Understanding omega-3's

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Omega-3 fatty acids are a subset of polyunsaturated fatty acids found in marine sources as eicosapentaenoic acid and docosahexaenoic acid and in some leafy vegetables, nuts, and oils as α-linolenic acid (ALA). The metabolism of omega-3's may explain the cardioprotective effects observed in epidemiologic and experimental studies. Although most data for cardioprotective effects come from studies of marine sources, vegetable sources of omega-3 fatty acids (α-linolenic acid) may have similar effects through in vivo conversion to eicosapentaenoic acid and docosahexaenoic acid. This document will provide an overview of omega-3 fatty acids with a focus on specific sources, metabolism, safety issues, and their potential indication for cardiovascular prevention. (Am Heart J 2006;151:564-70.)

Interest in omega-3 fatty acids has grown steadily since the observation that Greenland's Eskimos have a low incidence of cardiovascular disease (CVD) in the setting of a diet rich in fatty fish.[1] Importantly, both epidemiologic and experimental data have provided evidence for a beneficial effect of omega-3 fatty acids in the prevention of CVD. In 2002, the American Heart Association released a scientific statement endorsing the use of omega-3 fatty acids in both primary and secondary prevention.[2]

What are omega-3's?

There are 3 types of naturally occurring fats classified by the number of double bonds present in their fatty acid side chains: saturated, monounsaturated, and polyunsaturated (Figure 1). The food industry created a fourth class, trans fats, by adding hydrogen ions to polyunsaturated fats through a process called hydrogenation (Figure 1). Polyunsaturated fats can be further classified into 2 groups based on the position of the first double bond site: omega-3 fatty acids and omega-6 fatty acids (Figure 1). The most prominent omega-6 fatty acids in the human diet are arachidonic acid (found in animal meat) and linoleic acid (found in vegetable oils, seeds, and nuts), which can be converted into arachidonic acid by a desaturase enzyme (Figure 2). Major dietary sources of omega-3's are fish containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and nuts, seeds, and vegetable oils containing α-linolenic acid (ALA), which can be converted to EPA and then DHA by the same desaturase enzyme that converts linoleic acid to arachidonic acid (Figure 2).

The conversion of ALA to EPA is of interest because the cardioprotective effects of omega-3's have been most rigorously studied and closely associated with EPA. This conversion may explain, in part or in whole, ALA's potential benefit. Isotope-labeled ALA feeding trials have shown the conversion of ALA to EPA to vary between 0.2% and 21% and that of ALA to DHA to vary between 0% and 9%.[3] Most feeding studies that measure interval changes in membrane fatty acid composition show that ALA feeding will lead to an increase in EPA but has a null effect or slight decrease in DHA levels.[3] These studies, however, are somewhat limited because the conversion of ALA to EPA + DHA is likely influenced by multiple factors including, sex, competitive inhibition of desaturase by linoleic acid (Figure 2), negative feedback inhibition of desaturase by EPA + DHA (Figure 2), and timing of the sample collection.

Analysis of the Health Professional Follow-up Study cohort found that ALA's CVD protective properties were inversely related to EPA + DHA intake. The authors concluded that ALA's cardioprotective properties were contingent on conversion to EPA + DHA and that this conversion was inhibited by EPA + DHA intake[4] (Figure 2).

Where are omega-3's?

Dietary intake of omega-3 and omega-6 fatty acids varies within and between different populations. NHANES III, the largest database of nutrient consumption of Americans, reports a median intake of EPA + DHA of 0 and <1 g/d of ALA.[5] The ratio of omega-6 to omega-3 intake is estimated to be 20 to 1 in a modern Western diet, compared with that of our Paleolithic ancestors who ate a diet much richer in omega-3's (estimated

