

n-3 fatty acids from fish and coronary artery disease: implications for public health

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Abstract

Objective: To review and discuss the effect of n-3 polyunsaturated fatty acids (PUFA) from fish in the prevention and, primarily, in the treatment of coronary artery disease (CAD).

Design: Overview of the literature.

Setting: Denmark.

Results: There is good evidence that fish consumption may reduce the risk of CAD.

Conclusions: Fish can be recommended to reduce the risk of CAD both in healthy subjects and in patients with a high risk of CAD or with documented CAD. The use of fish oil concentrates can not be recommended in general, but may be considered in patients after a myocardial infarction or in patients with hypertriglyceridaemia. An increased intake of n-3 polyunsaturated fatty acids from fish may have substantial implications for public health and health economy by decreasing the risk of coronary events and sudden cardiac death.

Keywords

n-3 fatty acids
Fish oil
Coronary heart disease
Sudden cardiac death
Public health

In this paper we will discuss the evidence for a beneficial effect of long-chained n-3 PUFA, derived from fish, on the risk of CAD and the major cause of deaths in these patients, sudden cardiac death. We will focus on clinical trial data in patients with CAD and discuss the potential public health benefit from increasing the intake of n-3 PUFA from fish.

n-3 PUFA are members of an essential fatty acid family characterized by having their first double bond at carbon atom number 3, as opposed to the other essential fatty acid family n-6 PUFA whose first double bond is at carbon atom number 6, counted from the methyl end of the carbon chain constituting the backbone of fatty acids^{1,2}.

There are two subgroups of n-3 PUFA. One is α -linolenic acid derived from plant oils (canola oil, rapeseed oil and linseed oil) composed of 18 carbon atoms and three double bonds (nomenclature 18:3). The other group of n-3 PUFA is derived from seafood, and the major marine n-3 PUFA are eicosapentaenoic acid (EPA; 20:5) and docosahexaenoic acid (DHA; 22:6). Because of a larger number of carbon atoms (20 and 22, respectively), these are also called long-chained n-3 PUFA. α -linolenic acid can to a limited extent be elongated and desaturated in humans to EPA and DHA, otherwise they are only acquired from seafood.

The content of n-3 PUFA varies between fish species³, being high in fatty fish like mackerel and salmon and low in lean fish such as flounder and cod (Table 1). It is worth noting that the content of n-3 PUFA in seafood may vary considerably in relation to location and the time of year of capture^{3,4}. The intake of long-chained n-3 PUFA varies considerably between populations. It is very high in traditionally living Eskimos (10–14 g day⁻¹), low in western populations (< 0.2 g day⁻¹) and intermediate in areas like Japan and Norway (1–3 g day⁻¹). The content of n-3 PUFA in cod liver oil is about 20%, and can be up to 90% in fish oil capsules.

Marine n-3 PUFA, atherosclerosis and thrombosis

n-3 PUFA are readily incorporated into human atherosclerotic plaques⁵. Considering the importance of plaque composition for future clinical events^{6,7}, the effect of dietary n-3 PUFA on plaque characteristics is important, but has been scarcely studied. In a recent autopsy study it was reported that atherosclerosis was rare in Greenland Eskimos living on a traditional diet extremely rich in n-3 PUFA⁸. Advanced atherosclerosis was also less at necropsy in Alaskan Eskimos compared to other Alaskans eating less seafood⁹. Furthermore, pulse wave velocity of the aorta was slower (suggesting less atherosclerosis) in subjects living in Japanese

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Table 1 The approximate content of n-3 PUFA (g per 100 g of fish) in seafood (varies with season, place of capture, etc.)

Seafood	n-3 PUFA
Mackerel	1.8–5.3
Herring	1.2–3.1
Salmon	1.0–2.0
Trout	0.5–1.6
Tuna	0.5–1.6
Halibut	0.5–1.0
Shrimp	0.2–0.4
Cod, plaice, flounder	c. 0.2

fishing villages compared to people living in farming villages (and eating less fish) in Japan¹⁰.

