The Eskimo diet has a high fat content, but this group has a low incidence of deaths from coronary heart disease.1 Because the Eskimo diet contains large amounts of long-chain polyunsaturated fatty acids (PUFAs),2 many studies have been conducted to determine whether high dietary PUFAs may reduce death from coronary heart disease. These studies, which have focused on two n-3 PUFAs that are relatively abundant in fish, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), include many prospective epidemiological studies, a few case-control studies, and 2 secondary prevention trials.3–13 Most of the prospective population studies showed a statistically significant inverse relationship between fish consumption and the risk of death from coronary heart disease. The dose-response relationship was complex in these studies: the reduction in coronary risk was greatest when adding a modest amount of dietary fish to populations that previously had low fish intake. Increasing fish intake still more did not incrementally decrease risk. Many of these studies measured n-3 PUFA incorporation into the cell membranes of platelets, granulocytes, adipose tissue, or erythrocytes. Overall, there was a significant correlation between fish intake and the level of n-3 PUFA in cell membranes. The overall consistency in the observational studies is excellent and signals a survival benefit from dietary n-3 PUFA.

The epidemiological data suggest that the benefit of dietary fish is centered on a reduction in sudden cardiac death. A case-control study in Seattle compared 334 victims of out-of-hospital primary cardiac arrest with 493 population-based controls.11 Compared with no dietary intake of EPA, ≥5.5 g of n-3 PUFA per month was associated with a 50% decrease in the risk of primary cardiac arrest.

The US Physician’s Health Study studied the effect of dietary fish on sudden cardiac death in 20 551 US male physicians who were free of cardiovascular disease at baseline and then followed for up to 11 years.9 During follow-up, 133 sudden deaths (death within 1 hour) occurred. After adjusting for coronary risk factors and study treatments (aspirin and beta carotene), a dietary intake of ≥1 fish meal per week was associated with a 52% reduction in sudden death. Eating fish more often than once a week was also associated with a 30% reduction in total mortality but not with a decrease in total myocardial infarction or nonsudden death.

Stronger evidence of an effect of n-3 PUFA on sudden cardiac death was obtained in 2 randomized clinical trials. The Diet and Reinfarction Trial (DART), reported in 1989, was the first randomized, clinical trial to evaluate the effects of n-3 PUFA on survival.12 DART included 2033 men who were recruited in 21 British hospitals an average of 41 days after myocardial infarction. The trial had a 2×2×2 factorial design; patients were randomized to receive (or not receive) advice on the following 3 dietary interventions: lowering fat intake, increasing fatty fish intake to at least 2 fish meals per week, and increasing fiber intake. Diabetic patients and men who intended to eat one of the intervention diets were excluded. Compared with the group that did not get fat advice, the group that was counseled to decrease fat intake to 30% of total energy and increase their polyunsaturated/unsaturated fat ratio to 1.0 had no change in mortality rate at 2 years but did have a 26% decrease in nonfatal myocardial infarction. The group that was advised to eat 18 g of cereal fiber daily had a 23% increase in total mortality (P<NS).

After 2 years, participants in DART who were advised to eat fish (mackerel, herring, kipper, pilchard, sardine, salmon, or trout) had a 29% decrease in all-cause mortality (P<0.05). Separation in survival curves was apparent by 100 days. Reduction in mortality was almost completely due to a decrease in coronary heart disease mortality; however, the total number of coronary heart disease events (recurrent nonfatal myocardial infarction plus coronary heart disease mortality) did not change significantly (48% increase in nonfatal myocardial infarction). Adjustment for 10 postinfarction risk factors did not significantly change the relative risks. A decrease in total mortality and ischemic heart disease deaths with an increase in nonfatal myocardial infarction is compatible with conversion of fatal myocardial infarction to nonfatal myocardial infarction by preventing arrhythmic death during myocardial ischemia.