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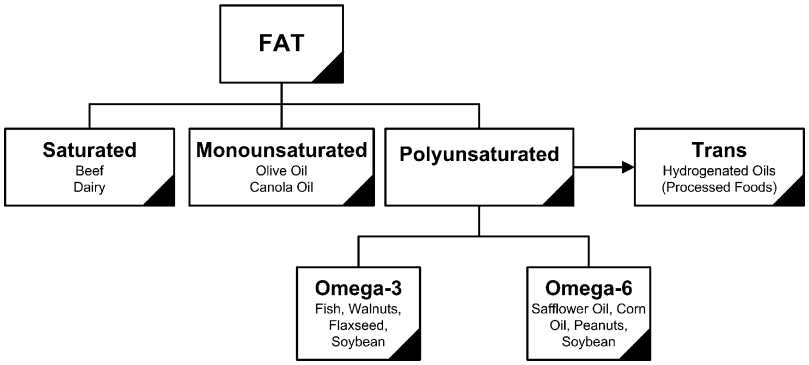
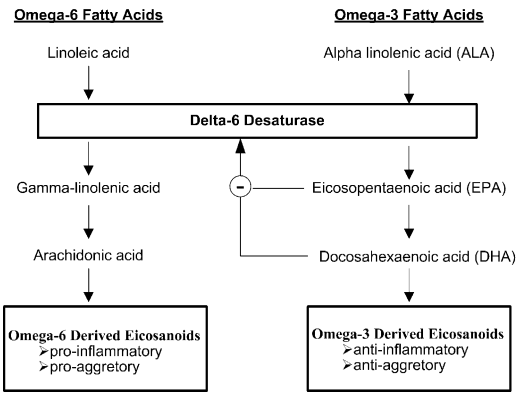
doi:10.1016/j.ahj.2005.03.051

Figure 1



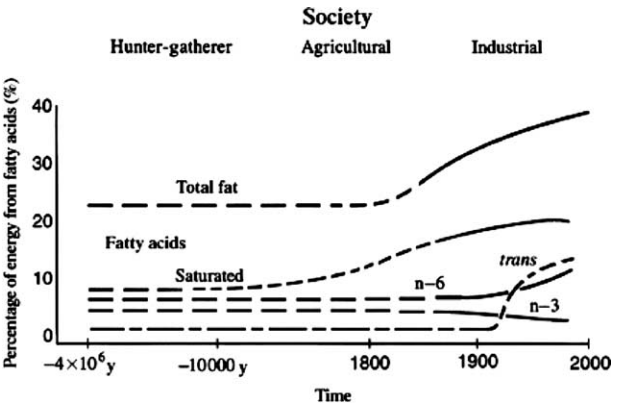
Classification of fats.

Figure 2



Metabolic pathway of omega-6 and omega-3 fatty acids.

Figure 3



Historical schematic of relative percentages of fat and intake of different fatty acids in human beings. Reproduced with permission by the *American Journal of Clinical Nutrition*. © Am J Clin Nutr. American Society for Clinical Nutrition.

omega-3/omega-6 ratio of 1-2:1) (Figure 3).[6,7] This dramatic dietary shift is thought to be related to an absolute reduction in fish consumption as well as a proportionate increased consumption of domestically raised fish. Meat and fish presently contain less omega-3 and more omega-6 fatty acids than in the past, secondary to use of commercial feeds high in omega-6 and low in omega-3 content.[8,9] Even cultivated vegetables are poor in omega-3 when compared with wild plants.[10]

The metabolism of omega-3's

A dietary shift toward less omega-3's and more omega-6's may significantly impact one's health because of their different metabolic pathways. Eicosanoids are a class of bioactive molecules derived from omega-3's and omega-6's that include leukotrienes, prostaglandins, and thromboxanes (Figure 2). Eicosanoids derived from omega-6's are generally proinflammatory and proaggretory, whereas those derived from omega-3's are predominantly anti-inflammatory and inhibit platelet aggregation.[6] This fundamental difference may account for the cardioprotective effects of omega-3's.

Inflammation is a central component in atheroma formation and plaque rupture,[11] and studies have linked systemic markers of inflammation to CVD risk.[12] A cross-sectional study of 727 women in the Nurses Health Study I found dietary intake of omega-3's to be inversely related to inflammatory markers C-reactive protein, IL-6,

E-selectin, soluble intercellular cell adhesion molecule 1, and soluble vascular cell adhesion molecule 1.[13] This relationship was consistent for ALA, EPA, and DHA independently and in aggregate.[13] An inverse relationship between EPA + DHA intake and soluble tumor necrosis factor receptors was demonstrated in a cohort of 405 healthy men in the Health Professionals Follow-up Study and 454 healthy women in the Nurses' Health Study II.[14] Levels of tumor necrosis factor receptors were lowest in subjects with a high ratio of EPA + DHA to omega-6 intake and highest in subjects with a low ratio of EPA + DHA to omega-6. In this study, ALA intake did not influence the levels of any of the inflammatory markers measured.

