

Fish Oil & Arrhythmias

Am J Cardiol. 2006 Apr 15;97(8):1127-1130. Epub 2006 Mar 3.

Effects of Omega-3 Fatty Acids on Resting Heart Rate, Heart Rate Recovery After Exercise, and Heart Rate Variability in Men With Healed Myocardial Infarctions and Depressed Ejection Fractions.

O'Keefe JH Jr, Abuissa H, Sastre A, Steinhaus DM, Harris WS.

We explored possible mechanisms by which recommended intakes of omega-3 fatty acids may decrease the risk for sudden cardiac death in patients with documented coronary heart disease. The cardioprotective effects of omega-3 fatty acids have been documented in epidemiologic and randomized controlled trials. These fatty acids are presumed to decrease susceptibility to fatal arrhythmias, but whether this is mediated by classic risk factors or direct cardiac mechanisms is not known. Eighteen white men with a history of myocardial infarction and ejection fractions <40% were randomized to placebo or omega-3 fatty acids (585 mg of docosahexaenoic acid and 225 mg of eicosapentaenoic acid) for two 4-month periods in a crossover design. At the end of each period, heart rate (HR), HR variability, and rate of HR recovery after exercise were determined, as were effects on arterial compliance, blood pressure, cardiac function, and fasting serum levels of lipids and inflammatory markers. Omega-3 fatty acids decreased HR at rest from 73 +/- 13 to 68 +/- 13 beats/min ($p < 0.0001$) and improved 1-minute HR recovery after exercise (-27 +/- 10 to -32 +/- 12 beats/min, $p < 0.01$). HR variability in the high-frequency band increased ($p < 0.02$), but no change was noted in overall HR variability. There were no significant effects on blood pressure, arterial compliance, lipids, or inflammatory markers. These changes are consistent with an increase in vagal activity and may in part explain the observed decrease in risk for sudden cardiac death seen with omega-3 fatty acid supplementation.

Metabolism. 2005 Dec;54(12):1557-65.

A systematic review and meta-analysis of the impact of omega-3 fatty acids on selected arrhythmia outcomes in animal models.

Matthan NR, Jordan H, Chung M, Lichtenstein AH, Lathrop DA, Lau J.

Epidemiological studies and clinical trials report the beneficial effects of fish or fish oil consumption on cardiovascular disease outcomes including sudden death. We performed a systematic review of the literature on controlled animal studies that assessed the effects of omega-3 fatty acids on selected arrhythmia outcomes. On the basis of predetermined criteria, 27 relevant animal studies were identified; 23 of these were feeding studies, and 4 were infusion studies. Across species, fish oil, eicosapentaenoic acid, and/or docosahexaenoic acid appear to have beneficial effects on ventricular tachycardia (VT) and fibrillation (VF) in ischemia- but not reperfusion-induced arrhythmia models; no effect on the incidence of death and infarct size; and inconsistent results with regard to arrhythmia score, VF threshold, ventricular premature beats or length of time in normal sinus rhythm, compared to omega-6, monounsaturated, or saturated fatty acids, and no treatment controls. In a meta-analysis of 13 studies using rat models, fish oil but not alpha-linolenic acid supplementation showed a significant protective effect for ischemia- and reperfusion-induced arrhythmias by reducing the incidence of VT and VF. It is not known whether omega-3 fatty-acid supplementation has antiarrhythmic effects in other disease settings not related to ischemia.

Circulation. 2005 Nov 1;112(18):2762-8.

Prevention of fatal arrhythmias in high-risk subjects by fish oil n-3 fatty acid intake.

Leaf A, Albert CM, Josephson M, Steinhaus D, Kluger J, Kang JX, Cox B, Zhang H, Schoenfeld D; Fatty Acid Antiarrhythmia Trial Investigators.

BACKGROUND: The long-chain n-3 fatty acids in fish have been demonstrated to have antiarrhythmic properties in experimental models and to prevent sudden cardiac death in a randomized trial of post-myocardial infarction patients. Therefore, we hypothesized that these n-3 fatty acids might prevent potentially fatal ventricular arrhythmias in high-risk patients. **METHODS AND RESULTS:** Four hundred two patients with implanted cardioverter/defibrillators (ICDs) were randomly assigned to

double-blind treatment with either a fish oil or an olive oil daily supplement for 12 months. The primary end point, time to first ICD event for ventricular tachycardia or fibrillation (VT or VF) confirmed by stored electrograms or death from any cause, was analyzed by intention to treat. Secondary analyses were performed for "probable" ventricular arrhythmias, "on-treatment" analyses for all subjects who had taken any of their oil supplements, and "on-treatment" analyses only of those subjects who were on treatment for at least 11 months. Compliance with double-blind treatment was similar in the 2 groups; however, the noncompliance rate was high (35% of all enrollees). In the primary analysis, assignment to treatment with the fish oil supplement showed a trend toward a prolonged time to the first ICD event (VT or VF) or of death from any cause (risk reduction of 28%; $P=0.057$). When therapies for probable episodes of VT or VF were included, the risk reduction became significant at 31%; $P=0.033$. For those who stayed on protocol for at least 11 months, the antiarrhythmic benefit of fish oil was improved for those with confirmed events (risk reduction of 38%; $P=0.034$). **CONCLUSIONS:** Although significance was not achieved for the primary end point, this study provides evidence that for individuals at high risk of fatal ventricular arrhythmias, regular daily ingestion of fish oil fatty acids may significantly reduce potentially fatal ventricular arrhythmias.

J Membr Biol. 2005 Jul;206(2):155-63.

Is fish oil good or bad for heart disease? Two trials with apparently conflicting results.

Burr ML, Dunstan FD, George CH.

Two successive randomized trials examined the effect of an increased intake of fatty fish, or the use of fish oil supplements, in reducing mortality in men with heart disease. The Diet and Reinfarction Trial (DART) was conducted in 2033 men who were recovering from acute myocardial infarction (MI). Those who were advised to eat fatty fish (or who opted to take fish oil capsules instead) had a 29% reduction in all-cause mortality over the following two years compared with those not so advised. The effect appeared in the first few months of the trial. The Diet and Angina Randomized Trial (DART 2) involved 3114 men with stable angina. Advice to eat fatty fish did not reduce mortality, and taking fish oil capsules was associated with a higher risk of cardiac and sudden death. The adverse effects of fish or fish oil were restricted to men not taking beta-blockers or dihydropyridine calcium-channel blockers, and were greater in those taking digoxin. Evidence from other sources strongly suggests an anti-arrhythmic action of fish oil, particularly after MI or in the presence of acute ischemia. The apparently conflicting results of the two trials may reflect different actions of n-3 fatty acids in acute and chronic conditions, together with different effects of eating fish and taking fish oil capsules. A mechanism is proposed that could account for these findings.

Europace. 2005 Jul;7(4):338-44.

n-3 Fatty acids and ventricular arrhythmias in patients with ischaemic heart disease and implantable cardioverter defibrillators.

Christensen JH, Riahi S, Schmidt EB, Molgaard H, Kirstein Pedersen A, Heath F, Cosedis Nielsen J, Toft E.

AIM: To investigate the relationship between serum content of n-3 polyunsaturated fatty acids (PUFA) and the incidence of ventricular arrhythmias in patients with an implantable cardioverter defibrillator (ICD). **METHODS:** We included 98 patients with ischaemic heart disease and an ICD. The numbers of ventricular fibrillation (VF) and ventricular tachycardia (VT) events were assessed during a 12-month period and related to the concentration of n-3 PUFA in serum phospholipids. **RESULTS:** Patients with more than one arrhythmic event had significantly lower n-3 PUFA levels compared with patients without arrhythmias (mean 7.1% vs 9.2%, $P<0.01$). Dividing the patients into quintiles according to their n-3 PUFA level those with the lowest content of n-3 PUFA had more ventricular arrhythmias than patients with the highest concentration of n-3 PUFA (mean 1.3 event vs 0.2 event, $P<0.05$). **CONCLUSION:** Patients with a low content of n-3 PUFA in serum had a higher incidence of ventricular arrhythmias compared with patients with high serum levels of n-3 PUFA. The data suggest that the protection offered by n-3 PUFA against sudden cardiac death observed in previous studies is mediated by a direct antiarrhythmic effect of n-3 PUFA.

J Membr Biol. 2005 Jul;206(2):85-102.

Membrane basis for fish oil effects on the heart: linking natural hibernators to prevention of human sudden cardiac death.

McLennan PL, Abeywardena MY.