Ten years later, the second randomized clinical trial, the GISSI-Prevenzione Trial, was reported.13 This open-label trial had a 2×2 factorial design in which patients were randomized, ≤3 months after myocardial infarction, to receive an 900-mg capsule of n-3 PUFA (EPA:DHA of 1:2) or a 300-mg capsule of synthetic α-tocopherol (vitamin E). The primary end points were the cumulative rate of the composite of all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke and the cumulative rate of the composite of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke. Secondary analyses evaluated each component of the primary end points and the main

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(Circulation. 2001;103:623-625.)

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causes of death. The trial included 11,324 persons from the 172 participating Italian centers (≈2800 in each of the 4 groups). Follow-up averaged 3.5 years. The primary end points decreased by 15% and 20%, respectively (P<0.05 and <0.01, respectively). There was a 20% decrease in all deaths, a 30% decrease in cardiovascular deaths, and a 45% decrease in sudden cardiac deaths.

No significant change occurred in the rates of nonfatal myocardial infarction or stroke between those who were on n-3 PUFA supplements and those who were not. No significant benefit was found for vitamin E treatment. The investigators concluded that n-3 PUFA supplementation significantly reduced death, particularly sudden death, but not reinfarction or stroke. An antiarrhythmic action of n-3 PUFA was supported by these findings.

The n-3 PUFA supplementation in GISSI-Prevenzione corresponds to ≈100 g of fish per day, an amount beyond what can be obtained with a balanced diet. However, several epidemiological studies suggest that a substantial benefit of fish intake is present at a level of ≈1 fish meal per week and that the benefit seems to plateau with higher fish intake.6-9 Importantly, neither the trial that increased dietary fish intake nor the trial that gave fish oil supplements for secondary prevention after myocardial infarction found any adverse effects from these inexpensive treatments. In GISSI-Prevenzione, n-3 PUFA supplements added benefit to conventional pharmacological therapy with aspirin, β-adrenergic blockers, and angiotensin-converting enzyme inhibitors.

The results of the 2 randomized trials provide strong evidence of benefit for dietary n-3 PUFA, and a body of epidemiological data supports these trial results. The mechanism of benefit has been the object of much laboratory and clinical research. The clinical observations and trials suggest that n-3 PUFAs have an antiarrhythmic action. The antiarrhythmic action is probably not due to the antithrombotic action of n-3 PUFAs, because nonfatal myocardial infarction and stroke are not reduced by n-3 PUFA treatment. The benefit of n-3 PUFA is not mediated through a decrease in cholesterol. In DART, an increase in fish consumption did not decrease serum cholesterol, and the benefit on survival was apparent within a few months. Clinical results suggest that myocardial infarction is not substantially less likely in patients taking n-3 PUFA, but infarction is less likely to be fatal because lethal arrhythmias are suppressed during acute myocardial infarction.

Kang and Leaf14 reviewed the electrophysiological effects of EPA and DHA in cultured cardiac myocytes and their antiarrhythmic effects in laboratory experiments done in rats, marmoset monkeys, and dogs. By partitioning into the membrane phospholipids, n-3 PUFAs exert antiarrhythmic effects on membrane ion channels. Effects on L-type calcium channels probably reduce cytosolic calcium concentrations during ischemia and during catecholamine or digitalis toxicity. Antiarrhythmic effects have also been described for sodium channels in cultured cardiac myocytes. The effects of n-3 PUFAs on sodium channels are novel and distinctly different from the effects of class I antiarrhythmic drugs. Adding de-lipidized serum albumin to the perfusate to remove PUFAs from isolated cardiac myocytes reverses the electrophysiological and antiarrhythmic effects of superfused n-3 PUFAs. In whole heart and intact animal models, arrhythmias evoked by coronary artery occlusion or occlusion and reperfusion are reduced substantially by n-3 PUFAs. The PUFAs can be supplied to the in vivo systems by feeding the experimental animal n-3 PUFAs for a period of time before coronary artery occlusion or by giving n-3 PUFAs intravenously just before occlusion.

