Omega-3 Fatty Acid Supplementation for the Prevention of Arrhythmias

Mina K. Chung, MD

Corresponding author
Mina K. Chung, MD
Department of Cardiovascular Medicine, Cleveland Clinic, 9500 Euclid Avenue, F-15, Cleveland, OH 44195, USA.
E-mail: chungm@ccf.org

Current Treatment Options in Cardiovascular Medicine 2008, **10:**398–407
Current Medicine Group LLC ISSN 1092-8464

Opinion statement

Fish oil, or omega-3 (n-3) polyunsaturated fatty acid (PUFA), supplements have been purported to produce potential health benefits. One of the strongest supported effects of n-3 PUFAs may be their potential benefits in reducing the risk of sudden cardiac death. This article reviews clinical and mechanistic studies that may explain the effects of these agents on ischemic arrhythmias, sudden death, and atrial fibrillation.

Introduction

The concept that omega-3 (n-3) polyunsaturated fatty acids (PUFAs) may have potential health benefits has been supported by early observations in populations with a high fish intake. Greenland Eskimos, Alaska Natives, and Japanese in fishing villages eat a diet high in fish and have a low incidence of cardiovascular disease. Since these early observations, favorable effects from n-3 PUFAs have been reported for triglyceride reduction, mild hypertension, coronary heart disease prevention, arrhythmias (ventricular arrhythmias, premature ventricular contractions, and atrial fibrillation [AF]), overall mortality, and sudden death mortality. Although variable efficacy has been reported for some of these areas, the data supporting beneficial effects on arrhythmias, particularly ischemic ventricular arrhythmias and sudden death prevention, are perhaps the most compelling. The aim of this review is to survey the data on n-3 PUFAs' effects on preventing cardiac arrhythmias, specifically sudden cardiac death and ischemic ventricular arrhythmias, premature ventricular complexes (PVCs), and AF.

OMEGA-3 VERSUS OMEGA-6 FATTY ACIDS

The two main classes of essential fatty acids are omega-6 (n-6) and n-3 PUFAs (Fig. 1). The n-6 PUFAs have a double-bond six carbons from the amino terminus, whereas the n-3 PUFAs have a double-bond three carbons from the amino terminus. These fatty acids are essential in that they are not manufactured de novo but must be taken in by diet. The n-6 PUFAs are derived from certain oils and meats. n-6 PUFA linoleic acid is metabolized to γ-linolenic acid and arachidonic acid, which is also derived from meat sources. These are metabolized to n-6–derived eicosanoids, such as thromboxane A_2, leukotriene B_4, and prostaglandins, which are considered proaggregatory, proinflammatory, and arrhythmogenic. In contrast, the n-3 PUFAs may be derived from certain vegetable oils, which supply α-linolenic acid (ALA). ALA is metabolized to eicosapentaenoic acid (EPA), but with low efficiency. Our main n-6 PUFA intake is from fish and fish oils, which supply EPA and docosahexaenoic acid (DHA). These are metabolized to n-3–derived eicosanoids, including prostacyclin, thromboxane A_3, and leukotriene B_5, which are considered anti-inflammatory and antithrombotic [1,2].

Omega-3 fatty acid supplementation

Omega-3 fatty acids in the prevention of sudden cardiac death

Free fatty acids and the risk of sudden death

- Elevated circulating free fatty acids have been reported to be a risk factor for sudden death. In the Paris Prospective Study reported by Jouven et al. [3], 5250 men were observed over a mean follow-up period of 22 years.