The concept that diet-induced changes in membrane lipids could modify heart function partly arose from observations that membrane composition and physical properties were closely associated with the capacity of the heart to respond appropriately to torpor and hibernation. Observations of natural hibernators further revealed that behavior of key membrane-bound enzymes could be influenced through the lipid composition of the cell membrane, either by changing the surrounding fatty acids through reconstitution into a foreign lipid milieu of different composition, or by alteration through diet. Myocardial

responsiveness to beta-adrenoceptor stimulation, including initiation of spontaneous dysrhythmic contractions, was altered by both hibernation and dietary modulation of membrane fatty acids, suggesting modified vulnerability to cardiac arrhythmia. Subsequent studies using whole-animal models recognized that vulnerability to ventricular fibrillation decreased as the polyunsaturated: saturated fat (P:S) ratio of the diet increased. However, dietary fish oils, which typically contain at least 30% saturated fatty acids and only 30% long-chain n-3 (omega-3) polyunsaturated fatty acids (PUFA), exhibit antiarrhythmic effects that exceed the predicted influence of the P:S ratio, suggesting properties unique to the long-chain n-3 PUFA. Large-scale clinical trials and epidemiology have confirmed the arrhythmia prevention observed in vitro in myocytes, papillary muscles, and isolated hearts and in whole-animal models of sudden cardiac death. Some progress has been made towards a biologically plausible mechanism. These developments highlight nature's ability to provide guidance for the most unexpected applications.

J Membr Biol. 2005 Jul;206(2):141-54.

The antiarrhythmic effect of n-3 polyunsaturated fatty acids: modulation of cardiac ion channels as a potential mechanism.

Xiao YF, Sigg DC, Leaf A.

Sudden cardiac death remains one of the most serious medical challenges in Western countries. Increasing evidence in recent years has demonstrated that the n-3 polyunsaturated fatty acids (PUFAs) can prevent fatal ventricular arrhythmias in experimental animals and probably in humans. Dietary supplement of fish oils or intravenous infusion of the n-3 PUFAs prevents ventricular fibrillation caused by ischemia/reperfusion. Similar antiarrhythmic effects of these fatty acids are also observed in cultured mammalian cardiomyocytes. Based on clinical observations and experimental studies in vitro and in vivo, several mechanisms have been postulated for the antiarrhythmic effect of the n-3 PUFAs. The data from our laboratory and others have shown that the n-3 PUFAs are able to affect the activities of cardiac ion channels. The modulation of channel activities, especially voltage-gated Na(+) and L-type Ca(2+) channels, by the n-3 fatty acids may explain, at least partially, the antiarrhythmic action. It is not clear, however, whether one or more than one mechanism involves the beneficial effect of the n-3 PUFAs on the heart. This article summarizes our recent studies on the specific effects of the n-3 PUFAs on cardiac ion channels. In addition, the effect of the n-3 PUFAs on the human hyperpolarization-activated cyclic-nucleotide-modulated channel is presented.

J Membr Biol. 2005 Jul;206(2):129-39.

Membrane effects of the n-3 fish oil fatty acids, which prevent fatal ventricular arrhythmias.

Leaf A, Xiao YF, Kang JX, Billman GE.

Fish oil fatty acids are known to exert beneficial effects on the heart and vascular systems. We have studied the membrane effects on ion channel conductance by the n-3 fish oil fatty acids that account for these beneficial effects. We have confirmed that these fatty acids prevent fatal cardiac arrhythmias in a reliable dog model of sudden cardiac death. This finding was followed by experiments indicating that the n-3 fatty acids electrically stabilize heart cells and do so largely through modulation of the fast voltage-dependent Na(+) currents and the L-type Ca(2+) channels in a manner, which makes the heart cells resistant to arrhythmias. Others and we have demonstrated that these membrane effects on the heart can prevent fatal cardiac arrhythmias in humans.

J Membr Biol. 2005 Jul;206(2):117-28.

Antiarrhythmic mechanisms of n-3 PUFA and the results of the GISSI-Prevenzione trial.

Marchioli R, Levantesi G, Macchia A, Maggioni AP, Marfisi RM, Silletta MG, Tavazzi L, Tognoni G, Valagussa F; GISSI-Prevenzione Investigators.

The purpose of this paper is twofold: on the one hand, to confirm the positive results on n-3 PUFA from the overall results Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione trial; on the other, to summarize and describe how the results of an important trial can help generate hypotheses either on mechanisms of action or on differential results in particular subgroups of patients, as well as test the pathophysiological hypotheses that have accompanied in the years the story of the hypothesized mechanisms of action of a drug. GISSI-Prevenzione was conceived as a pragmatic population trial on patients with recent myocardial infarction and it was conducted in the framework of the Italian public health system. In GISSI-Prevenzione, 11,323 patients were enrolled in a clinical trial aimed at testing the effectiveness of n-3 polyunsaturated fatty acids (PUFA) and vitamin E. Patients were invited to follow Mediterranean dietary habits, and were treated with up-to-date preventive pharmacological interventions. Long-term n-3 PUFA at 1 g daily, but not vitamin E at 300 mg daily, was beneficial for death and for combined death, non-fatal myocardial infarction, and stroke. All the benefit, however, was attributable to the decrease in risk for overall (-20%), cardiovascular (-30%), and sudden death (-45%). At variance from the orientation of a scientific scenario largely dominated by the "cholesterol-heart hypothesis", GISSI-Prevenzione results indicate n-3 PUFA (virtually devoid of any cholesterol-lowering effect) as a relevant pharmacological treatment for secondary prevention after myocardial infarction.

Br J Nutr. 2005 Jun;93(6):787-90.

Effect of n-3 fatty acids from fish on electrocardiographic characteristics in patients with frequent premature ventricular complexes.

Geelen A, Zock PL, Brouwer IA, Katan MB, Kors JA, Ritsema van Eck HJ, Schouten EG.

n-3 Fatty acids may protect against heart disease mortality by preventing fatal arrhythmias. Underlying effects on cardiac electrophysiology may be demonstrable in the standard electrocardiogram (ECG) and provide insight into the mechanism. Therefore, we investigated the effect of dietary n-3 fatty acids on heart-rate-corrected QT interval, T-loop width, spatial QRS-T angle and spatial U-wave amplitude in patients with frequent premature ventricular complexes. Seventy-four patients received either capsules providing 1.5 g n-3 fatty acids daily or placebo for approximately 14 weeks. ECG were recorded before and after intervention. None of the ECG characteristics was significantly affected by treatment. The present results do not provide additional support for the hypothesis that n-3 fatty acids prevent cardiac arrhythmia through generic electrophysiologic effects on heart cell membranes. However, we cannot exclude effects of n-3 fatty acids on clinical relevant endpoints that are not easily detected by prior changes in the ECG.

JAMA. 2005 Jun 15;293(23):2884-91.

Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implantable defibrillators: a randomized controlled trial.

Raitt MH, Connor WE, Morris C, Kron J, Halperin B, Chugh SS, McClelland J, Cook J, MacMurdy K, Swenson R, Connor SL, Gerhard G, Kraemer DF, Oseran D, Marchant C, Calhoun D, Shnider R, McNulty J.

CONTEXT: Clinical studies of omega-3 polyunsaturated fatty acids (PUFAs) have shown a reduction in sudden cardiac death, suggesting that omega-3 PUFAs may have antiarrhythmic effects. OBJECTIVE: To determine whether omega-3 PUFAs have beneficial antiarrhythmic effects in patients with a history of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF). DESIGN AND SETTING: Randomized, double-blind, placebo-controlled trial performed at 6 US medical centers with enrollment from February 1999 until January 2003. PATIENTS: Two hundred patients with an implantable cardioverter defibrillator (ICD) and a recent episode of sustained VT or VF. INTERVENTION: Patients were randomly assigned to receive fish oil, 1.8 g/d, 72% omega-3 PUFAs, or placebo and were followed up for a median of 718 days (range, 20-828 days). MAIN OUTCOME MEASURES: Time to first episode of ICD treatment for VT/VF, changes in red blood cell concentrations of omega-3 PUFAs, frequency of recurrent VT/VF events, and predetermined subgroup analyses. RESULTS: Patients randomized to receive fish oil had an increase in the mean percentage of omega-3 PUFAs in red blood cell membranes from 4.7% to 8.3% ($P < .001$), with no change observed in patients receiving placebo. At 6, 12, and 24 months, 46% (SE, 5%), 51% (5%), and 65% (5%) of patients randomized to receive fish oil had ICD therapy for VT/VF compared with 36% (5%), 41% (5%), and 59% (5%) for patients randomized to receive placebo ($P = .19$). In the subset of 133 patients whose qualifying arrhythmia was VT, 61% (SE, 6%), 66% (6%), and 79% (6%) of patients in the fish oil group had VT/VF at 6, 12, and 24 months compared with 37% (6%), 43% (6%), and 65% (6%) of patients in the control group ($P = .007$). Recurrent VT/VF events were more common in patients randomized to receive fish oil ($P < .001$). CONCLUSION: Among patients with a recent episode of sustained ventricular arrhythmia and an ICD, fish oil supplementation does not reduce the risk of VT/VF and may be proarrhythmic in some patients.

Naunyn Schmiedebergs Arch Pharmacol. 2005 Mar;371(3):202-11. Epub 2005 Apr 15.

Antiarrhythmic and electrophysiological effects of long-chain omega-3 polyunsaturated fatty acids.

Dhein S, Michaelis B, Mohr FW.

