Antiarrhythmic Effects of Omega-3 Fatty Acids

James A. Reiffel, MD,[a,*] and Arline McDonald, PhD[b]

Fish oil, and omega-3 fatty acids in particular, have been found to reduce plasma levels of triglycerides and increase levels of high-density lipoprotein in patients with marked hypertriglyceridemia, and a pharmaceutical-grade preparation has recently received approval from the US Food and Drug Administration to market for this purpose. However, in both bench research studies and clinical trials, evidence for clinically significant antiarrhythmic properties has also been detected in association with omega-3 fatty acid intake. Arguably the most significant finding in this data set was the reduction in the incidence of sudden death in survivors of myocardial infarction in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)–Prevenzione trial and the subsequent recommendation for administration of fish oil as part of the postinfarction regimen in Europe. This article reviews in detail the basic and clinical research studies of fish oil as an antiarrhythmic entity, the forms of preparation and/or administration that appear to possess these properties and those that do not, the types of arrhythmias (ventricular ectopy and atrial fibrillation as well as ventricular tachyarrhythmias) that have been beneficially affected by fish oil administration, and the presumed and known mechanisms by which the beneficial actions are exerted. **(Am J Cardiol 2006;98[suppl]:50i–60i)**

Sudden cardiac death is the most common cause of mortality among patients surviving a myocardial infarction (MI), accounting for 50% to 60% of all deaths due to coronary artery disease (CAD).[1] Postinfarction treatment of patients with fish oil supplements is now considered 1 component of an effective approach to preventing mortality due to sudden cardiac death in this group at high risk. In 2003, the European Society of Cardiology published guidelines that recommended inclusion of fish oils as standard therapy for postinfarction management.[2] This recommendation is supported by morbidity and mortality data obtained from secondary prevention studies of patients treated with fish oil supplements after MI and from prospective observational studies of healthy adults who regularly consumed fish.[3–10] These studies found significant reductions in total and cardiovascular mortality associated with intake of fish and fish oils, with the largest decreases in the incidence of sudden cardiac death. Overall, the magnitude of risk reduction ranged from 29% to 52% for cardiovascular-related mortality and from 45% to 81% for sudden cardiac death.[11–13] These findings are supported by those of other studies—in patients with ischemic heart disease (IHD), in subgroups of patients with implantable cardioverter defibrillators or supraventricular arrhythmias, or with protocols designed to assess antiarrhythmic mechanisms[14–72]—that will be discussed in this article.

Are Fish Oils Antiarrhythmic?

The proportionately larger decrease in risk of sudden cardiac death associated with fish consumption and fish oil therapy, relative to nonfatal MI or mortality due to other cardiovascular disease, suggests that fish oils may have antiarrhythmic properties underlying these cardioprotective effects.[5,6] The relatively short duration observed between initiating treatment and detection of effects on mortality (eg, ≤90 days)[3,4,10,14] and the independence of these effects from changes in serum lipid profiles[3,4] suggest a direct antiarrhythmic potential of fish oils. In addition, both fish and fish oils have been found to be beneficial when consumed at low to moderate levels, indicating that effects are achieved with physiologic levels of the active omega-3 fatty acid components.

In the largest secondary prevention clinical trial with fish oil conducted to date, the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)–Prevenzione found that mortality due to sudden cardiac death was reduced by 53% and total mortality by 41% after MI in 11,323 patients treated with a relatively low dose (1.0 g/day) of pharmaceutical-grade fish oil.[3] Divergence of survival curves for sudden cardiac death were observed ≤90 days after initiating fish oil therapy. Similar findings were also reported by the Indian Experiment on Infarct Survival Study, a randomized placebo-controlled study in 460 pa-

[a]Division of Cardiology, Department of Medicine, College of Physicians and Surgeons, Columbia University Medical Center, New York, New York, USA; and [b]Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA.

*Address for reprints: James A. Reiffel, MD, Division of Cardiology, Department of Medicine, Columbia University College of Physicians and Surgeons, Columbia University Medical Center, 161 Fort Washington Avenue, New York, New York 10032.

E-mail address: jar2@columbia.edu.

0002-9149/06/$ – see front matter
doi:10.1016/j.amjcard.2005.12.027

tients with suspected acute MI.[4] At 1 year, significantly fewer cardiac deaths were found among patients randomized to fish oil therapy (24.5% compared with 34.7% for controls; $p < 0.01$). This difference in cardiac mortality between fish oil and placebo groups was not associated with differences in blood lipoproteins between groups, but the total incidence of cardiac arrhythmias was significantly reduced in the fish oil group. In contrast were the findings with use of eicosapentaenoic acid (EPA) in the recently reported Japan EPA Lipid Intervention Study (JELIS).[15] In JELIS, fish oil supplements (1,800 mg/day) were given to 18,645 Japanese patients with hyperlipidemia who were taking statins and already consuming significant amounts of fish in their diets; only 20% of these patients had known CAD. No reduction in the incidence of sudden cardiac death was noted, although the supplements did decrease major coronary events in total by 19% ($p = 0.011$). Thus, there may be a dose for dietary omega-3 fatty acid consumption plus supplements beyond which additional antiarrhythmic benefit may not be demonstrable and/or the benefit may be most striking in patients with underlying IHD.

The cardioprotective effects of fish consumption and fish oil therapy have been attributed specifically to the antiarrhythmic effects of the long-chain omega-3 fatty acids EPA and docosahexaenoic acid (DHA), which make up the majority of fatty acids in fish-derived fats. Estimates of omega-3 fatty acid intake obtained indirectly from dietary recall of seafood consumption or directly from measurement of cell-membrane fatty acid concentrations have yielded similar findings. Siscovick and associates[9] demonstrated a relation between risk of primary cardiac arrest and omega-3 fatty acids using both methods of assessment in a population-based cohort of adults aged between 25 and 74 years who were free of prior heart disease, major comorbidity, or history of preventive fish-oil supplement use. Among 334 patients who had experienced primary cardiac arrest and 493 age- and sex-matched control subjects, risk of primary cardiac arrest was decreased significantly by 50% for those who consumed an estimated 5.5 g of omega-3 fatty acids over the prior month (based on dietary recall of fish consumption) compared with those who consumed no fish at all, after adjustment for potential confounders ($p < 0.05$). In a subset of 82 cases and 108 controls from this study,[9,16] erythrocyte membrane omega-3 fatty acids were 4.3% $\pm$ 1.1 % for cardiac arrest cases and 4.9% $\pm$ 1.4% for controls ($p = 0.002$). Risk of primary cardiac arrest was significantly decreased by 70% for those in the third quartile of membrane omega-3 fatty acid concentration (mean, 5.0% of total fatty acids) compared with those in the lowest quartile (mean, 3.3% of total fatty acids). Controlling for membrane omega-3 fatty acid differences eliminated the differences in risk attributed to dietary intake between cases and controls, suggesting that the benefits associated with consumption of fish in this study were related to the incorporation of the omega-3 fatty acid components into membrane phospholipids.

The prospective, cohort Cardiovascular Health Study (CHS) examined the relation between risk of IHD mortality due to arrhythmia and fish consumption, based on dietary recall and verified by plasma phospholipid omega-3 fatty acid content, in 3,910 adults aged $\geq$65 years without a history of cardiovascular disease at baseline.[8] At an average follow-up of 9.3 years, 148 arrhythmic deaths were identified among 247 incident IHD deaths. Arrhythmic IHD death was decreased 68% among those with a baseline fish consumption of $\geq$3 times weekly ($p = 0.001$) compared with those who consumed fish $<$1 time weekly, after adjustment for multiple dietary and cardiovascular disease risk factors. Total IHD mortality was decreased 53% ($p = 0.002$). In contrast, among the 363 cases of incident nonfatal MI, previous fish intake did not significantly affect mortality risk after adjustment for heart rate.