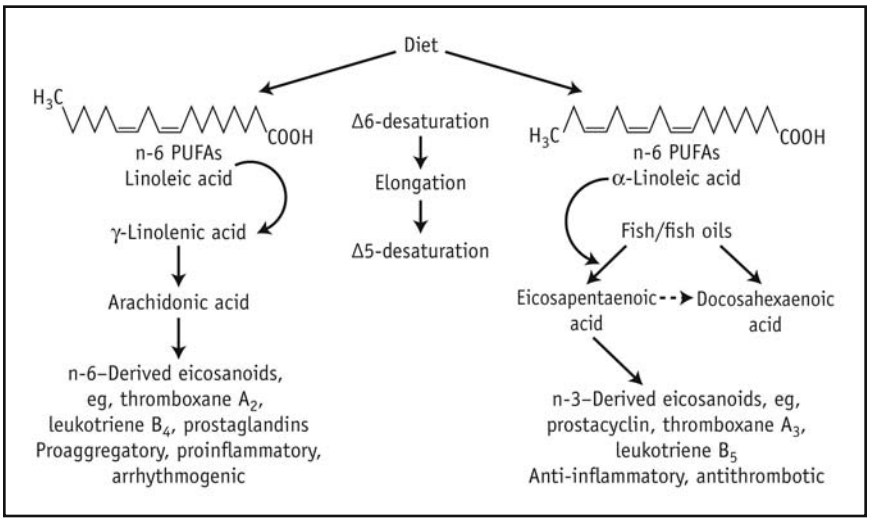

Figure 1. Omega-6 (n-6) versus omega-3 (n-3) polyunsaturated fatty acids (PUFAs): two classes of essential fatty acids. (*Modified from* Lee and Lip [1] and Leaf et al. [2].)

Circulating concentration of nonesterified free fatty acids was demonstrated to be an independent risk factor for sudden death ($P = 0.01$), although not for fatal myocardial infarction (MI). Risk of sudden death rose with increasing quintile of nonesterified free fatty acids.

- The arrhythmogenicity of fatty acids appears to depend highly on n-3 versus n-6 subtypes. In an epidemiologic study, Siscovick et al. [4] reported that n-3 PUFAs may prevent arrhythmias. Groups with a high fish intake experienced less fatal coronary disease. Specific effects were reported on sudden death and primary cardiac arrest, with lower risk associated with higher quartiles of n-3 fatty acids in red cell membranes. Albert et al. [5] reported that n-3 fatty acid blood levels were significantly associated with a lower risk of sudden death in the Physicians' Health Study. Patients with sudden cardiac death were compared with controls matched for age and smoking status. Baseline blood levels of long-chain n-3 fatty acids were inversely related to the risk of sudden death.

Trials with omega-3 PUFA supplementation

- Clinical studies of n-3 PUFA supplementation have included several large trials, such as the Diet and Reinfarction Trial (DART) [6] and the large Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione trial [7]. In DART [6], 2033 men who had an MI were randomly assigned to one of three dietary advice strategies:
  - Decrease fat intake to 30% of total energy and increase the ratio of polyunsaturated to saturated fat
  - Increase cereal fiber to 18 g daily
  - Increase fatty fish intake to at least two 200- to 400-g portions weekly or 1.5-g fish oil capsules.
- There was no significant change in mortality associated with the first strategy, a small but nonsignificant effect on mortality with the second strategy, and a 29% decrease in mortality with the third (fatty fish) strategy.
- In the GISSI-Prevenzione trial [7], 11,324 survivors of recent MI (within the preceding 3 months) were treated for a mean follow-up of 3.5 years with n-3 PUFA, 1 g/d (EPA + DHA); vitamin E, 300 mg/d; both therapies; or neither therapy. The primary end points were death, nonfatal MI, and cerebrovascular accident. n-3 PUFA, but not vitamin E, significantly

reduced the risk of the combined primary end point of death, nonfatal MI, and stroke. All the benefit was attributable to a decrease in risk for overall and cardiovascular death, particularly sudden death. With n-3 PUFA, there was a 28% decrease in total mortality and a 47% reduction in sudden death. The protective effect was most pronounced in patients with reduced left ventricular ejection fraction [8].

- In the Physicians' Health Study [9], 20,551 US male physicians were administered a baseline questionnaire regarding fish consumption. Dietary fish intake was associated with lower sudden death and total mortality. The threshold for the effect was at one fish meal per week. There was a 52% lower risk in men who consumed fish at least once a week compared with those who had fish less than once a month ($P = 0.04$).
- In the Indian Experiment on Infarct Survival, a placebo-controlled study, 360 patients were randomly assigned to receive fish oil (1.08 g/d EPA + 0.72 g/d DHA), mustard seed oil, or placebo (aluminum hydroxide) within 24 hours of suspected acute MI [10]. The primary end point was total cardiac events (sudden cardiac death, total cardiac deaths, nonfatal reinfarction). At 1 year, total cardiac events were reduced by 30% in the patients who received fish oil, and cardiac deaths occurred in 24.5% of the fish oil group compared with 34.7% of controls ($P < 0.01$).
- In the Japan EPA Lipid Intervention Study (JELIS) [11], 18,645 hyperlipidemic Japanese patients who were on statins and already consuming a significant amount of fish were randomly assigned to receive open-label EPA, 1.8 g/d. In this group, there was no reduction in sudden cardiac death, suggesting that supplementation over an ample baseline n-3 PUFA intake might not produce additional benefits. However, in this study, major coronary events were reduced 19% and trends toward reduced unstable angina and nonfatal coronary events were observed. It was postulated that fish oil might have plaque stabilization properties.
- Overall, these studies support a role for n-3 PUFAs in reducing sudden death. However, these studies also demonstrate the less-convincing effect n-3 PUFAs may have on reducing other end points, such as overall mortality and acute MI.

