

Antiatherosclerotic and Antithrombotic Effects of Omega-3 Fatty Acids

Jennifer G. Robinson, MD, MPH,^{a,*} and Neil J. Stone, MD^b

Omega-3 fatty acids from both marine and plant sources have been shown to reduce the risk of coronary artery disease death. Although their beneficial cardiovascular effects are thought to be due to their antiarrhythmic properties, omega-3 fatty acids also have been shown to have a wide range of antiatherosclerotic and antithrombotic effects in animal and human studies. Review of the findings of randomized, controlled trials published through August 2005 shows that omega-3 fatty acids of marine origin consistently lower elevated plasma triglyceride levels in a dose-dependent fashion, with greater efficacy at higher triglyceride levels. Smaller effects on lowering blood pressure, improving endothelial function, and increasing plasma levels of high-density lipoprotein cholesterol were also found. No consistent effects on other lipid, hemostatic, inflammatory, glucose tolerance, or plaque stabilization parameters were found. Epidemiologic studies show more consistent reductions in the incidence of nonfatal myocardial infarction and ischemic stroke than do the clinical trials of increased omega-3 fatty acid intake, which suggests important confounding factors in observational studies. Ongoing clinical trials may clarify the non-antiarrhythmic benefits of omega-3 fatty acid supplementation. © 2006 Elsevier Inc. All rights reserved. (Am J Cardiol 2006;98[suppl]:39i–49i)

Both epidemiologic studies and clinical trials have shown that the omega-3 fatty acids—eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)—reduce the risk of coronary artery disease (CAD) death. Fish intake reduces the risk of CAD death in a dose-response fashion in both men and women with or without CAD.¹ Randomized trials of increased omega-3 fatty acid intake, either from oily fish or supplements, resulted in 20% to 30% reductions in fatal CAD events after myocardial infarction (MI).² α -Linolenic acid (ALA) is a plant source of omega-3 fatty acids that is partly converted into EPA and DHA at a rate of 0.3% to 20%³ and has been associated with a reduction in CAD mortality.⁴ The reduction in CAD death in these studies was largely due to a striking reduction in the risk of sudden death that is generally attributed to early antiarrhythmic effects of omega-3 fatty acids.^{5,6} Whether the cardioprotective benefit of omega-3 fatty acids is mediated through other mechanisms, such as effects on cardiovascular risk factors, is less clear.

Animal and in vitro studies of omega-3 fatty acids have described a wide range of antiatherosclerotic and antithrombotic effects. This article focuses on the effects of omega-3 fatty acids in human epidemiologic and clinical trials. The

Agency for Health Research and Quality (AHRQ) recently commissioned a systematic review of the effects of omega-3 fatty acids on cardiovascular risk factors and intermediate markers of cardiovascular disease in humans.⁷ Data from >120 randomized trials published through 2003 were reviewed by the committee; their findings are summarized here and updated with randomized trials published through July 2005, identified through Medline searches. Most of these trials evaluated fish or other marine oils; a few evaluated plant oils or had <25 subjects in each treatment arm. Very few studies compared doses or sources of omega-3 fatty acids.

Lipid Effects

EPA and DHA increase intracellular degradation of apolipoprotein B-100-containing lipoproteins. This severely inhibits secretion of very-low-density lipoprotein (VLDL) and thereby lowers plasma triglyceride (TG) levels. EPA + DHA supplementation also appears to (1) accelerate chylomicron TG clearance by increasing lipoprotein lipase activity,⁸ (2) increase conversion of VLDL to low-density lipoprotein (LDL),⁹ (3) depress LDL synthesis, and (4) reduce postprandial lipemia.¹⁰ EPA and DHA are useful for treating severe hypertriglyceridemia, eg, TGs >11.3 mmol/L (1,000 mg/dL).¹¹ Marine fish oils are typically used in doses of 2 to 6 g/day of EPA + DHA to lower TG levels. In patients with severe hypertriglyceridemia, LDL cholesterol levels typically rise due to a shift toward larger LDL particles, which may be less atherogenic. In patients who

^aDepartments of Epidemiology and Medicine, University of Iowa, Iowa City, Iowa, USA; and ^bDepartment of Medicine, Section of Cardiology, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA.

*Address for reprints: Jennifer G. Robinson, MD, MPH, Departments of Epidemiology and Medicine, University of Iowa, 200 Hawkins Drive SE 226 GH, Iowa City, Iowa 52242.

E-mail address: jennifer-g-robinson@uiowa.edu.

have normal TG levels, however, LDL cholesterol levels often fall slightly.

The AHRQ meta-analysis included the largest 25 of 182 eligible randomized trials of omega-3 fatty acid consumption. There were ≥ 60 subjects in the parallel trials and 40 subjects in the crossover trials. Many of the smaller studies of patients with diabetes mellitus were excluded. All but 5 of the studies included patients with cardiovascular disease. The doses of EPA + DHA ranged from 0.045 to 5.4 g/day; 13 trials of supplements used >2 g/day. Three of the 4 plant-oil studies used 4 to 5 g/day of ALA.