In addition to markers of vascular inflammation, omega-3's may beneficially influence other factors related to CVD risk: ventricular arrhythmias, thrombosis, triglycerides, apolipoprotein B, high-density lipoprotein, adhesion molecule expression in plaque, platelet-derived growth factor, nitric oxide–induced endothelial relaxation, and blood pressure.[2,6,15-17] In general, these studies have been performed largely with EPA + DHA; few studies examine the impact of ALA on these intermediate markers of CVD. Importantly, vascular inflammation may be the common pathologic mechanism in which omega-3's impact all of these factors.

Epidemiologic data

Several important observational studies have concluded that omega-3 consumption is inversely related to CVD, especially cardiac death.[18-22] In a study of 22 071 male American physicians, those who consumed fish once a week had a 52% reduction of sudden cardiac death compared with those who ate fish less than once a month ($P = .04$).[20] There was no additional protective effect for men eating fish in amounts greater than once a week. Although a reduction in sudden cardiac death and total mortality was observed, there was no relationship between omega-3 consumption and myocardial infarction, nonsudden cardiac death, or CVD mortality. The Nurses Health Study of 84 688 women showed an inverse relationship between consumption of EPA + DHA and both fatal and nonfatal CVD events, whereas ALA intake was only significantly related to a reduction in fatal CVD events.[21] In the MRFIT trial of 12 866 men, dietary intake of both EPA + DHA and ALA was inversely related to coronary heart disease, all CVD events, and all-cause mortality.

In the Honolulu Heart Program study of 8006 men, low fish intake was defined as consumption of fish less than twice a week and high fish intake as that ≥2 times a week.[23] There was no difference in the incidence of coronary heart disease between the cohorts, but this lack of association may have been secondary to a threshold effect. Maximal reduction of sudden cardiac death in the Physicians Health Study was seen at a fish intake of once a week. A threshold effect may also explain the lack of association between fish consumption and coronary heart disease in the Health Professionals Follow-up Study.[24] Although a 4-fold difference in fish consumption existed between the highest and lowest quintile of participants in this study, the mean fish intake in the lowest quintile was still 1.2 servings/wk.

In addition to dietary intake studies, omega-3 fatty acid whole blood[25] and platelet phospholipid content[16] have been shown to be inversely related to CVD death.

Prospective randomized trials

The impact of omega-3's on cardiovascular end points has been evaluated in 4 well-designed secondary prevention trials. These trials evaluated omega-3's either as part of a comprehensive diet plan or as a capsule supplement, and although these trials differed in many respects, their findings were consistent and compelling—omega-3's are effective for secondary prevention of cardiovascular events.

The DART[26] randomized 2033 post–myocardial infarction Welsh men to one of the following groups: (1) sensible eating (placebo); (2) low fat with an increased polyunsaturated-to-saturated ratio; (3) fatty fish consumption twice a week or 1.5 g fish oil capsules/d; (4) increased dietary fiber; or (5) a combination of the above. At 2 years, there was a 4-fold increase in EPA intake in the fish advice group (22% were taking fish oil capsules instead of eating fish).

All-cause mortality and ischemic heart disease events were not reduced in the high-fiber and low-fat groups. The group advised to consume fatty fish twice a week or take fish oil capsules had a 29% (3.5% absolute risk, $P < .05$) reduction in all-cause mortality attributable to a reduction in ischemic deaths, whereas nonfatal ischemic heart disease events were not reduced. A survey of 47% of DART participants still living 10 years after the trial's conclusion showed no long-term survival benefit in any of the intervention groups.[27] This lack of sustained benefit may be caused by the substantial reduction in the difference in fish and fish oil intake between the intervention and placebo groups observed during the trial.[27]

