New Approaches to Therapy with Omega-3 Fatty Acids

Puneet Kakar, MRCP, Timothy Watson, MRCP, and Gregory Y.H. Lip, MD, FRCP

Corresponding author
Gregory Y.H. Lip, MD, FRCP
University Department of Medicine, City Hospital, Birmingham B18 7QH, UK.
E-mail: g.y.h.lip@bham.ac.uk

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With greater focus on chronic disease prevention, renewed attention has been directed toward understanding the pathophysiology of various medical conditions and the development of newer medical treatments to prevent and treat complications. There has been immense interest in evaluating societal lifestyles, cultural attitudes toward health, and dietary influences on health conditions. The omega-3 fatty acids have become a focus of interest, and recent research and trial evidence have highlighted their effects, including potential clinical advantages. Despite this progress, the precise mechanisms through which omega-3 fatty acids act remain poorly understood. These agents are now recommended as secondary prevention after acute myocardial infarction, and ongoing large clinical trials should provide insight into the use of omega-3 fatty acids in heart failure and the primary prevention of cardiovascular disease.

Introduction

The quest for protective dietary nutrients has spanned generations of scientific research. Almost all ingredients in our daily dietary consumption have been scrutinized and either vindicated or vilified. Linus Pauling explained the importance of vitamins in the human diet and extolled their beneficial effects. Similarly minerals, fats, and antioxidant-containing foods have been the focus of intense research in the past few decades. Of late, renewed interest and vigor has been showered on the role of omega fatty acids.

There are two broad types of omega fatty acids, the omega-3 (n-3) and the omega-6 (n-6) fatty acids. These are named based on the position of carbon-carbon unsaturation (double bond) in the fatty acid structure. Thus, n-3 fatty acids have their unsaturation at the third carbon atom from the terminal end of the molecule and n-6 fatty acids have their saturation at the sixth position. These two are essential fatty acid groups in that they cannot be produced by the body and thus need to be consumed through diet, from both plant and fish sources. These fatty acids play an important role in maintaining normal growth and development, reducing inflammation, and preventing cardiovascular disease. It has only recently been discovered that n-3 and n-6 fatty acids play opposing roles in the inflammatory process, with n-6 fatty acids having a proinflammatory effect and n-3 fatty acids having an anti-inflammatory effect. The net result may ultimately depend on the relative proportion of the two competing fatty acid groups.

The n-3 fatty acids have been extensively researched, and their biologic actions are thought to be protective. This review concentrates on this class of fatty acids. There are three main types of n-3 fatty acids: 1) α-linolenic acid (ALA), which is derived from plants; 2) eicosapentaenoic acid (EPA), which is derived from fish oil; and 3) docosahexaenoic acid (DHA), which is also derived from fish oil [1]. After consumption, the body converts ALA to EPA and DHA, the last two being more readily used. The extent of this conversion is under scrutiny [2], and fish oils are considered the major source of omega fatty acids.

Biologic Effects

The n-3 fatty acids have a number of positive effects in humans. These include modulation of endothelial function, antiarrhythmic effects, and antithrombotic effects. Each of these is described in detail.

Endothelial function

The n-3 fatty acids may have particular benefits on the endothelium, which may be the mechanism for their benefits in cardiovascular disease. On a biologic front and at a molecular level, it is thought that these fatty acids mediate this effect by regulating prostaglandin homeostasis, affecting endothelial-derived relaxation, improving plaque stability, and influencing endothelial adhesion molecules.

In one randomized, double-blind, placebo-controlled trial of hypercholesterolemic patients, recipients of fish

oil demonstrated improved relaxation to acetylcholine stress as compared with non–fish oil recipients [3]. Also, the placebo group showed poorer endothelial relaxation provoked by sodium nitroprusside as compared with the active group. Similarly, in a diabetic cohort of patients, arterial wall characteristics (specifically, arterial wall compliance) improved significantly after 6 weeks of fish oil administration. This was independent of changes in serum cholesterol and blood pressure levels, thus proving a direct effect of fish oils on improving arterial compliance [4]. Another study of healthy individuals that investigated nitric oxide synthesis showed that fish oil supplementation produced increased levels of urinary nitrate excretion while maintaining stable serum levels of nitrate, thus suggesting a relative increase in the systemic production of nitrates secondary to fish oil consumption [5]. These observations suggest that fish oils may directly improve endothelial function by improving endothelial relaxation in healthy and diseased states.

Soluble adhesion molecules, such as vascular cellular adhesion molecule (VCAM), E-selectin, and intercellular adhesion molecule (ICAM)-1, represent a proposed surrogate measure of endothelial adhesion and activation. Although some adhesion molecules are related to inflammatory status, the quantification of these adhesion molecules can be indicative of endothelial activation (eg, via cytokines). Nonetheless, conflicting data have been reported with omega fatty acids. For example, a reduction in ICAM-1 and soluble E-selectin was found in hypertriglyceridemic patients receiving n-3 fatty acids [6], whereas in a study of male smokers with hyperlipidemia, n-3 fatty acid supplementation increased soluble E-selectin and VCAM-1 [7]. In vitro evidence suggests that omega fatty acids reduce endothelial expression of VCAM-1, E-selectin, and ICAM-1 [8], but a study in patients with coronary artery disease reported increased plasma levels of these adhesion molecules [9]. Obviously, these data need to be interpreted with caution, as assessment of endothelial function based on adhesion molecule numbers is not entirely reliable. Correlation between soluble adhesion molecules and functional in situ adhesion molecules is not clear.