TGs: In the 27 studies that measured TG levels, all but 1 study with EPA + DHA doses ≥ 2 g/day found highly significant decreases.^{7,12-19} There was evidence of greater reduction in patients with higher baseline levels of TGs. Studies in individuals with baseline TG levels <1.70 mmol/L (150 mg/dL) found TG reductions between 10% and 25%. Studies in patients with cardiovascular disease and TGs ≥ 1.70 mmol/L (150 mg/dL) demonstrated 10% to 30% reductions in TG levels. Of the studies in patients with dyslipidemia, 2 of the 3 studies reported 20% to 33% reductions in TGs. Studies in individuals with severe hypertriglyceridemia (TGs >5.65 mmol/L [500 mg/dL]) reported TG reductions of 40% to 79% with EPA + DHA intake >3 g/day.¹⁹⁻²¹ Another review of the effects of EPA + DHA in patients with diabetes reported 25% to 45% reductions in TG levels, with evidence of a dose response.²² EPA + DHA effects do not appear to differ by sex or dietary fat intake. A clear linear trend toward greater TG reduction emerges with higher doses of EPA + DHA, regardless of source (Figure 1).⁷ Although results of some studies suggest that the TG-lowering effects of fish and fish oil diminish over time, studies of higher-dose EPA + DHA supplementation as long as 2.3 years showed that TG lowering did not diminish over time. There was also some evidence in these studies of a diminution of the LDL-raising effects over time.²³

In a study of pure ALA supplementation, doses of both 4.5 and 9.5 g/day from ALA margarine increased TG levels. Both studies in which ALA was provided as part of a Mediterranean diet found decreases in TG levels; however, fish intake increased as well.

Total cholesterol: Treatment effects were not consistent for changes in plasma total cholesterol levels in 33 studies.^{7,12-19} Most studies found net increases in total cholesterol of between 0% and 6% (approximately <0.36 mmol/L [14 mg/dL]); the results in only 3 studies were significantly different compared with control. No study evaluated a population exclusively of patients with diabetes. However, subgroup analysis in 1 study found that the effect of fish oil was similar in the 98 patients with diabetes compared with all participants, with a nonsignificant greater decrease in total cholesterol in the patients with diabetes. Source and dose of marine omega-3 fatty acids were not clearly related to total cholesterol changes. All 4 studies of ALA reported net increases in total cholesterol, but there was no apparent

difference compared with results of studies of marine omega-3 fatty acids. Interpretation of these findings is problematic because most studies either did not control for saturated fat intake or used omega-3 fatty acid preparations containing a significant amount of cholesterol.

LDL: Data on LDL was reported in 23 studies.^{7,12-19} A fairly uniform net increase in LDL cholesterol levels occurred across studies, with most studies finding a net increase of <0.26 mmol/L (10 mg/dL), with change ranging from -0.49 to $+0.54$ (-19 to $+21$ mg/dL). No clear pattern of LDL change emerged among the 10 studies of populations with cardiovascular disease, 4 dyslipidemia studies, 1 study in patients with chronic renal failure, or the 3 studies in healthy subjects. No difference related to source or dose of marine omega-3 fatty acids was found. The 2 studies of ALA reported smaller increases in LDL that were not significantly different from findings in the marine omega-3 fatty acid studies.

Apolipoprotein B: In a secondary analysis of randomized trials that measured apolipoprotein B levels, 26 trials had data on ≥ 20 subjects in parallel trials and 10 subjects in crossover trials.⁷ No consistent effects were identified for either total apolipoprotein B or apolipoprotein B-100, with approximately half the studies showing a small increase and the other half showing a small decrease.^{7,12,18} Some evidence of an inverse dose effect was apparent for total apolipoprotein B. In contrast, significant decreases in apolipoprotein B-100 of 0.20 to 0.45 g/L (20 to 45 mg/dL) were found in 4 of 6 studies.

Lipoprotein subfractions: Fish and fish oil may shift plasma lipoprotein composition to a less atherogenic pattern. A diet high in fish consumption was shown to decrease levels of medium and small VLDLs but to have no effect on LDL composition or particle size.^{24,25} Small studies of EPA and/or DHA supplementation did, however, demonstrate either a decrease in small, dense LDL particles or an increase in large, buoyant LDL.^{17,18,26}

LDL oxidation: Some studies have shown that omega-3 fatty acids from both marine and plant sources may increase the susceptibility of LDL to oxidation, whereas others have not.^{17,27-30}

High-density lipoprotein (HDL): Most of the 27 studies that measured plasma HDL cholesterol levels found a net increase in HDL of 0.08 to 0.13 mmol/L (3 to 5 mg/dL), with 8 studies finding a statistically significant increase.^{7,12,17} Seven of the trials found either a small net decrease or no effect. All but 1 study had baseline HDL levels >1.04 mmol/L (40 mg/dL), and more than half had baseline levels >1.30 mmol/L (50 mg/dL). The efficacy of omega-3 fatty acid supplementation for raising HDL levels <1.04 mmol/L (40 mg/dL) has yet to be determined. No dose effect was found, although DHA may raise HDL to a slightly greater extent than does EPA. No difference be-