Omega-3 PUFA supplementation in patients with an implantable cardioverter-defibrillator

- Although intravenous infusion of n-3 PUFA in patients with implantable cardioverter-defibrillators (ICDs) and recurrent sustained ventricular tachycardia (VT) reduced inducibility of monomorphic VT in one study [12], longer-term clinical studies using oral n-3 PUFA supplementation to reduce arrhythmias in patients with implantable defibrillators have shown variable results. Raitt et al. [13] reported that in 200 patients with ICDs and recent VT/ventricular fibrillation (VF), fish oil at 1.8 g/d did not reduce VT/VF. In this study, recurrent VT/VF was actually more common in patients taking fish oil. In contrast, Leaf et al. [14] reported a benefit to fish oil; there was a longer time to ICD therapy for VT/VF or death from any cause in patients with ICDs randomly assigned to receive fish oil compared with those who received olive oil. The differences were more significant in patients who were on therapy for at least 11 months. In the Study on Omega-3 Fatty Acids and Ventricular Arrhythmias (SOFA) [15], a randomized, placebo-controlled, double-blind trial, 546 primary prevention ICD patients in Europe with at least one ICD intervention for VT/VF over the previous year were assigned to treatment with fish oil 2 g/d (900 mg n-3 PUFA, equivalent to three to four fish meals per week) or placebo (high–oleic acid sunflower oil). The primary outcome of spontaneous ventricular tachyarrhythmias as

recorded by the ICD or all-cause mortality was not significantly different in the fish oil group; however, in patients with prior MI, there was a trend toward a benefit with fish oil ($P = 0.09$). Importantly, there was no evidence of harm from fish oil.

- In a meta-analysis of n-3 PUFAs in coronary heart disease, Bucher et al. [16] reported a benefit from n-3 PUFAs on fatal MI, sudden death, and overall mortality. In contrast, a meta-analysis by Hooper et al. [17•] showed only trends toward a benefit of n-3 fat.
- A potential explanation for the discrepant results in ICD patients and overall mortality is that ICD therapy for VT/VF may not be a proper surrogate for the development of VF secondary to an acute ischemic event. The mechanism of VT/VF in ICD patients may not be ischemia-based but myocardial scar–based reentry. The beneficial effects of n-3 fatty acids may be primarily on ischemic sudden death rather than on overall mortality.

Antiarrhythmic effects of PUFAs: animal studies

- Animal studies support an antiarrhythmic effect of PUFAs in ischemic arrhythmias. In ischemia/reperfusion models in rats and marmosets, tuna fish oil (dietary n-3 PUFA) and sunflower seed oil (n-6 PUFA) supplementation reduced the incidence of VF and increased fibrillation threshold [18–20]; however, n-3 PUFAs were more effective. In a canine model of ischemia after prior MI, a balloon was inflated in the left circumflex artery during treadmill exercise 1 month after acute anterior MI [21–23]. In these studies, ischemia-induced VF was prevented in up to 87% of dogs by intravenous purified n-3 PUFA (DHA or EPA). These studies support the potential benefits of n-3 PUFAs in preventing ischemic ventricular arrhythmias.

