

EDITORIAL

Fishing for heart protection<sup>1,2</sup>

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Fish do not die from heart attacks, but what about fish eaters? The most recent Finnish study on this question, which was authored by Erkkilä et al and appears in this issue of the Journal (1), showed that the serum cholesteryl ester content of eicosapentaenoic acid (primarily derived from fish fat) was inversely related to future coronary artery disease (CAD) mortality in subjects with established CAD. In contrast, the association with a combined endpoint of CAD death and myocardial infarction (MI) was not significant. These results fit perfectly with results from earlier prospective cohort studies (2): fish consumption is associated with decreased CAD mortality but not with total CAD morbidity in high-risk subjects.

In general terms, an average daily intake of 50 g fish was reported to halve CAD mortality. However, the apparent protection seemed to be limited to high-risk populations (2). The observational data lead us to pose questions like the following. Are we seeing a causal relation? Is fish just a marker of a healthier lifestyle? In the early days of the era relating fish consumption with heart health, Kromhout et al (3) also wondered about these questions because of their finding of decreased CAD mortality at surprisingly low intakes of fish and n-3 fatty acids. Our best chance to find the right answers is offered by the growing number of randomized intervention trials.

In the first study [Diet and Reinfarction Trial (DART); n = 2033], Burr et al (4) reported that 2-y CAD mortality and total mortality were 30% lower among post-MI, male patients who were advised to eat 200–400 g fatty fish/wk than among similar patients who did not receive that advice. The weekly intake of 200–400 g fatty fish corresponds to a combined daily intake of eicosapentaenoic acid and docosahexaenoic acid of a little less than 1 g. Ten years later, Italian researchers presented similar data from the large GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico)-Prevenzione trial, which included 11 324 post-MI patients of both sexes (5). The daily intake of 0.9 g eicosapentaenoic acid +docosahexaenoic acid in capsules was associated with a 20% reduction in CAD mortality at the 3.5-y follow-up, primarily because of fewer sudden deaths. Total mortality also decreased 14%. Both studies were nicely designed and performed, the results were impressive and convincing, and the interpretation of all the

available scientific evidence seemed obvious: CAD patients and high-risk subjects should be prescribed fish or fish oil. However, this conclusion has now been seriously challenged by data presented in 2 recently published papers.

The first of these papers presented long-term, post-trial follow-up data from the DART study (6). Surprisingly, the all-cause mortality in the 2–5-y follow-up period of the original group who received advice to consume fish was significantly higher (31%) than that of the control group. Thus, the all-cause mortality of the 2 groups after a mean follow-up of 15 y became almost identical [adjusted hazard ratio of the fish group: 0.95 (95% CI: 0.85, 1.07)]. The second recent paper presented data on the effect of advice to consume fatty fish or of 3 daily fish oil capsules on CAD mortality in a group of 3114 male patients with stable angina (7). Another surprising result was found: advice to consume fish and the intake of fish oil capsules were associated with increases in CAD mortality of 20% ( $P = 0.16$ ) and 45% ( $P = 0.02$ ), respectively! Furthermore, the increase in risk was even more prominent for sudden death. Such results force us to rethink our view on fish and fish oil in the primary and secondary prevention of CAD.

Currently, the available evidence may be best summarized by the following statements. 1) Consumption of fish and fish oil lowers CAD and total mortality in post-MI patients, but only as long as consumption of fish and fish oil is continued (4–6). 2) Fish is more beneficial than fish oil (4, 5, 7). 3) For patients with stable angina, there is no benefit from eating fish and there may even be harmful effects of consuming fish oil capsules (7). 4) We have insufficient evidence to conclude whether the consumption of fish and fish oil per se influences CAD morbidity and mortality in the general population.

The reduced CAD mortality in post-MI patients seems to be explained best by the solidly shown antiarrhythmic properties of n-3 fatty acids (8). This antiarrhythmic effect would tend to lower MI fatality rates and the incidence of sudden death, which is exactly what was seen in the intervention trials (4, 5). Consumption of fish and fish oil probably leads to similar reductions in mortality in other groups of CAD patients with highly vulnerable plaques, ie, in all cases of the acute coronary syndrome (patients with unstable angina or MI).

Fish may be more beneficial than fish oil for 3 reasons. First, fish contains potentially cardioprotective nutrients, such as selenium, various natural antioxidants, and fish protein, that are not present in fish oil. Second, fish intake may modify meals in a healthy direction: fish typically replaces red meat, and fish is often consumed with specific foods, such as mustard, dill, and broccoli, that may be healthy but are otherwise seldom eaten. Third, fish is an integrated part of the diet, whereas fish-oil supplementation means adding pure fat to the diet and increasing the risk of weight gain.

The apparent negative influence of fish oil on stable angina could be explained by a net proatherogenic effect of fish oil that may modify stable plaques into vulnerable ones. This almost heretical suggestion is primarily based on the facts that fish-oil supplementation does not lower LDL cholesterol and does not improve the LDL subclass profile of normotriglyceridemic persons but has an undisputed adverse effect on LDL

resistance to oxidation. We have no primary-prevention intervention trials in humans but have divergent results from preventive animal experiments (9, 10). The results of human observational studies also diverge, and some of the multiple metabolic effects of n-3 fatty acids may be beneficial, whereas others may be harmful, as exemplified above.

In conclusion, I believe that we should strongly recommend fatty fish or fish oil to all patients who have had an acute coronary event. Persons who have never had an acute coronary event should be informed that it is unknown whether fish consumption per se protects against future CAD. However, they should also know that fish is a tasteful food and contains essential nutrients, such as iodine, selenium, vitamin D, and n-3 fatty acids, that are only scarcely present in the remaining diet. In addition, they should know that any kind of fish, unless it comes from heavily polluted waters, can easily fit into a healthy and cardioprotective diet that is low in saturated fat and rich in vegetables, fruit, and whole-grain products. In my opinion, fish-oil supplementation cannot be recommended for the general population. It should be restricted to patients with a history of acute coronary disease, as an alternative to consumption of fatty fish, and to patients with other specific diseases, such as hypertriglyceridemia and rheumatoid arthritis, for which fish oil may be a valuable part of the treatment.

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