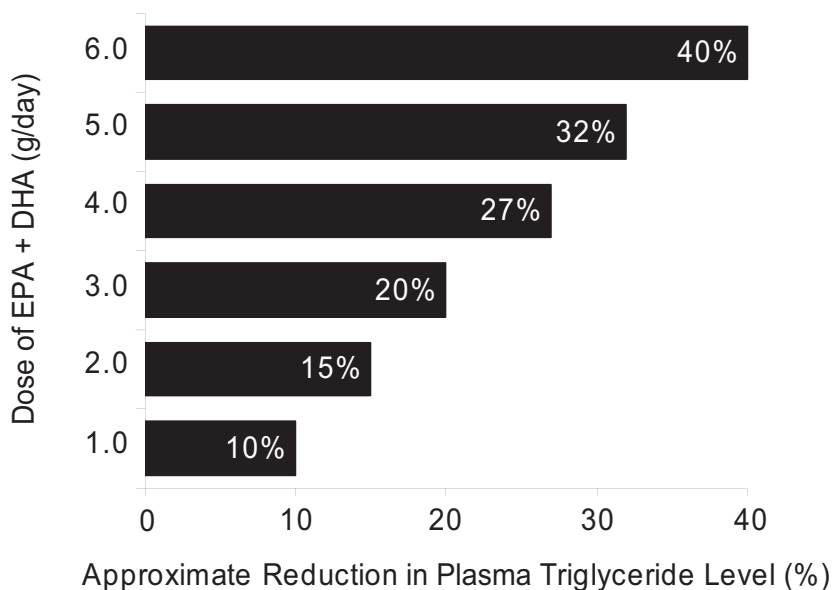


Figure 1. Approximate plasma triglyceride reduction per gram of combined eicosapentaenoic acid and docosapentaenoic acid (EPA + DHA) based on a meta-regression analysis of 19 studies. (Adapted from *Effects of Omega-3 Fatty Acids on Cardiovascular Risk Factors and Intermediate Markers of Cardiovascular Disease*.⁷)

tween dietary sources or supplements was identified. In the 2 ALA studies that measured HDL, there was no evidence of a treatment effect.

Apolipoprotein A-I: Levels of apolipoprotein A-I are strongly correlated with HDL levels, although the ratios of apolipoprotein A-I to HDL can vary. In a secondary analysis of 27 randomized trials with ≥ 20 subjects in parallel studies and 15 subjects in crossover trials, the effects of omega-3 fatty acid intake on apolipoprotein A-I levels varied between -5% and $+5\%$ (-0.07 to 0.10 g/L [-7 to $+10$ mg/dL]) in most studies.⁷ No study found a significant increase in apolipoprotein A-I; however, 2 studies did find small significant decreases. Effects did not differ according to source or dose of omega-3 fatty acids.

Lipoprotein(a): No consistent effect was found in 14 trials that evaluated lipoprotein(a).⁷ Baseline lipoprotein(a) levels varied widely in the studies, which limited the likelihood of statistically significant findings. Only 2 studies reported a statistically significant difference between omega-3 fatty acid treatment and control; both studies showed only a slight decrease in lipoprotein(a) of ≤ 0.03 g/L (3 mg/dL), which was largely limited to subjects with lipoprotein(a) levels ≥ 0.20 g/L (20 mg/dL). No difference among omega-3 fatty acid sources or doses was identified.

Blood Pressure

A meta-analysis of 36 randomized trials of fish-oil supplementation reported small but significant reductions in blood pressure of -2 mm Hg systolic and -1.5 mm Hg diastolic with a median dose of 3.7 g/day of fish oil.³¹ Blood pressure

effects were larger in those who had hypertension or were aged >45 years. Although a dose of fish oil <0.5 g/day did not have a significant effect on blood pressure, no dose effect was apparent with higher doses.^{7,32} A subsequent meta-analysis of 6 randomized trials of fish oil in patients with diabetes found similar results.⁷

Glucose Tolerance

Early reports of adverse effects of fish oil on blood glucose control and insulin activity were largely attributed to the high doses (≥ 10 g/day) used.²² More recent studies using lower doses of omega-3 fatty acids have shown no adverse effects on glucose tolerance.

