum fatty acid profiles of subjects in the Multiple Risk Factor Intervention Trial, α-linolenic acid was negatively associated with stroke incidence.[37] In both the Lyon Diet Heart Study[38] (testing a Mediterranean-style diet enriched with α-linolenic acid) and the GISSI-Prevention Study[39] (testing the effects of 850 mg of supplemental omega-3 fatty acids), there was no significant effect on the incidence of stroke.

The evidence to date is primarily for total stroke risk, and associations could differ if the data were analyzed for type-specific stroke incidence. For example, evidence exists for an inverse relationship between small intakes of fish (1 portion per week) and ischemic stroke[32] and for a possible increased risk for hemorrhagic stroke with "Eskimo" intakes of omega-3 fatty acids.[40] Thus, as Zhang et al[8] have noted, linking fish consumption with total stroke risk is likely to underestimate the strength of the real associations between fish consumption and type-specific stroke risk.

Randomized Controlled Trials

At the time of the first Advisory, the only RCT of omega-3 fatty acids in secondary prevention of CHD was the Diet And Reinfarction Trial (DART), which reported a 29% reduction in all-cause mortality over a 2-year period in male MI survivors advised to increase their intake of oily fish (200 to 400 g of fatty fish per week, which provided an additional 500 to 800 mg/d of omega-3 fatty acids).[41] The greatest benefit was seen in fatal MIs, and this observation led to the hypothesis that omega-3 fatty acids might protect the myocardium against the adverse sequela of acute ischemic stress. A post hoc analysis of patients receiving fish oil capsules (900 mg/d of EPA+DHA) in DART suggested that the protective effect was attributable to omega-3 fatty acids.[42]

The first of three recent RCTs designed to detect the effects of supplemental EPA and DHA on clinical events was reported by Singh et al.[43] Patients admitted to the hospital with suspected acute MIs were randomized to either fish oil capsules (containing 1.8 g/d of EPA+DHA), mustard oil (20 g/d providing 2.9 g α-linolenic acid), or placebo. After one year, total cardiac events were 25% and 28% in the fish oil and mustard oil groups, respectively, versus 35% in the placebo group ($P<0.01$). As in the DART, nonfatal MIs were significantly lower in the fish oil and mustard oil groups.

The largest prospective RCT to test the efficacy of omega-3 fatty acids for secondary prevention of CHD is the GISSI-Prevention Study.[39] In this study, 11 324 patients with preexisting CHD (who were receiving conventional cardiac pharmacotherapy) were randomized to either 300 mg of vitamin E, 850 mg of omega-3 fatty acid ethyl esters (as EPA and DHA), both, or neither. After 3.5 years of follow-up, the group given the omega-3 fatty acids alone experienced a 15% reduction in the primary end point of death, nonfatal MI, and nonfatal stroke ($P<0.02$). There was a 20% reduction in all-cause mortality ($P=0.01$) and a 45% reduction in sudden death ($P<0.001$) compared with the control group; vitamin E provided no additional benefit. Triglycerides decreased by 4% and LDL cholesterol levels increased by 2.5% after six months in the omega-3 fatty acid treatment groups compared with controls. This trial, although very large and carried out in a relatively "usual-care" setting, was not placebo controlled, and dropout rates were high (>25%). A follow-up study[44] assessed the time-course of the benefit of omega-3 fatty acids on mortality in subjects in the GISSI Study and found that survival curves diverged early after randomization. Total mortality was significantly lowered after 3 months of treatment (RR=0.59), and by 4 months, risk of sudden death was reduced (RR=0.47).

In contrast to the growing body of evidence supporting a protective effect of omega-3 fatty acids in secondary prevention, a recent study reported no effect of 3.5 g/d of DHA+EPA versus corn oil on cardiac events in post-MI patients (n=300) after 1.5 years of intervention.[45] The authors speculated that the lack of an omega-3 fatty acid effect may have been due to the high habitual fish intake in western Norway, which could have afforded maximal protection beyond which no additional effects would be expected. Thus, further research is needed to confirm and further define the role of omega-3 fatty acid supplements for secondary prevention of coronary disease.