Recent studies indicate that a diet enriched in omega-3 polyunsaturated fatty acids may prevent sudden cardiac death. The goal of the present study was to elucidate how omega-3 polyunsaturated fatty acids such as docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and alpha-linolenic acid (ALA; 1-20 microM) may affect the cardiac activation and repolarization pattern. For this reason, DHA, EPA or ALA was infused in spontaneously beating isolated rabbit heart (Langendorff technique) and subjected to 256 electrodes epicardial mapping. All compounds exhibited a negative inotropic and chronotropic effect. EPA and ALA, but not DHA, prolonged QTc. The dispersion was enhanced at higher concentrations (>5 microM) by DHA and less (or not affected) by the others. The total activation time, reflecting ventricular conduction, was prolonged predominantly by DHA and to a lower extent by the other drugs. Atrioventricular conduction time was slowed only by DHA and EPA. To analyze of the pattern of activation, we determined the timepoint of activation as $t(dU/dt(\min))$ for all 256 electrodes. The beat-to-beat similarity of these patterns was moderately reduced by all drugs. Regarding antiarrhythmic activity we found that the threshold for elicitation of a ventricular extrasystole was concentration-dependently enhanced by DHA and EPA, but not by ALA. DHA dose-dependently reduced longitudinal propagation velocity $V(L)$ and to a lower extent transverse velocity $V(T)$. Anisotropy was not significantly changed. EPA and ALA did not exhibit a systematic effect on $V(L)$ or $V(T)$. These results clearly demonstrate that DHA, EPA, and ALA exhibit direct electrophysiological effects with different profiles.

Ital Heart J. 2005 Mar;6(3):175-9.

Non-antiarrhythmic drugs for the prevention of cardiac arrhythmias.

Di Biase M, Troccoli R, Brunetti ND.

It is noteworthy that drugs having a significant impact in preventing arrhythmias (atrial or ventricular) are those with no direct specific antiarrhythmic electrophysiologic properties. Specifically, drugs able to interfere with the renin-angiotensin system and the n-3 fatty acids seem to play a relevant role as antiarrhythmics, even if they do not act in the typical manner. Angiotensin-converting enzyme (ACE) inhibitors decrease the incidence of arrhythmias in patients with decreased left ventricular function. The main reduction is linked to a decrease of ventricular arrhythmias, while several studies have suggested that ACE-inhibitors may also decrease the burden of atrial fibrillation. Furthermore, many of angiotensin receptor blockers and spironolactone have been shown to have antiarrhythmic properties. n-3 polyunsaturated fatty acids (PUFAs) are known to be antiarrhythmic as well. Their effects on the fast voltage-dependent sodium current I(Na), inhibition of I(Ca²⁺) and the K⁺ channel modulation explain their antiarrhythmic properties. For these reasons the renin-angiotensin system blockade and the n-3 PUFA intake may provide simple and safe protection from cardiac arrhythmias.

Am J Clin Nutr. 2005 Feb;81(2):416-20.

Effects of n-3 fatty acids from fish on premature ventricular complexes and heart rate in humans.

Geelen A, Brouwer IA, Schouten EG, Maan AC, Katan MB, Zock PL.

BACKGROUND: A large body of evidence suggests that n-3 fatty acids from fish prevent fatal heart disease. They may be an effective and safe alternative to drug treatment for reducing the risk of arrhythmia and sudden cardiac death. **OBJECTIVE:** We investigated the effect of n-3 fatty acids on heart rate and premature ventricular complexes (PVCs), a common form of arrhythmia that may trigger arrhythmias that are more life-threatening. **DESIGN:** Patients (n=84) with ≥ 1440 PVCs/24 h in a previous Holter recording were randomly assigned to receive 1.5 g/d of either n-3 fatty acids or placebo. Two 24-h Holter recordings were made at baseline, and 2 were made after an intervention of approximately 14 wk. **RESULTS:** Treatment did not significantly affect the number of PVCs. The number decreased in the fish-oil group by 867/24 h more than it decreased in placebo group (95% CI: -3187, 1453). However, the mean 24-h heart rate was significantly affected, decreasing in the fish-oil group by a mean of 2.1 beats/min more than it decreased in the placebo group (95% CI: -3.9, -0.3). **CONCLUSIONS:** Supplementation with 1.5 g n-3 fatty acids/d from fish does not substantially suppress the number of PVCs in a patient population with frequent PVCs. However, n-3 fatty acids decreased heart rate by 2.1 beats/min, a significant decrease that predicts a lower risk of sudden death.

Herz. 2004 Nov;29(7):673-85.

Risk stratification by the "EPA+DHA level" and the "EPA/AA ratio" focus on anti-inflammatory and antiarrhythmogenic effects of long-chain omega-3 fatty acids.

Rupp H, Wagner D, Rupp T, Schulte LM, Maisch B.

The identification of risks associated with sudden cardiac death requires further investigations. The question was addressed whether parameters can be established which not only describe an increased risk for an enhanced electrical instability of the heart but also of inflammatory events underlying plaque rupture. Emphasis is placed on dose-dependent effects of the long-chain omega-(omega)-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Since free acids of EPA and DHA are required for most of their biological effects, it appears essential not only to build up stores in the body for release of these fatty acids, but also to provide a sustained uptake of EPA and DHA in the form of ethyl esters. In contrast to rapidly absorbed triacylglycerols from fish, ethyl esters are taken up more slowly within 24 h. For the administration of 1 g/day highly purified EPA+DHA ethyl esters (Omacor) to healthy volunteers, it is shown that EPA is increased from 0.6% to 1.4% within 10 days, while DHA is increased from 2.9% to 4.3%. After withdrawal, EPA and DHA approach baseline values within 10 days. A gas chromatographic procedure was established which requires only 10 microl of whole blood for the identification of more than 35 fatty acids. Evidence is summarized strengthening the concept that a low "EPA+DHA level" presents a risk for sudden cardiac death and that the administration of 840 mg/day of EPA+DHA ethyl esters raises the "EPA+DHA level" to approximately 6% that is associated with a marked protection from sudden cardiac death. For reducing pro-inflammatory eicosanoids and cytokines, a higher "EPA+DHA level" is required which can be achieved with an intake of 2-4 g/day of 84% EPA+DHA ethyl esters. For assessing influences from pro-inflammatory eicosanoids and cytokines, the EPA/arachidonic acid ratio ("EPA/AA ratio") was identified as diagnostic parameter. To assess the dietary EPA+DHA intake, fatty acids were determined in fish dishes of the cafeteria of the Philipps University Hospital Marburg, Germany. The EPA+DHA content of the popular Alaska Pollock was 125 +/- 70 mg/100 g. A once daily fish dish can thus not provide the 840 mg/day EPA+DHA administered in the GISSI Prevention Study in the form of ethyl ester which markedly reduced the risk of sudden cardiac death in postmyocardial infarction patients. Nonetheless, at least two preferably oily fish meals per week should be consumed as preventive measure by persons without coronary artery disease. With documented coronary heart disease, it was advised to consume approximately 1 g/day of EPA+DHA.

Curr Atheroscler Rep. 2004 Nov;6(6):447-52.

Are omega-3 fatty acids the most important nutritional modulators of coronary heart disease risk?

Harris WS.

With each passing year, the evidence linking an increased risk for coronary heart disease (CHD) death with a chronic dietary deficiency in long-chain omega-3 (n-3) fatty acids (FAs) grows stronger. Recently, a federally mandated evidence-based review in the United States concluded that n-3 FAs, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have clear cardioprotective effects, and national and international expert panels and health organizations have begun to call for increased EPA and DHA intakes. Consumption of between 450 and 1000 mg/d is recommended for those without and with known CHD, respectively. Based on animal and isolated cell studies, these FAs were presumed to have antiarrhythmic effects. The first direct evidence for this in humans was recently published, as were new data linking low n-3 FA intakes with risk for developing atrial fibrillation. The strength of the n-3 story has now led to a proposal that blood levels of EPA plus DHA be considered a new, modifiable, and clinically relevant risk factor for death from CHD.

Biochem Biophys Res Commun. 2004 Aug 13;321(1):116-23.

Inhibitory effect of n-3 fish oil fatty acids on cardiac Na⁺/Ca²⁺ exchange currents in HEK293t cells.

Xiao YF, Ke Q, Chen Y, Morgan JP, Leaf A.

Abnormal activity of the cardiac Na⁺/Ca²⁺ exchanger (NCX1) can affect intracellular Ca²⁺ homeostasis and cause arrhythmias. The n-3 polyunsaturated fatty acids (PUFAs), however, may prevent arrhythmias. To test the effect of PUFAs on the cardiac NCX1 current (I(NCX1)), the canine NCX1 cDNA was expressed in human embryonic kidney (HEK293t) cells. The average density of I(NCX1) was 10.9±2.6 pA/pF (n=44) in NCX1-transfected cells and eicosapentaenoic acid (EPA, C20:5n-3) significantly inhibited I(NCX1). The suppression of I(NCX1) by EPA was concentration-dependent with an IC₅₀ of 0.82±0.27 μM. EPA had a similar effect on outward or inward I(NCX1). Docosahexaenoic acid (DHA, C22:6n-3) and arachidonic acid (AA, C20:4n-6) also significantly inhibited I(NCX1), whereas the saturated fatty acid, stearic acid (SA, C18:0), did not. Our data demonstrate that the n-3 PUFAs significantly suppress cardiac I(NCX1), which is probably one of their protective effects against lethal arrhythmias.