Glycosylated hemoglobin (hemoglobin A_{1c}) was measured in 19 randomized trials of omega-3 fatty acid consumption with ≥ 10 subjects in either parallel trials or crossover trials; 14 were trials in patients with diabetes.^{7,12} Most studies evaluated doses of EPA + DHA of 3.0 to 4.6 g/day. Omega-3 fatty acids had a very small effect, if any, on glycosylated hemoglobin levels both in patients with diabetes and in healthy subjects. No dose or source effect was apparent across the studies, nor was there evidence of an effect with treatment duration. An earlier meta-analysis of 26 studies in patients with type 1 and type 2 diabetes also found no adverse effect on either glycosylated hemoglobin or fasting glucose levels.³³

No consistent effect was found on fasting plasma glucose levels in the 17 randomized trials of omega-3 fatty acid consumption with ≥ 25 subjects in parallel trials and 15 subjects in crossover trials. Changes in fasting plasma glucose ranged from -1.61 to $+1.39$ mmol/L (-29 to $+25$

mg/dL) over 6 to 8 weeks of treatment. Of the few studies that found a significant difference between treatment groups, only 1 study in patients with diabetes found a significant increase in fasting plasma glucose levels. There was no evidence of an effect due to dose, source, or duration of treatment across the studies.

Fasting insulin levels were measured in 16 trials. Wide variation in insulin levels was present within each population studied as well as between populations of patients with diabetes (6 studies) and healthy persons (9 studies). Therefore, percentage change from baseline was used for the analysis. Studies were evenly distributed between the tertiles of $<-10\%$, -10% to $+10\%$, and $>+10\%$ changes in insulin levels. No dose, source, or treatment-duration effect was apparent. One study found daily fish intake added to a weight-loss diet further lowered leptin levels as well as insulin levels beyond the levels obtained with a weight-loss diet alone.³⁴

Anti-inflammatory and Antithrombotic Effects

Epidemiologic studies of Greenland Eskimos and Japanese populations, both groups with high marine omega-3 fatty acid intakes, revealed low rates of chronic inflammatory disorders and autoimmune disorders in addition to low rates of cardiovascular disease. Results of clinical trials in rheumatoid arthritis, psoriasis, asthma, inflammatory bowel disorders, and systemic lupus erythematosus suggest that omega-3 fatty acids have clinically important effects on chronic inflammation.^{35–37} Inflammation, thrombosis, and endothelial function all share several key molecular mechanisms and are, in fact, intrinsically linked processes.^{38,39}

Opposing effects of omega-6 and omega-3 fatty acids:

The anti-inflammatory effects of omega-3 fatty acids are thought to be mediated, at least in part, by reduced synthesis of inflammatory molecules from omega-6 fatty acids. Omega-6 fatty acids are the predominant polyunsaturated fatty acids in the diet of Western countries. Neither omega-3 fatty acids nor omega-6 fatty acids are synthesized by the human body and must be obtained through diet or supplements. In the United States, the ratio of omega-6 to omega-3 fatty acids is estimated to be $\geq 15:1$ to $20:1$, although a more optimal ratio may be closer to $1:1$.⁴⁰ The predominant omega-6 fatty acid is arachidonic acid. Products of arachidonic acid metabolism, including prostaglandins, leukotrienes, lipoxins, and epoxygenase products, are important regulators of cellular functions; many of these products have atherogenic and prothrombotic effects. The omega-3 fatty acid EPA is a competitive substrate for the enzymes of the arachidonic acid cascade; involvement of EPA results in different end products, many of which oppose the products resulting from arachidonic acid metabolism (Figure 2).³⁵ When EPA is available, thromboxane B_3 with its few physiologic effects is produced rather than thromboxane B_2 , a

potent vasoconstrictor and platelet activator derived from arachidonic acid. Available EPA further counteracts the adverse effects of thromboxane B_2 through the manufacture of prostaglandins that, along with those manufactured from arachidonic acid, inhibit platelet aggregation and promote vasodilation.⁴¹ Omega-3 fatty acids may also oppose omega-6 fatty acid metabolites by promoting the production of largely inactive leukotriene B_5 and competitively inhibiting the production of highly inflammatory leukotriene B_4 from arachidonic acid. Altering the balance of downstream products from omega-6 and omega-3 fatty acids may also influence the arrhythmia threshold because almost all the prostaglandins produced from arachidonic acid are proarrhythmic, whereas those produced from EPA are not.⁴² EPA also results in the production of less inflammatory and chemotactic eicosanoids than those derived from arachidonic acid.³⁶ Recently, an alternative pathway for the anti-inflammatory effects of omega-3 fatty acids has been proposed. Resolvin E1 is an oxidized derivative of EPA that reduces inflammation by suppressing the activation of nuclear factor- κB and consequently the synthesis of inflammatory cytokines and chemokines.⁴³

Inflammation: Elevation in C-reactive protein (CRP), an acute-phase reactant produced by the liver, is considered a summary index of inflammation. CRP levels detected with high-sensitivity assays have consistently been shown to be an independent risk factor for cardiovascular disease.^{44,45} Tumor necrosis factor- α ; serum amyloid A; and interleukins 1, 6, and 10 are proinflammatory cytokines produced by monocytes and macrophages that have also been associated with increased cardiovascular risk. In vitro studies have shown that both EPA and DHA inhibit production of interleukin-6, the only cytokine that stimulates the synthesis of all the acute-phase reactants involved in inflammation.³⁶ Soluble adhesion factors—soluble intercellular adhesion molecule-1, soluble vascular adhesion molecule-1, and sP-selectin—are involved in platelet reactivity, endothelial activation, and plaque development; they may provide a measure of the inflammatory processes underlying atherosclerosis.