The first study to explore the effects of omega-3 fatty acids on angiographic progression rates provided 59 patients either 6 g/d of omega-3 fatty acids or olive oil for 2 years.[46] No benefit was observed. More recently, a larger trial using lower and more practical intakes of omega-3 fatty acids has been reported.[47] Patients presenting for coronary angiography (n=223) were randomized to either placebo or omega-3 fatty acids (3 g/d for 3 months followed by 1.5 g/d for 21 months). The latter group exhibited significantly ($P=0.04$) less progression, more regression, and a trend toward fewer clinical events (7 versus 2, $P=0.1$). Finally, Eritsland et al[48] reported that in 610 patients undergoing coronary artery bypass grafting, the provision of 3.4 g of omega-3 fatty acid ethyl esters lowered vein graft occlusion rates from 33% (control) to 27% ($P=0.03$).

Several randomized trials of fish oil were conducted over the past 10 years to test the hypothesis that omega-3 fatty acids could prevent restenosis after percutaneous transluminal coronary angioplasty. Although a meta-analysis of seven early trials concluded that supplementation was beneficial,[49] more recent trials (with large study populations given 5 to 7 g/d of omega-3 fatty acids) have not supported this conclusion.[50,51] Most investigators have concluded that further trials are not warranted.

The question of the efficacy of α-linolenic acid in CHD prevention has been examined in four trials. The Indian

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Experiment of Infarct Survival[43] discussed above reported a significant decrease in total cardiac events in the group assigned to mustard seed oil. The Lyon Heart Trial was a secondary prevention trial designed to test whether a Mediterranean-type diet (including increased amounts of α-linolenic acid) would reduce reoccurrence rates of cardiac events compared with a prudent Western diet.[38,52] Marked reductions were seen in cardiac death and nonfatal MI, major secondary end points, and minor events. The difference in intakes of α-linolenic acid between groups was 0.5 versus 1.5 g/d. It is impossible, however, to ascribe the benefit unambiguously to α-linolenic acid because many other dietary variables were present: Saturated fat and cholesterol decreased and monounsaturated fat increased, as did the consumption of fruits and vegetables.

Although the Indian Experiment of Infarct Survival[43] and the Lyon Heart Trial[38] provide clinical trial evidence in support of a beneficial effect of α-linolenic acid, the Norwegian Vegetable Oil Experiment[53] and the Mediterranean Alpha-Linolenic Enriched Groningen Dietary Intervention (MARGARIN) Study[54] do not. The Norwegian Vegetable Oil Experiment was a double-blind RCT in which >13 000 men ages 50 to 59 with no history of MI were randomized to consume 5.5 g/d of α-linolenic acid (from 10 mL of linseed oil) or 10 mL of sunflower seed oil for one year. There were 27 cases of new CHD or sudden death in each group, and 40 versus 43 deaths from any cause in the control versus the linseed oil groups. In the MARGARIN Study, free-living subjects (n=124 men and 158 women) with multiple CVD risk factors were provided with margarines high in either α-linolenic acid or linoleic acid and followed up for 2 years.[54] According to effects on CVD risk factors, the 10-year estimated ischemic heart disease risk decreased similarly in both groups (2.1% and 2.5%, respectively). Of note, however, was a trend toward fewer CVD events in the α-linolenic acid group (1.8% versus 5.7%, $P=0.20$). It is important that additional studies be conducted to clarify the role of α-linolenic acid in reducing CHD risk.

In aggregate, available RCTs show a beneficial effect of dietary and supplemental omega-3 fatty acids, including both EPA+DHA and α-linolenic acid, on CHD. This has been summarized in a recent meta-analysis of 11 RCTs with 7951 patients in the intervention groups.[55] In this meta-analysis, the risk ratio of nonfatal MI was 0.8, for fatal MI it was 0.7, and for sudden death (in 5 trials) it was 0.7.

