Marine n-3 fatty acids, sudden cardiac death and coronary disease: Fish or supplements?

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Coronary heart disease (CHD) remains one of the most common causes of death despite a marked reduction in incidence during recent years. More than half of deaths from CHD are caused by sudden cardiac death (SCD) (1). A few high-risk patients, mainly with severe left ventricular dysfunction caused by heart failure, cardiomyopathies or genetic arrhythmic disorders may be recognized and protected from SCD by medications, pacemakers and implantable cardioverter defibrillators (ICDs). However, SCD is often the first manifestation of CHD and therefore mainly occurs unanticipated and outside of hospital. Hospital treatment of CHD including myocardial infarction (MI) and treatment post-MI have significantly improved during the last decades, but this does not help individuals who have no symptoms or for other reasons do not come to medical attention. To reduce fatalities from CHD there is an urgent need for preventive measures to reduce the risk of SCD.

One such option might be intake of n-3 polyunsaturated fatty acids (PUFAs), notably eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) derived from seafood. Thus, in-vitro studies (2) and research in monkeys and rats (3) have reported antiarrhythmic effects of marine n-3 PUFAs. These seminal studies indicated that marine n-3 PUFAs might possibly reduce the risk of SCD, bearing in mind that the doses investigated were high. Marine n-3 PUFAs may reduce the risk of malignant arrhythmias by several mechanisms including increasing the stability of myocardial cells, modulating intracellular calcium levels, lowering of heart rate reducing oxygen demand, and an effect on the autonomic nervous system with an increase in heart rate variability (4).

SCD is difficult to study because sudden death may be caused by a variety of cardiac and non-cardiac causes. Furthermore, fatalities are often difficult to precisely classify because autopsies are seldom performed. A beneficial effect of marine n-3 PUFAs may therefore perhaps be more clearly reflected in fatalities from CHD rather than in risk of non-fatal MI and this has indeed often been reported (5,6). However, spouses of 334 subjects without known heart disease but with primary cardiac arrest were interviewed concerning the victims fish consumption the month preceding the incident (7). There was a 50% reduced risk of primary cardiac arrest in subjects eating at least 5.5 g marine n-3 PUFAs the month before the incident, corresponding to one weekly main course of fatty fish compared to non-fish eaters. In a subgroup, the content of EPA and DHA was determined in red blood cells and a high content of these fatty acids was also associated with a lower risk of primary cardiac arrest. A beneficial effect of moderate consumption of fish compared to no or very little fish intake on SCD and CHD is supported by several observational studies (1,6,8), with little additive

effect of higher fish intakes (6). While an effect of fish on SCD would likely be mainly of an antiarrhythmic nature, this does not exclude a role for other effects of marine n-3 PUFAs, such as reduced inflammation, thrombosis and triacylglycerols although at least some of these effects may require higher intakes of n-3 PUFAs (9).

In this issue of the *Journal of Nutrition*, Macartney et al. (10) report results from a study where rats were fed fish oil (providing more DHA than EPA) at a low dose equivalent to 0.57 g/ day of n-3 PUFAs in humans or at a higher dose equivalent to 2.3 g/day or a control diet. After 4-5 weeks of feeding, the animals were subjected to cardiac ischemia by left coronary artery occlusion followed by reperfusion. Fish oil feeding led to an increase in DHA in myocardial tissue, a lowering of heart rate and a marked and significant reduction in ventricular tachycardia and ventricular fibrillation (VF). The effects were present at the low dose of fish oil but were slightly greater with the high dose of fish oil. These results could cautiously be interpreted as an intake of EPA+DHA around 0.6 g per day (or 4 g per week) - which can be achieved by consuming (fatty) fish twice weekly - might provide protection against SCD in humans bearing in mind that results from animal models cannot be directly extrapolated to humans. The results of the study, however, support current guidelines recommending consumption of (fatty) fish 1-2 times weekly for protection against CHD for the whole population (6,11).

In the Macartney study (10), 2.4 g/day of n-3 PUFAs also had beneficial (actually even better than the low dose) effects, but in humans such an intake cannot be realistically achieved by diet alone on a long-term basis apart from in very few populations with extremely high consumption of seafood and so would require the use of supplements. The first and largest trial investigating the effect of marine n-3 PUFA supplementation on CHD was the Italian multicenter Gissi-Prevenzione trial (12). In that trial, 11,324 patients were included post-MI and randomized to about 0.9 g per day of marine n-3 PUFAs as ethyl esters; there was a 26% reduction in SCD during 3.5 years of follow up compared to those not given n-3 PUFA supplement. Results from more recent trials with n-3 PUFA supplements have, however, been less convincing and have often produced null effects (13-16). However a recent trial (REDUCE-IT) with 3.6 g/day of EPA as an ethyl ester in at risk patients showed a significant reduction in the primary outcome (a composite of cardiovascular death, non-fatal MI, non-fatal stroke, coronary revascularisation or unstable angina), in the secondary outcome and in a range of exploratory outcomes (17). Nevertheless, another recent trial investigating the effect of marine n-3 PUFAs in patients with hypertriglyceridaemia (STRENGTH; not yet published in detail) was stopped early because no effect of n-3 PUFAs was observed in an interim analysis. A recent meta-analysis included data from 13 randomised controlled trials (127,477 patients; mean follow-up 5 years) (18): in an analysis excluding REDUCE-IT, marine n-3 PUFAs were associated with a significantly, albeit moderate, lower risk of MI, CHD death, cardiovascular death and total cardiovascular disease. These inverse associations for all outcomes were strengthened after including REDUCE-IT.

There is consensus that fish, preferably fatty with a high content of n-3 PUFAs, should be consumed 1-2 times weekly for prevention of CHD and cardiovascular disease (6,11). There is, however, much debate about the value of supplemental marine n-3 PUFAs for prevention of CHD. In the most recent American Heart Association Advisory on this topic, a minority of the authors found supplemental n-3 PUFA treatment of patients with high risk of cardiovascular disease reasonable, while the majority of the authors advocated n-3 PUFA supplements for secondary prevention of CHD (19). Important distinctions between fish intake and n-3 PUFA (“fish oil”) supplements are that fish contains many

health-promoting nutrients other than n-3 PUFAs, that supplements are taken on top of the usual diet, and that fish consumption reduces intake of other nutrients with potential detrimental effects on CHD e.g. those from meat (6,16). Furthermore, fish consumption may be an integral part of a healthy dietary pattern that may overall reduce cardiovascular disease (16).

Another important issue raised, although not directly investigated, by Macartney et al. (10) is that the failure of several randomized clinical trials to observe a beneficial effect of supplemental n-3 PUFAs might be at least partly because those not receiving the supplements might have had a moderate/high fish consumption making it difficult to obtain an effect of the supplements, especially since the major part of the effect on VF may be achieved from a low intake of marine n-3 PUFAs. Further studies are warranted to establish the optimal dose of n-3 PUFAs for prevention of vascular disease. Future clinical trials should systematically register the diet of the participants and ideally use biomarkers for intake of EPA and DHA; this has not always been done in the past.

Conflicts of interest

EBS No conflict of interest. PCC has received research funding from BASF AS and acts as a consultant to BASF AS, Smartfish, DSM, Cargill, Danone/Nutricia and Fresenius-Kabi.

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