Similarly, a nested case-control study of 5,021 patients enrolled in the CHS found that 67% (36 of 54 patients) of cases of fatal IHD were attributable to arrhythmias.[6] This study also found significantly lower plasma levels of phospholipid EPA and DHA, omega-3 fatty acids derived almost exclusively from fish, among cases compared with controls matched for age, sex, clinic site, and length of follow-up ($p = 0.02$). An increase of 1 standard deviation in plasma phospholipid EPA and DHA was associated with a 68% decrease in risk of incident fatal IHD ($p = 0.01$). At the same time, a comparable increase in the primary dietary omega-6 fatty acid, linoleic acid, was associated with a significant increase in risk of 2.5 times ($p = 0.03$). For nonfatal MI, no significant difference in risk related to either plasma phospholipid omega-3 or omega-6 fatty acids was found between patients and control subjects.

Clinical data supporting antiarrhythmic properties of fish oils have also been obtained from studies examining surrogate markers of lethal sustained ventricular arrhythmias, such as incidence of premature ventricular complexes, and from other arrhythmias, such as atrial tachycardia and atrial fibrillation.

In a double-blind placebo-controlled study in 65 patients with cardiac arrhythmias but without evidence of CAD or heart failure, the incidences of atrial and ventricular premature complexes, couplets, and triplets were reduced over a 6-month period among those randomized to treatment with 3 g/day of fish oil providing 1 g of omega-3 fatty acids compared with those randomized to 3 g/day of olive oil as a placebo.[17] At the end of the dietary period, the Lown classification grades switched from higher to lower values in the fish oil group whereas no change was observed in the olive oil group.

In 39 patients who were free of complex ventricular arrhythmias and severe heart failure at baseline, a significant trend toward a reduction in ventricular premature complexes was also reported after 16-week treatment with 15 mL/day of fish oil providing 0.9 g EPA and 1.54 g DHA or with a placebo of sunflower seed oil.[18] Data from 24-hour ambulatory Holter electrocardiographic (ECG) monitoring

showed a 48% decrease in ventricular premature complexes in the fish oil group compared with a 25% decrease in the placebo group. In addition, 38% (15 of 39 patients) in the fish oil group had a clinically relevant response of a >70% reduction compared with a 13% reduction (5 of 40 patients) in the placebo group ($p < 0.01$). Reductions in couplets (>80%) and triplets (>90%) also occurred more frequently in the fish oil group compared with the placebo group (response in 52% vs 44%, respectively).

Similarly, in a study in 40 patients with dual-chamber pacemakers who had paroxysmal atrial tachyarrhythmia recorded at periodic monitoring, treatment with 1 g/day of omega-3 fatty acids for 4 months significantly reduced the number of atrial tachyarrhythmia episodes by 59% ($p = 0.037$) and the burden by 67% ($p = 0.029$) without change in device programming or pharmacologic therapy.[19] During the 4-month follow-up after discontinuation of the omega-3 fatty acid therapy, both the number of episodes and burden of duration increased to levels comparable to pretreatment values.

Risk of atrial fibrillation was also inversely associated with fish intake in a prospective population-based cohort of 4,815 adults aged ≥65 years.[20] A total of 980 cases of incident atrial fibrillation were diagnosed from hospital discharge records and annual ECGs at 12-year follow-up. A 28% lower risk of atrial fibrillation was associated with consumption of tuna or other broiled or baked fish 1 to 4 times weekly compared with intakes of <1 time monthly. Risk was 31% lower when fish was consumed ≥5 times weekly. Adjusting for a history of or the presence of MI or congestive heart failure did not change the results. This study also confirmed a significant relation between plasma phospholipid EPA and DHA concentrations and consumption of tuna or other broiled or baked fish. In contrast, consumption of fried fish or fish sandwiches did not significantly influence risk of atrial fibrillation nor did it relate to plasma phospholipid concentration of EPA and DHA. An additional trial in atrial fibrillation is ongoing.[21]

The incidence of atrial fibrillation has also been reported to be reduced by fish oils when used following coronary artery bypass surgery.[22] In a prospective study, 160 patients were randomized to receive polyunsaturated fatty acids (2 g/day) or placebo control, starting 5 days before surgery and continuing until hospital discharge.[22] The incidence of atrial fibrillation was 33.3% in the control group and 15.2% in the fish oil group ($p = 0.013$), and hospital stay was 1 day shorter in the fish oil group ($p = 0.017$).

Supporting Data from Nonhuman Studies

Substantial data from studies in cultured neonatal cardiomyocytes and isolated perfused animal hearts support the antiarrhythmic properties of omega-3 fatty acids.[14,23–29] Prevention of ischemia-induced ventricular fibrillation by omega-3 fatty acids has also been observed in whole animal models, including dogs, rats, and marmosets.[24] In a reliable model of sudden cardiac death in dogs having a hydraulic inflatable cuff surgically inserted around the left circumflex artery, fatal ventricular fibrillation was prevented during exercise in every instance with prior infusion of EPA plus DHA and, following induction, was stopped with infusion of these fatty acids.[30]

In isolated neonatal rat cardiac myocytes, EPA plus DHA inhibited development of tachyarrhythmias induced by exposure to a broad spectrum of arrhythmogenic agents, including elevated calcium concentrations, toxic levels of ouabain, the β-adrenergic agent isoproterenol, lysophosphatidylcholine, and acylcarnitine.[28] Using an isolated working heart model perfused with porcine erythrocytes to demonstrate ischemia- and reperfusion-induced arrhythmias, researchers showed that previous feeding of a fish oil diet for 16 weeks to adult male rats reduced arrhythmias in ischemia and prevented reperfusion-induced ventricular fibrillation.[31] Neither effect was observed in hearts from animals previously fed isoenergetic saturated-fat or low-fat reference diets. Compared with the low-fat reference diet, the fish oil diet increased the threshold for programmed electrical induction of ventricular fibrillation during control perfusion, whereas the saturated-fat diet decreased the threshold. A small but not significant decrease in the incidence of ventricular fibrillation during acute myocardial ischemia was also observed in isolated perfused hearts from rats that had been fed fish oil in amounts as small as 0.4% of total energy for 4 weeks.[32]

Anesthetized marmosets underwent programmed electrical stimulation to induce ventricular fibrillation to compare the effects of omega-3 with omega-6 fatty acids in diets fed for 16 weeks. Ventricular fibrillation was induced in 6 of 10 monkeys on each diet. The threshold for ventricular fibrillation was significantly elevated in the saturated fat/fish oil group (33.3 ± 3.1 mA) compared with the saturated fat/sunflower seed oil group (14.3 ± 4.9 mA). The ventricular fibrillation threshold reduced during acute myocardial ischemia remained significantly higher with fish oil. With feeding of 3.8% of energy as fish oil, omega-3 fatty acid incorporation into myocardial membranes was 31% of total fatty acids. Omega-3 fatty acids reduced the vulnerability of normal or ischemic myocardium to arrhythmias in nonhuman primates.[33]

Are All the Available Data Consistent?

Not all studies have been able to demonstrate antiarrhythmic properties associated with fish oils. In humans, risk of atrial fibrillation or flutter did not appear to be influenced by fish consumption in a prospective cohort study in 47,949 adults aged 50 to 64 years who were free of CAD at baseline and were enrolled in the Danish Diet, Health, and Cancer Study.[34] At a mean follow-up of 5.7 years, baseline omega-3 fatty acid intake equivalent to a frequency of fish

consumption of ≥2 times weekly was not associated with a reduction in risk across any of the sex-specific quintiles of omega-3 fatty acid intake in this study.