Possible mechanisms of action

- Various mechanisms have been proposed to explain the effects of n-3 PUFAs on risk for cardiovascular disease and sudden death [24]. n-3 PUFAs may have antiarrhythmic, membrane stabilization, antithrombotic, and anti-inflammatory effects. They may also reduce fibrinogen and triglycerides and affect endothelial function. Investigators have shown membrane stabilization effects with reduced electrical excitability [2,25]. They have demonstrated suppression of L-type calcium channel ($I_{Ca\text{-}L}$) and sodium channel (I_{Na}) currents with a shift to a more negative resting membrane potential and suppression of automaticity. Protection in ischemic areas may be particularly important. In ischemic areas, the resting membrane is partially depolarized and the resting membrane potential is closer to threshold. Suppression of calcium currents would decrease calcium fluxes, calcium overload, and triggered arrhythmia from afterdepolarizations. Other possible cardioprotective mechanisms include inhibition of adhesion molecule expression, inhibition of arachidonic acid metabolism, protection against low-density lipoprotein (LDL) oxidation, and plaque stabilization [26–29]. These studies support a mechanism of membrane stabilization with reduced arrhythmogenesis, particularly in ischemic conditions, and may explain the reductions in sudden cardiac death observed in clinical studies.

Omega-3 PUFAs and atrial fibrillation

Postoperative atrial fibrillation

- Calo et al. [30] reported that n-3 PUFAs reduced the incidence of postoperative AF after coronary artery bypass grafting (CABG). In this study, 160 patients undergoing CABG were randomly assigned to receive n-3

PUFA, 2 g/d from 5 days preoperatively until discharge. Postoperative AF was reduced from 33% to 15% in this open-label study. A randomized, placebo-controlled trial is ongoing.

Non-postoperative atrial fibrillation

- Despite potential beneficial effects on prevention of postoperative AF, there do not seem to be consistent effects on non-postoperative AF in epidemiologic studies, although these studies have relied on assessment of n-3 PUFA intake by diet questionnaires. Mozaffarian et al. [31] reported that tuna or other broiled or baked fish, but not fried fish or fish sandwiches, was associated with lower incidence of AF. In contrast, in a Danish registry of 47,949 patients who were given a food questionnaire, AF occurred in 556 subjects after a mean follow-up of 5.7 years [32]. Consumption of n-3 PUFAs from fish was not associated with reduced risk of AF/atrial flutter. Similarly, in the Rotterdam Study, a prospective cohort study including dietary intake data for 5184 subjects, AF occurred in 312 subjects after a mean follow-up of 6.4 years [33]. EPA and DHA intake was not associated with risk of AF. Whether n-3 PUFA supplementation will reduce AF remains to be demonstrated in randomized, controlled trials.

Animal and in vitro studies

- n-3 PUFAs have been studied in various models of AF. In a canine model of AF vagally induced by atrial burst pacing and extrastimuli, Sarrazin et al. [34] reported that dogs fed EPA plus DHA for 14 days demonstrated a 42% to 79% reduction in AF inducibility as well as reduced expression of gap junction proteins connexin 40 and 43. Protection against AF was mostly related to reduced connexin 40 expression. In a rabbit model of stretch-induced AF produced by increasing intra-atrial pressure, Ninio et al. [35] reported that compared with rabbits given dietary sunflower oil, higher pressures were required to induce and sustain AF and there was less marked stretch-induced shortening of atrial refractory periods in fish oil–fed animals. The authors concluded that incorporation of dietary n-3 fatty acids into atrial tissue reduced stretch-induced susceptibility to AF. In canine experiments testing AF associated with electrical remodeling induced by rapid atrial pacing and AF associated with structural remodeling induced by rapid ventricular pacing, Sakabe et al. [36] demonstrated that oral n-3 PUFA pretreatment did not change atrial pacing effects on refractory period AF duration. However, n-3 PUFAs suppressed ventricular pacing–induced increases in AF duration, heart failure–related atrial fibrosis and conduction abnormalities, hemodynamic dysfunction, and activation of mitogen-activated protein kinases. In contrast, in a canine model of acute rapid atrial pacing, da Cunha et al. [37] reported that n-3 PUFA treatment significantly reduced shortening of atrial effective refractory periods and decreased occurrence of AF. The differing effects of n-3 PUFAs may reflect variable effects on the heterogeneous forms of AF, which may underlie the conflicting results of prior epidemiologic studies of n-3 PUFAs in AF prevention.

Omega-3 PUFAs and premature ventricular complexes

- In a randomized, placebo controlled study of 84 patients with frequent (≥ 1440/24 hours) PVCs, treatment with 1.5 g/d of n-3 PUFAs showed a trend toward PVC reduction but failed to significantly reduce PVCs compared with placebo [38].

Omega-3 PUFAs and other cardiovascular effects

Myocardial infarction

- Although n-3 PUFAs have been associated with reduction in sudden death mortality, demonstration of their effects on coronary artery disease or MI prevention has been less convincing. The meta-analysis by Bucher et al. [16] found a decrease in overall mortality, sudden death, and fatal MI, but no significant effects on nonfatal MI.