Antiarrhythmic effects

Effects on reduction of sudden cardiac death after myocardial infarction (MI) have led to the hypothesis that n-3 fatty acids may have an antiarrythmic potential. Mechanistic insights suggest a shift in cardiomyocte voltage potential from depolarizable to hyperpolarized, thus increasing cardiac refractoriness and reducing electrical "misfiring" [10]. This effect is mainly seen on sodium channels. Other possible explanations include calcium channel regulation, prevention of calcium overload [11], and increased heart rate variability [12].

A number of animal and in vitro human experiments also suggest a cardioprotective role for n-3 fatty acids. For example, supplementation of EPA in a canine model was shown to have a protective effect on the myocardium in terms of reducing arrythmogenic potential. These dogs were supplemented with EPA and it was found that after coronary occlusion, the control group had a higher incidence and severity of arrhythmias [13]. Similarly, in another experiment, 4 weeks after artificially inducing an MI, dogs pretreated with n-3 fatty acids had a lower incidence of ventricular fibrillation on exercise testing. The antiarrhythmic effect was associated with reduced heart rate, shortened QT interval, and prolonged PR interval [14].

A recently concluded clinical trial of fish oil in healthy humans, the ATTICA study [15•], showed that consumption lowered the arrythmogenic potential, even in healthy patients. The exact mode of action of channel stabilization remains to be determined. The Omega-Study group [16] is currently testing the effects of n-3 fatty acids after acute MI in a double-blind regimen under the conditions of modern treatment of MI (results are due in 2008).

Antithrombotic effects

The effects of n-3 fatty acids on coagulation have been controversial. A number of studies have investigated various surrogate indices of coagulation and fibrinolysis, and conflicting results have been reported.

Earlier experiments demonstrated an improved fibrinolytic state associated with n-3 fatty acid intake [17]. Increased fish intake was negatively associated with hemostatic markers, such as fibrinogen, factor VIII, and von Willebrand factor, in the Atherosclerosis Risk in Communities (ARIC) study [18], which was a population-based cross-sectional study. In contrast, Coronary Artery Risk Development in Young Adults (CARDIA) study [19] examined 1672 men and found no associations between these hemostatic markers and increased fish oil or n-3 fatty acid intake. Similarly, the recently concluded Quantification of the Optimal n-6/n-3 Ratio in the UK Fiet (OPTILIP) trial [20] showed no significant effects of fish oil consumption (or the alteration of n-6 to n-3 fatty acid ratio) on levels of plasma fibrinogen and factors XIIa, VIIc, and VIIa. Lee et al. [21] also demonstrated no improvement in hemostatic indices in patients who had suffered an MI and then were treated with n-3 fatty acids.

The n-3 fatty acids can inhibit platelet adhesion and platelet aggregation [22]. In an in vitro experiment using dietary fish oils, collagen-induced platelet aggregation was reduced in the fish oil and fish diet group [23]. In a group of middle-aged, nonsmoking men with hypertension and hypercholesterolemia, the intake of n-3 fatty acids was associated with a decrease in platelet aggregation to both collagen-induced and platelet activating factor–induced responses [24]. Indeed, the consumption of EPA and DHA may directly affect platelet thromboxane A2 synthesis, which may further inhibit platelet aggregation [25]. However, the effects of n-3 fatty acids on platelets in vitro may be quite different from the biologic effect in vivo. Cer-

tainly, there has been some evidence to suggest that platelet survival (which is shortened due to plaque-induced platelet damage) in atherothrombotic disease may be enhanced by the administration of n-3 fatty acids [26], suggesting that n-3 fatty acids reduce platelet–plaque "stickiness."

Cytokine modulation and anti-inflammatory effects

By influencing the production of biologically active cytokines [27], such as tumor necrosis factor and interleukin-1 [28], n-3 fatty acids may reduce systemic inflammation. The n-3 fatty acids are also known to inhibit cyclooxygenase, thus downregulating the arachidonic acid activation system and reducing active prostaglandins and leukotrienes [29].

Effects on lipids

The use of n-3 fatty acids has been shown to modulate the lipid profile. Although a 25% decrease in triglyceride levels was reported by Harris [30], this was associated with an increase in low-density lipoprotein cholesterol (LDL-C). The impact of this rise on cardiovascular health is unclear, as there have been suggestions that omega fatty acids may also lead to increased LDL-C oxidation, perhaps offsetting the effects of this modest increase in LDL-C and thereby allowing patients to benefit from the reduction in triglycerides [31].

Blood pressure lowering

The effect on blood pressure seems to be small, dose dependent, and also dependent on the magnitude of hypertension. Morris et al. [32] reported a reduction in blood pressure of 3.4/2.0 mm Hg with high-dose omega fatty acid use (5.6 g/d). The recently conducted International Study of Macro and Micro-nutrients and Blood Pressure (INTERMAP) study [33•], which was an international, cross-sectional, epidemiologic study of 4680 men and women from 17 population samples in China, Japan, the United Kingdom, and the United States, also corroborates the small but significant inverse effect these fatty acids have on blood pressure. After adjustment for 17 variables, the systolic/diastolic blood pressure differences were -0.55/-0.57 mm Hg for all participants, -1.01/-0.98 mm Hg for 2238 persons without medical or dietary interventions, and -0.91/-0.92 mm Hg for persons without hypertension.

