Fish and N-3 Fatty Acids for the Prevention and Treatment of Coronary Heart Disease: Nutrition Is Not Pharmacology

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Since investigators suggested that the lower mortality rate of coronary heart disease observed in Eskimos in Greenland may be due to a seafood-rich diet (1), the dietary benefits of fish have attracted considerable scientific interest. While most epidemiological studies have reported a protective effect associated with the consumption of even small amounts of fish, there have been negative reports (2,3), as well as inconsistent findings (4,5). This variability could be due to differences in the methods of assessing fish intake (4); consumption of different types of fish (e.g., fatty fish versus lean fish) or fish from various sources (Table) (5); potential contamination of fish by toxic heavy metals (6); subjects being aware of the cardioprotective effects of fish consumption, which may result in an "effect-cause" relation (2,3); differences in the methods used to validate and classify endpoints, with only a few studies reporting, for instance, on both sudden and nonsudden cardiac death; or differences in risk levels among different populations (7).

However, when assessing more precisely (whenever possible) the cause of cardiac death, the data suggest that the benefit of eating fish is a reduction in the risk of sudden cardiac death. Two studies (8,9) reported that modest fish intake is associated with a 50% decrease in the risk of sudden cardiac death but no decrease in the risk of nonsudden cardiac death or myocardial infarction (9). Other evidence of an effect of the long-chain n-3 fatty acids (Figure), which are abundant in fatty fish in the form of docosahexanoic and eicosapentaenoic acids, on sudden cardiac death come from laboratory and clinical research. For instance, the electrophysiological effects of n-3 fatty acids in cultured cardiac myocytes, as well as their antiarrhythmic effects in laboratory animals (10), have been reported, as has their administration intravenously to prevent sudden cardiac death during myocardial ischemia (11). Christensen et al. investigated the effects of n-3 fatty acids on heart rate variability in patients with recent acute myocardial infarction and a low left ventricular ejection fraction (12), and found a positive correlation between n-3 fatty acids in the diet (and blood) and baroreflex sensitivity (12), the latter being associated with good outcomes in patients who survive a recent acute coronary event (13). They also showed that the intake of n-3 fatty acids was associated with increased heart rate variability in a dose-dependent manner (14).

The beneficial effects of n-3 fatty acids on the risk of sudden cardiac death may therefore be partly related to an antiarrhythmic effect due to a favorable shift in the vagal/sympathetic balance, which decreases susceptibility to ventricular arrhythmias (15). Although the details of the antiarrhythmic action of n-3 fatty acids remain to be elucidated (relative importance of the effect on cardiac ion channels, on the autonomic nervous system or on the local production of proarrhythmic and antiarrhythmic eicosanoids), the consensus is that n-3 fatty acids have an important cardioprotective effect in patients with established coronary heart disease, and that physicians should recommend the inclusion of fish in their patients' diets (15–17). In addition, the cardioprotective effects of long-chain n-3 fatty acids at low doses are due to an effect on the ischemic myocardium, and not on blood lipids and hemostasis. Conversely, alpha-linolenic acid, the parent compound of long-chain n-3 fatty acids (Figure) that is found in some vegetable oils, may protect through both myocardial and nonmyocardial mechanisms.

Indeed, for persons who cannot (or will not) eat fish or other seafood that is rich in n-3 fatty acids, consumption of foods containing alpha-linolenic acid is an alternative. In addition to its own direct effect on cardiac arrhythmias (10,11), dietary alpha-linolenic acid does not accumulate within cells, induces a marked shift in the endogenous metabolism of n-6 fatty acids (18), and inhibits the elongation and desaturation of linoleic acid (18:2 n-6) into arachidonic acid (19). Because arachidonic acid (20:4 n-6), in competition with eicosapentaenoic acid, affects inflammation as the precursor of the proinflammatory eicosanoids and leukotrienes, modifying its amount and the amount of its fatty acid precursors would affect the prevalence and severity of eicosanoid-related disorders, including atherosclerotic complications and sudden cardiac death (18,19). Indeed, dietary alpha-linolenic acid has been shown to be associated inversely with the risk of fatal coronary heart disease (20). Thus, for many authors, it is the balance between n-3 and n-6 fatty acids, rather than the absolute amounts of n-3 fatty acids in the diet, which is critical for disease prevention (21–23), and the

