# Cardiovascular effects of marine omega-3 fatty acids

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**Much evidence shows that the marine omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid have beneficial effects in various cardiac disorders, and their use is recommended in guidelines for management of patients after myocardial infarction. However, questions have been raised about their usefulness alongside optimum medical therapies with agents proven to reduce risk of cardiac events in high-risk patients. Additionally, there is some evidence for a possible pro-arrhythmic effect in subsets of cardiac patients. Some uncertainly exists about the optimum dose needed to obtain beneficial effects and the relative merit of dietary intake of omega-3 polyunsaturated fatty acids versus supplements. We review evidence for the effects of omega-3 polyunsaturated fatty acids on various cardiac disorders and the risk factors for cardiac disease. We also assess areas of uncertainty needing further research.**

## Introduction

The marine omega-3 polyunsaturated fatty acids (n-3 PUFAs) eicosapentaenoic acid and docosahexaenoic acid are present mainly in oily fish and commercially available supplements, which are available either over the counter (as fish oils) or as concentrated pharmaceutical preparations. Such supplements are becoming increasingly popular, with several health benefits attributed to them. Substantial benefits are reported in relation to diseases of the cardiovascular system, and guidelines recommend use of these agents in some cardiac disorders.[1,2] Although much research has been focused on this area during the past three decades, an absence of clarity remains about some basic issues, such as the appropriate dose needed to achieve beneficial reduction in cardiovascular events. Additionally, some doubt exists about some established benefits and assumed mechanisms of action, whereas new areas of use and mechanisms are being identified. We review evidence for the effects of n-3 PUFAs on various cardiac disorders and the risk factors for cardiac disease. We also assess areas of uncertainty needing further research.

## Coronary artery disease

Researchers of observational studies[3,4] of the Greenland Inuit population and Okinawa islanders reported that the low risk of death from coronary artery disease in these populations was related to an abundance of n-3 PUFAs in their diet. Subsequently, researchers from several prospective epidemiological studies[5–8] reported that high fish consumption was associated with a lowered mortality from coronary artery disease. These finding formed the basis of a theory that n-3 PUFAs could prevent atherosclerosis, thrombosis, and their associated diseases.[9]

This hypothesis was supported by findings of the landmark DART study,[10] a randomised secondary prevention trial with long-term dietary intervention after myocardial infarction in men. A 30% reduction in total mortality and mortality related to coronary artery disease was reported in patients randomly assigned to consumption of fatty fish twice per week. In the GISSI Prevenzione study,[11] a large intervention trial of secondary prevention after myocardial infarction, researchers identified a substantial reduction in all-cause and cardiovascular mortality with 1 g per day of n-3 PUFA supplementation. Notably, findings from this study showed that incidence of sudden cardiac death was greatly reduced in this patient population within 4 months of starting therapy with n-3 PUFAs (figure 1). However, no benefit was shown for occurrence of non-fatal myocardial infarction or stroke.[11] Another study[13] assessed the role of n-3 PUFA in secondary prevention of cardiovascular diseases in patients treated with chronic haemodialysis, showing that supplementation with 1·7 g per day of n-3 PUFA for 2 years had no effect on total or cardiovascular mortality, but reduced incidence of myocardial infarction.

Data for the effect of n-3 PUFAs on risk of development of coronary artery disease in healthy participants are inconsistent.[8,14,15] A large prospective study[16] (JELIS) in Japanese patients with hypercholesterolaemia, with or without pre-existing coronary artery disease, showed that long-term use of 1·8 g of purified eicosapentaenoic acid daily reduced the risk of major coronary events by 18%. Further subgroup analysis showed much benefit for a subsets of patients known to have pre-existing coronary artery disease (figure 2), who had a high serum triglyceride concentration and a low serum HDL cholesterol concentration, or who had impaired glucose tolerance. Investigators for a prospective cohort study[17]