In a randomized, double-blind, placebo-controlled study in 92 patients aged ≥18 years, the number of ventricular premature complexes was not significantly reduced after 14 weeks of supplementation with 3.5 g/day of fish oil providing 700 mg of EPA and 560 mg of DHA compared with high–oleic acid sunflower oil supplementation.[35] Patients enrolled in this study had a history of frequent ventricular premature complexes over the previous 6 months, defined as a rate of ≥1 per minute or a frequency of 1,440 per 24-hour period on Holter monitoring. A total of 3 patients in the fish oil group had a reduction of >70%, indicating a positive response to treatment in a clinical setting, compared with 7 positive responses in the placebo group. Nevertheless, the incidence of these complexes was decreased by >867 in the fish oil group compared with placebo; heart rate, an established predictor of risk for sudden cardiac death, was decreased significantly by 2.1 beats per minute ($p = 0.022$).[36]

No effect due to treatment was observed in a study in 84 healthy adults aged 50 to 70 years that was conducted in the Netherlands.[37] In this study, subjects were randomized by sex and diastolic blood pressure (above or below median) and matched by fish intake within strata to receive either 3.5 g/day of fish oil—an amount equivalent to 2 servings of fish—or high–oleic acid sunflower oil for 12 weeks. End points consisted of ECG and blood pressure recorded for 10 minutes with standard respiration of 15 breaths per minute and heart rate variability (HRV) calculated from the standard deviation of the duration of all normal relative risk intervals from the recordings. Similarly, there was no demonstrable benefit on atrial fibrillation in a Danish study that examined the incidence of atrial fibrillation with the consumption of fish.[34] However, information concerning the use of fish oil supplementation was not available.

In anesthetized pigs, recovery of cardiac function and incidence of cardiac arrhythmias were not influenced by whether a mackerel diet or a lard diet had been fed over the previous 8 weeks.[38] These end points were measured following occlusion of the left anterior descending coronary artery 6 times, for periods of 5 minutes at 15-minute intervals, to mimic acute recurrent ischemia. The hyperemic responses in the last reperfusions were smaller in magnitude and of shorter duration in the lard-fed animals, and coronary venous blood thromboxane B_2 levels were also higher during peak hyperemia in these animals. Membrane omega-6 fatty acids had been partially replaced with omega-3 fatty acids in animals fed the mackerel diet, and reductions of 51% in plasma cholesterol and 48% in plasma triglycerides were also noted compared with pigs fed a lard diet. The differences in responses between the 2 diet groups was explained by differences in eicosanoid production because baseline blood levels of both thromboxane B_2 and 6-keto-prostaglandin F1-α were lower in mackerel-fed animals, reflecting the reduced content of precursor fatty acids in the membrane phospholipids.

Studies in patients with implantable cardioverter defibrillators: Results of studies in patients with implantable cardioverter defibrillators have also appeared to be conflicting. Some studies reported a trend toward an increased risk of ventricular arrhythmias, although not of mortality, with fish oil supplementation in patients with implantable cardioverter defibrillators.[39] A recent randomized placebo-controlled trial in 200 patients with newly implanted cardioverter defibrillators for ECG-documented ventricular tachycardia or fibrillation found that the number of episodes of ventricular tachycardia and fibrillation was not significantly different between groups supplemented with either fish oil consisting of 1.8 g/day of 42% EPA and 30% DHA ethyl esters or an olive oil placebo at 2-year follow-up.[40] An overall trend toward an increase in ventricular tachycardia and fibrillation was noted in those receiving fish oil supplements, which was significant among those patients with ventricular tachycardia as a qualifying entry rhythm ($p = 0.007$). In addition, the rate of recurrent episodes was significantly increased in this group ($p < 0.001$), suggestive of potential proarrhythmic effects of fish oil in this population. At study entry, none of these patients had a preexisting cardioverter defibrillator implant or had received implantable cardioverter defibrillator therapy for an episode of ECG-documented ventricular tachycardia or fibrillation during the previous 3 months.

In another series, omega-3 fatty acids were infused in 10 patients with implanted cardioverter defibrillators who underwent simultaneous electrophysiologic testing to ascertain the immediate effects of these fatty acids on the induction of sustained ventricular tachycardia.[41] Although omega-3 fatty acid infusion did not induce arrhythmia in these patients, it did sustain ventricular tachycardia in 5 of the 7 patients in whom this condition was observed. The rationale for an infusion study, however, can be questioned: incorporation into tissue membranes is needed for an effect, and clinical benefit is not conferred immediately with increased oral intake.

Of possible relevance, Burr and coworkers[7] had previously suggested possible proarrhythmic effects of fish oil supplementation based on data from 3,114 men with CAD in the Diet and Reinfarction Trial (DART). In this unblinded study, men who were randomized to increase their fish intake were instructed to consume either 2 portions of fatty fish weekly or 3 g of fish oil daily. A higher risk of sudden cardiac death was found among men who were randomized to the fish group ($n = 1,572$), compared with the effect observed among those taking fish oil supplements ($n = 462$).

In contrast, Leaf and colleagues[42] most recently reported a trend toward prolonged time to first implantable cardioverter defibrillator event or death due to any cause (risk reduction, 28%; $p = 0.057$) in 402 patients randomized to

fish oil compared with olive oil supplementation. When therapies for probable ventricular tachycardia or fibrillation were included in the end point, the risk reduction became significant: 31% ($p = 0.033$). Similarly, in the Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA)[43,44] reported at the annual scientific sessions of the European Society of Cardiology in September 2005, a trend toward improved survival free of ventricular tachycardia or fibrillation was seen in patients with implanted cardioverter defibrillators treated with fish oil supplementation (71% vs 63%), although only in the subpopulation with a prior MI.

Why Are the Data Inconsistent?

The most convincing support for antiarrhythmic properties of fish oils has come from epidemiologic studies relating fish consumption to risk of sudden cardiac death, fatal MI, or mortality due to IHD; from studies specifically in patients with prior MI; from populations with low intrinsic levels of fish in their diets; and from experimental studies that examined the effects of specific omega-3 fatty acids in isolated cell systems or whole animals. Attempts to reproduce these findings in all clinical settings have not shown the same consistency in results. Disparities among these data reflect in part the relatively small numbers of studies conducted to date, as well as substantial differences in the study protocols, including source, amount, and method of administration of omega-3 fatty acids tested; duration of supplementation; control of background diet, particularly intake of other fatty acids that may have proarrhythmic or antiarrhythmic effects; and either the end points used to assess arrhythmias or conditions to induce them experimentally.

The available data in humans have been obtained from a heterogeneous group of observational and interventional studies in healthy adults or in patients in whom different clinical criteria were used to determine eligibility for enrollment. Fish oils were either administered as supplements or obtained from consumption of fish. Doses of omega-3 fatty acids were not standardized across clinical studies, and when dietary intakes were assessed, estimates of omega-3 fatty acid intakes were based on fish consumption obtained from recall. In those studies that verified the level of omega-3 fatty acid intake by measuring plasma phospholipid fatty acid content, the antiarrhythmic effects associated with fish and fish oil have been confirmed.[8,16,20,35]

Another possible explanation for the absence of a uniformly observed protective effect of fish consumption on mortality due to IHD is that the relation between omega-3 fatty acids and mortality risk is nonlinear, suggesting a threshold and possibly a dose-limited nonincremental effect.[16] Several prospective cohort studies reported a maximum impact of fish consumption on mortality at intakes of $\geq$1 serving per month.[16] A nonlinear dose-response relationship was found between omega-3 fatty acid intake from seafood and risk of primary cardiac arrest.[16] Mean intakes of EPA plus DHA calculated over the month before the event were 4.3 ± 6.0 g for cases and 5.3 ± 5.6 g for controls ($p = 0.02$). No additional benefit was observed at total intakes averaging $>$5.5 g of omega-3 fatty acids per month (96 g of fish per week). The JELIS data are also consistent with a nonlinear dose response.[15]

Consequently, studies in populations in whom the lowest intakes of fish are above this theoretical maximum for observable benefit would not be likely to demonstrate a reduction in risk of mortality or a protective antiarrhythmic effect from incremental increases in omega-3 fatty acid intakes obtained from fish oil supplements. Geelen and associates[37] reported no benefit of 12-week supplementation with fish oils at 3.5 g/day on HRV in healthy adults aged 50 to 70 years who resided in the Netherlands. In this study, the average monthly baseline intake of omega-3 fatty acids estimated from habitual fish intake (obtained from 24-hour dietary recall) was 8.4 g in the supplemented group and 8.7 g in the placebo group. These levels of intake are equivalent to $>$4 servings of fish per month or 1 serving weekly, which is the threshold level of intake suggested by Siscovick and associates.[16]

Does the Type of Oil Matter?