Possible Mechanisms

The mechanisms responsible for the observed effects of omega-3 fatty acids on cardiovascular health are not known with confidence, especially at the low intakes utilized in the DART and GISSI Prevention Study. Those possibly involved are summarized in Table 1.[56]

TABLE 1. Potential Mechanisms by Which Omega-3 Fatty Acids May Reduce Risk for Cardiovascular Disease

Reduce susceptibility of the heart to ventricular arrhythmia
Antithrombogenic
Hypotriglyceridemic (fasting and postprandial)
Retard growth of atherosclerotic plaque
Reduce adhesion molecule expression
Reduce platelet-derived growth factor
Antiinflammatory
Promote nitric oxide-induced endothelial relaxation
Mildly hypotensive

Adapted from Connor.[56]

Triglycerides

The hypotriglyceridemic effects of omega-3 fatty acids from fish oils are well established. In a comprehensive review of human studies, Harris[57] reported that ≈4 g/d of omega-3 fatty acids from fish oil decreased serum triglyceride concentrations by 25% to 30%, with accompanying increases in LDL cholesterol of 5% to 10% and in HDL cholesterol of 1% to 3%. A dose-response relationship exists between omega-3 fatty acid intake and triglyceride lowering.[57] Postprandial triglyceridemia is especially sensitive to chronic omega-3 fatty acid consumption,[58,59] with quite small intakes (<2 g/d) producing significant reductions.[60] The plasma lipid and lipoprotein responses to fish oil are comparable in diabetic and nondiabetic subjects.[61] In addition, a recent meta-analysis of 26 trials of subjects with type 1 or type 2 diabetes mellitus reported no effects of fish oil on hemoglobin A_{1c},[62] although fasting blood glucose levels rose slightly in the latter group.

Fish oil can have a therapeutic role in the treatment of marked hypertriglyceridemia (>750 mg/dL). Effective doses of omega-3 fatty acids range from 3 to 5 g/d, which can only be obtained consistently by supplementation. At present, it seems that both EPA and DHA have triglyceride-lowering properties.[63] Patients taking >3 g of EPA+DHA from supplements should do so only under a physician's care because the FDA has noted that an intake in excess of this level could result in excessive bleeding in some individuals.[64] In contrast, cardioprotective intakes seem to be considerably lower (≈1 g/d), have almost no potential for adverse effects, and can be achieved by diet.

Blood Pressure

Omega-3 fatty acids seem to have a small, dose-dependent, hypotensive effect, the extent of which seems to be dependent on the degree of hypertension.[65] In a meta-analysis, Morris et al[66] found a significant reduction in blood pressure of −3.4/−2.0 mm Hg in studies with hypertensive subjects who consumed 5.6 g/d of omega-3 fatty acids. Likewise, Appel et al[67] found that blood pressure was decreased −5.5/−3.5 mm Hg in trials of untreated hypertensives given >3 g/d of omega-3 fatty acids. DHA seems to be more effective than EPA in lowering blood pressure.[68] Still, in view of the high dose required to lower blood pressure and the proven efficacy of other nutritional factors and of antihypertensive medications, an increased intake of omega-3 fatty acids has a limited role in the management of hypertension.

Thrombosis and Hemostasis

Omega-3 fatty acids decrease platelet aggregation,[69,70] resulting in a modest prolongation of bleeding times (reviewed by Knapp[71]). Some evidence indicates that fish oil supplemen-

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tation may enhance fibrinolysis.[72] Although omega-3 fatty acid intake has been negatively associated with levels of fibrinogen, Factor VIII, and von Willebrand factor,[73] more recent evidence from the Coronary Artery Risk Development In young Adults (CARDIA) study found no significant associations between customary intakes of fish (4 to 39 g/d) and omega-3 fatty acids (0.9 to 4.1 g/d) and these coagulation factors.[74] Marckmann et al[75] also found no effect of omega-3 fatty acids (0.9 g/d) on levels of Factor VII, fibrinogen, endogenous fibrinolysis, β-thromboglobulin, and von Willebrand factor. In contrast, a recent study reported that coronary patients taking 5.1 g/d of omega-3 fatty acids for 6 months experienced a reduction in von Willebrand factor (128% versus 147% for controls) and thrombomodulin (25 versus 33 ng/mL).[76] Although it seems clear that omega-3 fatty acids beneficially influence collagen-induced platelet aggregation (thereby affecting hemostasis), their effects on thrombosis remain unclear. There is little evidence to suggest that an intake <3 g/d of omega-3 fatty acids would cause clinically significant bleeding.