Blood lipids

- In the GISSI-Prevenzione trial, n-3 PUFA supplementation was not associated with any significant effect on total or LDL cholesterol but was associated with a slight increase in high-density lipoprotein cholesterol and significant reduction in triglycerides [7].

Omega-3 PUFA sources

- Predominant essential fatty acids in common oils include n-3 and n-6 PUFAs [39]. n-3 PUFAs are present in canola, fish, flaxseed, soybean, and walnut oils. n-6 PUFAs are found in borage, corn, cottonseed, grapeseed, peanut, primrose, safflower, sesame, soybean, and sunflower oils. However, conversion of ALA, found in plant and nut sources, to the more active longer-chain n-3 PUFAs (DHA and EPA) is inefficient (2%–5% for DHA, < 5%–10% for EPA) [40]. The main source of DHA and EPA is fish. Fish species rich in n-3 PUFAs include anchovies, bass, bluefish, mackerel, pompano, herring, salmon, sardines, trout, and sablefish [41]. One fish meal typically consists of approximately 227 g of fish [41]. Table 1 lists the approximate n-3 PUFA content of common fish. The American Heart Association (AHA) recommendations for n-3 PUFA, discussed under "Recommendations," include at least two oily fish meals per week, or 1 g/d of n-3 PUFA.

Safety of omega-3 PUFAs

- Potential limitations to high fish intake include fishy aftertaste and gastrointestinal symptoms (nausea, bloating, belching). The risks of clinical bleeding, worsening glycemia in patients with impaired glucose intolerance or diabetes, and a rise in LDL cholesterol, mainly in patients with hypertriglyceridemia, are low to very low at doses up to 1 g/d and low to moderate at greater than 3 g/d [42]. Another concern is exposure to environmental contaminants, which should be considered with frequent intake of certain fish. Fortunately, most concentrated and purified n-3 PUFA supplements appear to have essentially no mercury and very low levels of organochloride contaminants, although less-controlled preparations may have some amounts [42].

Recommendations

- Based on the potential for reducing the risk of sudden death, current recommendations for n-3 PUFA supplementation can be supported. The AHA's recommendations for n-3 fatty acid intake are listed in Table 2 [43]. They include eating a variety of preferably oily fish at least two

Table 1. Approximate omega-3 PUFA (EPA + DHA) content in common fish*

Fish	Fat, *g*	n-3 PUFA/100 g, *g*	n-3 PUFA/3 oz, *g*	Alternative portion size: n-3 PUFA/fish meal, *g*
Anchovy	4.8	1.5	1.3	
Canned in oil, drained	9.7	2.1	1.8	0.4 (5 anchovies, 20 g)
Bass				
Freshwater	3.7	0.7	0.6	0.5 (1 fillet, 79 g)
Striped	2.3	0.8	0.6	1.2 (1 fillet, 159 g)
Sea	2.0	0.7	0.6	0.9 (1 fillet, 129 g)
Bluefish	4.2	0.8	0.7	1.25 (1 fillet, 150 g)
Carp	5.6	0.4	0.4	0.9 (1 fillet, 218 g)
Catfish				
Channel, farmed	7.6	0.4	0.3	0.6 (1 fillet, 159 g)
Channel, wild	2.8	0.5	0.4	0.7 (1 fillet, 159 g)
Cod				
Atlantic	0.7	0.2	0.2	0.4 (1 fillet, 231 g)
Pacific	0.6	0.2	0.2	0.3 (1 fillet, 116 g)
Flounder/sole	1.2	0.2	0.2	0.4 (1 fillet, 163 g)
Halibut				
Atlantic and Pacific	2.3	0.5	0.4	0.9 (0.5 fillet, 204 g)
Greenland	13.8	1.0	0.9	2.1 (0.5 fillet, 204 g)
Herring				
Atlantic	9.0	1.6	1.4	3.0 (1 fillet, 184 g)
Pacific	13.9	1.8	1.6	3.4 (1 fillet, 184 g)
Mackerel				
Atlantic	13.9	2.5	2.1	2.8 (1 fillet, 112 g)
King	2.0	0.3	0.3	0.7 (0.5 fillet, 198 g)
Pacific, Jack, mixed species	7.0	1.6	1.3	3.5 (1 fillet, 225 g)
Pompano	9.5	0.8	0.7	0.9 (1 fillet, 112 g)
Salmon				
Atlantic, farmed	10.9	1.9	1.6	3.4 (0.5 fillet, 198 g)
Atlantic, wild	6.3	1.72	1.5	3.4 (0.5 fillet, 198 g)
Chinook	10.4	2.3	1.9	4.5 (0.5 fillet, 198 g)
Coho, farmed	7.7	1.2	1.0	1.9 (1 fillet, 159 g)
Coho, wild	5.9	1.3	1.1	2.6 (0.5 fillet, 198 g)
Pink	3.5	1.1	0.9	1.8 (0.5 fillet, 159 g)
Sockeye	8.6	1.2	1.0	2.4 (0.5 fillet, 198 g)
Sardine, canned in oil, drained	11.5	1.0	0.9	0.9 (3.75-oz can, 92 g)
Swordfish	4.0	0.6	0.5	0.9 (1 piece, ~ 4½ × 2 × 1 in, 136 g)
Tilapia	1.7	0.2	0.15	