Lack of control of background dietary intakes, particularly of other fatty acids with effects that may modulate the antiarrhythmic effects of omega-3 fatty acids, also likely contributes significantly to the inconsistencies in some of the studies. Use of placebo oils such as safflower oil, which has a high content of omega-6 fatty acids that have antiarrhythmic effects, although weaker than those of omega-3 fatty acids, may have diminished the ability to detect a significant difference between the effects of fish oils and placebo. In addition, failure to account for methods of preparation of fish that use highly saturated fat may also be involved. Data from the prospective, population-based CHS did not support a relation between risk of either atrial fibrillation or incident nonfatal MI and fried fish in $>$3,500 adults aged $\geq$65 years at an average follow-up of $>$9 years; however, risk of both were significantly reduced with consumption of tuna and other broiled or baked fish.[8,20]

Both omega-3 and omega-6 classes of polyunsaturated fatty acids appear to have antiarrhythmic effects, with the possible exception of arachidonic acid ($C_{20:4\ n\text{-}6}$), which may exhibit proarrhythmic activity through its cyclooxygenase metabolites[45] (Figure 1).[46] For this reason, Leaf and colleagues[24] recommended that only omega-3 polyunsaturated fatty acids be tested as antiarrhythmic agents in clinical trials. Dietary fatty acid composition influences development of cardiac arrhythmias experimentally induced by coronary occlusion and reperfusion. In an anesthetized whole animal model of arrhythmia and sudden cardiac death, incidence and severity of arrhythmias were decreased by supplementation with tuna fish oil, whereas sunflower

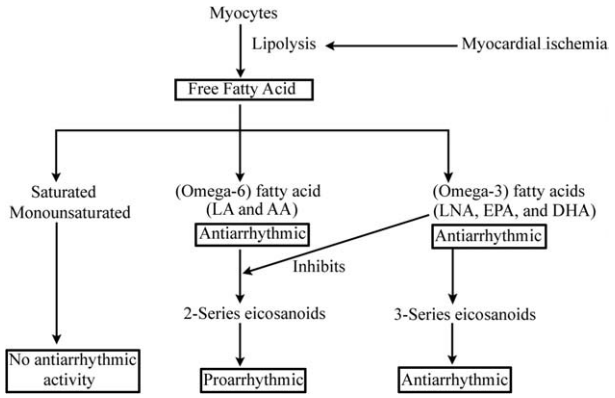

Figure 1. The effect of different dietary fatty acids on cardiac arrhythmia. AA = arachidonic acid; DMA = docosahexaenoic acid; EPA = eicosapentaenoic acid; LA = linoleic acid; LNA = α-linoleic acid. (Adapted with permission from *J Nutr*.[46])

seed oil (comprising 77% linoleic acid and <1% linolenic acid) decreased arrhythmias induced during occlusion but not during reperfusion.

A review of experimental data demonstrated that diets with a high ratio of linoleic acid to saturated fat protect against ventricular fibrillation and are thus antiarrhythmic.[47] Under experimental conditions, significant reductions in arrhythmias have been observed when fish oil was compared with saturated fat but not with omega-6 fatty acids. Although fatal ventricular fibrillation induced by coronary artery ligation was reduced 70% with sunflower oil compared with saturated-fat and monounsaturated-fat diets, reduction with fish oil was almost 100%.[48] Intravenous infusion of omega-3 fatty acids, but not soybean oil, also reversed the ventricular fibrillation induced in conscious exercising dogs by inflated cuff occlusion of the left circumflex artery.[30]

How May End Points Matter?

Choice of end points may also contribute to the inconsistency in data supporting the antiarrhythmic effects of fish oils. Animal studies have relied exclusively on assessment of ventricular fibrillation, with mixed results at omega-3 fatty acid intakes ranging from 0.4% to 30% of total energy, despite marked incorporation into cell membranes over this range.[32] In contrast to animal studies, studies in humans have used a broad spectrum of end points to assess antiarrhythmic potential in both healthy adults and patient populations. These include mortality due to IHD, sudden cardiac death, and fatal MI[3–6,14,31] as well as various intermediate markers such as ventricular fibrillation and tachycardia,[17,40,41,49] atrial fibrillation,[19,20,34] HRV and baroreceptor sensitivity,[50] ECG findings such as corrected QT interval,[37] and premature ventricular complexes.[18,35]

Although the mechanism of action of antiarrhythmic drugs involves a direct effect on the electrophysiology of cardiac muscle, comparable effects of omega-3 fatty acids on electrophysiologic predictors of arrhythmia such as HRV, premature ventricular complexes, or ECG findings have not been consistently found, although most of the studies using end points have been small and conducted in healthy populations.[13] Favorable effects on HRV have been found in patients after MI, suggesting that autonomic control may be affected by omega-3 fatty acids in a population in whom ischemic damage may already be present. In addition, the individual effects of EPA and DHA were not examined, despite the vast majority of experimental evidence supporting antiarrhythmic properties specific to these fatty acids that may not generalize to other omega-3 fatty acids found in fish oils.

Although surrogate markers are more closely linked with arrhythmic properties than are the mortality end points they represent, individual markers do not represent every aspect of the pathology underlying development of fatal arrhythmias that may be influenced by omega-3 fatty acids. For example, HRV and baroreceptor sensitivity reflect cardiac autonomic regulation such that reduced values predict arrhythmic events and mortality, but most sudden cardiac deaths are caused by acute ventricular tachyarrhythmias.[50] Although the effects of omega-3 fatty acids on ventricular tachycardia and fibrillation address influences on ventricular arrhythmias, these end points nevertheless have not been considered an ideal surrogate for sudden cardiac death. According to Raitt and associates,[40] who did not demonstrate a benefit of fish oils in patients with implanted cardioverter defibrillators, ischemic ventricular fibrillation may be the primary cause of sudden cardiac death in patients with recent MI and preserved left ventricular function but not among patients similar to those enrolled in their study—patients who had not had a recent MI, had significantly reduced left ventricular function, and had a history of sustained ventricular arrhythmias. In these patients, sustained ventricular tachycardia or fibrillation, especially ventricular tachycardia, in the absence of MI would not likely be ischemic (like myocardial scar-based reentry), and thus antiarrhythmic effects based on electrical stabilization of cardiomyocytes as proposed by Leaf and colleagues[23] would not apply.

HRV and baroreceptor sensitivity have been suggested as surrogate markers predictive of arrhythmic events and mortality because both of these indices represent cardiac autonomic regulation.[49] In a double-blind placebo-controlled study in 55 patients with a previous MI, the effect of fish oil on cardiac autonomic control was assessed by measurement of HRV (as an indicator of cardiac autonomic control) by means of 24-hour Holter monitoring.[12] The group randomized to receive 5.2 g/day of omega-3 fatty acids showed a significant increase in HRV from baseline that was also significantly different from that in the placebo group. Although the number of ventricular extrasystoles over the 24-hour monitoring was decreased in both groups, the difference between groups was not significant. Addi-

tionally, correlations between membrane fatty acids in platelets or granulocytes and HRV were examined in a randomized placebo-controlled trial in 60 healthy men and women.[51] Membrane DHA was positively and significantly correlated with HRV indices at baseline (correlation coefficient, 0.50; $p < 0.01$). After supplementation with either 6.6 g/day or 2.0 g/day of omega-3 fatty acids or an olive oil placebo for 12 weeks, a dose-dependent relation was observed in men but not in women. In contrast, neither HRV nor baroreceptor sensitivity was influenced over 12 weeks by a fish oil supplement of 3.5 g/day, equivalent to 2 servings of fish, compared with high–oleic acid sunflower oil in a group of healthy adults aged 50 to 70 years. This finding can be taken as evidence against fish oils having an effect on cardiac autonomic function but, alternatively, it may indicate that sunflower oil has similar actions. Regarding fish oils having an effect on autonomic function, the recent meta-analysis by Mozaffarian and coworkers[52] found that fish oil supplementation reduced heart rate, particularly in trials of ≥12 weeks and particularly in patients with higher baseline heart rates.