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Table. Fatty Acid Composition of Some Common Fish Species, by Location, Season, and Means of Preparation

		Fatty Acid				
		Grams Per 100 g of Edible Portion of Fish				
Fish	Fat	18:3(n-3)	20:5(n-3)	22:5(n-3)	22:6(n-3)	Sum of (n-3)
Fatty Fish						
Herring						
United States* (Atlantic, cooked)	11.6	0.13	0.91	0.07	1.10	2.21
Norway† (North Sea, raw)	14	0.14	1.32	0.10	1.40	2.96
Mackerel (Atlantic)						
United States* (cooked)	17.8	0.11	0.50	0.11	0.70	1.42
Norway† (spring, raw)	10	0.11	0.57	0.12	1.40	2.20
Norway† (autumn, raw)	30	0.33	1.71	0.36	4.17	6.57
Salmon (Atlantic)						
United States* (wild, raw)	6.3	0.30	0.32	0.28	1.12	2.02
United States* (farm, cooked)	12.4	0.11	0.69	NA	1.46	2.26
Red Tuna						
United States* (cooked)	6.3	NA	0.36	0.16	1.14	1.66
Lean Fish						
Cod (Atlantic)						
United States* (cooked)	0.9	0.001	0.004	0.01	0.15	0.17
Plaice (North Sea)						
Norway† (raw)	1.4	0.01	0.24	0.07	0.15	0.47
Pollock (Atlantic)						
United States* (cooked)	1.3	NA	0.09	0.03	0.45	0.57

* From the food composition database of the United States Department of Agriculture. Available at: http://www.usda.gov.
† From the fish composition database of the Norwegian Seafood Export Council (Eksportutvalget for fisk, Tromso, Norway).
NA = data not available.

importance of alpha-linolenic acid in health and disease is now recognized (24,25).

It is in this context that Bucher et al. report the results of a meta-analysis of randomized controlled trials of n-3 fatty acids in the secondary prevention of coronary heart disease in this issue of **The Green Journal** (26). This systematic review of trials of both long-chain n-3 fatty acids and alpha-linolenic acid provides a rapid overview of the topic. The authors identified 11 trials with a follow-up of at least 6 months, which included 7951 patients in the intervention group and 7855 patients in the control group. In patients who were assigned to n-3 fatty acid–enhanced diets, the risk ratios were 0.81 for overall mortality, 0.74 for fatal myocardial infarction, and 0.71 for sudden death (all $P < 0.01$, compared with controls), which supports the consensus that dietary and nondietary intake of n-3 fatty acids reduces mortality, in particular sudden death (by 30%), in patients with coronary heart disease. Its effects on nonfatal myocardial infarction, however, were not significant ($P = 0.16$).

However, as noted by the authors, their meta-analysis has limitations. Beyond those of publication bias and the technical and methodological heterogeneity of the studies, one limitation involves the hypothesis—that there is no major difference between dietary and pharmacologic applications, and hence intake of n-3 fatty acid by eating fish or taking a supplement is equivalent and can therefore be analyzed in the same way. Accordingly, whatever the form of n-3 fatty acid intake, the biological and physiological effect of the nutrient should be similar to that of the molecule; nonetheless, the authors may have overlooked some critical information. For example, can the Gruppo Italiano per lo Studio della Sopravvienza nell-infarto miocardico (GISSI) trial (27) be compared consistently with the Diet and Reinfarction Trial (DART) (28)? The two trials may have had similar results, but their settings were so different that the interpretation of the data may have been affected. In GISSI (27), patients were advised to follow a Mediterranean diet, and more than 82% were using olive oil regularly at the end of the trial. Marchioli et al. (29) reported that patients who followed a Mediterranean diet the most closely were also the most protected, compared with patients who did not comply, who were 3 times less protected. However, while the clinical effectiveness of capsules containing 0.8 g of n-3 fatty acids was observed in patients following a Mediterranean diet, the exact relation between the Mediterranean diet (or some of its characteristics) and n-3 fatty acids remains to be elucidated.