### Search strategy and selection criteria

We searched Medline, Embase, the Cochrane Library, PubMed, CINAHL, IPA, Web of Science, Scopus, and Pascal for reports published between January, 1970, and January, 2010. We used the search terms "omega-3 fatty acids" or "n-3 PUFA" in combination with the terms "cardiac", "cardio-vascular", "sudden cardiac death", "arrhythmia", "ion channels", "atrial fibrillation", "stroke", "hypertension", "triglycerides", "immunology", and "inflammation". We largely selected publications from the past 15 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles and book chapters are cited to provide readers with more details and references than this Review provides. Our reference list was modified on the basis of comments from peer reviewers.

of 25 573 men and 28 653 women reported that intake of fatty fish was associated with a 30% lowered risk of acute coronary syndrome in men (but not in women) during a mean follow-up of 7·6 years, when comparing participants in the lowest quintile (≤6 g fatty fish per day) with those in the higher quintiles (>6 g fatty fish per day) of intake.

Findings from initial studies[18] for patients who underwent percutaneous coronary revascularisation procedures with conventional balloon angioplasty showed

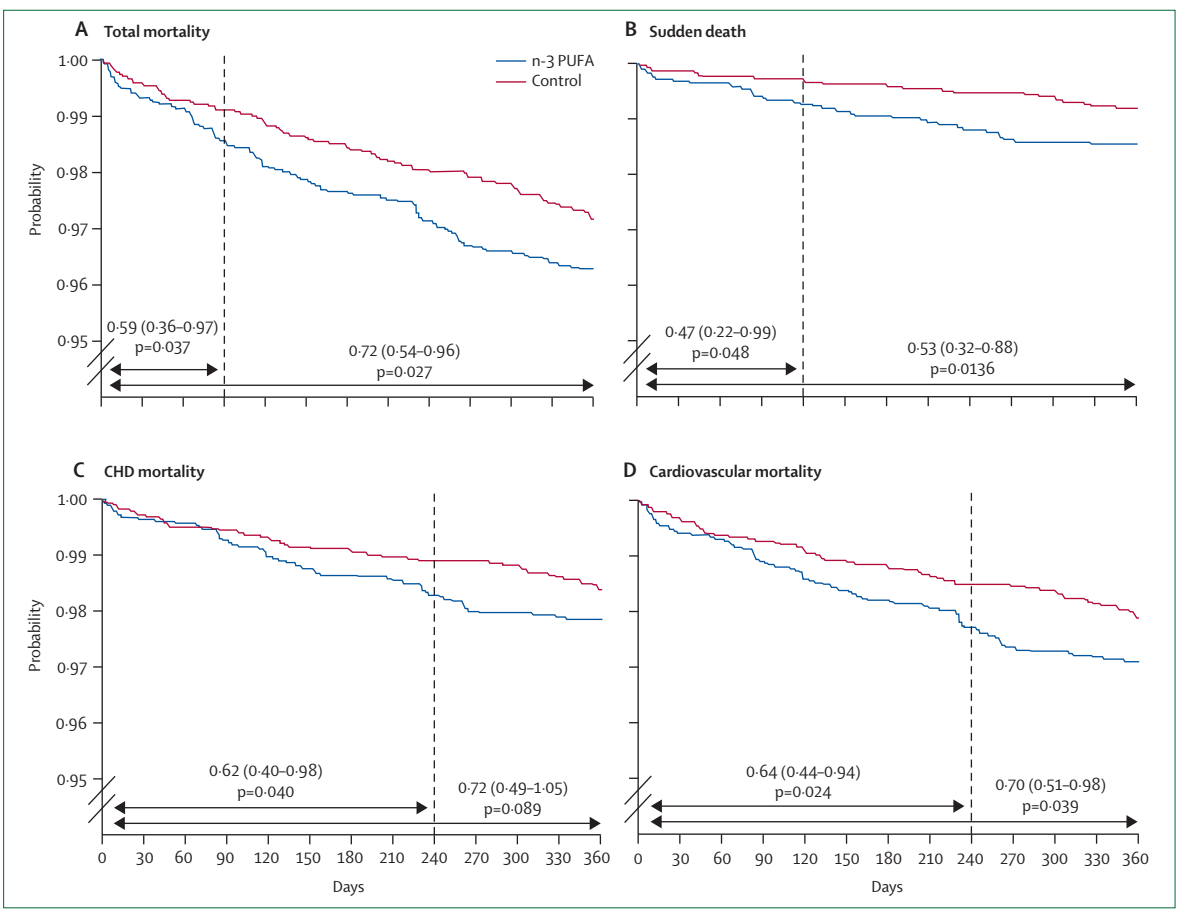


***Figure 1:*** **Early protection from mortality with n-3PUFA supplementation in GISSI-Prevenzione study[12]—a time course analysis**
Data are hazard ratio (95% CI). n-3 PUFA=omega-3 polyunsaturated fatty acid. CHD=coronary heart disease. Reproduced from reference 12 with permission of Wolters Kluwer Health.