The Indian Experiment of Infarct Survival 4 trial[28] randomized 360 patients with acute coronary syndrome to 1 of 3 interventions: (1) placebo; (2) fish oil capsules (1.8 g/d EPA + DHA); and (3) 20 g/d of mustard oil (2.9 g/d of ALA). After 1 year, total cardiac events (sudden cardiac death, nonfatal reinfarction, cardiac death) were reduced from 34.7% in the placebo group to 28% in the mustard oil group ($P < .01$) and to 24.5% in the fish oil group ($P < .01$). Statistically significant reductions were seen in patients in both the fish oil and the mustard oil

groups for nonfatal infarctions, angina, arrhythmias, heart failure, and left ventricular hypertrophy. Only patients in the fish oil group had a statistically significant reduction in all cardiac deaths when compared with those in the placebo group.

The Lyon Heart Study[29] compared a Mediterranean ALA-rich diet with a prudent diet in 608 post–myocardial infarction patients. After an average follow-up of 27 months, the Mediterranean ALA-rich diet group achieved a 70% reduction in all deaths ($P = .02$), 76% reduction in cardiac death ($P = .02$), and a 73% reduction in the primary end point of cardiac death and nonfatal myocardial infarction ($P = .001$) after multivariant adjustment. A follow-up assessment at 46 months revealed continued good compliance with the Mediterranean ALA-rich diet and similar reductions in total mortality and cardiovascular events.[30] Because subjects in the Mediterranean diet group made multiple dietary changes, it is not possible to determine if ALA was specifically responsible for the positive results; nonetheless, it is clear from this study that ALA can be part of a cardioprotective Mediterranean diet.

The GISSI-Prevenzione trial,[31] an open-label design trial, randomized 11 324 post–myocardial infarction patients to 1 of 4 groups: (1) 1 g/d of fish oil supplement; (2) 300 mg/d of vitamin E supplement; (3) both; or (4) neither in addition to intensive post–myocardial infarction care and good adherence to a Mediterranean diet with >70% of the participants eating fish at least once a week. This care did not differ between the intervention and control groups and data were collected on 99.9% of participants during the 3.5 years of intervention. The fish oil supplement group had a 15% reduction in the combined end point of death, nonfatal myocardial infarction, and nonfatal stroke ($P = .023$) when compared with the control group (no supplement). Analysis of individual end points showed a 20% reduction in death ($P < .05$), 30% reduction in cardiovascular deaths ($P = .02$), and a 45% reduction in sudden death ($P = .01$). There was no reduction in nonfatal cardiovascular events in the fish oil group. Vitamin E did not impact CVD outcomes in the presence or absence of fish oil.

All 4 trials report a reduction in secondary cardiac events with either 1.0 to 1.8 g/d of fish oil capsules/1 serving of fish per day (DART, the Indian Experiment of Infarct Survival 4 trial, GISSI) or ALA supplementation (Indian Experiment of Infarct Survival 4 trial, Lyon Heart Study). Results are similar with fish/fish oil supplemented as part of a comprehensive dietary intervention and as a single intervention (DART), fish oil capsules alone (GISSI), and ALA as a single intervention (Indian Experiment of Infarct Survival 4 trial) or as part of a comprehensive diet plan (Lyon). Of the 4 trials, GISSI provides the most convincing data because of its large size (11 324), randomized intervention with a controlled dose (1 g/d) of fish oil, and 99.9% follow up rate, although it can be criticized for its open-label design.

Clinical use

In addition to being useful in the secondary prevention of CVD events, a prescription formulation of omega-3 fatty acids, Omacor, has gained Food and Drug Administration (FDA) approval as an adjunct to diet to reduce very high (>500 mg/dL) triglycerides in adults. Two studies of 4 g/d of Omacor demonstrated a 50% reduction in triglycerides and a 44.5% increase in low-density lipoprotein (LDL) cholesterol in 84 adults with primary hypertriglyceridemia.[32] A review of 10 trials in 606 subjects with primary hypertriglyceridemia (triglycerides >150 mg/dL and/or total cholesterol >200 mg/dL) supplemented with 3.4 to 4 g/d of fish oil for 4 to 16 weeks was notable for a 16% to 45% reduction in triglycerides in all but one study.[33] Total cholesterol decreased 0% to 9.3%, high-density lipoprotein increased 0% to 13%, and changes in LDL ranged from −11.3% to +32%. Although fish oil may increase total LDL (at doses >1 g/d), the resultant LDL population may have an increased particle size that is potentially less atherogenic than small, dense LDL.[34] In normotriglyceridemic diabetics, fish oil supplementation modestly lowers triglycerides without any clinically significant effect on glycemic control. In hypertriglyceridemic diabetics, fish oil supplementation reduces triglycerides; however, it may increase LDL.[35] In three small studies (n = 41, n = 48, n = 55), fish oil supplementation has been used as a safe adjunct to statin therapy to further reduce triglycerides, while maintaining a reduction in LDL.[36-38] The impact of ALA on triglycerides remains uncertain given that a single study of 30 adults supplemented with 4.5 g/d of ALA demonstrated no significant change in a baseline triglyceride level of 147 mg/dL.[39]