A beneficial effect of marine n-3 PUFA on atherogenesis is also supported from the majority of animal studies showing that feeding with fish oil decreases atherosclerosis¹¹. n-3 PUFA may also reduce thrombogenesis and thereby decrease the risk of thrombotic complications to plaque rupture/fissure. Thus, Hornstra has shown an antithrombotic effect of n-3 PUFA in rats, in particular when n-3 PUFA were given in combination with a diet low in saturated fat¹². Cod liver oil reduced platelet deposition to carotid arteries subjected to deep intimal injury by balloon angioplasty in pigs and reduced injury-related vasoconstriction¹³. Also, when blood obtained from cod liver oil-treated pigs perfused normal pig aortas, platelet deposition to the aortas was lower than when blood from control pigs was used. These results indicate a beneficial effect of n-3 PUFA on the platelet–vessel wall interaction¹³. In a comprehensive study in baboons, a very high dose of fish oil was fed for 22 weeks¹⁴. Femoral arteriovenous Dacron shunts were surgically implanted, and thrombotic responses of blood to segments of the grafts were studied. Later, endarterectomies were performed on carotid arteries. Vascular thrombus formation and lesions were inhibited by n-3 PUFA. These results fit with a reduction in microthrombi over atherosclerotic lesions found in hyperlipidaemic swine fed fish oil¹⁵.

Overall, there is some evidence that intake of n-3 PUFA may be antiatherogenic and antithrombotic.

Marine n-3 PUFA and risk factors for CAD

The risk of CAD depends on inherited genetic traits, age and gender. Known modifiable risk factors for CAD include tobacco smoking, hypertension, adipositas, high plasma levels of low-density-lipoprotein (LDL) cholesterol and low levels of high-density-lipoprotein (HDL) cholesterol, while the impact of hypertriglyceridaemia on cardiac risk is controversial^{16,17}. High levels of plasma homocysteine, fibrinogen and of coagulation factor VII as well as impaired fibrinolysis are also associated with an increased risk of CAD^{16,17}. Several

other risk factors for CAD have been proposed, and the above mentioned is not a complete listing of risk factors.

The effect of n-3 PUFA on risk factors for CAD has been investigated in many studies. While dietary n-3 PUFA in practical doses – in contrast to common public belief – have no effect on LDL cholesterol levels, they do slightly increase the antiatherogenic HDL₂ cholesterol and substantially decrease plasma triglycerides^{1,18,19}. n-3 PUFA may also decrease blood pressure by 2–5 mmHg^{20,21}. Most studies have indicated no effect of n-3 PUFA on plasma fibrinogen and coagulant factor VII levels^{1,2}, but n-3 PUFA do reduce platelet reactivity and may impair fibrinolysis². Other potential effects of n-3 PUFA, with respect to preventing atherosclerosis and thrombosis by modifying risk factors for CAD, include a reduction in leukocyte reactivity, an improvement of vessel wall function and a beneficial effect on blood rheology^{2,22,23}. The biochemical effects of n-3 PUFA are usually seen after daily doses of between 2 and 5 g, but these effects are dose-dependent and the most favourable effects are achieved with high doses of n-3 PUFA. There is limited evidence that n-3 PUFA may reduce some of the health problems caused by smoking^{24,25}, but this clearly needs further documentation.

The concept of assessing the individual risk of CAD as the sum of risk factors, instead of focusing on single risk factors such as high plasma cholesterol, is very important and has been stressed in the recently published European guidelines on the prevention of CAD¹⁷. n-3 PUFA induce several beneficial changes in risk factors (Table 2), which in our view makes n-3 PUFA very attractive in the prophylaxis and treatment of the multifactorial disease, CAD.

