
Editorial

New evidence in support of the cardiovascular benefit of long-chain n-3 fatty acids

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Despite the high fat content of their traditional diet, Eskimo populations in Greenland and elsewhere were found to have much lower cardiovascular mortality than predicted¹⁻³. The protective component of the Eskimo diet was considered to be the long-chain n-3 polyunsaturated fatty acids (PUFAs) consumed in very high amounts due to the regular intake of seal meat and whale blubber. These long-chain n-3 PUFAs include eicosapentaenoic acid (EPA), docosapentaenoic acid, and docosahexaenoic acid (DHA). Oily fish such as tuna, herring, salmon and mackerel also contain significant amounts of long-chain n-3 PUFAs. The Japanese exhibit low cardiovascular mortality⁴ and the traditional Japanese diet is rich in seafood including oily fish. Epidemiological studies indicate that consumption of fish or of long-chain n-3 PUFAs reduces the risk of cardiovascular mortality in North American and European populations⁵⁻¹¹ and also in the Chinese¹². Several recent studies have confirmed the cardio-protective effects of the long-chain n-3 PUFAs¹³⁻¹⁷.

N-3 PUFAs could protect against the pathological processes leading to cardiovascular disease (i.e. atherosclerosis) or against the processes that ultimately cause death (e.g. myocardial infarction, stroke) or against both. Long-chain n-3 PUFAs favourably affect several risk factors for development of atherosclerosis, suggesting that they might slow its progression. For example, long-chain n-3 PUFAs lower fasting and post-prandial plasma triacylglycerol concentrations^{18,19}, both of which are now recognised to increase the risk of cardiovascular disease. Long-chain n-3 PUFAs also lower blood pressure in both nor-

motensive and hypertensive individuals, as confirmed in a recent meta-analysis²⁰. Fish oil contains significant amounts of EPA and DHA, and including fish oil in the diet of various types of animal has been demonstrated to decrease atherosclerosis. This might be due to:

- lipid lowering, so making less lipid available for deposition in atherosclerotic plaques;
- decreased production of growth factors involved in atherosclerosis;
- decreased inflammation, so impeding development of plaques, which involves an inflammatory component²¹;
- a combination of these mechanisms.

Epidemiologic studies indicate a strong protective effect of n-3 PUFAs towards fatal myocardial infarction^{8,9}, particularly towards sudden death^{10,14,15}. Several studies also report protection against non-fatal myocardial infarction^{8,11,13,15}. These findings suggest that n-3 PUFAs lower risk of acute coronary events. Placebo-controlled, secondary prevention studies providing long-chain n-3 PUFAs (as fish oil) to patients post-myocardial infarction have shown significant reduction in mortality²², in cardiovascular events, non-fatal myocardial infarction and cardiac death²³, and in fatal cardiovascular events, especially sudden death²⁴. In the GISSI-Prevenzione study the protective effects of n-3 PUFAs occurred in the absence of lipid lowering. A recent publication reports that the reduction in risk of sudden death at 2 years in those patients consuming fish oil was already apparent at 4 months and the reductions in risk of cardiovascular mortality and coronary heart disease mortality were apparent within 6 to 8 months of initiating fish oil treatment²⁵.

Two mechanisms are considered to contribute to the strong protective effect of long-chain n-3 PUFAs towards acute events, especially those that are fatal. These are antithrombotic effects²⁶ and antiarrhythmic effects²⁷. However, a recent study²⁸ suggests that anti-inflammatory actions²⁹⁻³¹ may provide a further, novel, mechanism for the cardioprotective effects of n-3 PUFAs. The rupture of an atherosclerotic plaque, which is the acute event that exposes the plaque contents to the highly pro-thrombotic environment of the vessel lumen, is, essentially, an inflammatory event^{32,33}. The characteristics of an atherosclerotic plaque that make it vulnerable to rupture include a thin fibrous cap and increased numbers of inflammatory cells such as macrophages³⁴⁻³⁶. N-3 PUFAs might act to stabilise atherosclerotic plaques by decreasing infiltration of inflammatory and immune cells (e.g. monocyte/macrophages and lymphocytes) into the plaques and/or by decreasing the activity of those cells once in the plaque. Thies et al.²⁸ addressed whether n-3 PUFAs influence atherosclerotic plaque stability.