Heart rate variability

Increased heart rate variability is known to be associated with a decreased mortality risk in MI survivors by reducing arrhythmias. Christensen et al. [12] demonstrated a significant positive correlation between consumption of n-3 fatty acids (ie, DHA) through fish eating and increased heart rate variability in 52 patients with a previous MI and left ventricular dysfunction. This association was further confirmed in a double-blind, randomized controlled trial using fish oil supplements (4.3 g/d of n-3 fatty acids) [34]. However, other studies have not demonstrated similar findings. For example, Hamaad et al. [35] showed no difference in indices of heart rate variability in 38 stable post-MI patients despite being supplemented with n-3 fatty acids for 3 months.

The exact mode of action to explain the benefits of n-3 fatty acids in cardiovascular disease has not clearly been established. There have been a number of postulated mechanisms through which fish-derived omega fatty acids exert their protective and anti-inflammatory effects, and these relate to blood pressure lowering, plaque stabilization, lipid-profile stabilizing, and other antiatherogenic effects.

The Epidemiologic Evidence for the Benefits of Omega-3 Fatty Acids

Based on the mechanistic explanations detailed in the preceding text, people who consume a diet rich in n-3 fatty acids would (theoretically, at least) have better lipid profiles, lower triglycerides, and lower blood pressures. This should translate into increased survival, but the results are not always so forthcoming (Table 1).

Early observational studies in the Eskimos of Greenland confirmed that consumption of fish oil indeed had a favorable outcome on serum lipid profile as compared with other Western populations [36]. Similarly, in a small study of 852 men based in the town of Zutphen, Netherlands, cardiovascular mortality and fish oil consumption were inversely related [37]. This was also seen in an elderly Dutch population, in whom a similar inverse relation was shown between fish oil consumption and cardiovascular mortality [38], as well as in a case-control subgroup study of the Multiple Risk Factor Intervention (MRFIT) study [39], which demonstrated that consumption of ALA and the risk of stroke were inversely related. Other epidemiologic data from the Chicago Western Electric Study [40] also confirm these associations. Furthermore, a multinational review of fish consumption data [41] showed an inverse relation between fish consumption and all-cause and ischemic heart disease mortality in both sexes. Finally, the Nurses' Health Study [42] also showed that increased consumption of n-3 fatty acids was associated with a lower risk of MI and coronary heart disease in women.

Not all studies demonstrate an inverse relationship between n-3 fatty acid intake and cardiovascular risk. Although a number of reasons have been cited, including mercury levels in fish, other unaccounted risk factors, and faulty study design, the data on dietary fish oil consumption per se has not always been positive. For example, the European Multicenter Case-Control Study on Antioxidants, Myocardial Infarction and Breast Cancer [EURAMIC] [43] and the Seven Countries data study [44] failed to confirm the association between omega fatty acids and reduced cardiovascular mortality. Similarly, the Health Professionals Follow-up Study [45] and the US Physicians' Health Study [46] did not show any relationship between fish oil consumption and cardiovascular mortality but did

Table 1. Epidemiologic data for omega fatty acids

Study	Subjects, *n*	Key findings
Chicago Western Electric Study [40]	1822 men	Inverse relation between fish consumption and death from coronary artery disease, especially nonsudden death from myocardial infarction
Nurses' Health Study [42]	84,688 female nurses	Omega fatty acids were associated with a lower coronary heart disease risk and mortality
Health Professionals Study [45]	44,895 men	Increasing fish intake in healthy individuals did not substantially reduce the risk of coronary heart disease among men who were initially free of cardiovascular disease
US Physicians' Health Study [46]	20,551 men	No association between fish consumption (or omega-3 fatty acid intake) and reduced risk of total myocardial infarction, nonsudden cardiac death, or total cardiovascular mortality; however, fish consumption was related to a reduced risk of total mortality
EURAMIC study [43]	1339	Docosahexaenoic acid did not have a protective effect on the risk of myocardial infarction
Alpha-Tocopherol, Beta-Carotene Cancer Prevention study [47]	21,930 men	Intake of fatty fish was directly related to coronary death

EURAMIC—European Multicenter Case-control Study on Antioxidants, Myocardial Infarction and Breast Cancer.

suggest a reduction in sudden cardiac death in the n-3 fatty acid group. One study, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study [47] found that n-3 fatty acid intake from fish was associated with a trend toward an increased relative risk of coronary death.

Randomized controlled trial evidence in cardiovascular disease

The Diet and Reinfarction Trial (DART) [48] was the first experimental design used to assess the effects of omega fatty acids prospectively. The trial was designed to assess the effects of three dietary interventions on the survival and secondary prevention of MI in 2033 men. These three interventions were 1) reducing of fat intake and increasing the ratio of unsaturated to saturated fats, 2) increasing fatty fish intake, and 3) increasing fiber intake. The group that increased fatty fish intake had a 29% reduced all-cause mortality over 2 years as compared with the "no dietary advice" group. A subgroup analysis of those who took fish oil capsules showed a 56% reduction in total mortality and a 62% reduction in coronary heart disease mortality [49]. This led the investigators to conclude that fish-derived n-3 fatty acids have a strong cardiovascular protective effect in patients at high cardiovascular risk.

The largest intervention clinical trial was the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio (GISSI)-Prevenzione trial [50]. This was an open-label, multicenter, non–placebo-controlled randomized study of 11,324 patients who had experienced a recent MI. The primary combined efficacy end point was death, nonfatal MI, and stroke. Intention-to-treat analyses were done according to a two-way factorial design and by treatment group (four-way analysis). These patients were assigned to receive vitamin E, omega fatty acids (EPA plus DHA), both, or neither. After 3.5 years of follow-up, the group that received the n-3 fatty acids alone experienced a 15% reduction in the primary end point of death, nonfatal MI, and nonfatal stroke, a 20% reduction in all-cause mortality, and a 45% reduction in sudden death as compared with the control group. Further post hoc analysis reveals that n-3 supplementation was most beneficial in preventing mortality and sudden cardiac death in those with heart failure [51]. Vitamin E provided no benefit either by itself or in addition to omega fatty acids. A favorable response was also seen in lowering triglyceride and cholesterol levels.