Fish oil supplementation at 1 to 2 g/d titratable to 4 g/d in single or divided doses can be considered for patients with modest hypertriglyceridemia (200-499 mg/dL) who do not have a reversible secondary cause of hypertriglyceridemia and have failed dietary intervention. Periodic monitoring of LDL and triglycerides levels is prudent until a safe, steady, therapeutic dose is achieved. Treatment recommendations for severe hypertriglyceridemia (>500 mg/dL) are beyond the scope of this article.

Safety

The US Department of Health and Human Services Agency for Healthcare Research and Quality identified 148 omega-3 fatty acid studies that reported on adverse events in >20 000 subjects.[5] In summary, gastrointestinal complaints were reported in 6.6% of the subjects

Table I. Mercury level in 5 popular fish oil supplements

Supplement brand name	Mercury level (μg/L)
CVS	10
Kirkland	<6
Nordic Ultimate	<6
Omega Brite	12
Sundown	<6

Data from Foran et al.[44]

Table II. Omega-3 fatty acid content of select food

Food item	EPA	DHA	ALA
Fish			
Catfish	Trace	0.2	0.1
Cod	Trace	0.1	Trace
Mackerel	0.9	1.4	0.2
Salmon			
Farmed	0.6	1.3	Trace
Wild	0.3	1.1	0.3
Canned	0.9	0.8	Trace
Salmon, Chinook	1.0	0.9	Trace
Swordfish	0.1	0.5	0.2
Tuna, Bluefin	0.3	0.9	–
Tuna, Light			
Canned in oil	Trace	0.1	Trace
Canned in water	Trace	0.2	Trace
Tuna, White			
Canned in oil	Trace	0.2	0.2
Canned in water	0.2	0.6	Trace
Shellfish			
Lobster	–	–	–
Mussels	0.2	0.3	Trace
Shrimp	0.3	0.2	Trace
Nuts and seeds			
Butternuts	–	–	8.7
Flaxseed	–	–	18.1
Walnuts	–	–	9.1
Plant oils			
Canola	–	–	9.3
Flaxseed	–	–	53.3

Measurements are expressed in grams per 100 grams (3.5 oz) of food item.
Trace = <0.1; (–) = 0 or no data.
Adapted from the US Department of Health and Human Services.[5]

Table III. Summary of American Heart Association recommendations for omega-3 fatty acid intake

Population	Recommendation
Patients without documented CHD	Eat a variety of (preferably fatty) fish at least twice a week. Include food and oils rich in ALA in your diet.
Patients with documented CHD	Consume approximately 1 g of EPA + DHA (3 g of fish oil) everyday, preferably from fatty fish. EPA + DHA (fish oil) supplements could be considered in consultation with a physician.

Data from Kris-Etherton et al.[2]

taking omega-3's versus 4.3% in the placebo groups. An increased incidence of bleeding was not observed, and only 1 of the 148 studies reviewed reported such an association in patients randomized to 6 g/d of omega-3. There are no reported deaths or life-threatening illness as a consequence of omega-3 consumption, and 77 of the studies reported no adverse events at all. The agency concluded that adverse events related to consumption of fish oil or ALA supplements appear to be minor. In addition, the FDA has ruled that up to 3 g/d of EPA + DHA is safe,[40] although most data are limited to <6 months. Importantly, caution should be exercised when applying safety data generated in a clinical research setting to patients in the general population.