Arrhythmias

The possibility that omega-3 fatty acids (including α-linolenic acid) may reduce risk for sudden cardiac death is based on evidence from a prospective cohort study,[12] a case-control study,[22] and four prospective dietary intervention trials.[38,39,41,43] Proposed mechanisms to explain these observations center not on lipid or blood pressure lowering or on antithrombotic effects, but on a novel stabilizing effect of omega-3 fatty acids on the myocardium itself. Evidence for a direct effect of these fatty acids on the heart has come from several observations. First, increased heart rate variability in survivors of MI was associated with the consumption of one fish meal per week[77] or fish oil supplements (4.3 g/d of omega-3 fatty acids).[78] Increases in this parameter predict a lower risk of mortality due to arrhythmic events in post-MI patients. EPA and DHA also have been shown to reduce resting heart rate and increase left ventricular filling capacity.[79] Animal experiments and cell culture studies have shown that fish oil has potent antiarrhythmic effects. For example, studies with rats[80] and dogs[81,82] have shown that pretreatment with omega-3 fatty acids reduced damage to cardiac tissue and forestalled the development of ventricular dysrhythmias when heart attacks were induced. Similar observations were made in fish oil–fed cats that were protected from cerebral damage after stroke induction.[83] In vitro induction of tachyarrhythmias in cultured neonatal rat ventricular myocytes by various pharmacological agents (such as ouabain) can be prevented or abolished by the addition of omega-3 fatty acids to the culture medium (reviewed by Kang and Leaf[84]). This seems to be due to the ability of omega-3 fatty acids to prevent calcium overload by maintaining the activity of L-type calcium channels during periods of stress,[85] and to increase the activity of cardiac microsomal Ca^{2+}/Mg^{2+}-ATPase.[79] In addition, omega-3 fatty acids (including α-linolenic acid) are potent inhibitors of voltage-gated sodium channels in cultured neonatal cardiac myocytes, which may contribute to the reduction in arrhythmia.[84]

Other Biological Effects

Goode et al[86] showed that acetylcholine-stimulated relaxation of small arteries taken from hypercholesterolemic patients was significantly improved after three months of supplementation with 3 g/d of EPA+DHA. Fish oil feeding has also been shown to improve endothelial function (reviewed by Chin and Dart[87]) and to increase arterial compliance.[88] These effects may be secondary to fish oil's ability to enhance nitric oxide production[89] and may be the mechanism by which fish oil elicits a small hypotensive effect.

Mechanisms to explain the antiatherogenic (inhibition of new plaque development) effect of omega-3 fatty acids have recently been proposed.[48] For example, EPA and DHA seem to alter the metabolism of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1), E-selectin, and intercellular adhesion molecule-1 (ICAM-1). Abe et al (1998)[90] reported a 9% reduction in soluble ICAM-1 and a 16% reduction in soluble E-selectin but not in soluble VCAM-1 in hypertriglyceridemic subjects receiving 3.4 g/d of highly purified omega-3 fatty acid ethyl esters for 7 to 12 months. There is also in vitro evidence that DHA reduces endothelial expression of VCAM-1 and the expression of E-selectin, ICAM-1, interleukin (IL)-6, and IL-8 in stimulated cells.[91,92] On the other hand, a study in male smokers with hyperlipidemia showed that six weeks of omega-3 fatty acid supplementation (4.8 g/d) increased soluble forms of E-selectin and VCAM-1.[93] A subsequent study in coronary patients given supplemental omega-3 fatty acids (5.1 g/d for 6 months) found similar results.[76] Fish oil also affects the metabolism of inflammatory mediators like the interleukins and tumor necrosis factor-α,[94] molecules also believed to play a role in atherogenesis and plaque stability.[95]