Two small studies, one of which was performed in patients with rheumatoid arthritis, found a significant reduction in CRP.^{46,47} Of the remaining 8 randomized trials that measured CRP, none found a significant effect of omega-3 fatty acid from fish oil on CRP, although some did observe a reduction in inflammatory cytokines.^{7,9,36,48–55} Trials of ALA supplementation, however, have shown consistent reductions in CRP. A study in 103 individuals with hypercholesterolemia who were treated with ALA-enriched margarine showed a significant reduction in CRP but not in soluble intercellular adhesion molecule-1, interleukin-6, or interleukin-10.⁵⁶ CRP was also significantly reduced in another study of ALA supplementation, along with levels of serum amyloid A and interleukin-6.⁵⁷ In a trial of an ALA-enriched diet, both CRP and adhesion molecule reductions

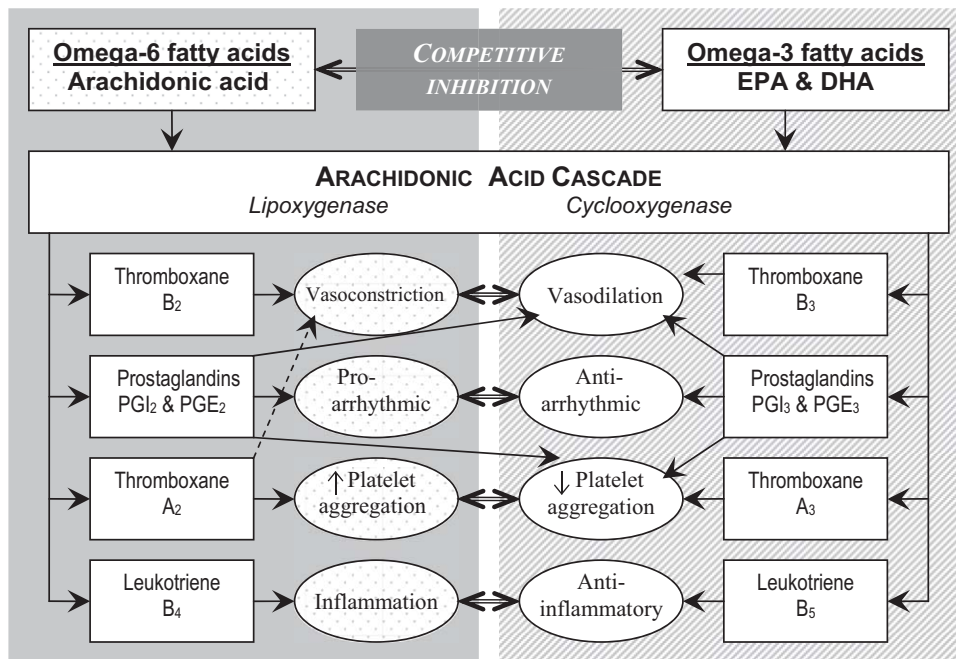


Figure 2. Opposing effects of omega-6 and omega-3 fatty acids on the arachidonic acid cascade that may influence vascular function, inflammation, platelet aggregation, and arrhythmia threshold. DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; PGE = prostaglandin E; PGI = prostacyclin; ↑ = increased; ↓ = decreased.

were observed.⁵⁸ A trial of a Mediterranean diet that resulted in a lower ratio of omega-6 to omega-3 fatty acids also showed a reduction in CRP, as well as in other markers of inflammation.⁵⁹

Although most studies of EPA and DHA have shown a decrease in soluble vascular adhesion molecules and decreased monocyte adhesion, some studies have not.^{39,49,54,60–63} Immunomodulatory effects may vary between EPA and DHA as well as by dose.^{35,54,63} Increased levels of adhesion molecules were found in 2 studies of higher-dose EPA + DHA (4.8 to 5.1 g/day).^{60,61} Moderate doses of 2 g/day had no effect. Lower doses, such as 1 g/day, were shown to decrease some markers of endothelial activation although they did not affect inflammatory cell numbers or function.⁴⁹ The clinical importance of these findings is unclear. In a study of a National Cholesterol Education Program step 2 diet, the decreased cell-mediated immunity that occurred with the step 2 diet was ameliorated in part when the diet was supplemented with a high intake of fish.⁶⁴ Dietary supplementation with ALA was shown to decrease adhesion molecules in 1 study.⁶⁵

Antithrombotic effects: Elevated levels of the procoagulant factors fibrinogen, factor VII, factor VIII, von Willebrand factor, and plasminogen activator inhibitor-1 have been associated with increased cardiovascular risk in epidemiologic studies.^{66–68} Platelets have been implicated in both thrombosis and inflammation.⁶⁹ Large doses of marine omega-3 fatty acids increase bleeding time, although the relationship of bleeding time to coagulation and fibrinolysis is unclear.⁴⁹ Doses of 4 g/day of fish oil did not affect bleeding time or the number of bleeding episodes in a study

of 511 patients who received either aspirin or warfarin following coronary artery bypass grafting.⁷⁰ However, because of the potential for prolongation of bleeding time and interaction with warfarin, patients receiving anticoagulant therapy should be monitored and the dose of anticoagulant adjusted if necessary.⁷¹