Primary prevention of CAD

There is no randomized clinically controlled trial that has investigated an increased intake of n-3 PUFA (fish or n-3 PUFA supplements) in the primary prevention of CAD. Unfortunately, it is unlikely there will ever be such a trial, due to the costs involved and the non-patentability of seafood (and fish oil capsules) making funding unrealistic, as no pharmaceutical company is

Table 2 Major beneficial effects of n-3 PUFA in CAD

Triglycerides	↓
HDL ₂ cholesterol	↑
Platelet reactivity	↓
Monocyte reactivity	↓
Neutrophil reactivity	↓
Blood pressure	↓
Improvement of blood rheology	
Improvement of vasoreactivity	
Antiarrhythmic properties	

↑, increase; ↓, decrease.

going to finance such a trial. However, there is some evidence from epidemiological data that ingestion of marine n-3 PUFA reduces the risk of CAD. This has most clearly been shown in Greenland Eskimos²⁶, but a low occurrence of CAD has also been reported in Alaskan Eskimos⁹. In studies from Japan the incidence of CAD was lower in fishing villages compared to farming villages with a lower intake of fish^{10,27}. The possible association between consumption of seafood and CAD has also been studied in western populations with an average intake of n-3 PUFA below 1 g day⁻¹. In Zutphen, a Dutch area included in the classic Seven Countries Study, an inverse correlation between fish consumption and CAD was reported in middle-aged men during 20 years of follow up²⁸. A similar inverse correlation between heart disease and fish consumption in Caucasian populations was reported by some²⁹⁻³⁴, but not by other investigators^{23,35-40}. In the Health Professionals Follow-up Study there was an unexplained increased risk of coronary artery bypass surgery grafting in men with higher fish consumption⁴⁰. Finally, it is of interest that while fish consumption in the Physician's Health Study offered no protection against cardiovascular mortality³⁵, total mortality and the risk of sudden cardiac death were indeed reduced in those who ate fish⁴¹. It is puzzling why an intake of fish (and n-3 PUFA) of this order of magnitude may offer protection against CAD, because the beneficial biochemical effects of n-3 PUFA mentioned previously have not been shown at this low dosage^{1,2}. The possibility that other components in fish might be contributing to this effect therefore should be kept in mind.

We would, however, like to stress that epidemiological data can neither prove nor reject the hypothesis of a beneficial effect of n-3 PUFA in the prevention of CAD.

Clinical studies in patients with CAD

Patients with established CAD have a substantially increased risk of future coronary events¹⁷. This patient population should therefore be given high priority and be treated vigorously.

Angina pectoris

Saynor *et al.* in 1984 reported a marked symptomatic effect (fewer anginal attacks and reduced consumption of glyceryl trinitrate) in 12 patients with stable angina pectoris supplemented with 6 g n-3 PUFA per day for 9 months in an open trial⁴². We were, however, unable to confirm this in a controlled trial⁴³, where 36 patients were randomized to 12 weeks' treatment with 4.5 g n-3 PUFA per day or matching placebo. Other studies on small groups of patients with stable angina have also been negative².

No studies have been published on the effect of n-3 PUFA in patients with unstable angina pectoris.

Secondary prevention after myocardial infarction

Burr *et al.*⁴⁴ randomized approximately 2000 men with a recent myocardial infarction to various dietary changes including an increased intake of n-3 PUFA (fatty fish twice weekly or, alternatively, fish oil capsules) for 2 years. There was a significant 29% reduction in total mortality and deaths from CAD in the group increasing their dietary intake of n-3 PUFA to 0.5–1 g day⁻¹ by eating fish or taking supplements with fish oil. The number of non-fatal infarctions increased, although not significantly, in the group given fish advice. This makes the underlying mechanism of protection in the fish group unlikely to be antithrombotic, and the authors suggested an antiarrhythmic effect of n-3 PUFA as an explanation for their findings. This study was a clinical landmark trial and still provides the best evidence for a protective role of n-3 PUFA in CAD.

In the more recent Lyon study, the effect of a Mediterranean type of diet with an increased intake of fish, bread, fruit, vegetables and α -linolenic acid was investigated in 600 patients with a recent myocardial infarction⁴⁵. There was a 70% reduction in morbidity and mortality in the patients randomized to the Mediterranean diet. However, in this trial an increased intake of fish was only one of several dietary changes, making it impossible to know what role the (marginally) increased intake of marine n-3 PUFA had on the outcome.