Concerns have been raised regarding potential mercury exposure from fish and fish oil consumption. However, there have been no cases of mercury poisoning related to fish consumption reported in the United States over the last 35 years. Subclinical neural damage from chronic exposure to low levels of mercury found in fish is controversial.[41] One observational study reported subtle neuropsychological changes in children who had been exposed to high levels of mercury through frequent maternal consumption of whales (1.6 μg methyl-mercury/g) during pregnancy.[41,42] A similar study found no adverse effects in children whose mothers consumed an average of 12 servings of fish per week that contained average levels of methyl mercury (0.3 μg/g).[41,42]

Although the risk posed by mercury exposure through fish consumption is speculative, the FDA recommends limiting consumption of fish that are high in mercury (>1 ppm or approximately 1 μg/g) to one serving (7 oz) per week.[43] Because the fetal brain is more susceptible than the adult brain to mercury-induced damage, the FDA and the Environmental Protection Agency recommend that pregnant women, nursing mothers, and young children avoid eating fish with high mercury content. The FDA maintains a web page (http://www.cfsan.fda.gov) that currently lists shark, swordfish, king mackerel, and tilefish as having a high mercury content. With the exception of Omacor, available by prescription, the FDA does not regulate fish oil supplements, and, at the time of this review, we were able to identify only one peer-reviewed English language study that had evaluated fish oil supplements for mercury content. This study examined 5 popular fish oil supplements: 3 were found to have undetectable levels of mercury (<6 μg/L) and 2 had levels between 10 and 12 μg/L of mercury by cold vapor atomic absorption spectroscopy (Table I).[44] This level of mercury is considered negligible.

Several cohort and case-control studies evaluating the relationship between omega-3's and prostate cancer have been conducted with varying results. A meta-analysis combining the results of 4 cohort and 5 case-control studies concluded that high intake of ALA is associated with an increased risk of prostate cancer (relative risk 1.70, 95% CI 1.12-2.58).[45] The authors note that the studies were quite heterogeneous, with only 1 of the 4 prospective cohort trials and 3 of the 5 case-control studies showing a statistically significant positive association to prostate cancer. To date, null and inverse associations between EPA + DHA and prostate cancer have been reported.[45,46]

Conclusion

Omega-3's are a unique group of polyunsaturated fats that can be found most abundantly in fatty fish, flaxseed, walnuts, soy, and canola oil (Table II). The metabolism of omega-3's from fish (EPA + DHA) and vegetables (ALA) results in the production of the same eicosanoids (thromboxane, leukotrienes, prostaglandins); however, it is unclear as to what extent ALA is metabolized into these eicosanoids and if this metabolism is directly related to its effect on CVD. It does seem clear from the 4 prospective randomized trials outlined above that both fish and plant sources of omega-3's can favorably impact cardiovascular health. The impact of omega-3's is most consistently related to the use of fish oil. Although data on reduction in cardiovascular events with plant sources of omega-3's (ALA) exist, the number of subjects studied in the Indian Experiment of Infarct Survival 4 was small and ALA supplementation was part of multiple dietary interventions in the Lyon Heart Study. Clearly, a prospective randomized controlled trial, similar to GISSI, with ALA would be very valuable. Strong cohort trial data exist for the primary prevention of cardiovascular events with omega-3's (EPA, DHA, ALA), but no prospective randomized controlled trial has adequately evaluated the effect of omega-3 fatty acids on the primary prevention of CVD. To date, no serious adverse effects of omega-3's have been identified despite trial data on 20 000 subjects. Potential harm from mercury exposure can be avoided with prudent fish and fish oil supplement selection. Data on the association between ALA and prostate cancer are inconsistent and limited to case-control and cohort trials. Given this concern, if omega-3 supplementation is going to be implemented in men, fish oil may be a more prudent choice than ALA.

It is recommended that patients with known CVD consume one serving (200-400 g) of fatty fish (Table II) or 1 g/d of fish oil supplement and maintain a healthy diet that is rich in ALA (Table II). Patients with a CVD risk equivalent (diabetes, peripheral vascular disease, etc) should consider consumption of a single serving of fatty fish or 1 g/d of fish oil supplement and eat a healthy diet rich in ALA. Fish oil supplements may be particularly helpful in patients with known CVD or CVD risk equivalents and hypertriglyceridemia. For patients without known CVD, a single serving of fatty fish approximately once or twice a week and a diet rich in ALA should be encouraged. It is prudent to avoid fish that contain high levels of mercury as defined by the FDA. These recommendations are in agreement with the American Heart Association's scientific statement (Table III).