Another potential antiatherogenic mechanism of omega-3 fatty acids is their interference with the arachidonic acid cascade that generates a wide variety of eicosanoids (reviewed by Uauy et al[96]). EPA not only can replace arachidonic acid in phospholipid bilayers, but it is also a competitive inhibitor of cyclooxygenase, reducing the production of the 2-series prostaglandins, thromboxanes, and prostacyclins and the 4-series leukotrienes. The 3- and 5-series (respectively) produced from EPA are generally less biologically active. DHA, although not a direct inhibitor of arachidonic acid metabolism, nevertheless can inhibit platelet aggregation by reducing the affinity of platelet TxA_2/PGH_2 receptor for its ligand.[97] The net effects of omega-3 fatty acids are thus to reduce inflammatory processes, vasoconstriction, and platelet aggregation, all known to be antiatherogenic.

Some studies have shown that omega-3 fatty acids may increase the susceptibility of LDL to oxidation,[98,99] whereas others have not.[100–102] It therefore remains to be established whether LDL oxidative status in vivo is affected by omega-3 fatty acids and, if so, whether this has any adverse clinical implications. Our current inability to identify and quantify in vivo oxidative damage and to relate it to clinical outcomes makes it difficult to draw firm conclusions about the impact of omega-3 fatty acids on these processes.

Intake of Omega-3 Fatty Acids

The intake of total omega-3 fatty acids in the United States is $\approx$1.6 g/d ($\approx$0.7% of energy intake).[103] Of this, α-linolenic

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TABLE 2. α-Linolenic Acid Content of Selected Vegetable Oils, Nuts, and Seeds

	α-Linolenic Acid Content, g/tbsp
Olive oil	0.1
Walnuts, English	0.7
Soybean oil	0.9
Canola oil	1.3
Walnut oil	1.4
Flaxseeds	2.2
Flaxseed (linseed) oil	8.5

Adapted from USDA Nutrient Data Laboratory.[104]

acid accounts for ≈1.4 g/d, and only 0.1 to 0.2 g/d comes from EPA and DHA. The major food sources of α-linolenic acid are vegetable oils, principally canola and soybean oils. Other food sources that are rich in α-linolenic acid (Table 2)[104] include flaxseed (23 g/100 g) and English walnuts (7 g/100 g). Although some α-linolenic acid is converted to the longer-chain omega-3 fatty acids, the extent of this conversion is modest and controversial. For example, Emken et al[105] reported a 15% conversion, whereas Pawlosky et al[106] found 0.2%; both reported that the conversion to DHA was much less than that to EPA. Fish are the major food source of EPA and DHA (Table 3).[104] All fish contain EPA and DHA; however, the quantities vary among species and within a species according to environmental variables such as diet and whether fish are wild or farm-raised. Farm-raised catfish tend to have less EPA and DHA than do wild catfish, whereas farm-raised salmon and trout contain similar amounts versus their wild counterparts.

A number of countries (Canada, Sweden, United Kingdom, Australia, Japan) as well as the World Health Organization and North Atlantic Treaty Organisation have made formal population-based dietary recommendations for omega-3 fatty acids. Typical recommendations are 0.3 to 0.5 g/d of EPA+DHA and 0.8 to 1.1 g/d of α-linolenic acid. Recently, the Food and Nutrition Board, Institute of Medicine, and The National Academies, in collaboration with Health Canada, released the Dietary Reference Intakes for Energy and Macronutrients.[107] The Acceptable Macronutrient Distribution Range (AMDR) for α-linolenic acid is estimated to be 0.6% to 1.2% of energy, or 1.3 to 2.7 g/d on the basis of a 2000-calorie diet. This is ≈10 times the current intake of EPA+DHA. The lower boundary of the range is based on an Adequate Intake set for α-linolenic acid, which represents median intake levels that prevent an essential fatty acid deficiency. The upper boundary corresponds to the highest α-linolenic acid intakes from foods consumed by individuals in the United States and Canada. Thus, the intent of the AMDR range for omega-3 fatty acids is to provide guidance for healthy people, not to prevent chronic disease. These recommendations can easily be met by following the AHA Dietary Guidelines to consume two fish meals per week, with an emphasis on fatty fish (ie, salmon, herring, and mackerel), and by using liquid vegetable oils containing α-linolenic acid. Commercially prepared fried fish (eg, from restaurants and fast food establishments, as well as many frozen, convenience-type fried fish products) should be avoided because they are low in omega-3 and high in trans-fatty acids.