Another post hoc analysis assessed the time frame of action of n-3 fatty acids and the impact on total and cardiovascular mortality [51]. Survival curves for n-3 fatty acid treatment diverged early after randomization, total mortality was significantly lowered after 3 months of treatment, and the risk reduction of sudden death was statistically significant at 4 months and cardiovascular mortality at 8 months. These results indicated that not only did n-3 fatty acid supplementation have an impact on survival after MI, but the effect was observed early after the index event.

Although there have been concerns regarding the validity of the Indian Infarct Survival study [52,53], the results apparently support a favorable effect of n-3 fatty acid supplementation in acute MI survivors. In the study, patients were randomized to receive mustard oil (ALA), fish oil (EPA and DHA), or placebo. Treatments were administered about (mean) 18 hours after MI and the patients were followed for 1 year. The total cardiac events (ie, nonfatal infarctions, cardiac arrhythmias, left ventricular enlarge-

Table 2. Randomized controlled data for omega fatty acids

Study	Subjects, *n*	Key findings
GISSI-Prevenzione [50]	11,324 post-MI	Omega-3 fatty acids were associated with a 15% reduction in the primary end point of death, nonfatal MI, and nonfatal stroke; a 20% reduction in all-cause mortality; and a 45% reduction in sudden death, and with preventing arrythmias in those with heart failure
Indian Infarct Survival study [52]	360 post–acute MI	Nonfatal MIs were significantly lower in the fish oil and mustard oil groups
Diet and Reinfarction Trial (DART) [48]	2033 men post-MI	Fish consumption had a 29% reduction in all-cause mortality over a 2-year period in male MI survivors, with the greatest benefit seen in fatal MIs
Coronary Angioplasty Restenosis Trial (CART) [59]	500	Fish oil supplementation 2 weeks prior to angioplasty did not reduce restenosis rates

GISSI—Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; MI—myocardial infarction.

ment, and angina) were significantly less in the fish oil and mustard oil groups compared with the placebo group. Of note was the finding that total cardiac deaths in the mustard oil group were no less than those in the placebo group, although the fish oil group did show a reduction.

Other studies have demonstrated a favorable effect of omega fatty acids on infarct size. In one prospective cohort study of 745 post–acute MI patients in Norway, peak serum creatine kinase levels (used as a surrogate for Q-wave infarction) correlated negatively with fish consumption [54].

While the case for omega fatty acids was being made in acute MI, other investigators studied patients with angiographically established coronary atherosclerosis [55]. n-3 Fatty acid treatment in these patients resulted in a lower rate of progression, increased regression (at repeat angiography), and fewer clinical events. In patients undergoing coronary bypass grafting, recipients of n-3 fatty acids had a lower graft occlusion rate as compared with recipients of placebo [56]. Regarding coronary angioplasty and fish oil consumption, Gapinski et al. [57] reported a meta-analysis demonstrating a favorable effect of fish oils on restenosis rates. However, the Enoxaparin MaxEPA Prevention of Angioplasty Restenosis (EMPAR) [58] study and the Coronary Angioplasty Restenosis Trial (CART) [59] failed to show any significantly positive effects after angioplasty. Thus, the beneficial effects of omega fatty acids remain largely in patients with acute MI (Table 2).

Meta-analyses

A number of meta-analyses have tried to collate useful evidence of n-3 fatty acids in the prevention and treatment of cardiovascular disease.

One meta-analysis published in 2002 incorporated data from 11 randomized controlled trials of dietary and nondietary consumption of n-3 fatty acids in coronary heart disease [60]. The results demonstrated that the risk ratio of nonfatal MI in patients who were on n-3 polyunsaturated fatty acid–enriched diets compared with control diets or placebo was 0.8 (95% CI, 0.5–1.2; $P = 0.16$), and the risk ratio of fatal MI was 0.7 (95% CI, 0.6–0.8). Sudden death was associated with a risk ratio of 0.7 (95% CI, 0.6–0.9), whereas the risk ratio of overall mortality was 0.8 (95% CI, 0.7–0.9), thus suggesting an overall benefit of both dietary and nondietary omega-3 fatty acids in patients with coronary heart disease.

A Cochrane review published in 2004 included data from 48 randomized controlled trials and 41 cohort analyses [61]. The relative risk of death in those participants randomized to n-3 supplementation or advice compared with those on placebo or no such dietary advice was 0.87 (95% CI, 0.73–1.03). Subgrouping by fish or vegetable source of n-3 and dose of n-3 did not suggest a significant difference in either group. Meta-analysis of both randomized controlled studies (95% CI, 0.87–1.37) and cohort studies (95% CI, 0.73–1.13) did not reveal a significant effect of n-3 fatty acids on cardiovascular events. Overall, pooled trial results did not show a reduction in the risk of total mortality or combined cardiovascular events in those taking additional n-3 fatty acids [61].

n-3 Fatty acids in stroke

Whereas the GISSI-Prevenzione trial, DART, and Indian Infarct Survival study examined patients with acute MI, there have been no randomized prospective studies in other vascular conditions, such as acute stroke. As compared with epidemiologic studies in coronary artery disease, the data on stroke are more limited, but there are enough to suggest some beneficial effects of n-3 fatty acids (Table 3).