Lancet. 2004 May 1;363(9419):1441-2.

Immediate effects of n-3 fatty acid infusion on the induction of sustained ventricular tachycardia.

Schrepf R, Limmert T, Claus Weber P, Theisen K, Sellmayer A.

Increased consumption of n-3 fatty acids reduces mortality from sudden cardiac death, indicating that such acids have anti-arrhythmic effects. We did electrophysiological testing in ten patients with implanted cardioverter defibrillators who were at high risk of sudden cardiac death. To assess their immediate effects on the induction of sustained ventricular tachycardia, n-3 fatty acids were infused. Such tachycardia was not induced in five of seven patients. Our findings show that infusion of n-3 polyunsaturated fatty acids does not induce arrhythmia, but did result in a reduction of sustained ventricular tachycardia in some patients.

Curr Opin Lipidol. 2004 Feb;15(1):25-30.

Antiarrhythmic effects of n-3 fatty acids: evidence from human studies.

Geelen A, Brouwer IA, Zock PL, Katan MB.

PURPOSE OF REVIEW: N-3 fatty acids from fish reduce cardiovascular mortality including sudden cardiac death. In this paper, the authors discuss the results of human studies with regard to the hypothesis that n-3 fatty acids reduce the risk of fatal coronary heart disease through antiarrhythmic effects. **RECENT FINDINGS:** Results from two recent clinical trials do not support a protective effect of n-3 fatty acids. In light of the earlier published bulk of evidence that n-3 fatty acids reduce cardiovascular mortality and sudden cardiac death, it is hard to explain these findings. Two recent observational studies confirmed that intake of n-3 fatty acids from fish is associated with less cardiovascular disease in the general population. They indicated that the protective effect of a fish meal may depend on the n-3 fatty acid content or preparation method and suggested a protective effect on arrhythmia rather than on atherosclerosis. Intervention studies on electrophysiological predictors of arrhythmia do not clearly confirm a beneficial effect of n-3 fatty acids. However, most of these studies were small or performed in healthy populations. **SUMMARY:** The available evidence still suggests that n-3 fatty acids may prevent fatal cardiac arrhythmia, but more conclusive studies are urgently needed.

Eur J Heart Fail. 2004 Jan;6(1):109-15.

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.

Cleland JG, Freemantle N, Kaye G, Nasir M, Velavan P, Lalukota K, Mudawi T, Shelton R, Clark AL, Coletta AP.

The American Heart Association meeting reported the results of several clinical trials of particular interest to those who care for patients with heart failure. Omega-3 fatty acids were associated with a trend to increased recurrence of ventricular arrhythmias but not mortality in patients with an implantable defibrillator. The ACTIV in CHF study provides more evidence of a therapeutic role for arginine vasopressin antagonists in the treatment of heart failure. The VALIANT study provides further evidence to suggest that a combination of angiotensin receptor antagonist and ACE inhibitor does not reduce mortality but may reduce morbidity in post-MI patients with heart failure or major LV systolic dysfunction. A study of autologous bone marrow cell transplantation into myocardial scar gave encouraging results. SPORTIF V showed ximelagatran to be as effective as warfarin but with improved safety. ORBIT and PAD showed public access defibrillators saved lives but questioned their cost effectiveness. DEFINITE supported a role for ICDs in patients with non-ischemic cardiomyopathy, although cost-effectiveness remains in doubt.

Cardiovasc Res. 2003 Nov 1;60(2):337-46.

Effects of eicosapentaenoic acid on cardiac SR Ca(2+)-release and ryanodine receptor function.

Swan JS, Dibb K, Negretti N, O'Neill SC, Sitsapesan R.

n-3 polyunsaturated fatty acids (PUFAs) can prevent life-threatening arrhythmias but the mechanisms responsible have not been established. There is strong evidence that part of the antiarrhythmic action of PUFAs is mediated through inhibition of the Ca(2+)-release mechanism of the sarcoplasmic reticulum (SR). It has also been shown that PUFAs activate protein kinase A (PKA) and produce effects in the cardiac cell similar to beta-adrenergic stimulation. We have investigated whether the inhibitory effect of PUFAs on the Ca(2+)-release mechanism is caused by direct inhibition of the SR Ca(2+)-release channel/ryanodine receptor (RyR) or requires activation of PKA. Experiments in intact cells under voltage-clamp show that the n-3 PUFA eicosapentaenoic acid (EPA) is able to reduce the frequency of spontaneous waves of Ca(2+)-release while increasing SR Ca(2+) content even when PKA activity is inhibited with H-89. This suggests that the EPA-induced inhibition of SR Ca(2+)-release is not dependent on activation of PKA. Consistent with this, single-channel studies demonstrate that EPA (10-100 microM), but not saturated fatty acids, reduce the open probability (Po) of the cardiac RyR incorporated into phospholipid bilayers. EPA also inhibited the binding of [3H]ryanodine to isolated heavy SR. Our results indicate that direct inhibition of RyR channel gating by PUFAs play an important role in the overall antiarrhythmic properties of these compounds.

Eur J Clin Nutr. 2003 Oct;57(10):1323-30.

Rationale and design of a randomised controlled clinical trial on supplemental intake of n-3 fatty acids and incidence of cardiac arrhythmia: SOFA.

Brouwer IA, Zock PL, Wever EF, Hauer RN, Camm AJ, Bocker D, Otto-Terlouw P, Katan MB, Schouten EG.

BACKGROUND: Evidence from earlier studies indicates that intake of very long-chain n-3 polyunsaturated fatty acids (n-3 PUFA, also named omega-3 fatty acids) as present in fish oil reduces the risk of sudden death. Sudden death forms a major part of mortality from cardiovascular disease and is in most cases a direct consequence of cardiac arrhythmia. n-3 PUFA may exert their protective effect through reducing the susceptibility for cardiac arrhythmia. **OBJECTIVE:** To investigate the effect of n-3 PUFA on the incidence of recurrent ventricular arrhythmia. This paper presents the rationale, design and methods of the Study on Omega-3 Fatty acids and ventricular Arrhythmia (SOFA) and discusses problems encountered in conducting a multi-centre clinical trial on food. **DESIGN:** A randomised, parallel, placebo-controlled, double blind intervention study, which obeys the guidelines for Good Clinical Practice. **SETTING:** Multiple cardiology centres in Europe. **SUBJECTS:** A total of 500 patients with an implantable cardioverter defibrillator (ICD). An ICD detects, treats and stores cardiac arrhythmic events in its memory chip. **INTERVENTIONS:** Patients receive either 2 g/day of fish oil, containing approximately 450 mg eicosapentaenoic acid and 350 mg docosahexaenoic acid, or placebo for 12 months. **PRIMARY OUTCOME:** Spontaneous ventricular tachyarrhythmias as recorded by the ICD or all-cause mortality. **CONCLUSION:** SOFA is designed to answer the question whether intake of n-3 PUFA from fish-a regular food ingredient-can reduce the incidence of life-threatening cardiac arrhythmia. If this proves to be true, increasing the intake of n-3 PUFA could be an easy, effective and safe measure to prevent fatal arrhythmia in the general population.

QJM. 2003 Jul;96(7):465-80.

The role of omega-3 fatty acids in the secondary prevention of cardiovascular disease.

Lee KW, Lip GY.

It has long been recognized from epidemiological studies that Greenland Eskimos have substantially reduced rates of acute myocardial infarction (MI) compared with Western controls. From these epidemiological observations, the benefits of fatty fish consumption have been explored in cell culture and animal studies, as well as randomized controlled trials investigating the cardioprotective effects of omega-3 fatty acids. Dietary omega-3 fatty acids seem to stabilize the myocardium electrically, resulting in reduced susceptibility to ventricular arrhythmias, thereby reducing the risk of sudden death. These fatty acids also have potent anti-inflammatory effects, and may also be antithrombotic and anti-atherogenic. Furthermore, the recent GISSI-Prevention study of 11 324 patients showed a marked decrease in risk of sudden cardiac death as well as a reduction in all-cause mortality in the group taking a highly purified form of omega-3 fatty acids, despite the use of other secondary prevention drugs, including beta-blockers and lipid-lowering therapy. The use of omega-3 fatty acids should be considered as part of a comprehensive secondary prevention strategy post-myocardial infarction.

Panminerva Med. 2003 Jun;45(2):99-107.

Omega-3 polyunsaturated fatty acids role in postmyocardial infarction therapy.

Imazio M, Forno D, Quaglia C, Trincherò R.