In 24 trials that evaluated fibrinogen, approximately half showed a net increase in fibrinogen level with omega-3 fatty acid consumption; the rest of the studies showed either a net decrease or no effect. Statistically significant decreases in fibrinogen of 5% to 20% were found in 3 studies, although 1 study reported an increase of 11%, nor was any consistent effect found in 19 trials evaluating factor VII or the 9 trials evaluating factor VIII. Most of the 9 trials evaluating von Willebrand factor found a small, nonsignificant decrease with omega-3 fatty acids. No effect on plasminogen activator inhibitor-1 was observed in 3 studies,⁴⁹ on tissue-type plasminogen activator antigen in 1 study,⁶² or on factor VII in 1 study.¹⁶ ALA does not appear to affect levels of hemostatic or fibrinolytic factors.⁴⁹ Omega-3 fatty acids do not appear to influence homocysteine levels.⁷²

EPA and DHA are incorporated in a dose-response fashion into platelet phospholipids.⁷ Omega-3 fatty acids from fish oil have been shown to influence gene regulation by downregulating gene expression of platelet-derived growth factors A and B.⁷³ Omega-3 fatty acids also suppress platelet activating factor, a potent platelet aggregator and leukocyte activator. However, using heterogeneous methodologies, most of the 11 studies of platelet aggregation found no effect due to omega-3 fatty acids.

Similarly, EPA and DHA are incorporated into leukocyte^{63,74} and monocyte⁷⁵ membranes, although data regarding the dose-response relationship are not available. In 1 study, fish oil supplementation suppressed monocyte synthesis of the prothrombotic thromboplastin and thromboxane B₂; no effect on fibrinolysis was evident, with no change in whole-blood clot lysis time or tissue plasminogen activator level.⁷⁵ Another study demonstrated decreased T-lymphocyte activation only with DHA and no effect on inflammatory cytokines with either DHA or EPA supplementation.⁶³ Fish oil has also been shown to suppress cyclooxygenase-2 expression in circulating monocytes through inhibition of Toll-like receptor-mediated signaling pathways.⁷⁶

Plaque Stabilization

A reduced risk of stroke with increased omega-3 fatty acid intake may be mediated by changes in plaque morphology that reduce the risk of acute plaque rupture. In a study in 188 patients awaiting carotid endarterectomy, those who received fish oil (1.4 g/day EPA + DHA) had higher levels of omega-3 fatty acids incorporated into their carotid plaques and more changes that can enhance plaque stability, such as thicker fibrous caps, absence of inflammation, and fewer macrophages.⁷⁷ Such changes may be expected to occur in coronary atheromas as well.

Endothelial Function

Endothelial dysfunction has been shown to predict future risk of CAD events.⁷⁸ Four studies demonstrated improved endothelial function with a dose of EPA and/or DHA of ≥ 3 g/day,^{39,79} although a study of a high-fiber Mediterranean diet enriched with omega-3 fatty acids did not.³⁰ Supplementation with 20 g/day of ALA from flaxseed oil also improved arterial compliance even though LDL oxidation was increased.⁸⁰ These effects, as well as the hypotensive effect of omega-3 fatty acids, may be mediated through enhanced nitric oxide production.⁸¹

Coronary Artery Restenosis

Restenosis following coronary angioplasty is primarily due to negative arterial remodeling and neointimal hyperplasia rather than an atherosclerotic process, although acute thrombosis may occur.⁸² In the 12 trials included in the analysis, fish oil was usually initiated prior to angioplasty. Although the end points used and the results were heterogeneous, an overall trend toward a 14% reduction in the risk of restenosis emerged with meta-analysis. Fish oil supplementation has not been evaluated in the modern era of coated coronary artery stents.

Table 1
Antiatherogenic and antithrombotic effects of omega-3 fatty acids: summary of results from randomized trials

Variable	Effect
Lipids	
Total cholesterol	↑ 0–6%
Triglycerides	↓ 10–40%
High-density lipoprotein cholesterol	↑ 0.08–0.13 mmol/L (3–5 mg/dL)
Low-density lipoprotein (LDL) cholesterol	↑ <0.26 mmol/L (10 mg/dL)
LDL particle size	Variable
Glucose tolerance	
Glycosylated hemoglobin	No effect
Fasting plasma glucose	No consistent effect
Fasting plasma insulin	No consistent effect
Inflammation	
C-reactive protein	No effect
Leukotriene B ₄	↓ Urinary excretion
Adhesion molecules	No consistent effect
Lipid oxidation	
EPA or DHA	= no effect
ALA	= ↑ with high dose
Hemostatic factors	
Bleeding time	↑
Coagulation factors	No effect on fibrinogen, factors VII and VIII, von Willebrand factor, plasminogen activator inhibitor-1
Platelets	No effects
Plaque stabilization	Possible effect
Endothelial function	Improved
Restenosis	↓ 14%
Exercise capacity	Slight ↑

ALA = α -linolenic acid; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; ↑ = increase; ↓ = decrease.