What about DART? Was it simply a fish or fish oil trial? Although DART is often seen as a testing of the effect of a single factor, it is actually a trial of the effect of intensive dietary advice on the risk of recurrent cardiovascular events in patients with established coronary heart disease

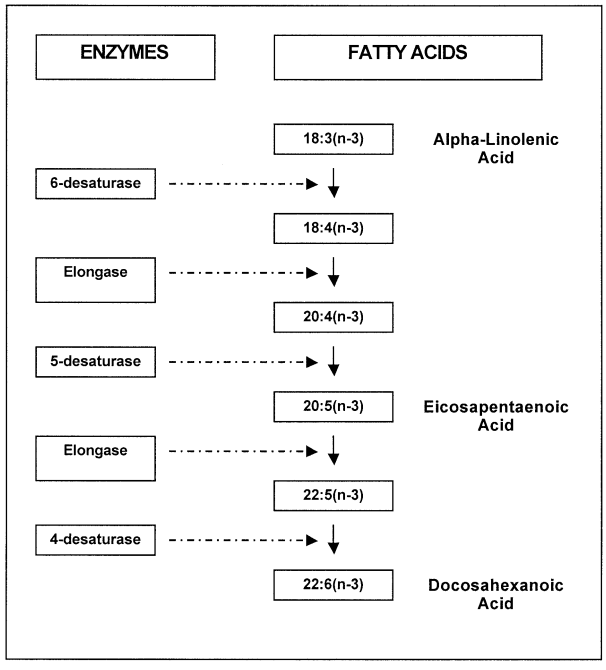

Figure. The desaturation and elongation pathway of the n-3 fatty acids departing from the essential alpha-linolenic acid found in some natural vegetable foods, such as walnut and canola oil. Note that, in competition with arachidonic acid, eicosapentaenoic acid is the starting point for the synthesis of prostaglandins and eicosanoids. Increasing the intake of eicosapentaenoic and docosahexanoic acids through increased consumption of marine foods and increased intake of alpha-linolenic acid are therefore two different preventive strategies in cardiology.

(28). In DART, patients were initially seen in their homes by a nutritionist and were randomly assigned to one of three diets. They were visited after 1 month, 3 months, and 5 months. Thereafter, they were contacted at three monthly intervals until 2 years after the entry into the trial. Those who were assigned to a fish diet with advice from a dietitian were encouraged to eat two portions of fatty fish a week and as much as they could eat of other fish. Increased consumption of fish is likely to reduce consumption of non-fish sources (e.g., meat), leading to decreased intake of saturated fat. Because of the dietary advice, patients also may have avoided using butter and cream to prepare the fish, as well as avoided other forms of prepared fish, such as deep fat fried and highly salted fish. Furthermore, fish and other types of seafood are one of the main sources of certain essential nutrients, such as selenium, which also have beneficial effects in cardiovascular (30) and other (31) diseases.

Likewise, other dietary trials, such as the Lyon Diet Heart Study (32) or the Indian Heart trial (33), may not be compared so easily with other trials. These two studies included patients who were randomly assigned to receive increased intake of n-3 fatty acids (specifically, alpha-linolenic acid) through the consumption of foods (e.g., canola oil and tree nuts) that also contain other nutrients (e.g., oleic acid, alpha-tocopherol, folates, arginine) that have cardioprotective effects. The effects of a specific nutrient or food were not studied, but rather a global dietary pattern, namely a Mediterranean diet (32) and an Asian vegetarian diet (33). In the two trials, the rate of both fatal and nonfatal complications due to coronary heart disease was reduced, suggesting that the protective effect of alpha-linolenic acid was not restricted to a myocardial antiarrhythmic effect that has been observed with long-chain n-3 fatty acids (27,28). In these food-based trials, however, it is often difficult to determine if the health benefits result from n-3 fatty acids, other nutrients, or the interaction between the two types of nutrients.

In summary, it could be said that dietary alpha-linolenic acid is different from a long-chain n-3 fatty acid (Figure); n-3 fatty acids from fish are not the same as those from plants because, besides the varying amounts of n-3 fatty acids (long chain in fish, alpha-linolenic acid in vegetables) found in these foods, there are other nutrients that have cardioprotective effects; fish contain many nutrients other than lipids and taking capsules of fish oil is not the same as eating fatty fish; and not all fish is safe because contaminants such as mercury can reduce the cardioprotective effect of n-3 fatty acids (34). Thus, nutrition is not pharmacology, and nutritional data should be analyzed carefully before being extrapolated to pharmacologic applications.

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