Largely initiated by studies among Eskimos in the early 1970s, great attention has been given to possible effects of omega-3 polyunsaturated fatty acids (PUFA) in cardiovascular diseases. A series of positive effects on pathogenetic mechanisms of cardiovascular disease has been discovered from laboratory studies in cell cultures, animal models and in humans. omega-3 PUFA can reduce platelets and leucocytes activities as well as plasma triglycerides. Moreover they can have antiarrhythmic properties. Nowadays patients who experienced myocardial infarction have decreased risk of total and cardiovascular mortality by treatment with omega-3 PUFA (1 g daily). This effect is present irrespective of high or low fish intake or simultaneous intake of other drugs for secondary prevention of coronary heart disease. Mainly on the basis of GISSI Prevention trial results, dietary supplementation with omega-3 PUFA is now recommended as a new component of secondary prevention after myocardial infarction in national and international guidelines.

Pharmacol Ther. 2003 Jun;98(3):355-77.

Prevention of sudden cardiac death by n-3 polyunsaturated fatty acids.

Leaf A, Xiao YF, Kang JX, Billman GE.

This is a review of our present understanding of the mechanism by which the n-3 polyunsaturated fatty acids (PUFA) in fish oils prevent fatal ventricular arrhythmias in animals and cultured heart cells. A brief review of three clinical trials that suggest that these PUFAs prevent sudden cardiac death is also included in order to emphasize the potential importance of these fatty acids in human nutrition. The PUFAs act by stabilizing electrically every cardiac myocyte by modulating conductance of ion channels in the sarcolemma, particularly the fast, voltage-dependent sodium current and the L-type calcium currents, though other ion currents are also affected. Work in progress suggests that the primary site of action of the PUFAs may be on the phospholipid bilayer of the heart cells in the microdomains through which the ion channels penetrate the membrane bilayer in juxtaposition with the ion channels rather than directly on the channel protein itself. These PUFAs then allosterically alter the conformation and conductance of the channels. Both potential benefits and possible adverse effects of the PUFAs in man will be discussed. Knowing that the ion channels have been structurally conserved among all excitable tissues, we tested their effects on the electrophysiology of rat hippocampal CA1 neurons and found that the sodium and calcium ion channels in these neurons were also affected by PUFAs. An attempt to show the place of the PUFAs in human nutrition during the 2-4 million years of our evolution will conclude the review.

Eur J Clin Nutr. 2003 Feb;57(2):193-200.

Lack of benefit of dietary advice to men with angina: results of a controlled trial.

Burr ML, Ashfield-Watt PA, Dunstan FD, Fehily AM, Breay P, Ashton T, Zotos PC, Haboubi NA, Elwood PC.

OBJECTIVE: To see whether mortality among men with angina can be reduced by dietary advice. DESIGN: A randomized controlled factorial trial. SETTING: Male patients of general practitioners in south Wales. SUBJECTS: A total of 3114 men under 70 y of age with angina. INTERVENTIONS: Subjects were randomly allocated to four groups: (1) advised to eat two portions of oily fish each week, or to take three fish oil capsules daily; (2) advised to eat more fruit, vegetables and oats; (3) given both the above types of advice; and (4) given no specific dietary advice. Mortality was ascertained after 3-9 y. RESULTS: Compliance was better with the fish advice than with the fruit advice. All-cause mortality was not reduced by either form of

advice, and no other effects were attributable to fruit advice. Risk of cardiac death was higher among subjects advised to take oily fish than among those not so advised; the adjusted hazard ratio was 1.26 (95% confidence interval 1.00, 1.58; $P=0.047$), and even greater for sudden cardiac death (1.54; 95% CI 1.06, 2.23; $P=0.025$). The excess risk was largely located among the subgroup given fish oil capsules. There was no evidence that it was due to interactions with medication. **CONCLUSIONS:** Advice to eat more fruit was poorly complied with and had no detectable effect on mortality. Men advised to eat oily fish, and particularly those supplied with fish oil capsules, had a higher risk of cardiac death. This result is unexplained; it may arise from risk compensation or some other effect on patients' or doctors' behaviour.

Prostaglandins Leukot Essent Fatty Acids. 2002 Aug-Sep;67(2-3):113-20.

Interactions of n-3 fatty acids with ion channels in excitable tissues.

Leaf A, Xiao YF, Kang JX.

In summary, we have shown that the conventional explanation for the site of action of a ligand which alters the conductance of a membrane ion channel is that the ligand interacts or binds with the ion channel protein, changing its conductance, is inadequate to explain the primary site of action of the antiarrhythmic n-3 PUFAs. We have shown that when a neutral asparagine is replaced by a positively charged lysine in the N406 amino acid site in the alpha-subunit of the human cardiac sodium channel, the n-3 fatty acids lose their inhibitory action on the sodium current. The inadequacy of this finding to explain the primary site of action of the n-3 PUFAs is demonstrated by the inhibitory effect on all other cardiac ion channels, so far tested. We show that ion channels, which share no amino acid homology with the PUFAs, have their conductance also reduced in the presence of the PUFAs. Thus a more general conceptual framework or paradigm is needed to account for the broad action of the PUFAs on diverse different ion channels lacking amino acid homology. We have been testing the membrane tension hypothesis of Andersen and associates. According to this hypothesis, the fatty acids are not acting directly on the ion channel protein but accumulating in the phospholipid membrane in immediate juxtaposition to the site in the membrane where the ion channel protein penetrates the membrane phospholipid bilayer. This alters membrane tensions exerted by the phospholipid membrane on the ion channel, which in turn causes conformational changes in the ion channel, altering the conductance of the ion channel. Our preliminary data seem to support this membrane tension hypothesis.

Circulation. 2002 Apr 23;105(16):1897-903.

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.

Marchioli R, Barzi F, Bomba E, Chieffo C, Di Gregorio D, Di Mascio R, Franzosi MG, Geraci E, Levantesi G, Maggioni AP, Mantini L, Marfisi RM, Mastrogiuseppe G, Mininni N, Nicolosi GL, Santini M, Schweiger C, Tavazzi L, Tognoni G, Tucci C, Valagussa F; GISSI-Prevenzione Investigators.

BACKGROUND: Our purpose was to assess the time course of the benefit of n-3 polyunsaturated fatty acids (PUFAs) on mortality documented by the GISSI-Prevenzione trial in patients surviving a recent (<3 months) myocardial infarction. **METHODS AND RESULTS:** In this study, 11 323 patients were randomly assigned to supplements of n-3 PUFAs, vitamin E (300 mg/d), both, or no treatment (control) on top of optimal pharmacological treatment and lifestyle advice. Intention-to-treat analysis adjusted for interaction between treatments was carried out. Early efficacy of n-3 PUFA treatment for total, cardiovascular, cardiac, coronary, and sudden death; nonfatal myocardial infarction; total coronary heart disease; and cerebrovascular events was assessed by right-censoring follow-up data 12 times from the first month after randomization up to 12 months. Survival curves for n-3 PUFA treatment diverged early after randomization, and total mortality was significantly lowered after 3 months of treatment (relative risk [RR] 0.59; 95% CI 0.36 to 0.97; $P=0.037$). The reduction in risk of sudden death was specifically relevant and statistically significant already at 4 months (RR 0.47; 95% CI 0.219 to 0.995; $P=0.048$). A similarly significant, although delayed, pattern after 6 to 8 months of treatment was observed for cardiovascular, cardiac, and coronary deaths. **CONCLUSIONS:** The early effect of low-dose (1 g/d) n-3 PUFAs on total mortality and sudden death supports the hypothesis of an antiarrhythmic effect of this drug. Such a result is consistent with the wealth of evidence coming from laboratory experiments on isolated myocytes, animal models, and epidemiological and clinical studies.

Lipids. 2001;36 Suppl:S111-4.

Myocardial membrane fatty acids and the antiarrhythmic actions of dietary fish oil in animal models.

McLennan PL.

Epidemiologic studies, animal studies, and more recently, clinical intervention trials all suggest a role for regular intake of dietary fish oil in reducing cardiovascular morbidity and mortality. Prevention of cardiac arrhythmias and sudden death is demonstrable at fish or fish oil intakes that have little or no effect on blood pressure or plasma lipids. In animals, dietary intake of fish oil [containing both eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3)] selectively increases myocardial membrane phospholipid content of DHA, whereas low dose consumption of purified fatty acids shows antiarrhythmic effects of DHA but not EPA. Ventricular fibrillation induced under many conditions, including ischemia, reperfusion, and electrical stimulation, and even arrhythmias induced in vitro with no circulating fatty acids are prevented by prior dietary consumption of fish oil. The preferential accumulation of DHA in myocardial cell membranes, its association with arrhythmia prevention, and the selective ability of pure DHA to prevent ventricular fibrillation all point to DHA as the active component of fish oil. The antiarrhythmic effect of dietary fish oil appears to depend on the accumulation of DHA in myocardial cell membranes.

Lipids. 2001;36 Suppl:S107-10.

The electrophysiologic basis for the antiarrhythmic and anticonvulsant effects of n-3 polyunsaturated fatty acids: heart and brain.

Leaf A.