Exercise Capacity

Each of 3 randomized trials ($n \leq 10$ for all studies) found a small relative improvement in exercise capacity with exercise stress testing in those receiving fish oil compared with those receiving olive oil supplements.

The effects of marine and plant omega-3 fatty acids on intermediate markers of cardiovascular disease are summarized in Table 1.

Cardiovascular End Point Studies

Although omega-3 fatty acids have been shown to have beneficial antithrombotic and antiatherogenic effects, the clinical trials of omega-3 fatty acid supplementation do not show consistent reductions in the incidence of nonfatal MI.² The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI)-Prevenzione study was by far the largest trial of omega-3 fatty acid supplementation, with >11,000 participants.⁸³ Patients with a recent MI (primarily men), who consumed a Mediterranean-type diet with

Table 2
Summary of the Japan EPA Lipid Intervention Study (JELIS) results

Design/Duration	Patient Characteristics	Interventions (mg/day)	Main Results	Safety
Prospective, randomized trial, mean of 4.6 years	N = 18,645 Mean age, 61 yr Men (aged 40–75 yr), 31% Women (postmenopausal, aged \leq 75 yr) 69% Hypertension, 36% Diabetes mellitus, 15% CAD, 20% Mean LDL, 4.6 mmol/L (180 mg/dL)	Pravastatin 10 or simvastatin 5 vs EPA 1,800 + pravastatin 10 or EPA 1,800 + simvastatin 5	Primary end point: sudden cardiac death, fatal or nonfatal MI, unstable angina pectoris, CABG/PCI EPA + statin vs statin only: RRR = 19%, $p < 0.05$ ARR = 0.7	Higher incidence of adverse events, especially GI and skin disorders, and abnormal liver function tests with EPA + statin vs statin only (25.3% vs 21.7%; $p < 0.0001$); most were mild Treatment-related drug discontinuation: EPA + statin 11.7% vs statin only 7.2%

ARR = absolute risk reduction; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; EPA = eicosapentaenoic acid; GI = gastrointestinal; LDL = low-density lipoprotein cholesterol; MI = myocardial infarction; PCI = percutaneous coronary intervention; RRR = relative risk reduction; statin = 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor.

Adapted from *Am Heart J*⁸⁶ and American Heart Association Scientific Sessions.⁸⁷

moderate fish consumption, were randomly assigned to open-label omega-3 fatty acids (850 mg/day EPA + DHA) or to usual care alone. The primary combined efficacy end points were (1) the cumulative rate of all-cause death, nonfatal MI, and nonfatal stroke; and (2) the cumulative rate of cardiovascular death, nonfatal MI, and nonfatal stroke. After a mean follow-up of 3 years, the 10% relative decrease in risk for the combined primary end point of all-cause death, nonfatal MI, and nonfatal stroke was significant (95% confidence interval [CI], 1 to 18; $p = 0.048$), but the 11% decrease in risk for the other combined end point of cardiovascular death, nonfatal MI, and nonfatal stroke was not (CI, 1 to 20; $p = 0.053$). All-cause mortality was reduced by 21% and cardiovascular disease death was reduced by 30%, primarily resulting from the 45% reduction in incidence of sudden death. Post-hoc analysis revealed early divergence of the survival curves for the omega-3 fatty acids group, with a statistically significant 53% reduction in sudden death after just 4 months of treatment.⁵ Although delayed, significant 36% to 38% reductions in coronary and cardiovascular deaths emerged after 6 to 8 months of treatment. However, despite criticisms of potentially biased outcome assessment, there was no reduction in nonfatal MI by the end of 3.5 years of follow-up (relative risk [RR], 0.91; 95% CI, 0.70 to 1.18). A small study of fish oil supplementation in a population with a high level of background fish intake also showed no effect on a variety of cardiovascular disease outcomes.⁸⁴ Another small trial, however, did demonstrate significant reductions in the occurrence of both CAD death and nonfatal MI.⁸⁵

The Japan EPA Lipid Intervention Study (JELIS) recently reported the effects of EPA in addition to statin treatment in patients with hypercholesterolemia (Table 2).^{86–89} JELIS randomized 15,000 patients for primary prevention and 3,645 patients for secondary prevention to treatment with a statin only (pravastatin 10 mg/day or simvastatin 5 mg/day) or statin treatment plus EPA 1,800 mg/day. The primary end point was sudden cardiac death, fatal or nonfatal MI, unstable angina pectoris, and revascularization (coronary artery bypass graft or

percutaneous coronary intervention). After a mean 4.6 years of follow-up, those receiving a statin plus EPA had a significant 19% reduction in the primary end point compared with the statin-only group. Unstable angina was the only individual CAD event that was significantly reduced with the addition of EPA (RR, 0.76; 95% CI, 0.62 to 0.95; $p = 0.014$); RRs for nonfatal MI (0.75; CI, 0.54 to 1.04; $p = 0.86$), fatal MI (0.79; CI, 0.36 to 1.74; $p = 0.86$), and sudden death (1.06; CI, 0.55 to 2.07; $p = 0.95$) were not. However, this trial is not necessarily generalizable to non-Japanese populations, given the high levels of fish consumption in the study population. Furthermore, since this trial used only EPA, it cannot be considered either to confirm or refute the findings of the GISSI trial, which used both EPA and DHA.