Patients with CHD should be encouraged to increase their consumption of EPA and DHA to ≈1 g/d, which is the dose used in the GISSI-Prevention Study. Table 3 presents omega-3 fatty acid content of various fish and supplements as well as the amount required each day to provide ≈1 g/d of EPA+DHA. Although this level of EPA and DHA intake potentially can be attained through fish consumption, the requisite amount of fish intake may be difficult to achieve and sustain over the long term. For those individuals who do not eat fish, have limited access to a variety of fish, or cannot afford to purchase fish, a fish oil supplement may be considered. 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.

Safety of Omega-3 Fatty Acids

Omega-3 fatty acids have been a part of the human diet for millennia. It has been estimated that the ratio of omega-6 to omega-3 fatty acids in the diet of early humans was 1:1.[108] The ratio in the United States today has risen to ≈10:1 because of the combination of reduced omega-3 fatty acid intake and the widespread use of vegetable oils rich in linoleic acid.[103] Because of the well-known competition between the omega-6 linoleate and the omega-3 α-linolenate for metabolic conversion to longer-chain, physiologically active metabolites, reducing the former while increasing the latter (or simply increasing the latter) is a strategy for increasing tissue levels of omega-3 fatty acids.[109] Another obvious strategy is to simply consume more EPA and DHA, an approach that minimizes the significance of the ratio.

Since the first omega-3 fatty acid advisory,[1] the FDA has ruled that intakes of up to 3 g/d of marine omega-3 fatty acids are GRAS (Generally Recognized As Safe) for inclusion in the diet.[110] This ruling included specific consideration of the reported effects of omega-3 fatty acids on glycemic control in patients with diabetes, on bleeding tendencies, and on LDL cholesterol. Moreover, the FDA recently has approved a qualified health claim for EPA and DHA omega-3 fatty acids in dietary supplements.[64]

Although the safety of low intakes does not seem to be an issue, and supplements are essentially mercury free, some side effects of omega-3 fatty acid supplementation do occur (Table 4).[111] Perhaps the most common is a fishy aftertaste. In the GISSI Prevention study, which provided 0.85 g of omega-3 fatty acids per day for 3.5 years, 3.8% of patients discontinued taking their supplements (compared with 2.1% for the vitamin E group). Gastrointestinal disturbances and nausea were the most commonly reported side effects, with 4.9% and 1.4% reported, respectively, compared with 2.9% and 0.4% in the vitamin E group. When 12 capsules contain-

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TABLE 3. Amounts of EPA+DHA in Fish and Fish Oils and the Amount of Fish Consumption Required to Provide ≈1 g of EPA+DHA per Day