The absence of an effect of fish oil supplementation on ECG findings (including corrected QT interval and QRS duration) in a healthy population may suggest that the protective effects of fish oils do not involve electrophysiologic effects on cardiac repolarization.[37] However, a nonsignificant decrease of 0.2% or 0.8 msec in the corrected QT interval with fish oil supplementation compared with placebo in this healthy population cannot rule out the possibility that fish oil supplements may have a greater impact on these end points in a population at high risk. In addition, baseline omega-3 fatty acid intake estimated for both the fish oil and placebo groups in both of these studies[37,52] was also at or above the proposed threshold effect level. Other studies that did not find an effect of fish oil supplementation on surrogate markers of arrhythmias also did not enroll patients at high risk. Geelen and associates[35] did not include patients with left ventricular dysfunction, and only 25% of patients had a history of MI. Frost and Vestergaard[34] measured effects of fish intake on atrial fibrillation but only in those patients who were symptomatic.

What Are the Likely Mechanisms for the Antiarrhythmic Effects of Fish Oils?

A number of plausible mechanisms have been proposed to explain the antiarrhythmic effects attributed to fish oils: structural, metabolic, autonomic, and electrophysiologic. Omega-3 fatty acids satisfy the structural requirements of antiarrhythmic agents identified by in vitro studies to consist of a long acyl hydrocarbon tail, ≥2 unsaturated carbon-carbon double bonds, and a free carboxyl group at 1 end. Fatty acids are essential fuels for mechanical, electrical, and synthetic activities of the heart.[53] EPA and DHA are preferentially bound at the *sn*-1 position in storage triglycerides, where lipases are most active and thus are mobilized more rapidly from adipose tissue stores in response to physiologic demand than are saturated fat and monounsaturated fat. Omega-3 fatty acids are not active in triglyceride storage form and require phospholipases to be activated.[30] Free fatty acids alter excitability and activity of sodium and L-type calcium channels.[36]

The antiarrhythmic properties of omega-3 fatty acids likely involve modulation of the biochemical processes underlying fatal ventricular arrhythmias.[54] The specific mechanisms that have been proposed include direct effects on cardiac microsomal calcium/magnesium adenosine triphosphatase and voltage-gated sodium channels, as demonstrated in cultured neonatal cardiac myocytes. Also included may be effects on the inositol lipid cycle and cell signaling; on the cell membrane, via modification of membrane phospholipids; or anti-inflammatory effects mediated by eicosanoids. Support for a particular mechanism of action appears to depend on the type of study.[53] Whereas dietary studies support mechanisms mediated by changes in omega-3 fatty acids or their metabolites in plasma and vascular tissues, studies in isolated animal hearts and cultured neonatal cardiac myocytes support mechanisms related to direct effects on the electrophysiology of the heart.

Although human data have not yielded consistent findings on whether omega-3 fatty acids influence cardiac arrhythmias through autonomic control, they have not ruled out the possibility of additional direct effects on ion channels in cardiomyocytes. Autonomic regulation involves control of inward sodium and calcium currents, which promote depolarization, and the outward potassium current, which opposes depolarization.[55] Omega-3 fatty acids have prevented or attenuated β-adrenergic agonist–induced arrhythmias in cultured myocytes in the absence of confounders such as hormones and neurotransmitters.

Effects on Sodium and Calcium Currents

The majority of experimental studies indicate that omega-3 fatty acids may prevent fatal ventricular arrhythmias at least in part by correcting electrolyte disturbances that electrically destabilize the myocardium.[20,25,26,55] Fatal arrhythmias underlying sudden cardiac death most often arise from ischemia-induced electrical instability in the heart. Ischemia depolarizes the cardiac membrane by decreasing the activity of sodium/potassium adenosine triphosphatase, which increases interstitial potassium concentration, making the resting membrane potential more positive.[56] The result is that the voltage threshold for gating of inward sodium current (which initiates action potential) is approached, making the myocytes more vulnerable to any small further depolarization stimulus or injury currents. Under these conditions, a smaller than normal depolarizing current can elicit a premature action potential and initiate an arrhythmia.

Omega-3 fatty acids are thought to act on the final

common pathway affecting excitability of the myocyte. This involves inhibition of voltage-gated sodium channels and maintenance of L-type calcium channels to prevent calcium overload during stress.[20,22,26,53,57–60] By shifting the membrane to a more negative or hyperpolarized state, omega-3 fatty acids cells ensure that these cells cannot become sufficiently negative to return from the prolonged inactivated state to an activatable one, so that any further action potential can be generated only in nonischemic tissue. Researchers found that the effectiveness of an antiarrhythmic agent depends on its ability to inhibit voltage-gated sodium current by a voltage-dependent mechanism, producing a large leftward shift of steady-state inactivation.[57,61] Because partially depolarized myocytes at the periphery of an ischemic zone require only a small depolarization stimulus (eg, the current of injury) to elicit an action potential, shifting steady-state inactivation to physiologically unattainable negative potentials would prevent fatal arrhythmias. These partially depolarized myocytes would be removed from the functional pool because the requirement for a more negative resting potential to revert the channel to an activatable resting state would render it unresponsive and eliminate it as an arrhythmic risk.[22,56] In studies to date, a large shift in the hyperpolarization of the membrane potential necessary to close the voltage-gated sodium channel is the only effect on sodium current that has been observed with omega-3 fatty acids.[56] The activated opening of the sodium channel in α-subunits of human myocardial sodium channels expressed in stable human embryonic kidney cells was not affected.

In contrast, with inhibition of L-type calcium channels, omega-3 fatty acids have been found to prevent the increase in calcium concentration that trigger arrhythmic afterpotential discharges caused by excessive cytosolic calcium fluctuations.[26,57,62] Contracture and fibrillation in isolated neonatal myocytes exposed to toxic levels of ouabain (0.1 mmol/L) were inhibited by EPA and DHA, which were associated with prevention of excessively high calcium concentrations in these cells.[61] Calcium currents through L-type calcium channels were modulated within a few minutes of adding these fatty acids to the medium. Under experimental conditions, the presence of omega-3 fatty acids in the medium increases the voltage requirement for gating (opening) of sodium channels so that the strength of the stimulus needed to elicit an action potential is increased by 50%. At the same time, omega-3 fatty acids decrease L-type calcium current so that the refractory period is prolonged by 150%.[63] The net effect of these actions would be an increased electrical stability of the myocardium.

Other effects of omega-3 fatty acids on ion conductance have also been noted. DHA produces a direct open channel block of the major voltage-dependent potassium channel cloned in cardiac cells through binding to an external site on the channel structure.[64] By accelerating the apparent activation and decreasing the peak current in cardiac cells, omega-3 fatty acids act similarly to the class III antiarrhythmic drug tedisamil.