The n-3 polyunsaturated fatty acids (PUFA) have been shown to be antiarrhythmic in animals and probably in humans. PUFA stabilize the electrical activity of isolated cardiac myocytes by modulating sarcolemmal ion channels, so that a stronger electrical stimulus is required to elicit an action potential and the refractory period is markedly prolonged. Inhibition of voltage-dependent sodium currents, which initiate action potentials in excitable tissues, and of the L-type calcium currents, which initiate release of sarcoplasmic calcium stores, thus increasing cytosolic free calcium concentrations and activating the contractile proteins in myocytes, appears at present to be the probable major antiarrhythmic mechanisms of PUFA. Because the ion channels in neurons have channel proteins essentially homologous to those in the heart, the n-3 fatty acids would appear to be likely to affect the electrical activity in the brain in a manner similar to their effects in the heart, and accumulating evidence supports this notion. Evidence of important beneficial neurological effects of dietary n-3 PUFA are emerging with more likely to be discovered.

J Nutr Health Aging. 2001;5(3):173-8.

Diet and sudden cardiac death.

Leaf A.

The purpose of this paper is to review the evidence that dietary factors, namely the ingestion of the n-3 (or w-3) polyunsaturated fatty acids of fish oils can prevent fatal cardiac arrhythmias (so-called sudden cardiac death) in experimental animals, and probably in humans as well. The mechanism for this striking effect results from the ability of these fatty acids to directly stabilize electrically every contractile myocyte in the heart. This is accomplished by modulation by the free n-3 fatty acids of the ionic currents in heart cells; particularly the voltage-dependent sodium currents which initiate action potentials and the L-type calcium currents, which initiate release of sarcoplasmic reticulum stores of calcium into the cytosol of heart cells. The resultant rise in cytosolic calcium concentration initiates contraction of the heart cells and the beating rate of the heart. The gradually accumulating clinical evidence that these fish oil fatty acids are potent preventors of cardiac sudden death in humans will be reviewed. With some 250,000 deaths occurring within one hour of the onset of acute myocardial infarctions annually in the USA alone and millions more in the whole world, the potential large public health benefit from this understanding is evident.

Am J Clin Nutr. 2000 Jan;71(1 Suppl):202S-7S.

Prevention of fatal cardiac arrhythmias by polyunsaturated fatty acids.

Kang JX, Leaf A.

In animal feeding studies, and probably in humans, n-3 polyunsaturated fatty acids (PUFAs) prevent fatal ischemia-induced cardiac arrhythmias. We showed that n-3 PUFAs also prevented such arrhythmias in surgically prepared, conscious, exercising dogs. The mechanism of the antiarrhythmic action of n-3 PUFAs has been studied in spontaneously contracting cultured

cardiac myocytes of neonatal rats. Adding arrhythmogenic toxins (eg, ouabain, high Ca²⁺), lysophosphatidylcholine, beta-adrenergic agonist, acylcarnitine, and the Ca²⁺ ionophore) to the myocyte perfusate caused tachycardia, contracture, and fibrillation of the cultured myocytes. Adding eicosapentaenoic acid (EPA: 5-15 micromol/L) to the superfusate before adding the toxins prevented the expected tachyarrhythmias. If the arrhythmias were first induced, adding the EPA to the superfusate terminated the arrhythmias. This antiarrhythmic action occurred with dietary n-3 and n-6 PUFAs; saturated fatty acids and the monounsaturated oleic acid induced no such action. Arachidonic acid (AA; 20:4n-6) is anomalous because in one-third of the tests it provoked severe arrhythmias, which were found to result from cyclooxygenase metabolites of AA. When cyclooxygenase inhibitors were added with the AA, the antiarrhythmic effect was like those of EPA and DHA. The action of the n-3 and n-6 PUFAs is to stabilize electrically every myocyte in the heart by increasing the electrical stimulus required to elicit an action potential by approximately 50% and prolonging the relative refractory time by approximately 150%. These electrophysiologic effects result from an action of the free PUFAs to modulate sodium and calcium currents in the myocytes. The PUFAs also modulate sodium and calcium channels and have anticonvulsant activity in brain cells.

Circulation. 1999 May 11;99(18):2452-7.

Prevention of sudden cardiac death by dietary pure omega-3 polyunsaturated fatty acids in dogs.

Billman GE, Kang JX, Leaf A.

BACKGROUND: Rat diets high in fish oil have been shown to be protective against ischemia-induced fatal ventricular arrhythmias. Increasing evidence suggests that this may also apply to humans. To confirm the evidence in animals, we tested a concentrate of the free fish-oil fatty acids and found them to be antiarrhythmic. In this study, we tested the pure free fatty acids of the 2 major dietary omega-3 polyunsaturated fatty acids in fish oil: cis-5,8,11,14, 17-eicosapentaenoic acid (C20:5omega-3) and cis-4,7,10,13,16, 19-docosahexaenoic acid (C22:6omega-3), and the parent omega-3 fatty acid in some vegetable oils, cis-9,12,15-alpha-linolenic acid (C18:3omega-3), administered intravenously on albumin or a phospholipid emulsion. **METHODS AND RESULTS:** The tests were performed in a dog model of cardiac sudden death. Dogs were prepared with a large anterior wall myocardial infarction produced surgically and an inflatable cuff placed around the left circumflex coronary artery. With the dogs running on a treadmill 1 month after the surgery, occlusion of the left circumflex artery regularly produced ventricular fibrillation in the control tests done 1 week before and after the test, with the omega-3 fatty acids administered intravenously as their pure free fatty acid. With infusion of the eicosapentaenoic acid, 5 of 7 dogs were protected from fatal ventricular arrhythmias (P<0.02). With docosahexaenoic acid, 6 of 8 dogs were protected, and with alpha-linolenic acid, 6 of 8 dogs were also protected (P<0.004 for each). The before and after control studies performed on the same animal all resulted in fatal ventricular arrhythmias, from which they were defibrillated. **CONCLUSIONS:** These results indicate that purified omega-3 fatty acids can prevent ischemia-induced ventricular fibrillation in this dog model of sudden cardiac death.

Lipids. 1997 Nov;32(11):1161-8.

Prevention of ischemia-induced cardiac sudden death by n-3 polyunsaturated fatty acids in dogs.

Billman GE, Kang JX, Leaf A.

The objective of this study was to obtain functional information associated with the prevention by n-3 polyunsaturated fatty acids (PUFA) of ischemia-induced fatal cardiac ventricular arrhythmias in the intact, conscious, exercising dog. Thirteen dogs susceptible to ischemia-induced ventricular fibrillation were prepared surgically by ligation of their anterior descending left coronary artery and placement of an inflatable cuff around their left circumflex artery. After 4 wk of recovery, exercise-plus-ischemia tests were performed without and then with an intravenous infusion of an emulsion of free n-3 PUFA just prior to occluding the left circumflex artery while the animals were running on a treadmill. One week later the exercise-plus-ischemia test was repeated but with a control infusion replacing the emulsion of n-3 PUFA. The infusion of the free n-3 PUFA in quantities of 1.0 to 10 g prevented ventricular fibrillation in 10 of the 13 dogs tested (P < 0.005), apparently without esterification of the PUFA into membrane phospholipids. The antiarrhythmic effect of the n-3 PUFA was associated with slowing of the heart rate, shortening of the QT-interval (electrical action potential duration), reduction of left ventricular systolic pressure, and prolongation of the electrocardiographic atrial-ventricular conduction time (P-R interval). These effects are comparable with those we have reported in studies with cultured neonatal rat cardiac myocytes.

Prostaglandins. 1997 Aug;54(2):511-30.

Differential effects of various eicosanoids on the production or prevention of arrhythmias in cultured neonatal rat cardiac myocytes.

Li Y, Kang JX, Leaf A.

To identify the arrhythmogenic and the antiarrhythmic eicosanoids, cultured, spontaneously beating, neonatal rat cardiac myocytes were used to examine the effects of various eicosanoids added to the medium superfusing the cells at different

concentrations on the contraction of the myocytes. Superfusion of the myocytes with the prostaglandins (PGD₂, PGE₂, PGF₂ alpha) or the thromboxane (TXA₂)-mimetic, U 46619, induced reversible tachyarrhythmias characterized by an increased beating rate, chaotic activity and contractures. These effects are concentration-dependent. PGF₂ alpha and U 46619 were much more potent than PGD₂ or PGE₂ in the production of tachyarrhythmias. Prostacyclin (PGI₂) induced a marked reduction in the contraction rate of the cells with a slight increase in the amplitude of the contractions and showed a protective effect against the arrhythmias induced by PGF₂ alpha and TXA₂ (U 46619). PGE₁ exerted a dose-dependent dual effect on the contraction of the myocytes. At low concentrations (< 2 microM), PGE₁ reduced the contraction rate of the cells with an increase in the amplitude of the contractions and effectively terminated the tachyarrhythmias induced by arrhythmogenic agents, such as isoproterenol, ouabain and U 46619. At higher concentrations (> 5 microM), PGE₁ caused cell contractures and chaotic activity. In contrast, the lipoxygenase products [leukotriene (LT) B₄, LTC₄, LTD₄ & LTE₄] of arachidonic acid (AA) had no significant effect on the myocyte contractions. The eicosanoids derived from eicosapentaenoic acid (EPA), including both the cyclooxygenase products (PGD₃, PGE₃, PGF₃ alpha, TXB₃) showed lesser effects on the contraction of the myocytes. The lipoxygenase products (LTB₅, LTC₅, LTD₅ & LTE₅), as with the AA metabolites showed little effect on the contraction of cardiac myocytes. The arrhythmias induced by the arrhythmogenic prostaglandins and thromboxane A₂ could be suppressed by the nonmetabolizable AA analog eicosatetraenoic acid (ETYA) or free AA and EPA, indicating a distinction in the effect on cardiac arrhythmia between the precursor fatty acids (AA & EPA) themselves and their metabolites. In conclusion, the major arrhythmogenic eicosanoids are the cyclooxygenase products of AA, whereas those products of EPA are much less or not effective; PGE₁, PGI₂, ETYA and EPA have antiarrhythmic effects.