References

1. Dyerberg J, Bang HO, Stoffersen E, et al. Eicosapentaenoic acid and prevention of thrombosis and atherosclerosis? Lancet 1978;2:117-9.
2. Kris-Etherton PM, Harris WS, Appel LJ, et al. Nutrition C. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease [erratum appears in Circulation 2003;107:512]. Circulation 2002;106:2747-57.
3. Burdge G. Alpha-linolenic acid metabolism in men and women: nutritional and biological implications. Curr Opin Clin Nutr Metab Care 2004;7:137-44.
4. Mozaffarian DM, Ascherio A, Hu FB, et al. Interplay between different polyunsaturated fatty acids and risk of coronary heart disease in men. Circulation 2005;111:166-73.
5. US Department of Health and Human Services AfHRaQ. Effects of omega-3 fatty acids on cardiovascular disease. Evid Rep Technol Assess (Summ) 2004;1-8.
6. Simopoulos AP. Essential fatty acids in health and chronic disease. Am J Clin Nutr 1999;70(3 Suppl):560S-9S.
7. Eaton SB, Konner M. Paleolithic nutrition. A consideration of its nature and current implications. N Engl J Med 1985;312:283-9.
8. Crawford MA. Fatty-acid ratios in free-living and domestic animals. Possible implications for atheroma. Lancet 1968;1:1329-33.
9. van Vliet T, Katan MB. Lower ratio of n-3 to n-6 fatty acids in cultured than in wild fish. Am J Clin Nutr 1990;51:1-2.
10. Simopoulos AP, Salem Jr N. Purslane: a terrestrial source of omega-3 fatty acids. N Engl J Med 1986;315:833.
11. Ross R. Atherosclerosis—an inflammatory disease. N Engl J Med 1999;340:115-26.
12. Ridker PM, Hennekens CH, Buring JE, et al. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000;342:836-43.
13. Lopez-Garcia E, Schulze MB, Manson JE, et al. Consumption of (n-3) fatty acids is related to plasma biomarkers of inflammation and endothelial activation in women. J Nutr 2004;134:1806-11.
14. Pischon T, Hankinson SE, Hotamisligil GS, et al. Habitual dietary intake of n-3 and n-6 fatty acids in relation to inflammatory markers among US men and women. Circulation 2003;108:155-60.
15. Weber PC, Leaf A. Cardiovascular effects of omega 3 fatty acids. Atherosclerosis risk factor modification by omega 3 fatty acids. World Rev Nutr Diet 1991;66:218-32.
16. Weber PC. Clinical studies on the effects of n-3 fatty acids on cells and eicosanoids in the cardiovascular system. J Intern Med Suppl 1989;225:61-8.
17. Harper CR, Jacobson TA. The fats of life: the role of omega-3 fatty acids in the prevention of coronary heart disease. Arch Intern Med 2001;161:2185-92.