In the National Health and Nutrition Examination Survey (NHANES) Epidemiologic Follow-up Study [62], white female patients who consumed fish more than once per week had a lower age-adjusted stroke incidence compared with women who did not consume fish. Similarly, a trend toward reduced stroke risk with increasing fish consumption was reported in the Nurses' Health Study [63]. As previously mentioned, in the MRFIT study, ALA

Table 3. Omega fatty acid consumption and stroke risk

Study	Subjects, *n*	Key findings
Multiple Risk Factor Intervention Trial (MRFIT) subgroup [39]	192 men	High α-linolenic acid consumption was associated with lower stroke risk
National Health and Nutrition Examination Survey [62]	4584	Fish consumption was inversely related to stroke risk
Nurses' Health Study [63]	84,688 female nurses	Higher consumption of fish and omega-3 polyunsaturated fatty acids was associated with a reduced risk of thrombotic infarction, primarily among women who did not take aspirin
GISSI-Prevenzione [50]	11,324 post-MI	No effect on the incidence of stroke by consuming fish oils

GISSI—Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; MI—myocardial infarction.

intake was negatively associated with stroke incidence. In contrast, both the Chicago Western Electric Study [64] and the Physicians' Health Study [65] failed to find any relationship between reported fish intake and reduced stroke risk. Similarly, in both the Lyon Diet Heart Study [66] and the GISSI-Prevenzione trial [50], there was no significant effect on the incidence of stroke.

Plant versus fish oils: which is better?

The ability of the body to convert ALA into the more usable forms of omega fatty acids, such as EPA and DHA, remains under investigation. The determinants and rate-limiting steps of this pathway, including enzymes and co-factors, have not yet been clearly established.

The few studies that provide positive evidence for ALA include the Indian Infarct Survival Study [52] and the Lyon Diet Study [66], whereas the Mediterranean Alpha-Linolenic Enriched Groningen Dietary Intervention (MARGARIN) study [67] did not show a clear benefit of ALA. Bearing in mind the favorable results of ALA in a recent meta-analysis of 11 randomized controlled trials of 7951 patients, the overall conclusion is that all essential fatty acids (ie, EPA, DHA, and ALA) have a somewhat favorable effect on cardiovascular disease [60]. Similarly, the INTERMAP study [33•] found a small blood pressure–lowering effect in the diet high in n-3 fatty acids, and the differences were greater in the fish-derived fatty acids as compared with the plant-derived fatty acids.

Current Opinion: Eat More Fish or Take Fish Oil Capsules?

Omega fatty acid supplementation is favorable not only for secondary prevention but also for primary prevention of cardiovascular disease. However, the question remains as to how we can increase the amount of consumption of these essential fatty acids. The obvious answer is by increasing fatty fish consumption, but this may prove difficult for a number of reasons.

The most widely available source of omega fatty acids is cold-water oily fish such as wild salmon, anchovies, mackerel, herring, and sardines. Oil from these fish has around seven times as much n-3 as n-6, whereas farmed (grain-fed) salmon have a higher proportion of omega-6. Omega fatty acids are also present at high concentration in over-the-counter fish oil preparations [68]. As with fresh fish, concern had been raised that these oils may contain unacceptably high levels of contaminants, such as mercury and organochlorines. This claim appears to be unfounded, and processed oil may even prove safer from this aspect than consumption of unprocessed fish [69,70].

The amount of fatty fish required may be quantitatively and proportionately larger than what many dietary regimes may actually allow. The environmental pollutants in the fish, such as methyl mercury, dioxins, and polychlorinated biphenyls, may make consumption hazardous [71]. The quality of fish may also be circumspect, and this may play an important role in actual delivery of omega fatty acids to the body. All these reasons make a concentrated fatty acid capsule an attractive option [72]. Advantages of the capsules are preparation from a purified source, exact dose administration, and convenience. Side effects of a concentrated fish oil capsule, including odor, aftertaste, and other systemic effects, may prove to be important determinants of compliance.

Current Guidelines for Cardiovascular Prevention

The data for secondary prevention after MI were largely gleaned from the GISSI-Prevenzione trial. It is generally agreed that the data are clinically robust and the measures cost effective in this patient group [73]. Prescription of omega fatty acid extract for hypertriglyceridemia was approved by the US Food and Drug Administration in 2006 after careful evaluation of cost and clinical effectiveness [74]. The American Heart Association has made clear recommendations to augment fatty fish supplementation for both healthy and "at risk" individuals (Table 4).

The recent National Institute for Health and Clinical Evidence guidelines have also highlighted the role of omega fatty acids in secondary prevention for those who have suffered an MI within the past 3 months and categorically state the following: "Patients should be advised to eat a Mediterranean-style diet, to consume at least 7 g of omega

Table 4. American Heart Association recommendations for omega fatty acid intake

Population subtype	Fish oil recommendation
Patients without documented CHD	Eat a variety of (preferably fatty) 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 about 1 g/d of EPA + DHA, preferably from fatty fish. EPA + DHA in capsule form could be considered in consultation with the physician.
Patients who need to lower triglycerides	2–4 g/d of EPA + DHA provided as capsules under a physician's care

CHD—coronary heart disease; DHA—docosahexaenoic acid; EPA—eicosapentaenoic acid.

3 fatty acids per week from two to four portions of oily fish and for those not reaching this target a prescription of supplemental fish oil extract should be considered." [75•].