In the study of Thies et al.²⁸ patients destined to undergo carotid endarterectomy were randomised to consume 6 g placebo, sunflower oil or fish oil per day until surgery. The placebo was an 80:20 mix of palm and soybean oils, which has a similar fatty acid composition to the average UK diet. Patients in the fish oil group consumed an extra 1.4 g EPA plus DHA per day, fairly similar to the amounts used in the various secondary prevention trials in post-myocardial infarction patients. Exclusions and dropout accounted for about 15% of enrolled patients, so that data for 57, 52 and 53 patients were available in the placebo, sunflower oil and fish oil groups, respectively. Duration of treatment was 7 to 189 days with a median of 42 days, and did not differ between the three groups. As expected, fish oil decreased mean fasting plasma triacylglycerol concentration (by approximately 30%) and increased in the proportion of EPA and DHA in plasma low-density lipoprotein lipid fractions. The proportions of EPA and DHA were higher in carotid plaque lipids in the fish oil group than in either of the other two groups. Thus, even when provided at a modest dose and for a relatively short duration, long-chain n-3 PUFAs are able to enter advanced atherosclerotic plaques. These findings suggest that atherosclerotic plaques are fairly dynamic with some degree of lipid turnover, even at an advanced stage of atherosclerosis. The observed higher content of EPA and DHA in atherosclerotic plaques from patients consuming fish oil has been reported previously by Rapp et al.³⁷. However, the study of Rapp et al.³⁷ provided a very high dose of fish oil (48 to 64 g/day providing 16 to 21 g EPA plus DHA per day), was not placebo-controlled or blinded, investigated a heterogeneous group of atherosclerotic plaques (carotid, femoral, aortic, iliac) removed from

11 patients, and provided no structural details of the plaques. In contrast, Thies et al.²⁸ used a modest dose of fish oil in a placebo-controlled, double-blind, randomised trial, studied one type of plaque removed from a large number of patients and provided some detail about plaque structure. The morphology of plaque sections was characterised according to the American Heart Association (AHA) classification³⁴. Almost all (approximately 90%) plaques were of the AHA type IV (well-formed necrotic core with an overlying thick fibrous cap) or type V (thin fibrous cap infiltrated by macrophages and lymphocytes) classification. Thus, type IV plaques appear to be more stable than type V plaques. Plaques from patients treated with fish oil were more likely to be type IV than those from the other two groups (odds ratio 1.19 vs placebo and 1.16 vs sunflower oil). Conversely, plaques from patients treated with fish oil were less likely to be type V than those from the other two groups (odds ratio 0.52 vs placebo and 0.49 vs sunflower oil). Thus, there were more plaques with a well formed fibrous cap, rather than a thin inflamed cap, in the fish oil group than in either of the other groups. The EPA and DHA contents of type IV plaques were higher than those of type V plaques, which, in turn, were higher than those of type VI plaques, further suggesting that n-3 PUFAs are associated with plaque stability. Infiltration by macrophages was investigated using immunohistochemistry. It was found that plaques from patients given fish oil were less heavily infiltrated with macrophages than those in the other two groups. Plaques with a higher content of EPA and DHA showed lower macrophage infiltration²⁸.

While the rapid effects of fish oil on plaque morphology and macrophage infiltration observed by Thies et al.²⁸ may be surprising, they are consistent with the time course of the reported effects of n-3 PUFAs on mortality in secondary prevention studies. In the DART study, the survival curves of the control and n-3 PUFA groups began to diverge after about 60 days, although it is not clear when the groups became significantly different²². In the GISSI study, the survival curve for patients receiving fish oil diverged from that of the controls also after about 60 days and statistically significant differences in total mortality and sudden death were apparent by 3 and 4 months, respectively²⁵. These studies support the idea that atherosclerotic plaques are dynamic and responsive to dietary modification, which may impact on plaque stability, as suggested by the results of Thies et al.²⁸. Since it is the vulnerability of the plaque to rupture rather than the degree of atherosclerosis that is the primary determinant of thrombosis-mediated acute cardiovascular events³⁶, it is likely that the findings of Thies et al.²⁸ are clinically relevant. Furthermore, they may explain the significant protective effects of n-3 PUFAs towards both fatal and non-fatal cardiovascular events.

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