In a trial from India, 360 patients with suspected myocardial infarction were randomized to daily supplementation with approximately 1.1 g of n-3 PUFA, 2.9 g of α -linolenic acid or placebo⁴⁶. Cardiac events were significantly reduced after 1 year with both the active treatments compared to the placebo, but cardiac deaths were only reduced in the fish oil group.

A large study from Italy (Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto Miocardico: GISSI) was presented in March 1999 in New Orleans, USA at the 48th meeting of the American College of Cardiology. More than 11 000 patients with CAD were randomized to daily supplementation with either one fish oil capsule containing approximately 0.85 g of EPA + DHA; 300 mg of vitamin E; a combination of fish oil and vitamin E; or to placebo. After 3.5 years those randomized to fish oil had a 15–20% reduction in total mortality which was mainly due to an approximately 45% reduction in sudden cardiac death. In line with the results from the Diet and Reinfarction Trial (DART) there was no significant difference in non-fatal myocardial infarctions between the groups. The publication of this extremely important study is eagerly awaited.

Restenosis after PTCA

A large proportion of patients treated for CAD with percutaneous transluminal coronary angioplasty (PTCA) develop restenosis. Accordingly, the effect of dietary n-3 PUFA in the prevention of restenosis has been evaluated in several trials. The results were initially promising with significant beneficial effects reported in five of eight randomized controlled trials and in a meta-analysis⁴⁷. However, recent larger trials set up to finally prove this effect of n-3 PUFA on restenosis rate failed to do so^{48–50}.

Nowadays, perhaps more than two-thirds of patients are treated with stents (metal frames that keep the vessel dilated) during PTCA, which has reduced the risk of restenosis. The studies with n-3 PUFA in the prevention of restenosis were all performed in the present era, and studies investigating the possible effect of n-3 PUFA in stented patients after PTCA have not yet been published.

Coronary artery bypass surgery

The incidence of late vein graft occlusion after coronary artery bypass surgery did not differ between patients randomized to fish oil or to aspirin⁵¹. However, in a study from Norway, 610 patients undergoing coronary artery bypass surgery were supplemented with 3.5 g n-3 PUFA daily as fish oil capsules or with placebo capsules for 1 year. Graft patency for venous, but not for arterial (mammary), grafts was significantly better after 1 year of follow-up in those randomized to fish oil⁵².

Arrhythmias and sudden cardiac death

In a series of studies in rats and monkeys McLennan *et al.* have convincingly shown that dietary n-3 PUFA reduce the incidence and severity of malignant ventricular tachyarrhythmias after coronary artery ligation and during reperfusion^{53,54}. Why n-3 PUFA protect against malignant tachyarrhythmias remains to be established, but several mechanisms have been proposed:

1. Changes in the formation of eicosanoids⁵⁵. Several studies have shown that an increase in the prostacyclin/thromboxane balance may protect against arrhythmias⁵⁵.
2. A reduction of calcium flux across cell membranes⁵⁶.
3. A modulating effect of n-3 PUFA on β -receptors⁵⁷.
4. A blockade of potassium channels by n-3 PUFA⁵⁸.

It is likely that these and perhaps other mechanisms as well may act in concert⁵⁹. This may involve a common pathway, namely a change in the (patho)physiological function of cell membranes induced by alteration in their lipid composition as found after an increased intake of n-3 PUFA.

Human studies lend support to an antiarrhythmic effect of n-3 PUFA. Thus, the content of long-chained

n-3 PUFA in coronary arteries was lower in subjects dying from sudden cardiac death than in controls dying of other causes⁶⁰, and intake of n-3 PUFA was associated with a reduced risk of cardiac arrest in previously healthy subjects⁶¹. Furthermore, as previously mentioned in the Physician's Health Study the risk of sudden cardiac death was reduced by fish consumption⁴¹. Also, a reduction in ventricular extrasystoles has been reported from small studies in humans eating n-3 PUFA^{62,63}. Heart rate variability is, however, a better indicator for the risk of sudden cardiac death than the number of ventricular extrasystoles⁶⁴. An increased heart rate variability indicates a beneficial alteration in cardiac vagal tone⁶⁴, that may relate to the experimental findings with n-3 PUFA discussed above. We therefore believe it is of major interest that our group has found that n-3 PUFA increase heart rate variability in patients with CAD, patients with renal failure and healthy men^{65–68}. Our studies thus suggest that the major cause of death from CAD, sudden cardiac death, may be reduced by dietary n-3 PUFA.