	EPA+DHA Content, g/3-oz Serving Fish (Edible Portion) or g/g Oil	Amount Required to Provide ≈1 g of EPA+DHA per Day, oz (Fish) or g (Oil)
Fish		
Tuna		
Light, canned in water, drained	0.26	12
White, canned in water, drained	0.73	4
Fresh	0.24–1.28	2.5–12
Sardines	0.98–1.70	2–3
Salmon		
Chum	0.68	4.5
Sockeye	0.68	4.5
Pink	1.09	2.5
Chinook	1.48	2
Atlantic, farmed	1.09–1.83	1.5–2.5
Atlantic, wild	0.9–1.56	2–3.5
Mackerel	0.34–1.57	2–8.5
Herring		
Pacific	1.81	1.5
Atlantic	1.71	2
Trout, rainbow		
Farmed	0.98	3
Wild	0.84	3.5
Halibut	0.4–1.0	3–7.5
Cod		
Pacific	0.13	23
Atlantic	0.24	12.5
Haddock	0.2	15
Catfish		
Farmed	0.15	20
Wild	0.2	15
Flounder/Sole	0.42	7
Oyster		
Pacific	1.17	2.5
Eastern	0.47	6.5
Farmed	0.37	8
Lobster	0.07–0.41	7.5–42.5
Crab, Alaskan King	0.35	8.5
Shrimp, mixed species	0.27	11
Clam	0.24	12.5
Scallop	0.17	17.5
Capsules		
Cod liver oil*	0.19	5
Standard fish body oil	0.30	3
Omega-3 fatty acid concentrate	0.50	2
Omacor (Pronova Biocare)†	0.85	1

Data from the USDA Nutrient Data Laboratory.[104]

The intakes of fish given above are very rough estimates because oil content can vary markedly (>300%) with species, season, diet, and packaging and cooking methods.

*This intake of cod liver oil would provide approximately the Recommended Dietary Allowance of vitamins A and D.

†Not currently available in the United States.

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TABLE 4. Risk for Side Effects From Ingestion of Omega-3 Fatty Acids

	Gastrointestinal Upset	Clinical Bleeding	Fishy Aftertaste	Worsening Glycemia*	Rise in LDL-C†
Up to 1 g/d	Very low	Very low	Low	Very low	Very low
1 to 3 g/d	Moderate	Very low	Moderate	Low	Moderate
>3 g/d	Moderate	Low	Likely	Moderate	Likely

*Usually only in patients with impaired glucose tolerance and diabetes.
†Usually only in patients with hypertriglyceridemia.

ing 6 g of omega-3 fatty acids were fed to 41 patients for 2.4 years, three patients dropped from the study claiming intolerance to the capsules.[46] In a 6-month trial providing 275 patients with 6.9 g of EPA+DHA in 10 capsules daily, there was no difference between the fish oil and corn oil control groups for any adverse event.[112] Gastrointestinal upset was reported by 8% of the latter and 7% of the former. Finally, although refined and concentrated omega-3 fatty acid products contain virtually no methylmercury and are very low in organochloride contaminants,[113] less well-controlled preparations can contain appreciable amounts.[114]

Safety of Fish

Some species of fish may contain significant levels of methylmercury, polychlorinated biphenyls (PCBs), dioxins, and other environmental contaminants. These substances are present at low levels in fresh waters and oceans, and they bioconcentrate in the aquatic food chain such that levels are generally highest in older, larger, predatory fish and marine mammals.

Fish and seafood are a major source of human exposure to these contaminants. PCBs and methylmercury have long half-lives in the body and can accumulate in people who consume contaminated fish on a frequent basis. Consumers can reduce their exposure to PCBs by removing the skin and fat from these fish before cooking them; however, because methylmercury is distributed throughout the muscle, skinning and trimming does not significantly reduce mercury concentrations in filets.