Cardiovasc Drugs Ther. 1997 Jul;11(3):485-91.

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.

Singh RB, Niaz MA, Sharma JP, Kumar R, Rastogi V, Moshiri M.

In a randomized, placebo-controlled trial, the effects of treatment with fish oil (eicosapentaenoic acid, 1.08 g/day) and mustard oil (alpha-linolenic acid, 2.9 g/day) were compared for 1 year in the management of 122 patients (fish oil, group A), 120 patients (mustard oil, group B), and 118 patients (placebo, group C) with suspected acute myocardial infarction (AMI). Treatments were administered about (mean) 18 hours after the symptoms of AMI in all three groups. The extent of cardiac disease, rise in cardiac enzymes, and lipid peroxides were comparable among the groups at entry into the study. After 1 year total cardiac events were significantly less in the fish oil and mustard oil groups compared with the placebo group (24.5% and 28% vs. 34.7%, $p < 0.01$). Nonfatal infarctions were also significantly less in the fish oil and mustard oil groups compared with the placebo group (13.0% and 15.0% vs. 25.4%, $p < 0.05$). Total cardiac deaths showed no significant reduction in the mustard oil group; however, the fish oil group had significantly less cardiac deaths compared with the placebo group (11.4% vs. 22.0%, $p < 0.05$). Apart from the decrease in the cardiac event rate, the fish oil and mustard oil groups also showed a significant reduction in total cardiac arrhythmias, left ventricular enlargement, and angina pectoris compared with the placebo group. Reductions in blood lipoproteins in the two intervention groups were modest and do not appear to be the cause of the benefit in the two groups. Diene conjugates showed a significant reduction in the fish oil and mustard oil groups, indicating that a part of the benefit may be caused by the reduction in oxidative stress. The findings of this study suggest that fish oil and mustard oil, possibly due to the presence of n-3 fatty acids, may provide rapid protective effects in patients with AMI. However, a large study is necessary to confirm this suggestion.

Proc Natl Acad Sci U S A. 1997 Mar 18;94(6):2724-8.

Regulation of sodium channel gene expression by class I antiarrhythmic drugs and n - 3 polyunsaturated fatty acids in cultured neonatal rat cardiac myocytes.

Kang JX, Li Y, Leaf A.

Previous studies have shown that chronic administration of class I antiarrhythmic drugs, which have definite inhibitory action on the fast Na⁺ channel, result in up-regulation of cardiac Na⁺ channel expression, and suggest that this effect may contribute to their deleterious effects during chronic administration. Recent studies have shown that the antiarrhythmic effects of free n - 3 polyunsaturated fatty acids (PUFA) are associated with an inhibition of the Na⁺ channel. Whether the PUFA when used chronically will mimic the effect of the class I drugs on the expression of the Na⁺ channel is not known. To answer this question, we determined the level of mRNA encoding cardiac Na⁺ channels and the number of the Na⁺ channels per cell in cultured neonatal rat cardiac myocytes after supplementation of the cells with the n - 3 PUFA eicosapentaenoic acid (EPA), the class I drug mexiletine, or both EPA and mexiletine for 3-4 days. The number of sodium channels was assessed with a radioligand binding assay using the sodium channel-specific toxin [³H]batrachotoxinin benzoate ([³H]BTXB). The supplementation of myocytes with mexiletine (20 microM) induced a 4-fold increase in [³H]BTXB specific binding to the cells. In contrast, chronic treatment with EPA (20 microM) alone did not significantly affect [³H]BTXB binding. However, the combination of EPA with mexiletine produced a 40-50% reduction in the [³H]BTXB binding, compared with that seen with mexiletine alone. RNA isolated from cardiac myocytes was probed with a 2.5-kb cRNA transcribed with T7 RNA polymerase from the clone Na-8.4,

which encodes nucleotides 3361-5868 of the alpha-subunit of the R(IIA) sodium channel subtype. The changes in the level of mRNA encoding sodium channel alpha-subunit were correlated with comparable changes in sodium channel number in the cultured myocytes, indicating that regulation of transcription of mRNA or its processing and stability is primarily responsible for the regulation of sodium channel number. These data demonstrate that chronic EPA treatment not only does not up-regulate the cardiac sodium channel expression but also reduces the mexiletine-induced increase in the cardiac sodium channel expression.

Biochem Biophys Res Commun. 1995 Mar 17;208(2):629-36.

Prevention and termination of beta-adrenergic agonist-induced arrhythmias by free polyunsaturated fatty acids in neonatal rat cardiac myocytes.

Kang JX, Leaf A.

Polyunsaturated omega-3 fatty acids, which have been shown to prevent ischemia-induced ventricular fibrillation in prepared dogs, were tested in cultured neonatal rat cardiac myocytes for their ability to prevent the tachyarrhythmias induced by isoproterenol, a beta-adrenergic agonist. We found that polyunsaturated fatty acids (5-10 microM), especially the fish oil omega-3 fatty acids, but not monounsaturated and saturated fatty acids were able to effectively prevent and terminate the arrhythmias induced by isoproterenol (as well as by cAMP and cholera toxin) without affecting the cell contractility, and that their action was independent of their metabolites and incorporation into membrane phospholipid. These protective effects of the free fatty acids may contribute, at least in part, to their reported preventive effects on ischemia-induced ventricular fibrillation and sudden cardiac death.

Proc Natl Acad Sci U S A. 1994 May 10;91(10):4427-30.

Prevention of ischemia-induced ventricular fibrillation by omega 3 fatty acids.

Billman GE, Hallaq H, Leaf A.

A specially prepared dog model of myocardial infarction was used to test the efficacy of the long-chain polyunsaturated fish oil omega 3 fatty acids eicosapentaenoic (20:5 n-3) and docosahexaenoic (22:6 n-3) acids to prevent ischemia-induced malignant cardiac arrhythmias. The dogs had sustained a prior experimental myocardial infarction from ligation of the left anterior descending coronary artery, and a hydraulic cuff was implanted around the left circumflex artery at that operation. After recovery from that procedure the animals were tested during a treadmill exercise test. With compression of the left circumflex artery sensitive animals will predictably develop ventricular fibrillation (VF). In such prepared dogs an emulsion of fish oil fatty acids was infused i.v. over a 50- to 60-min period just before the exercise-plus-ischemia test, and the effect on development of VF was recorded. The infusion was 100 ml of a 10% (vol/vol) emulsion of a fish oil concentrate containing 70% omega 3 fatty acids with free eicosapentaenoic acid and docosahexaenoic acid composing 33.9% and 25.0% of that total, respectively. Alternatively, some animals similarly received an emulsion containing 5 ml of the free fatty acid concentrate plus 5 ml of a triacylglycerol concentrate containing 65% omega 3 fatty acids with eicosapentaenoic acid and docosahexaenoic acid composing 34.0% and 23.6% of that total, respectively. In seven of eight animals the infusion of the fish oil emulsion completely prevented the acute occurrence of VF in the susceptible animals ($P < 0.005$). In five of five of these animals the subsequent exercise-plus-ischemia test after a similar infusion of an emulsion in which soy bean oil replaced the fish oil fatty acid concentrates resulted in prompt development of VF. Possible mechanisms for this protective effect of omega 3 fatty acids against exercise and ischemia-induced malignant arrhythmias are considered.

Proc Natl Acad Sci U S A. 1994 Oct 11;91(21):9886-90.

Effects of long-chain polyunsaturated fatty acids on the contraction of neonatal rat cardiac myocytes.

Kang JX, Leaf A.