Coronary anatomy

As previously stated there is some epidemiological evidence for less coronary atherosclerosis in populations with a high intake of fish^{8–10} and for less atherosclerosis in animals fed n-3 PUFA¹¹. Furthermore, case-control studies have suggested an inverse correlation between coronary atherosclerosis and the content of n-3 PUFA in various tissues^{60,69}.

Two clinical trials have evaluated the effect of n-3 PUFA on regression/progression of atherosclerosis in patients with proven CAD^{70,71}. In the first study treatment with 6 g n-3 PUFA per day for 2 years to 31 patients with CAD did not promote beneficial effects on coronary atherosclerosis compared to a group of 28 patients given placebo⁷⁰. However, in a larger trial of 223 patients, those randomized to 1.6 g n-3 PUFA daily for 2 years had a borderline significant beneficial effect on coronary atherosclerosis compared to patients receiving placebo⁷¹.

Types and safety of n-3 PUFA

Seafood is the natural source of long-chained n-3 PUFA. Lean fish provides low amounts of n-3 PUFA, but contains little saturated fat and cholesterol and can be recommended for reducing the risk of CAD. Fatty fish have a lower content of saturated fat than some servings containing meat and may for this reason, independent of likely beneficial effects of n-3 PUFA, be a better food source.

The concept of substituting fish for other food sources, and not just adding fish oil supplements to the habitual diet, must be emphasized. If fish oils are to

be used, products of high quality should be chosen with declared amounts of EPA and DHA, and with added antioxidants.

Concern has been expressed about an increased consumption of fish due to intake of heavy metals and pesticides from contaminated fish⁷². The risk is low, but must not be neglected, and pollution of the sea and its fish should be monitored by international organizations. During industrial processing it is possible to remove toxic substances from fish oil concentrates.

PUFA (including n-3 PUFA) are susceptible to oxidation. This may be very important, because of the probable pivotal role of oxidation of LDL in atherogenesis⁷³. Epidemiological data do not, however, suggest increased atherosclerosis in fish consumers. Whether an increased intake of n-3 PUFA leads to a clinically relevant enhanced *in vivo* oxidation of LDL is debatable^{74,75}. Anyway, oxidation of n-3 PUFA in fish oil concentrates should be minimized before their intake, which can be achieved by the addition of antioxidants (vitamin E), proper storage and encapsulation.

There has also been concern about an increased risk of bleeding, especially after consumption of larger doses of fish oil concentrates, but there is very little clinical evidence in support of this^{76–78}. It has been claimed, based on limited data, that n-3 PUFA may deteriorate glycaemic control in patients with diabetes, but recent data have discarded this hypothesis^{21,79,80}. While immune responses may be reduced by n-3 PUFA, there is no evidence that intake of n-3 PUFA is associated with an increased risk of cancer or serious infections^{1,2,78}.

Public health implications

As our understanding of the atherosclerotic process progresses, one thing becomes more and more clear, namely that atherosclerosis is due to a maladaptation of fundamental protective systems evolved over the evolution of mammals (i.e. haemostasis, inflammation, etc.). Studies of the nutrition of humans have pointed out that drastic changes have taken place over the last 100–200 years, coinciding with the industrialization of our culture. During this timespan the consumption of saturated fats increased, following the increased ingestion of dairy products, hydrogenated oils and meat. In the same period dietary levels of n-3 PUFA diminished and those of n-6 PUFA increased⁸¹. Along with these changes CAD made its debut. In line with this, death from CAD has significantly decreased in western countries during the last decades probably partly due to a decreased intake of saturated fatty acids.