Effects on Repolarization

The delayed-rectifier potassium channel current, which is responsible for the repolarization phase of ventricular more so than atrial cardiac action potential, may also be inhibited by these fatty acids in some circumstances, as demonstrated in rat and mouse cultured myocytes. Additionally, a reperfusion-induced increase in D-*myo*-inositol 1,4,5-triphosphate in perfused hearts was prevented in rats after 8 weeks of supplementation with omega-3 fatty acids compared with control.[65] Ventricular tachycardia was repressed 38% and ventricular fibrillation was repressed 13% in this study ($p < 0.01$). Omega-3 fatty acids may also influence the sodium-calcium exchanger that is responsible for accumulation of calcium in the cytoplasm, a stimulus for myocardial contractile proteins.[66] In a canine sodium/calcium exchanger system expressed in human embryonic kidney cells, EPA suppressed both inward and outward modes of operation in a concentration-dependent manner.[67] Accumulation of hydrogen during ischemia stimulates activity of the sodium/hydrogen exchanger to remove hydrogen in exchange for sodium. Increased activity of the exchanger causes an accumulation of intracellular sodium, which stimulates sodium/calcium exchange for removal of sodium at the expense of increasing calcium entry. Overloading the cells with calcium through this mechanism can also generate arrhythmia.

Different fatty acids appear to target different ion channels.[68] Sensitivity may be determined by 1 of the 2 protein subunits (eg, *hminK*) that produce slowly activating delayed-rectifier potassium current. Among the omega-3 fatty acids, DHA augmented the delayed-rectifier potassium channel current. EPA did not affect the magnitude of the current but reduced the rate of activation. The effects of lauric acid were similar to those of DHA; oleic acid had a lesser effect. Cardiac sarcolemmal sodium/hydrogen exchange in isolated cell membranes was inhibited 30% to 50% by exposure to EPA and DHA at physiologic concentrations, whereas no effect was observed with exposure to linoleic acid or linolenic acid. Passive sodium efflux, however, was not increased after treatment.[67]

Site of Action

The primary site of action of omega-3 fatty acids has not been determined. Data have been presented to support both direct effects on ion-channel proteins and indirect effects on ion conductance mediated through modification of the lipid bilayer contiguous with the ion channels in the microdomains in the cardiac sarcolemma. By allosterically altering the conformation of the membrane phospholipid bilayer in

juxtaposition with the ion channels, omega-3 fatty acids can influence sodium and calcium currents.[12] Membrane fluidity is influenced by the packaging of lipids in phospholipids in the membrane bilayer. When omega-3 fatty acids are packaged within the cell membrane phospholipids, the mismatch between the length of the hydrophobic transmembrane portion of the protein and lipid bilayer creates a molecular strain that interferes with the lipid microdomains contiguous with the channel protein.[69]

Membrane ion-channel conductance has been modified experimentally by partitioning of omega-3 fatty acids within the cell membrane with specific effects on the fast, voltage-gated sodium current and L-type calcium current.[26] Using whole-cell voltage clamp measurements, omega-3 fatty acids inhibited voltage-dependent sodium and potassium currents (transient outward current and delayed rectifier current, respectively), as well as the L-type calcium current.[66] Because omega-3 fatty acids noncompetitively displaced ^{3}H-nitrendipine (a specific L-type calcium channel antagonist) from its binding site at the external pore of the calcium channel protein, it cannot be said for certain what the primary effect is: that omega-3 does not bind to specific ion-channel proteins directly or that omega-3 changes the conformation of the transmembrane protein channels.

The protective effects of omega-3 fatty acids cannot be solely attributed to replacement of omega-6 fatty acids in membrane phospholipids because both types of fatty acids have demonstrated antiarrhythmic effects.[70] In a study of isolated hearts from male rats fed diets providing different types of fats (10% wt/wt) and a low-fat control group for 10 weeks, the incidence of ventricular fibrillation under experimentally induced conditions of both ischemia and reperfusion was 10% in the fish oil–fed group compared with 44% in the corn oil group, 67% in the coconut oil group, and 75% in controls.

Yang and coworkers[71] demonstrated that the antiarrhythmic effects of omega-3 fatty acids in rats were not mediated by plasma and blood cells. Animals fed diets enriched in fish oil for 5 days had significantly increased myocardial content of omega-3 fatty acids compared with controls fed butter-enriched diets. In isolated hearts from fish oil–fed rats, myocardial dysfunction was significantly attenuated following 15 minutes of global ischemia and 10 minutes of reperfusion compared with butter-fed rats, as evidenced by a smaller change in the force of contraction ($p < 0.05$) and coronary perfusion pressure ($p < 0.001$), as well as lower concentrations of creatine kinase and thromboxane B_2 in the coronary effluent ($p < 0.01$), accompanied by a lower incidence of ventricular arrhythmias.

The antiarrhythmic effects of omega-3 fatty acids may differ from those of antiarrhythmic drugs in that they do not involve changes in the number of sodium channels. Although EPA did not upregulate cardiac sodium channels, it reduced the increase in cardiac sodium channel expression observed with mexiletine by 40% to 50%. The toxicity of class I antiarrhythmic drugs is associated with upregulation of sodium channel expression, which can cause arrhythmias secondary to therapy.[72] Despite successful suppression of premature ventricular complexes by inhibiting cardiac sodium channels, short-term use of commonly used class I antiarrhythmic drugs (ie, encainide or flecainide) was associated with a poorer outcome and higher mortality in the Cardiac Arrhythmia Suppression Trial.[73]

Conclusion

The consumption of fish and fish oils appears in some large-scale clinical trials to have beneficial effects on survival, particularly or at least in ischemic substrates and particularly or at least in populations without high ambient consumption of fish intake. Evidence for a reduction in incidence of sudden death, in ischemic ventricular fibrillation, and in reperfusion ventricular fibrillation has been noted. Other antiarrhythmic effects may also exist, such as in some circumstances of atrial fibrillation, including a well-performed perioperative study of patients undergoing coronary artery bypass grafting. There is likely a dose-ranging or dose-threshold effect; there may be similar effects of other unsaturated vegetable oils; and there may be a sex difference, favoring effects in men. The manner in which the fish is prepared when eaten as part of the diet also likely alters the benefit seen, as does the background diet used by the patient. When fish oil supplements are taken, the variability in formulation, purity, and specific contaminants of the current over-the-counter preparations are likely a concern with respect to the effects sought in and by the patient. Responses to fish oil therapy do not appear to be immediate; rather, they require incorporation of the fatty acids into cell membranes. Accordingly, the effects may not be demonstrable in trials with too short a duration, too low a dose, and/or suboptimal dosing compliance.

Possible mechanisms for the antiarrhythmic benefit of fish oil therapy appear to be multiple and may, or likely, include effects on cardiac ion currents, effects on cardiac autonomic properties, and a resultant increase in fibrillation threshold. From the data reviewed, it also seems likely the antiarrhythmic effects are most pronounced in functionally mediated arrhythmias, in which an acute process alters the electrical properties of the cell and/or its autonomic modulation, rather than in anatomic-based (eg, scar-related) arrhythmias, a conclusion supported by the more impressive findings with ischemic substrates and sudden cardiac death than with ventricular tachycardia. Alterations in cell membrane properties by inclusion of fish oil derivatives may be a prominent part of the mechanism behind arrhythmia reduction. Future studies should include a focus on these issues rather than just observational counts of changes in arrhythmias with fish oil therapy.

In the United States, a pharmaceutical-grade fish oil preparation similar to that used in the GISSI study has been approved by the US Food and Drug Administration and was

released in the last quarter of 2005 (Reliant Pharmaceuticals, Liberty Corner, NJ). However, the indication sought, and received, was only for the reduction of significant elevations of triglycerides. Use for cardiac antiarrhythmic and/or survival benefit would be off-label until such time that approval for this purpose is attained; moreover, approval for such purposes will likely require more definitive studies than the ones performed to date. Prospective trials of dose, preparation (both as food and as supplement), patients in whom benefit may be seen, and information about active comparators will all have to be obtained.