*Content is for raw fish unless otherwise stated.
DHA—docosahexaenoic acid; EPA—eicosapentaenoic acid; n-3—omega-3; PUFA—polyunsaturated fatty acid.
(*Data from* the US Department of Agriculture [46].)

Table 1. Approximate omega-3 PUFA (EPA + DHA) content in common fish* ***(Continued)***

Fish	Fat, *g*	n-3 PUFA/100 g, *g*	n-3 PUFA/3 oz, *g*	Alternative portion size: n-3 PUFA/fish meal, *g*
Trout				
Mixed species	6.6	0.9	0.8	0.7 (1 fillet, 79 g)
Rainbow, farmed	5.4	0.9	0.8	0.7 (1 fillet, 79 g)
Rainbow, wild	3.5	0.7	0.6	1.1 (1 fillet, 159 g)
Tuna				
Bluefin	4.9	1.3	1.1	
Yellowfin	1.0	0.2	0.2	0.1 (1 oz, 28 g)
Light, canned in water, drained	0.8	0.3	0.2	0.5 (1 can, 165 g)
White, canned in water, drained	3.0	0.9	0.7	1.5 (1 can, 172 g)

*Content is for raw fish unless otherwise stated.
DHA—docosahexaenoic acid; EPA—eicosapentaenoic acid; n-3—omega-3; PUFA—polyunsaturated fatty acid.
(*Data from* the US Department of Agriculture [46].)

Table 2. American Heart Association recommendations for omega-3 PUFA intake

Population	Recommendation
Patients without documented CHD	Eat a variety of (preferably oily) fish at least 2 times per week. Include oils and foods rich in α-linolenic acid (flaxseed, canola, and soybean oils; flaxseeds; and walnuts).
Patients with documented CHD	Consume ~ 1 g/d of EPA + DHA, preferably from oily fish. EPA + DHA supplements may be considered in consultation with a physician.
Patients needing triglyceride lowering	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; PUFA—polyunsaturated fatty acid.
(*From* Kris-Etherton et al. [43].)

times per week. Depending on the fish type consumed, this could be approximately equivalent to taking 1 g/d of an n-3 PUFA supplement. For patients with documented coronary heart disease, the AHA recommends consuming the equivalent of 1 g/d of EPA plus DHA, preferably from oily fish. EPA plus DHA supplements may be considered in consultation with a physician. For patients with hypertriglyceridemia, the AHA recommends 2 to 4 g/d of EPA plus DHA.

- The American College of Cardiology Foundation Complementary Medicine Expert Consensus Document—Integrating Complementary Medicine Into Cardiovascular Medicine recommends the following:
  - n-3 PUFA supplements, 1 to 2 g/d, if there is insufficient n-3 intake from fish
  - Choosing oils and margarines low in saturated and trans fat and high in n-3 fat, such as canola, soybean, walnut, and flaxseed oils, including those fortified with stanols and sterols [44•].
- The use of fish oil or n-3 PUFA supplements needs to be balanced with the risk of toxicity. The US Environmental Protection Agency and US Food and Drug Administration recommend that young children and women who are pregnant, might become pregnant, or are breastfeeding avoid shark, swordfish, king mackerel, and tilefish because of the mercury risk. Instead they recommend up to 12 oz/wk of a variety of fish and shellfish lower in mercury, including shrimp, canned light tuna, salmon, pollock, and catfish. Albacore tuna should be limited to 6 oz/wk. Smaller portions should be given to children [45].