The responsibility for regulating the quality of the fish for human consumption is shared by the states and two federal agencies. The Environmental Protection Agency regulates sport-caught fish, whereas the FDA regulates all commercial fish—including farm-raised, imported, and marine fish. The Environmental Protection Agency's 2000 National Listing of Fish and Wildlife Advisories may be found on the Environmental Protection Agency web site.[115] The Environmental Protection Agency advises women who are pregnant or may become pregnant and nursing mothers to limit their consumption of sport-caught fish to one 6-ounce meal per week.[116] The Environmental Protection Agency also recommends that young children consume ≤2 ounces of sport-caught fish per week. The FDA recommends that women who are pregnant or nursing and young children eliminate shark, swordfish, king mackerel in the mackerel family, and tilefish (also referred to as golden bass or golden snapper) from their diets completely and limit their consumption of other fish to 12 ounces per week (≈3 to 4 servings/wk) to minimize exposure to methylmercury.[117] The FDA has concluded that persons other than pregnant women and women who may become pregnant can consume up to 7 ounces per week of fish with methylmercury levels around 1 ppm (eg, shark, swordfish, king mackerel, tilefish) and 14 ounces per week of fish with mercury levels averaging 0.5 ppm (eg, fresh tuna, orange roughy, marlin, red snapper).[118] In July 2002, an FDA Scientific Committee advised the FDA to conduct a more detailed analysis of the contribution of methylmercury from tuna (with emphasis on large tuna consumed as steaks rather than canned tuna) to total methylmercury levels in women and children. Although more data are needed, information currently available about the methylmercury content of selected fish can be found on the FDA web site.[119]

In summary, consumers need to be aware of both the benefits and risks of fish consumption for their particular stage of life. Children and pregnant and lactating women may be at increased risk for mercury intoxication from fish consumption but also are at low risk for CHD. Thus, avoidance of potentially contaminated fish is a higher priority for this group. For middle-aged and older men and postmenopausal women, the benefits of fish consumption far outweigh the risks within the guidelines established by the FDA and Environmental Protection Agency. Consumption of a wide variety of species within the guidelines is the best approach to both minimizing mercury exposure and increasing omega-3 fatty acid intake.

Summary

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

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TABLE 5. Summary of Recommendations for Omega-3 Fatty Acid Intake

Population	Recommendation
Patients without documented CHD	Eat a variety of (preferably oily) fish at least twice a week. Include oils and foods rich in α-linolenic acid (flaxseed, canola, and soybean oils; flaxseed and walnuts)
Patients with documented CHD	Consume $\approx$1 g of EPA+DHA per day, preferably from oily fish. EPA+DHA supplements could be considered in consultation with the physician.
Patients needing triglyceride lowering	Two to four grams of EPA+DHA per day provided as capsules under a physician's care

effects due to environmental pollutants and, at the same time, achieve desired CVD health outcomes.

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 ($\approx$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.

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KEY WORDS: AHA Scientific Statements ■ nutrition ■ fatty acids, omega-3 ■ fish oils ■ cardiovascular diseases

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Corrections

After the publication of the AHA Scientific Statement "Fish Consumption, Fish Oil, Omega-3 Fatty Acids, and Cardiovascular Disease" by Kris-Etherton et al, which appeared in a previous issue of the journal (*Circulation*. 2002;106:2747–2757), the following errors were noted in Table 3. First, two other sources for the fatty acid composition of fish should have been included.[1,2] Secondly, the footnote to "cod liver oil" should have read, "This intake of cod liver oil would provide approximately the Recommended Daily Allowance (RDA) of vitamin A and twice the RDA for vitamin D." Finally, the EPA+DHA content for four fish was given incorrectly, and should have been as follows:

TABLE 3. Amounts of EPA+DHA in Fish and Fish Oils and the Amount of Fish Consumption Required to Provide ≈1 g of EPA+DHA per Day

Fish	EPA+DHA Content, g/3-oz Serving Fish (Edible Portion) or g/g Oil	Amount Required to Provide ≈1 g of EPA+DHA per Day, oz (Fish) or g (Oil)
Sockeye salmon	1.05	2.5 oz
Eastern oysters	0.95	3 oz
Atlantic cod	0.13	23 oz
Pacific cod	0.24	12.5 oz

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In the "ACC/AHA 2002 Guideline Update for the Management of Patients With Chronic Stable Angina—Summary Article: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina)" by Gibbons et al that appeared in the January 7/14, 2003, issue of *Circulation* (*Circulation*. 2003;107:149–158), page numbers were not included in the Guideline's internal Table of Contents. The complete corrected Guideline follows this page. The page numbers shown are consistent with the pagination of the January 7/14 issue.

(*Circulation*. 2003;107:512.)

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