1. Lee KW, Hamaad A, MacFadyen RJ, Lip GY. Effects of dietary fat intake in sudden death: reduction of death with omega-3 fatty acids. *Curr Cardiol Rep* 2004;6:371–378.
2. De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, Ebrahim S, Faergeman O, Graham I, Mancia G, et al, for the Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. European guidelines on cardiovascular disease prevention in clinical practice: Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Eur Heart J* 2003; 24:1601–1610.
3. Marchioli R, Barzi F, Bomba E, Chieffo C, Di Gregorio D, Di Mascio R, Franzosi MG, Geraci E, Levantesi G, Maggioni AP, et al. Early protection against sudden death by omega-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.
4. Singh RB, Niaz MA, Sharma JP, Kumar R, Rastogi V, Moshiri M. 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.
5. Albert CM, Campos H, Stampfer MJ, Ridker PM, Manson JE, Willett WC, Ma J. Blood levels of long-chain omega-3 fatty acids and the risk of sudden death. *N Engl J Med* 2002;346:1113–1118.
6. Lemaitre RN, King IB, Mozaffarian D, Kuller LH, Tracy RP, Siscovick DS. Omega-3 polyunsaturated fatty acids, fatal ischemic heart disease, and nonfatal myocardial infarction in older adults: the Cardiovascular Health Study. *Am J Clin Nutr* 2003;77:319–325.
7. Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, Elwood PC, Deadman NM. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: Diet and Reinfarction Trial (DART). *Lancet* 1989;2:757–761.
8. Mozaffarian D, Lemaitre RN, Kuller LH, Burke GL, Tracy RP, Siscovick DS. Cardiac benefits of fish consumption may depend on the type of fish meal consumed: the Cardiovascular Health Study. *Circulation* 2003;107:1372–1377.
9. Siscovick DS, Raghunathan TE, King I, Weinmann S, Wicklund KG, Albright J, Bovbjerg V, Arbogast P, Smith H, Kushi LH, et al. Dietary intake and cell membrane levels of long-chain omega-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. *JAMA* 1995; 274:1363–1367.
10. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. 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.
11. Carroll DN, Roth MT. Evidence for the cardioprotective effects of omega-3 fatty acids. *Ann Pharmacother* 2002;36:1950–1956.
12. De Caterina R, Madonna R, Zucchi R, La Rovere MT. Antiarrhythmic effects of omega-3 fatty acids: from epidemiology to bedside. *Am Heart J* 2003;146:420–430.
13. Geelen A, Brouwer IA, Zock PL, Katan MB. Antiarrhythmic effects of omega-3 fatty acids: evidence from human studies. *Curr Opin Lipidol* 2004;15:25–30.
14. Richter WO. Long-chain omega-3 fatty acids from fish reduce sudden cardiac death in patients with coronary heart disease. *Eur J Med Res* 2003;8:332–336.
15. Yokoyama M, for the JELIS Investigators. Effects of eicosapentaenoic acid (EPA) on major cardiovascular events in hypercholesterolemic patients: the Japan EPA Lipid Intervention Study (JELIS). Paper presented at the American Heart Association Scientific Sessions 2005; November 13–16, 2005; Dallas, TX.
16. Siscovick DS, Raghunathan T, King I, Weinmann S, Bovbjerg VE, Kushi L, Cobb LA, Copass MK, Psaty BM, Lemaitre R, Retzlaff B, Knopp RH. Dietary intake of long-chain omega-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. *Am J Clin Nutr* 2000;71(suppl):208S–212S.
17. Singer P, Wirth M. Can omega-3 polyunsaturated fatty acids reduce cardiac arrhythmias? Results of a clinical trial. *Prostaglandins Leukot Essent Fatty Acids* 2004;71:153–159.
18. Sellmayer A, Witzgall H, Lorenz RL, Weber PC. Effects of dietary fish oil on ventricular premature complexes. *Am J Cardiol* 1995;76:974–977.
19. Biscione F, Totteri A, De Vita A, Lo BF, Altamura G. Effect of omega-3 fatty acids on the prevention of atrial arrhythmias [in Italian]. *Ital Heart J Suppl* 2005;6:53–59.
20. Mozaffarian D, Psaty BM, Rimm EB, Lemaitre RN, Burke GL, Lyles MF, Lefkowitz D, Siscovick DS. Fish intake and risk of incident atrial fibrillation. *Circulation* 2004;110:368–373.
21. Harrison RA, Elton PJ. Is there a role for long-chain ω3 or oil-rich fish in the treatment of atrial fibrillation? *Med Hypotheses* 2005;64:59–63.
22. Calo L, Bianconi L, Colivicchi F, Lamberti F, Loricchio ML, de Ruvo E, Meo A, Pandozi C, Staibano M, Santini M. 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.
23. Leaf A, Kang JX, Xiao YF, Billman GE. Clinical prevention of sudden cardiac death by omega-3 polyunsaturated fatty acids and mechanism of prevention of arrhythmias by omega-3 fish oils. *Circulation* 2003; 107:2646–2652.
24. Leaf A, Xiao YF, Kang JX, Billman GE. Prevention of sudden cardiac death by omega-3 polyunsaturated fatty acids. *Pharmacol Ther* 2003; 98:355–377.
25. Segal-Isaacson CJ, Wylie-Rosett J. The cardiovascular effects of fish oils and omega-3 fatty acids. *Heart Dis* 1999;1:149–154.
26. Von Schacky C. Omega-3 fatty acids and cardiovascular disease. *Curr Opin Clin Nutr Metab Care* 2004;7:131–136.
27. Jones PJ, Lau VW. Effect of omega-3 polyunsaturated fatty acids on risk reduction of sudden death. *Nutr Rev* 2002;60:407–409.
28. Leaf A, Kang JX. Prevention of cardiac sudden death by N-3 fatty acids: a review of the evidence. *J Intern Med* 1996;240:5–12.
29. Lee KW, Lip GY. The role of omega-3 fatty acids in the secondary prevention of cardiovascular disease. *QJM* 2003;96:465–480.
30. 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.
31. Pepe S, McLennan PL. Dietary fish oil confers direct antiarrhythmic properties on the myocardium of rats. *J Nutr* 1996;126:34–42.
32. Riemersma RA, Sargent CA. Dietary fish oil and ischaemic arrhythmias. *J Intern Med Suppl* 1989;731:111–116.
33. McLennan PL, Bridle TM, Abeywardena MY, Charnock JS. Comparative efficacy of n-3 and n-6 polyunsaturated fatty acids in modulating ventricular fibrillation threshold in marmoset monkeys. *Am J Clin Nutr* 1993;58:666–669.
34. Frost L, Vestergaard P. Omega-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.
35. Geelen A, Brouwer IA, Schouten EG, Maan AC, Katan MB, Zock PL. Effects of omega-3 fatty acids from fish on premature ventricular