Disclosure

Dr. Chung is participating in a study using an n-3 fatty acid supplement sponsored by Reliant Pharmaceuticals/GlaxoSmithKline.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Lee KW, Lip GY: **The role of omega-3 fatty acids in the secondary prevention of cardiovascular disease.** *QJM* 2003, **96:**465–480.
2. 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.
3. Jouven X, Charles MA, Desnos M, Ducimetiere P: **Circulating nonesterified fatty acid level as a predictive risk factor for sudden death in the population.** *Circulation* 2001, **104:**756–761.
4. Siscovick DS, Raghunathan TE, King I, et al.: **Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest.** *JAMA* 1995, **274:**1363–1367.
5. 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:**1113–1118.
6. 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.
7. Marchioli R, Barzi F, Bomba E, et al.: **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.
8. Macchia A, Levantesi G, Franzosi MG, et al.: **Left ventricular systolic dysfunction, total mortality, and sudden death in patients with myocardial infarction treated with n-3 polyunsaturated fatty acids.** *Eur J Heart Fail* 2005, **7:**904–909.
9. Albert CM, Hennekens CH, O'Donnell CJ, et al.: **Fish consumption and risk of sudden cardiac death.** *JAMA* 1998, **279:**23–28.
10. 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.
11. Yokoyama M, Origasa H, Matsuzaki M, et al.: **Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis.** *Lancet* 2007, **369:**1090–1098.
12. Schrepf R, Limmert T, Claus Weber P, et al.: **Immediate effects of n-3 fatty acid infusion on the induction of sustained ventricular tachycardia.** *Lancet* 2004, **363:**1441–1442.
13. Raitt MH, Connor WE, Morris C, et al.: **Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implantable defibrillators: a randomized controlled trial.** *JAMA* 2005, **293:**2884–2891.
14. Leaf A, Albert CM, Josephson M, et al.: **Prevention of fatal arrhythmias in high-risk subjects by fish oil n-3 fatty acid intake.** *Circulation* 2005, **112:**2762–2768.
15. Brouwer IA, Zock PL, Camm AJ, et al.: **Effect of fish oil on ventricular tachyarrhythmia and death in patients with implantable cardioverter defibrillators: the Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA) randomized trial.** *JAMA* 2006, **295:**2613–2619.
16. 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.
17. • Hooper L, Thompson RL, Harrison RA, et al.: **Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review.** *BMJ* 2006, **332:**752–760.
Meta-analysis of the effects of n-3 fatty acids on mortality and cardiovascular end points.
18. McLennan PL, Abeywardena MY, Charnock JS: **Dietary fish oil prevents ventricular fibrillation following coronary artery occlusion and reperfusion.** *Am Heart J* 1988, **116:**709–717.
19. McLennan PL, Abeywardena MY, Charnock JS. **Reversal of the arrhythmogenic effects of long-term saturated fatty acid intake by dietary n-3 and n-6 polyunsaturated fatty acids.** *Am J Clin Nutr* 1990, **51:**53–58.
20. McLennan PL, Bridle TM, Abeywardena MY, Charnock JS: **Dietary lipid modulation of ventricular fibrillation threshold in the marmoset monkey.** *Am Heart J* 1992, **123:**1555–1561.
21. Billman GE, Hallaq H, Leaf A: **Prevention of ischemia-induced ventricular fibrillation by omega 3 fatty acids.** *Proc Natl Acad Sci U S A* 1994, **91:**4427–4430.
22. 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.
23. Billman GE, Kang JX, Leaf A: **Prevention of sudden cardiac death by dietary pure omega-3 polyunsaturated fatty acids in dogs.** *Circulation* 1999, **99:**2452–2457.
24. Jones PJ, Lau VW: **Effect of n-3 polyunsaturated fatty acids on risk reduction of sudden death.** *Nutr Rev* 2002, **60:**407–409.
25. Pepe S, McLennan PL: **Cardiac membrane fatty acid composition modulates myocardial oxygen consumption and postischemic recovery of contractile function.** *Circulation* 2002, **105:**2303–2308.
26. Sethi S, Ziouzenkova O, Ni H, et al.: **Oxidized omega-3 fatty acids in fish oil inhibit leukocyte-endothelial interactions through activation of PPAR alpha.** *Blood* 2002, **100:**1340–1346.
27. Holub BJ: **Clinical nutrition: 4. Omega-3 fatty acids in cardiovascular care.** *CMAJ* 2002, **166:**608–615.
28. Calabresi L, Villa B, Canavesi M, et al.: **An omega-3 polyunsaturated fatty acid concentrate increases plasma high-density lipoprotein 2 cholesterol and paraoxonase levels in patients with familial combined hyperlipidemia.** *Metabolism* 2004, **53:**153–158.
29. Thies F, Garry JM, Yaqoob P, et al.: **Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomised controlled trial.** *Lancet* 2003, **361:**477–485.