Because of the ability of certain long-chain polyunsaturated fatty acids (PUFAs) to prevent lethal cardiac arrhythmias, we have examined the effects of various long-chain fatty acids on the contraction of spontaneously beating, isolated, neonatal rat cardiac myocytes. The omega 3 PUFA from fish oils, eicosapentaenoic acid [EPA; C20:5 (n-3)] and docosahexaenoic acid [DHA; C22:6 (n-3)], at 2-10 microM profoundly reduced the contraction rate of the cells without a significant change in the amplitude of the contractions. The fatty acid-induced reduction in the beating rate could be readily reversed by cell perfusion with fatty acid-free bovine serum albumin. Addition of either oxygenase inhibitors or antioxidants did not alter the effect of the fatty acids. Arachidonic acid [AA; C20:4 (n-6)] produced two different effects on the beating rate, an increase or a decrease, or it produced no change. In the case of the increased or unchanged beating rate in the presence of AA, addition of AA oxygenase inhibitors subsequently reduced the contraction rate. The nonmetabolizable AA analog eicosatetraenoic acid (ETYA) always reduced the beating rate, as did EPA or DHA. Two other PUFAs, linoleic acid [C18:2 (n-6)] and linolenic acid

[C18:3 (n-3)] also exhibited similar but less potent effects compared with EPA or ETYA. In contrast, neither the monounsaturated fatty acid oleic acid [C18:1 (n-9)] nor the saturated fatty acids stearic acid (C18:0), myristic acid (C14:0), and lauric acid (C12:0) affected the contraction rate. The inhibitory effect of these PUFAs on the contraction rate was similar to that produced by the class I antiarrhythmic drug lidocaine. The fatty acids that are able to reduce the beating rate, particularly EPA and DHA, could effectively prevent and terminate lethal tachyarrhythmias (contracture/fibrillation) induced by high extracellular calcium concentrations or ouabain. These results suggest that free PUFAs can suppress the automaticity of cardiac contraction and thereby exert their antiarrhythmic effects.

Am J Clin Nutr. 1993 Nov;58(5):666-9.

Comparative efficacy of n-3 and n-6 polyunsaturated fatty acids in modulating ventricular fibrillation threshold in marmoset monkeys.

McLennan PL, Bridle TM, Abeywardena MY, Charnock JS.

Programmed electrical stimulation in anesthetized marmoset monkeys was used to examine relative antiarrhythmic efficacies of dietary n-3 and n-6 polyunsaturated fatty acids (PUFAs) from fish and plant oils. Diets contained 31% of energy (en%) as fat, comprising 15 en% saturated fat and 7 en% PUFAs, obtained by blending sheep fat with sunflower seed (SF/SSO) or fish oil (SF/FO) and a base diet. After 16-wk feeding, ventricular fibrillation (VF) was inducible in 6 of 10 animals on each diet under control conditions. The VF threshold (VFT) was significantly elevated in the SF/FO group (33.3 +/- 3.1 mA; n = 6) compared with the SF/SSO group (14.3 +/- 4.9 mA; n = 6). VFT, reduced during acute myocardial ischemia with 10 of 10 animals inducible per diet, remained significantly higher with SF/FO feeding. The SF/FO diet contained 3.8 en% as n-3 PUFAs, which was incorporated as 31% of myocardial membrane fatty acids. Dietary n-3 PUFA reduced vulnerability of normal or ischemic myocardium to arrhythmias in a nonhuman primate.

Am J Clin Nutr. 1993 Feb;57(2):207-12.

Relative effects of dietary saturated, monounsaturated, and polyunsaturated fatty acids on cardiac arrhythmias in rats.

McLennan PL.

This study compared monounsaturated oleic acid with n-6 and n-3 polyunsaturated fatty acids (PUFAs) for their ability to modify the vulnerability to cardiac arrhythmias during ischemia or reperfusion in rats. Replacement of saturated animal fat in the diet with oleic acid-rich olive oil did not significantly alter the incidence of ventricular fibrillation or other cardiac arrhythmias. Replacement with either n-6-rich sunflower seed oil or n-3-rich fish oil reduced the incidence and severity of arrhythmias occurring in ischemia. The fish oil significantly reduced reperfusion arrhythmias independently of antecedent ischemic arrhythmias. Fatal ventricular fibrillation was significantly reduced by n-6 (8%; n = 25) and n-3 (0%; n = 24) PUFA but not by monounsaturates (36%; n = 25) compared with saturated fat (42%; n = 24). The results suggest that dietary replacement of saturated fats by n-6 and especially n-3 PUFA but not monounsaturated fatty acids can reduce the likelihood of an ischemic event leading to sudden cardiac death.

Am Heart J. 1992 Jun;123(6):1555-61.

Dietary lipid modulation of ventricular fibrillation threshold in the marmoset monkey.

McLennan PL, Bridle TM, Abeywardena MY, Charnock JS.

Programmed electrical stimulation was used to examine the ability of long-term dietary lipid modulation to influence myocardial vulnerability to the induction of ventricular fibrillation in adult marmoset monkeys (*Callithrix jacchus*). Marmosets fed diets supplemented (to a total of 28.5% of the energy as fat) with polyunsaturated fatty acid (PUFA)-rich tuna fish oil or sunflower seed oil had significantly elevated mean ventricular fibrillation threshold compared with those fed a saturated animal fat supplemented diet or a reference diet not supplemented with fat (11.2% of the energy as fat). Fibrillation threshold was reduced during acute myocardial ischemia induced by coronary artery occlusion but still remained higher in the PUFA-fed animals than either the control or the ischemic threshold in reference or saturated fat supplemented animals. Dietary tuna fish oil was associated with a low incidence of sustained fibrillation episodes and no fatalities. These results indicate that myocardial substrate vulnerability to arrhythmic stimuli is increased during ischemia in a nonhuman primate model but dietary PUFA can reduce vulnerability under both normal and ischemic conditions. Reduced dietary fat intake alone was without effect.

Lancet. 1989 Sep 30;2(8666):757-61.

Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART).

Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, Elwood PC, Deadman NM.

A randomised controlled trial with a factorial design was done to examine the effects of dietary intervention in the secondary prevention of myocardial infarction (MI). 2033 men who had recovered from MI were allocated to receive or not to receive advice on each of three dietary factors: a reduction in fat intake and an increase in the ratio of polyunsaturated to saturated fat, an increase in fatty fish intake, and an increase in cereal fibre intake. The advice on fat was not associated with any difference in mortality, perhaps because it produced only a small reduction (3-4%) in serum cholesterol. The subjects advised to eat fatty fish had a 29% reduction in 2 year all-cause mortality compared with those not so advised. This effect, which was significant, was not altered by adjusting for ten potential confounding factors. Subjects given fibre advice had a slightly higher mortality than other subjects (not significant). The 2 year incidence of reinfarction plus death from ischaemic heart disease was not significantly affected by any of the dietary regimens. A modest intake of fatty fish (two or three portions per week) may reduce mortality in men who have recovered from MI.

Am Heart J. 1988 Sep;116(3):709-17.

Dietary fish oil prevents ventricular fibrillation following coronary artery occlusion and reperfusion.

McLennan PL, Abeywardena MY, Charnock JS.

Coronary artery occlusion and reperfusion in the anesthetized rat was used as a whole animal model of arrhythmia and sudden cardiac death to examine the influence of long-term dietary lipid modulation of myocardial membrane fatty acids on the development of cardiac arrhythmias. Feeding rats a diet supplemented with tuna fish oil significantly reduced the incidence and severity of arrhythmias, preventing ventricular fibrillation during both occlusion and reperfusion. Dietary sunflower seed oil reduced arrhythmias during occlusion but not in reperfusion. Dietary fat can modify the vulnerability of the myocardium to arrhythmic stimuli. The efficacy of tuna fish oil in reducing vulnerability to both ischemic and reperfusion arrhythmias suggests a potential beneficial effect of dietary n-3 fatty acids in addition to their influence on hemostasis, plasma lipids, and atherosclerosis that may contribute to their proposed role in lowering cardiovascular disease mortality and morbidity.

Br J Pharmacol. 1981 Aug;73(4):909-15.

Effect of fatty acids on the ventricular arrhythmia threshold in the isolated heart of the rabbit.

Murnaghan MF.

1 The ventricular arrhythmia threshold (VAT) was measured in the isolated Ringer-perfused rabbit heart (Langendorff preparation) by applying a single 10 ms square-wave pulse of current to the left ventricle during the vulnerable period of the late systole under normoxic and hypoxic conditions. 2 The sodium salt of the fatty acid was bound to albumen and incorporated in the Krebs-Henseleit solution which was maintained at 37 degrees C and gassed with 95% O₂ and 5% CO₂ (normoxia) or 5% CO₂ in air (hypoxia). 3 Saturated fatty acids failed to alter the VAT under normoxia. 4 Naturally occurring long-chained saturated and mono-unsaturated fatty acids with chain lengths varying from 14 to 20 carbons, but not the 12 carbon lauric acid, potentiated the effect of the hypoxia in lowering the VAT. 5 Short-chained 8 and 10 carbon saturated and long-chained polyunsaturated fatty acids antagonized the effect of hypoxia on the VAT. 6 In addition the polyunsaturated acids antagonized the potentiating effect of the long-chained saturated and mono-unsaturated acids on the hypoxia in lowering the VAT. 7 The fatty acids did not alter the duration or type of the induced arrhythmia.

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