To generally recommend a reversion of dietary fat intake towards a composition more in harmony with that of the long evolutionary period of humankind seems rather straightforward and with few risks of unwanted side effects. Along this line we would like

to point to a study from Iceland, a country with a population characterized by high fish and n-3 PUFA consumption and a long life expectancy⁸². The investigation was a comparative study of cardiovascular risk factors in two genetically comparable, but geographically and culturally separated, populations – an Icelandic and an Islandic–Canadian one. The mortality rates for CAD were significantly higher in the latter population than in the Icelandic population in spite of higher levels of the major risk factor for CAD, serum total cholesterol (LDL cholesterol), in the Islandic population. The Islandic population had, however, lower levels of n-6 PUFA and three times higher levels of n-3 PUFA in their plasma phospholipids⁸². The Icelanders hold the European record for fish consumption (73 g day⁻¹ person⁻¹), and the use of cod liver oil as a food supplement is widespread. The findings seem to indicate that an increased consumption of n-3 PUFA may be cardioprotective in the context of an otherwise atherogenic diet. It has been argued that people would accrue measurable benefits by increasing dietary intake of n-3 PUFA to 1–2 g day⁻¹, which is far above the average daily estimated intake of 0.1–0.2 g long-chained n-3 PUFA in most industrialized nations⁸³.

Not many countries have yet translated this issue into specific dietary recommendations. However, in Canada official recommendations including sex- and age-dependent values were issued in 1990 regarding the intake of n-6 and n-3 PUFA⁸⁴, and in the UK an intake of 8–10 g EPA + DHA per week (2–3 medium servings of oil-rich fish) has been recommended⁸⁵.

The importance of sudden cardiac death for public health is illustrated from a recent British study reporting that 74% of fatal events among patients with heart disease happened outside hospital⁸⁶. Any substantial decrease in coronary deaths can therefore only be obtained by reducing CAD or by preventing its complication of sudden cardiac death. In-hospital mortality from CAD is around 15%⁸⁶, and even a total elimination of these fatalities will only have a minor effect on total cardiac mortality. Add to this that many patients die from sudden cardiac death as their first symptom of CAD. Over the years clinical trials with expensive pharmacotherapy to prevent arrhythmic death after myocardial infarction have shown disappointing results and even deleterious effects⁸⁷.

Dietary measures should therefore be included in the search for prevention of one of the most common causes of death in the western world, sudden cardiac death. Results obtained so far suggest that sudden cardiac death may be reduced by higher intakes of n-3 PUFA.

Conclusions

Data from epidemiological studies, animal experiments and clinical trials in humans lend support for a

beneficial role of n-3 PUFA on CAD. Effects of n-3 PUFA may be mediated through several mechanisms. Among these are: (i) a reduction in leukocyte and platelet reactivity; (ii) an improvement of the lipid profile; (iii) an improvement of vessel wall characteristics; (iv) a decrease in blood pressure; (v) an improvement of blood rheology; and (vi) an antiarrhythmic effect.

Further clinical studies with substitution/supplementation with n-3 PUFA to patients with acute myocardial ischaemia, previous myocardial infarction, patients undergoing coronary artery bypass surgery, patients with arrhythmias and patients at high risk of CAD should be undertaken, because only results from controlled clinical trials can establish whether n-3 PUFA reduce the risk of CAD. It is important to be aware that only studies with hard end points (total mortality, mortality from CAD and mortality from cardiovascular disease) are likely to have an impact on the treatment modalities chosen by clinicians. Such studies must be randomized, controlled and include many patients.

If the published results from the GISSI trial confirm the orally presented data as expected, we believe that all patients with CAD should increase their intake of n-3 PUFA (fish or fish oil capsules) to approximately 0.85 g day^{-1} . In the meantime, we advocate the incorporation of fish in the diet of healthy subjects and in particular to patients with or at high risk for CAD. This is in line with the recommendations of a recently published expert workshop summary⁸⁸.

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