30. Calo L, Bianconi L, Colivicchi F, et al.: **N-3 Fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a randomized, controlled trial.** *J Am Coll Cardiol* 2005, **45:**1723–1728.
31. Mozaffarian D, Psaty BM, Rimm EB, et al.: **Fish intake and risk of incident atrial fibrillation.** *Circulation* 2004, **110:**368–373.
32. Frost L, Vestergaard P: **n-3 Fatty acids consumed from fish and risk of atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study.** *Am J Clin Nutr* 2005, **81:**50–54.
33. Brouwer IA, Heeringa J, Geleijnse JM, et al.: **Intake of very long-chain n-3 fatty acids from fish and incidence of atrial fibrillation. The Rotterdam Study.** *Am Heart J* 2006, **151:**857–862.
34. Sarrazin JF, Comeau G, Daleau P, et al.: **Reduced incidence of vagally induced atrial fibrillation and expression levels of connexins by n-3 polyunsaturated fatty acids in dogs.** *J Am Coll Cardiol* 2007, **50:**1505–1512.
35. Ninio DM, Murphy KJ, Howe PR, Saint DA: **Dietary fish oil protects against stretch-induced vulnerability to atrial fibrillation in a rabbit model.** *J Cardiovasc Electrophysiol* 2005, **16:**1189–1194.
36. Sakabe M, Shiroshita-Takeshita A, Maguy A, et al.: **Omega-3 polyunsaturated fatty acids prevent atrial fibrillation associated with heart failure but not atrial tachycardia remodeling.** *Circulation* 2007, **116:**2101–2109.
37. da Cunha DN, Hamlin RL, Billman GE, Carnes CA: **n-3 (omega-3) polyunsaturated fatty acids prevent acute atrial electrophysiological remodeling.** *Br J Pharmacol* 2007, **150:**281–285.
38. Geelen A, Brouwer IA, Schouten EG, et al.: **Effects of n-3 fatty acids from fish on premature ventricular complexes and heart rate in humans.** *Am J Clin Nutr* 2005, **81:**416–420.
39. Covington MB: **Omega-3 fatty acids.** *Am Fam Physician* 2004, **70:**133–140.
40. Davis BC, Kris-Etherton PM: **Achieving optimal essential fatty acid status in vegetarians: current knowledge and practical implications.** *Am J Clin Nutr* 2003, **78(3 Suppl):**640S–646S.
41. Sidhu KS: **Health benefits and potential risks related to consumption of fish or fish oil.** *Regul Toxicol Pharmacol* 2003, **38:**336–344.
42. Kris-Etherton PM, Harris WS, Appel LJ: **Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease.** *Circulation* 2002, **106:**2747–2757.
43. Kris-Etherton PM, Harris WS, Appel LJ: **Omega-3 fatty acids and cardiovascular disease: new recommendations from the American Heart Association.** *Arterioscler Thromb Vasc Biol* 2003, **23:**151–152.
44.• Vogel JH, Bolling SF, Costello RB, et al.: **Integrating complementary medicine into cardiovascular medicine. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents (Writing Committee to Develop an Expert Consensus Document on Complementary and Integrative Medicine).** *J Am Coll Cardiol* 2005, **46:**184–221.
American College of Cardiology Consensus Document including recommendations regarding n-3 fatty acids.
45. US Environmental Protection Agency: **Fish advisory: what you need to know about mercury in fish and shellfish.** Available at http://www.epa.gov/waterscience/fish/advice/. Accessed July 2008.
46. US Department of Agriculture: **National Nutrient Database for Standard Reference, Release 20.** Available at http://www.ars.usda.gov/main/site_main.htm. Accessed April 13, 2008.