Conclusions

The role of omega fatty acids in cardiovascular disease prevention and treatment is becoming increasingly established. The potential role for omega fatty acids in treating and preventing a host of other disorders, including psychiatric illnesses, gastrointestinal disease, neoplasms, and even multiple sclerosis, is under further investigation.

Although historical evidence suggests that fatty fish consumption improves health outcomes, it is perhaps unexpected that in the era of advanced pharmaceutical design, a naturally occurring substance could apparently offer substantial impact in terms of cardiovascular protection in certain patient groups. It is clear that as the mechanistic processes involved remain poorly understood, the advent of this treatment is likely to be met with a degree of skepticism.

Disclosures

No potential conflict of interest relevant to this article was reported.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. **USDA Nutrient Data Laboratory.** Available at http://www.nalusda.gov/fnic/ foodcomp. Accessed on August 1, 2007.
2. Emken EA, Adlof RO, Gulley RM: **Dietary linoleic acid influences desaturation and acylation of deuterium-labeled linoleic and linolenic acids in young adult males.** *Biochim Biophys Acta* 1994, **1213:**277–288.
3. Goode GK, Garcia S, Heagerty AM: **Dietary supplementation with marine fish oil improves in vitro small artery endothelial function in hypercholesterolemic patients: a double-blind placebo-controlled study.** *Circulation* 1997, **96:**2802–2807.
4. McVeigh GE, Brennan GM, Cohn JN, et al.: **Fish oil improves arterial compliance in non-insulin-dependent diabetes mellitus.** *Arterioscler Thromb* 1994, **14:**1425–1429.
5. Harris WS, Rambjor GS, Windsor SL, Deirdrech D: **N-3 fatty acids and urinary excretion of nitric oxide metabolites in humans.** *Am J Clin Nutr* 1997, **65:**459–464.
6. Abe Y, El-Masri B, Kimball KT, et al.: **Soluble cell adhesion molecules in hypertriglyceridemia and potential significance on monocyte adhesion.** *Arterioscler Thromb Vasc Biol* 1998, **18:**723–731.
7. von Schacky C: **n-3 PUFA in CVD: influence of cytokine polymorphism.** *Proc Nutr Soc* 2007, **66:**166–170.
8. De Caterina R, Liao JK, Libby P: **Fatty acid modulation of endothelial activation.** *Am J Clin Nutr* 2000, **71(Suppl 1):**213S–223S.
9. Johansen O, Seljeflot I, Hostmark AT: **The effect of supplementation with omega-3 fatty acids on soluble markers of endothelial function in patients with coronary heart disease.** *Arterioscler Thromb Vas Biol* 1999, **19:**1681–1686.
10. Leaf A, Kang JX, Xiao YF, Billman GE: **Clinical prevention of sudden cardiac death by n–3 polyunsaturated fatty acids and mechanism of prevention of arrhythmias by n–3 fish oils.** *Circulation* 2003, **107:**2646–2652.
11. Hallaq H, Smith TW, Leaf A: **Modulation of dihydropyridine-sensitive calcium channels in heart cells by fish oil fatty acids.** *Proc Natl Acad Sci U S A* 1992, **89:**1760–1764.
12. Christensen JH, Korup E, Aaroe J, et al.: **Fish consumption, n-3 fatty acids in cell membranes, and heart rate variability in survivors of myocardial infarction with left ventricular dysfunction.** *Am J Cardiol* 1997, **79:**1670–1673.
13. Kinoshita I, Itoh K, Nishida-Nakai M, et al.: **Antiarrhythmic effects of eicosapentaenoic acid during myocardial infarction--enhanced cardiac microsomal (Ca(2+)-Mg2+)-ATPase activity.** *Jpn Circ J* 1994, **58:**903–912.
14. Billman GE, Kang JX, Leaf A: **Prevention of ischemia-induced cardiac sudden death by n-3 polyunsaturated fatty acids in dogs.** *Lipids* 1997, **32:**1161–1168.
15.• Chrysohoou C, Panagiotakos DB, Pitsavos C, et al.: **Long-term fish consumption is associated with protection against arrhythmia in healthy persons in a Mediterranean region—the ATTICA study.** *Am J Clin Nutr* 2007, **85:**1385–1391.

This study demonstrates that the long-term consumption of fish is associated with lower QTc interval in people without any evidence of cardiovascular disease. These data imply that even at the population level, fish intake may provide antiarrhythmic protection.

16. Rauch B, Schiele R, Schneider S, et al.: the Omega-Study group: **Highly purified omega-3 fatty acids for secondary prevention of sudden cardiac death after myocardial infarction-aims and methods of the OMEGA-study.** *Cardiovasc Drugs Ther* 2006, **20:**365–375.
17. Barcelli U, Glas-Greenwalt P, Pollak VE: **Enhancing effect of dietary supplementation with omega-3 fatty acids on plasma fibrinolysis in normal subjects** *Thromb Res* 1985, **39:**307–312.
18. Shahar E, Folsom AR, Wu KK, et al.: **Associations of fish intake and dietary n-3 polyunsaturated fatty acids with a hypocoagulable profile. The Atherosclerosis Risk in Communities (ARIC) Study.** *Arterioscler Thromb* 1993, **13:**1205–1212.