18. Kromhout D, Bosschieter EB, de Lezenne Coulander C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. N Engl J Med 1985;312:1205-9.
19. Daviglus ML, Stamler J, Orencia AJ, et al. Fish consumption and the 30-year risk of fatal myocardial infarction. N Engl J Med 1997;336:1046-53.
20. Albert CM, Hennekens CH, O'Donnell CJ, et al. Fish consumption and risk of sudden cardiac death. JAMA 1998;279:23-8.
21. Hu FB, Bronner L, Willett WC, et al. Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. JAMA 2002;287:1815-21.
22. Dolecek TA. Epidemiological evidence of relationships between dietary polyunsaturated fatty acids and mortality in the multiple risk factor intervention trial. Proc Soc Exp Biol Med 1992;200: 177-82.
23. Rodriguez BL, Sharp DS, Abbott RD, et al. Fish intake may limit the increase in risk of coronary heart disease morbidity and mortality among heavy smokers. The Honolulu Heart Program. Circulation 1996;94:952-6.
24. Ascherio A, Rimm EB, Stampfer MJ, et al. Dietary intake of marine n-3 fatty acids, fish intake, and the risk of coronary disease among men. N Engl J Med 1995;332:977-82.
25. Albert CM, Campos H, Stampfer MJ, et al. Blood levels of long-chain n-3 fatty acids and the risk of sudden death. N Engl J Med 2002;346:1113-8.
26. Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). Lancet 1989;2:757-61.
27. Ness AR, Hughes J, Elwood PC, et al. The long-term effect of dietary advice in men with coronary disease: follow-up of the Diet and Reinfarction Trial (DART). Eur J Clin Nutr 2002;56:512-8.
28. Singh RB, Niaz MA, Sharma JP, et al. Randomized, double-blind, placebo-controlled trial of fish oil and mustard oil in patients with suspected acute myocardial infarction: the Indian experiment of infarct survival–4. Cardiovasc Drugs Ther 1997;11:485-91.
29. de Lorgeril M, Renaud S, Mamelle N, et al. Mediterranean alpha-linolenic acid–rich diet in secondary prevention of coronary heart disease [erratum appears in Lancet 1995;345:738]. Lancet 1994; 343:1454-9.
30. de Lorgeril M, Salen P, Martin JL, et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. Circulation 1999;99:779-85.
31. Anonymous. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico [erratum appears in Lancet 2001;357:642]. Lancet 1999;354:447-55.
32. Omacor [package insert]. Liberty Corner (NJ): Reliant Pharmaceuticals, Inc; 2004.
33. Lewis A, Lookinland S, Beckstrand RL, et al. Treatment of hypertriglyceridemia with omega-3 fatty acids: a systematic review. J Am Acad Nurse Pract 2004;16:384-95.
34. Green ML. Management of dyslipidemias in the age of statins. Prim Care Clin Off Pract 2003;30:641-69.
35. Farmer A, Montori V, Dinneen S, et al. Fish oil in people with type 2 diabetes mellitus. Cochrane Database Syst Rev 2001; CD003205.
36. Chan DC, Watts GF, Barrett PH, et al. Regulatory effects of HMG CoA reductase inhibitor and fish oils on apolipoprotein B-100 kinetics in insulin-resistant obese male subjects with dyslipidemia. Diabetes 2002;51:2377-86.
37. Chan DC, Watts GF, Mori TA, et al. Factorial study of the effects of atorvastatin and fish oil on dyslipidaemia in visceral obesity. Eur J Clin Invest 2002;32:429-36.
38. Nordoy A, Bonaa KH, Nilsen H, et al. Effects of simvastatin and omega-3 fatty acids on plasma lipoproteins and lipid peroxidation in patients with combined hyperlipidaemia. J Intern Med 1998;243:163-70.
39. US Department of Health and Human Services AfHRaQ. Effects of omega-3 fatty acids on cardiovascular risk factors and intermediate markers of cardiovascular disease. Evid Rep Technol Assess 2004;1-6.
40. Administration USFaD. Safety reporting requirements for human drug and biological products. 2003:21 CFR Part 310, 312, 314, 320, 600, 606.
41. Clarkson TW, Magos L, Myers GJ. The toxicology of mercury—current exposures and clinical manifestations. N Engl J Med 2003; 349:1731-7.
42. Myers GJ, Davidson PW, Cox C, et al. Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study. Lancet 2003;361:1686-92.
43. Administration USFaD. Center for food safety and applied nutrition. 2004 [12/1/2004].
44. Foran SE, Flood JG, Lewandrowski KB. Measurement of mercury levels in concentrated over-the-counter fish oil preparations: is fish oil healthier than fish? Arch Pathol Lab Med 2003;127: 1603-5.
45. Brouwer IA, Katan MB, Zock PL. Dietary alpha-linolenic acid is associated with reduced risk of fatal coronary heart disease, but increased prostate cancer risk: a meta-analysis. J Nutr 2004;134: 919-22.
46. Terry PD, Terry JB, Rohan TE. Long-chain (n-3) fatty acid intake and risk of cancers of the breast and the prostate: recent epidemiological studies, biological mechanisms, and directions for future research. J Nutr 2004;134(12 Suppl):3412S-20S.