complexes and heart rate in humans. *Am J Clin Nutr* 2005;81:416–420.
36. Dyer AR, Persky V, Stamler J, Paul O, Shekelle RB, Berkson DM, Lepper M, Schoenberger JA, Lindberg HA. Heart rate as a prognostic factor for coronary heart disease and mortality: findings in three Chicago epidemiologic studies. *Am J Epidemiol* 1980;112:736–749.
37. Geelen A, Brouwer IA, Zock PL, Kors JA, Swenne CA, Katan MB, Schouten EG. (n-3) Fatty acids do not affect electrocardiographic characteristics of healthy men and women. *J Nutr* 2002;132:3051–3054.
38. Hartog JM, Lamers JM, Verdouw PD. The effects of dietary mackerel oil on plasma and cell membrane lipids, on hemodynamics and cardiac arrhythmias during recurrent acute ischemia in the pig. *Basic Res Cardiol* 1986;81:567–580.
39. Cleland JG, Freemantle N, Kaye G, Nasir M, Velavan P, Lalukota K, Mudawi T, Shelton R, Clark AL, Coletta AP. Clinical trials update from the American Heart Association meeting: omega-3 fatty acids and arrhythmia risk in patients with an implantable defibrillator, ACTIV in CHF, VALIANT, the Hanover autologous bone marrow transplantation study, SPORTIF V, ORBIT and PAD and DEFINITE. *Eur J Heart Fail* 2004;6:109–115.
40. Raitt MH, Connor WE, Morris C, Kron J, Halperin B, Chugh SS, McClelland J, Cook J, MacMurdy K, Swenson R, 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.
41. Schrepf R, Limmert T, Claus WP, Theisen K, Sellmayer A. Immediate effects of omega-3 fatty acid infusion on the induction of sustained ventricular tachycardia. *Lancet* 2004;363:1441–1442.
42. Leaf A, Albert CM, Josephson M, Steinhaus D, Kluger J, Kang JX, Cox B, Zhang H, Schoenfeld D, for the Fatty Acid Antiarrhythmia Trial Investigators. Prevention of fatal arrhythmias in high-risk subjects by fish oil n-3 fatty acid intake. *Circulation* 2005;112:2762–2768.
43. Brouwer IA, Zock PL, Wever EF, Hauer RN, Camm AJ, Bocker D, Otto-Turlouw P, Katan MB, Schouten EG. Rationale and design of a randomised controlled clinical trial on supplemental intake of omega-3 fatty acids and incidence of cardiac arrhythmia: SOFA. *Eur J Clin Nutr* 2003;57:1323–1330.
44. Brouwer I, for the SOFA Investigators. Presented at the 2005 Annual Scientific Sessions of the European Society of Cardiology; September 16, 2005; Amsterdam, Netherlands.
45. Li Y, Kang JX, Leaf A. Differential effects of various eicosanoids on the production or prevention of arrhythmias in cultured neonatal rat cardiac myocytes. *Prostaglandins* 1997;54:511–530.
46. Nair SS, Leitch JW, Falconer J, Garg ML. Prevention of cardiac arrhythmia by dietary (n-3) polyunsaturated fatty acids and their mechanism of action. *J Nutr* 1997;127:383–393.
47. Riemersma RA, Sargent CA. Dietary fish oil and ischaemic arrhythmias. *J Intern Med Suppl* 1989;731:111–116.
48. 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.
49. Christensen JH, Gustenhoff P, Korup E, Aaroe J, Toft E, Moller JM, Rasmussen K, Dyerberg J, Schmidt EB. Omega-3 polyunsaturated fatty acids, heart rate variability and ventricular arrhythmias in post-AMI-patients: a clinical controlled trial [in Danish]. *Ugeskr Laeger* 1997;159:5525–5529.
50. Geelen A, Zock PL, Swenne CA, Brouwer IA, Schouten EG, Katan MB. Effect of omega-3 fatty acids on heart rate variability and baroreflex sensitivity in middle-aged subjects. *Am Heart J* 2003;146:E4.
51. Christensen JH, Korup E, Aaroe J, Toft E, Moller J, Rasmussen K, Dyerberg J, Schmidt EB. Fish consumption, omega-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.
52. Mozaffarian D, Geelen A, Brouer IA, Geleijnse JM, Zock PL, Katan MB. Effect of fish oil on heart rate in humans: a meta-analysis of randomized controlled trials. *Circulation* 2005;112:1945–1952.
53. Leaf A. Plasma nonesterified fatty acid concentration as a risk factor for sudden cardiac death: the Paris Prospective Study. *Circulation* 2001;104:744–745.
54. Alberte C, Zipes DP. Use of nonantiarrhythmic drugs for prevention of sudden cardiac death. *J Cardiovasc Electrophysiol* 2003;14(suppl): S87–S95.
55. Kang JX, Leaf A. Prevention and termination of beta-adrenergic agonist-induced arrhythmias by free polyunsaturated fatty acids in neonatal rat cardiac myocytes. *Biochem Biophys Res Commun* 1995;208: 629–636.
56. Chung MK. Vitamins, supplements, herbal medicines, and arrhythmias. *Cardiol Rev* 2004;12:73–84.
57. Leaf A. The electrophysiologic basis for the antiarrhythmic and anticonvulsant effects of omega-3 polyunsaturated fatty acids: heart and brain. *Lipids* 2001;36(suppl):S107–S110.
58. Leaf A, Xiao YF, Kang JX, Billman GE. Prevention of sudden cardiac death by omega-3 polyunsaturated fatty acids. *Pharmacol Ther* 2003; 98:355–377.
59. Leaf A, Kang JX, Xiao YF, Billman GE. Omega-3 fatty acids in the prevention of cardiac arrhythmias. *Lipids* 1999;34(suppl):S187–S189.
60. Leaf A, Kang JX, Xiao YF, Billman GE. Dietary omega-3 fatty acids in the prevention of cardiac arrhythmias. *Curr Opin Clin Nutr Metab Care* 1998;1:225–228.
61. Leaf A, Kang JX. Dietary omega-3 fatty acids in the prevention of lethal cardiac arrhythmias. *Curr Opin Lipidol* 1997;8:4–6.
62. Leaf A. Omega-3 fatty acids and prevention of ventricular fibrillation. *Prostaglandins Leukot Essent Fatty Acids* 1995;52:197–198.
63. Honore E, Barhanin J, Atalli B, Lesage F, Lazdunski M. External blockage of the major cardiac delayed-rectifier K^+ channel (Kv 1.5) by polyunsaturated fatty acids. *Proc Natl Acad Sci U S A* 1997;91:1937–1944.
64. Kang JX, Leaf A. Prevention of fatal cardiac arrhythmias by polyunsaturated fatty acids. *Am J Clin Nutr* 2000;71(suppl):202S–207S.
65. Anderson KE, Du XJ, Sinclair AJ, Woodcock EA, Dart AM. Dietary fish oil prevents reperfusion Ins(1,4,5)P3 release in rat heart: possible antiarrhythmic mechanism. *Am J Physiol* 1996;271(pt 2):H1483–H1490.
66. Xiao YF, Ke Q, Chen Y, Morgan JP, Leaf A. Inhibitory effect of omega-3 fish oil fatty acids on cardiac Na^+/Ca^{2+} exchange currents in HEK293t cells. *Biochem Biophys Res Commun* 2004;321:116–123.
67. Goel DP, Maddaford TG, Pierce GN. Effects of ω-3 polyunsaturated fatty acids on cardiac sarcolemmal Na^+/H^+ exchange. *Am J Physiol Heart Circ Physiol* 2002;283:H1688–H1694.
68. Doolan GK, Panchal RG, Fonnes EL, Clarke AL, Williams DA, Petrou S. Fatty acid augmentation of the cardiac slowly activating delayed rectifier current (IKs) is conferred by *hminK*. *FASEB J* 2002;16:1662–1664.
69. Xiao YF, Ke Q, Wang SY, Yang Y, Chen Y, Wang GK, Morgan JP, Cox B, Leaf A. Electrophysiologic properties of lidocaine, cocaine, and omega-3 fatty-acids block of cardiac Na^+ channels. *Eur J Pharmacol* 2004;485:31–41.
70. Isensee H, Jacob R. Differential effects of various oil diets on the risk of cardiac arrhythmias in rats. *J Cardiovasc Risk* 1994;1:353–359.
71. Yang B, Saldeen TG, Nichols WW, Mehta JL. Dietary fish oil supplementation attenuates myocardial dysfunction and injury caused by global ischemia and reperfusion in isolated rat hearts. *J Nutr* 1993; 123:2067–2074.
72. Kang JX, Li Y, Leaf A. Regulation of sodium channel gene expression by class I antiarrhythmic drugs and n-3 polyunsaturated fatty acids in cultured neonatal rat cardiac myocytes. *Proc Natl Acad Sci U S A* 1997;94:2724–2728.
73. The CAPS Investigators. The Cardiac Arrhythmia Pilot Study. *Am J Cardiol* 1986;57:91–95.