In addition, there is no evidence of a significant effect on atherosclerotic progression assessed by quantitative coronary angiography. In the Study on Prevention of Coronary Atherosclerosis by Intervention with Marine Omega-3 Fatty Acids (SCIMO), 223 patients with angiographically proven CAD were randomized to fish oil supplementation with 1.6 g/day of EPA + DHA for 2 years.⁹⁰ Although a significant reduction in incidence of cardiovascular events occurred, the slight trend toward preserved coronary luminal diameter did not reach statistical significance. A second angiographic trial, the Harvard Atherosclerosis Reversibility Project, which treated 59 participants with 4.8 g/day of EPA + DHA, also showed no favorable change in any angiographic parameter after 2 years of treatment.⁹¹ In contrast, angiographic trials of lipid-lowering therapy in ≤ 100 participants demonstrated significant angiographic regression over a similar follow-up.^{92,93} Omega-3 fatty acids may cause clinically important beneficial changes in hemostatic factors, however. An angiographic trial in 610 patients following coronary artery bypass grafting showed a trend (odds ratio, 0.72; 95% CI, 0.51 to 1.01) toward reduction in vein graft occlusion at 1 year with 2 g/day of EPA + DHA.⁹⁴

An inverse relationship between dietary ALA consumption and coronary artery calcification was shown in 1

study,⁹⁵ but no trial of the effect of omega-3 fatty acids on coronary calcification has been performed. ALA consumption has been associated with reduced risk of nonfatal MI in some but not all epidemiologic studies.^{4,96,97}

Some evidence of a reduction in the risk of ischemic stroke may be found in epidemiologic studies of omega-3 fatty acids. Meta-analysis of findings in 9 prospective cohort studies revealed an inverse dose-response relationship between fish intake and stroke of any type.⁹⁸ The RR of stroke was 0.87 (95% CI, 0.77 to 0.98) for fish eaten 2 to 4 times a week and 0.69 (95% CI, 0.54 to 0.88) for ≥ 5 times a week. For the 3 studies with data on stroke subtypes, an inverse dose-response relationship between fish intake and ischemic stroke was significant for all levels of fish intake >1 time a month. There was also evidence of a trend toward an inverse relationship between fish intake and hemorrhagic stroke that did not reach statistical significance. In contrast, an impact on stroke is not evident in clinical trials of omega-3 fish oil. Meta-analysis of findings in 7 clinical trials of omega-3 fatty acid supplements or diet showed a nonsignificant RR reduction of 0.91 for stroke (95% CI, 0.56 to 1.48).⁹⁹ In the GISSI-Prevenzione study, although there were more fatal and nonfatal strokes in the group receiving omega-3 fatty acids than in the placebo group (92 vs 77, respectively), this did not reach statistical significance RR, 1.22 (0.81 to 1.85).⁵ The type of stroke—ischemic or hemorrhagic—was not characterized in this study.

Epidemiologic studies have shown that higher levels of EPA + DHA intake or blood levels were inversely related to carotid intimal-medial thickness.^{88,100–102} The SCIMO study also evaluated the effect of 2 years of EPA + DHA supplementation on the progression of carotid atherosclerosis. Of the 171 patients who completed the study, a nonsignificant net thickening of carotid intimal-medial thickness occurred with fish oil supplementation.⁸⁹ A study of ALA margarine as part of a dietary intervention to reduce saturated fat had similar results.⁵⁶

Additional data regarding stroke in addition to CHD will be forthcoming from the ongoing French SU.FOL.OM3 study, which will randomize 3,000 patients with CAD or stroke to folic acid plus B vitamins, omega-3 fatty acids, or placebo in a factorial design and follow them for 5 years.¹⁰³

Conclusions

Systematic review of randomized, controlled trials shows that omega-3 fatty acids have beneficial effects on several markers of increased cardiovascular risk. The most notable are a major effect on lowering elevated TG levels and smaller effects on lowering blood pressure and increasing HDL cholesterol levels. However, these changes only partly explain the 25% to 40% reduction in cardiovascular events seen primarily with fish oil supplements.⁷ Epidemiologic studies show more consistent reductions in incidence for nonfatal MI and ischemic stroke than do the clinical trials of

increased omega-3 fatty acid intake, suggesting important confounding dietary (such as background diet) or other factors in observational studies. Ongoing clinical trials may clarify the non-antiarrhythmic benefits of omega-3 fatty acid supplementation.

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