19. Archer SL, Green D, Chamberlain M, et al.: **Association of dietary fish and n-3 fatty acid intake with hemostatic factors in the Coronary Artery Risk Development in Young Adults (CARDIA) study.** *Arterioscler Thromb Vasc Biol* 1998, **18:**1119–1123.
20. Sanders TA, Lewis F, Slaughter S, et al.: **Effect of varying the ratio of n-6 to n-3 fatty acids by increasing the dietary intake of alpha-linolenic acid, eicosapentaenoic and docosahexaenoic acid, or both on fibrinogen and clotting factors VII and XII in persons aged 45-70 y: the OPTILIP study.** *Am J Clin Nutr* 2006, **84:**513–522.
21. Lee KW, Blann AD, Lip GY: **Effects of omega-3 polyunsaturated fatty acids on plasma indices of thrombogenesis and inflammation in patients post-myocardial infarction.** *Thromb Res* 2006, **118:**305–312.
22. Bayon Y, Croset M, Daveloose D, et al.: **Effect of specific phospholipid molecular species incorporated in human platelet membranes on thromboxane A2/prostaglandin H2 receptors.** *J Lipid Res* 1995, **36:**47–56.
23. Agren JJ, Vaoisaonen S, Haonninen O, et al.: **Hemostatic factors and platelet aggregation after a fish-enriched diet or fish oil or docosahexaenoic acid supplementation.** *Prostagland Leukot Essent Fatty Acids* 1997, **57:**419–421.
24. Mori TA, Beilin LJ, Burke V, et al.: **Interactions between dietary fat, fish, and fish oils and their effects on platelet function in men at risk of cardiovascular disease.** *Arterioscler Thromb Vasc Biol* 1997, **17:**279–286.
25. Croset M, Lagarde M: **In vitro incorporation and metabolism of icosapentaenoic and docosahexaenoic acids in human platelets—effect on aggregation.** *Thromb Haemost* 1986, **56:**57–62.
26. Levine PH, Fischer M, Schneider PB, et al.: **Dietary supplementation with omega-3 fatty acids prolongs platelet survival in hyperlipidemic patients with atherosclerosis.** *Arch Intern Med* 1989, **149:**1113–1117.
27. von Schacky C: **n-3 PUFA in CVD: influence of cytokine polymorphism.** *Proc Nutr Soc* 2007, **66:**166–170.
28. Endres S, von Schacky C: **n-3 polyunsaturated fatty acids and human cytokine synthesis.** *Curr Opin Lipidol* 1996, **7:**48–52
29. Uauy R, Mena P, Valenzuela A: **Essential fatty acids as determinants of lipid requirements in infants, children and adults.** *Eur J Clin Nutr* 1999, **53(Suppl 1):**S66–S77.
30. Harris WS: **n-3 Fatty acids and serum lipoproteins: human studies.** *Am J Clin Nutr* 1997, **65(Suppl 5):**1645S–1654S.
31. Hau MF, Smelt AH, Bindels AJ, et al.: **Effects of fish oil on oxidation resistance of VLDL in hypertriglyceridemic patients.** *Arterioscler Thromb Vasc Biol* 1996, **16:**1197–1202.
32. Morris MC, Sacks F, Rosner B: **Does fish oil lower blood pressure? A meta-analysis of controlled trials.** *Circulation* 1993, **88:**523–533.
33.• Ueshima H, Stamler J, Elliott P, et al.: **Food omega-3 fatty acid intake of individuals (total, linolenic acid, long-chain) and their blood pressure. INTERMAP Study.** *Hypertension* 2007, **50:**313–319.

Demonstrates a positive impact of omega-3 polyunsaturated fatty acid intake on blood pressure reduction, even in those people without hypertension.

34. Christensen JH, Gustenhoff P, Korup E, et al.: **Effect of fish oil on heart rate variability in survivors of myocardial infarction: a double blind randomised controlled trial.** *BMJ* 1996, **312:**677–678.
35. Hamaad A, Kaeng Lee W, Lip GY, MacFadyen RJ: **Oral omega n3-PUFA therapy (Omacor) has no impact on indices of heart rate variability in stable post myocardial infarction patients.** *Cardiovasc Drugs Ther* 2006, **20:**359–364.
36. Bang HO, Dyerberg J, Hjoorne N: **The composition of food consumed by Greenland Eskimos.** *Acta Med Scand* 1976, **200:**69–73.
37. 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:**1205–1209.
38. Kromhout D, Feskens EJ, Bowles CH: **The protective effect of a small amount of fish on coronary heart disesae mortality in an elderly population.** *Int J Epidemiol* 1995, **24:**340–345.
39. Simon JA, Fong J, Bernert JT Jr, Browner WS: **Serum fatty acids and the risk of stroke.** *Stroke* 1995, **26:**778–782.
40. Daviglus ML, Stamler J, Orencia AJ: **Fish consumption and the 30-year risk of fatal myocardial infarction.** *N Engl J Med* 1997, **336:**1046–1053.
41. Zhang J, Sasaki S, Amano K, Kestleloot H: **Fish consumption and mortality from all causes, ischemic heart disease, and stroke: an ecological study.** *Prev Med* 1999, **28:**520–529
42. 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:**1815–1821.
43. Guallar E, Aro A, Jimenez FJ, et al.: **Omega-3 fatty acids in adipose tissue and risk of myocardial infarction: the EURAMIC study.** *Arterioscler Thromb Vasc Biol* 1999, **19:**1111–1118.
44. Kromhout D, Bloemberg BP, Feskens EJ, et al.: **Alcohol, fish, fibre and antioxidant vitamins intake do not explain population differences in coronary heart disease mortality.** *Int J Epidemiol* 1996, **25:**753–759.
45. 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:**977–982.
46. Albert CM, Hennekens CH, O'Donnell CJ: **Fish consumption and risk of sudden cardiac death.** *JAMA* 1998, **279:**23–28.
47. Pietinen P, Ascherio A, Korhonen P, et al.: **Intake of fatty acids and risk of coronary heart disease in a cohort of Finnish men: the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study.** *Am J Epidemiol* 1997, **145:**876–887.
48. 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:**757–761.
49. Burr ML, Sweetham PM, Fehily AM: **Diet and reinfarction.** *Eur Heart J* 1994, **15:**1152–1153
50. **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.** *Lancet* 1999, **354:**447–455.
51. Marchioli R, Barzi F, Bomba E, et al.; GISSI-Prevenzione Investigators: **Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione.** *Circulation* 2002, **105:**1897–1903.
52. 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:**485–491.
53. White C: **Suspected research fraud: difficulties of getting at the truth.** *BMJ* 2005, **331:**281–288.
54. Landmark K, Abdelnoor M, Urdal P, et al.: **Use of fish oils appears to reduce infarct size as estimated from peak creatine kinase and lactate dehydrogenase activities.** *Cardiology* 1998, **89:**94–102.
55. von Schacky C, Angerer P, Kothny W, et al.: **The effect of dietary omega-3 fatty acids on coronary atherosclerosis: a randomized, double-blind, placebo-controlled trial.** *Ann Intern Med* 1999, **130:**554–562.
56. Eritsland J, Arnesen H, Gronseth K, et al.: **Effect of dietary supplementation with n-3 fatty acids on coronary artery bypass graft patency.** *Am J Cardiol* 1996, **77:**31–36.
57. Gapinski JP, VanRuiswyk JV, Heudebert GR, Schectman GS: **Preventing restenosis with fish oils following coronary angioplasty: a meta-analysis.** *Arch Intern Med* 1993, **153:**1595–1601.