Billman et al15 showed that intravenous administration of EPA or DHA prevented ventricular fibrillation in a dog model of ischemic sudden death. This is a model that has been used to elucidate the role of the autonomic nervous system on ischemic ventricular fibrillation.16,17

Dogs with greater baroreflex sensitivity and vagal activity are more likely to survive ischemia during exercise in the presence of a healed myocardial infarction. In dogs that are susceptible, ventricular fibrillation reproducibly occurs when the left circumflex coronary artery is occluded during exercise.16,17 All the dogs in the study by Billman et al15 developed ventricular fibrillation during control runs 1 week before and 1 week after the experiment with n-3 PUFA, but only a few fibrillated when the exercise/ischemia challenge was delivered after intravenous infusion of n-3 PUFA.

In this issue of Circulation, Christensen et al18 report an epidemiological study of wine and fish consumption and their relationship with n-3 PUFA in adipose tissue, granulocytes, and heart rate variability (HRV). The patient sample was composed of 291 patients who were referred to Aalborg Hospital in Denmark for coronary angiography. Fish and wine intake was quantified by food questionnaires and related to n-3 PUFA and HRV. High wine intake was associated with high fish consumption but was not independently associated with HRV. High fish consumption was associated with high n-3 PUFA in adipose tissue and granulocyte membranes. High values of n-3 PUFA, especially DHA, in granulocytes were significantly, if weakly, correlated with several measures of HRV. The strongest correlation was with the average standard deviation of normal RR intervals (called the SDNN index in this article). The SDNN index is a measure of low frequency power and reflects baroreflex activity.19,20 High values for baroreflex sensitivity were previously associated with good outcomes in animal models of sudden cardiac death17 and after myocardial infarction in humans.21

Christensen et al previously reported a randomized 12-week trial comparing n-3 PUFA supplements to olive oil in 49 patients with recent myocardial infarction and a left ventricular ejection fraction <0.40 and found an increase in the standard deviation of normal RR intervals over a 24-hour period (SDNN).22,23 Before treatment, there was an association between the DHA concentration in platelets and the SDNN. In another study, Christensen et al treated 60 normal subjects (25 women and 35 men; average age, 38±11 years) with n-3 PUFAs and showed an increase in SDNN for men but not women.24 The effect of n-3 PUFAs on SDNN was greatest in men who had low values for SDNN and low levels of n-3 PUFAs in platelet or granulocyte membranes before therapy.

Christensen et al take the increase in SDNN and SDNN index to indicate an antiarrhythmic effect of n-3 PUFA due to
a favorable shift in vagal/sympathetic balance. This evidence is indirect but concordant with a large body of experimental and clinical evidence that a shift in vagal/sympathetic balance in favor of vagal modulation of the heart decreases susceptibility to cardiac arrhythmias and arrhythmic death. In addition, several cardiovascular drugs that increase survival also increase HRV (vagal modulation of the heart); these include β-adrenergic blockers and angiotensin-converting enzyme inhibitors. With β-adrenergic blockers, the brain is an important site of action for the increase in HRV.

The details of the antiarrhythmic action for n-3 PUFA remain to be elucidated (relative importance of cardiac ion channel, brain, or autonomic effects), but the overall body of evidence from epidemiological studies and clinical trials suggest that n-3 PUFAs have an important antiarrhythmic effect in patients with coronary heart disease. Unfortunately, coronary heart disease is often announced by sudden cardiac death.

Given the safety and low cost of implementing a recommendation for a modest amount of fish in the diet, adequate dietary fish intake has a significant role to play in the primary and secondary prevention of out-of-hospital sudden cardiac death.

References


Key Words: Editorials | arrhythmia | lipids | prevention | death, sudden | nervous system, autonomic | ischemia
Polyunsaturated Fatty Acids and Cardiovascular Events: A Fish Tale
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Circulation. 2001;103:623-625
doi: 10.1161/01.CIR.103.5.623
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/103/5/623

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