58. Cairns JA, Gill J, Morton B, et al.: **Fish oils and low-molecular-weight heparin for the reduction of restenosis after percutaneous transluminal coronary angioplasty. The EMPAR Study.** *Circulation* 1996, **94:**1553–1560.
59. Johansen O, Brekke M, Seljeflot I, et al.: **n-3 fatty acids do not prevent restenosis after coronary angioplasty: results from the CART study. Coronary Angioplasty Restenosis Trial.** *J Am Coll Cardiol* 1999, **33:**1619–1626.
60. Bucher HC, Hengstler P, Schindler C, Meier G: **n-3 polyunsaturated fatty acids in coronary heart disease: a meta-analysis of randomized controlled trials.** *Am J Med* 2002, **112:**298–304.
61. Hooper L, Thompson RL, Harrison RA, et al.: **Omega 3 fatty acids for prevention and treatment of cardiovascular disease.** *Cochrane Database of Systematic Reviews* 2004, **Issue 4. Art. No.:** CD003177. DOI: 10.1002/14651858. CD003177.pub2.
62. Gillum RF, Mussolino ME, Madans JH: **The relationship between fish consumption and stroke incidence: the NHANES I Epidemiologic Follow-up Study (National Health and Nutrition Examination Survey).** *Arch Intern Med* 1996, **156:**537–542.
63. Iso H, Rexrode KM, Stampfer MJ: **Intake of fish and omega-3 fatty acids and risk of stroke in women.** *JAMA* 2001, **285:**304–312.
64. Orencia AJ, Daviglus ML, Dyer AR, et al.: **Fish consumption and stroke in men: 30-year findings of the Chicago Western Electric Study.** *Stroke* 1996, **27:**204–209.
65. Morris MC, Manson JE, Rosner B, et al.: **Fish consumption and cardiovascular disease in the Physicians' Health Study: a prospective study.** *Am J Epidemiol* 1995, **142:**166–175.
66. 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:**779–785.
67. Bemelmans WJ, Broer J, Feskens EJ, et al.: **Effect of an increased intake of alpha-linolenic acid and group nutritional education on cardiovascular risk factors: the Mediterranean Alpha-linolenic Enriched Groningen Dietary Intervention (MARGARIN) study.** *Am J Clin Nutr* 2002, **75:**221–227.
68. Kris-Etherton PM, Harris WS, Appel LJ; American Heart Association: **Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease.** *Circulation* 2002, **106:**2747–2757.
69. Melanson SF, Lewandrowski EL, Flood JG, Lewandrowski KB: **Measurement of organochlorines in commercial over-the-counter fish oil preparations: implications for dietary and therapeutic recommendations for omega-3 fatty acids and a review of the literature.** *Arch Pathol Lab Med* 2005, **129:**74–77.
70. 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:**1603–1605.
71. US Environmental Protection Agency: **Fish Advisories web page.** Available at http://www.epa.gov/waterscience/fish. Accessed on August 1, 2007.
72. Weber HS, Selimi D, Huber G: **Prevention of cardiovascular diseases and highly concentrated n-3 polyunsaturated fatty acids (PUFAs).** *Herz* 2006, **31:**24–30.
73. Lamotte M, Annemans L, Kawalec P, Zoellners Y: **A multi-country health-economic evaluation of highly concentrated n-3 polyunsaturated fatty acids in the secondary prevention after myocardial infarction.** *Herz* 2006, **31:**74–82.
74. McKenney JM, Sica D: **Prescription omega-3 fatty acids for the treatment of hypertriglyceridemia.** *Am J Health Syst Pharm* 2007, **64:**595–605.
75.• National Collaborating Centre for Primary Care: *Post myocardial infarction: secondary prevention in primary and secondary care for patients following a myocardial infarction*. London: Royal College of General Practitioners; 2007.
This work provides recommendations for secondary prevention of MI. It recommends consuming at least 7 g/wk of n-3 fatty acids.