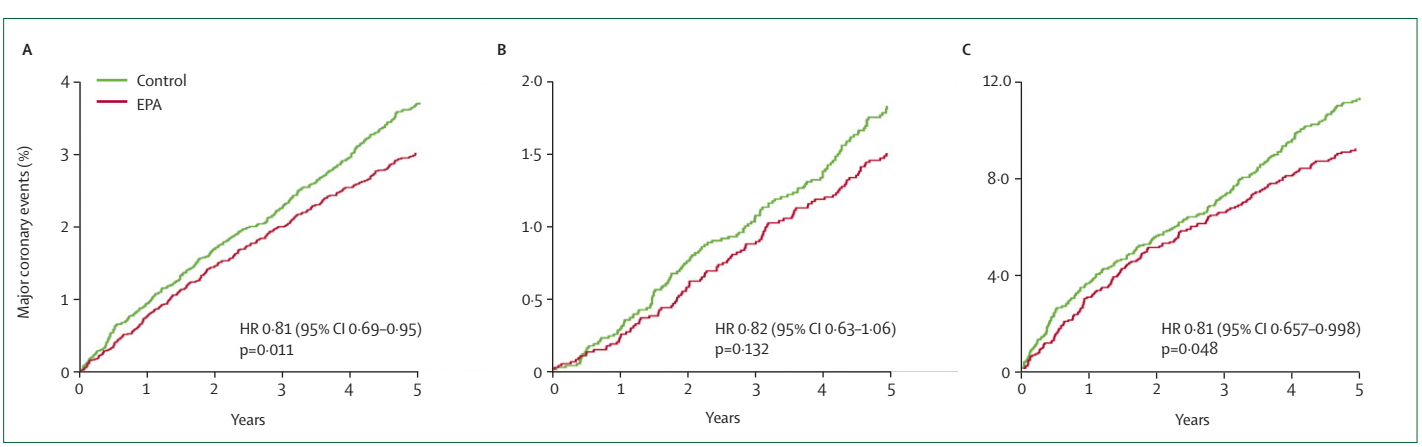


***Figure 2:*** **Kaplan-Meier estimates of incidence of coronary events in JELIS study[16]**
Total study population (A); primary prevention group (B); secondary prevention group (C). EPA=eicosapentaenoic acid. HR=hazard ratio. Reprinted from reference 16 with permission from Elsevier.

| | Study type | Main findings |
|---|---|---|
| Bang et al[3] | Observational | Low rates of CHD death in Greenland Eskimos consuming large amounts of seafood |
| Albert et al[8] (US Physicians Health Study) | Observational | Consumption of fish at least once per week associated with reduced risk of SCD in men |
| Albert et al[21] | Epidemiological | Raised blood content of n-3 PUFA associated with reduced risk of sudden death in men without evidence of previous cardiovascular disease |
| Lemaitre et al[22] (Cardiovascular Health Study) | Epidemiological | Raised intake of n-3 PUFA associated with reduced risk of fatal ischaemic heart disease in older adults (≥65 years) |
| Streppel et al[23] | Epidemiological | Consumption of fatty fish associated with reduced risk of SCD. No clear relation between dose of n-3 PUFA and risk of SCD |
| Burr et al[10] (DART study) | Clinical trial (after MI with dietary intervention) | A modest intake of fatty fish (two or three portions per week) reduced mortality in men who had recovered from MI |
| GISSI-Prevenzione Investigators[11] | Clinical trial (post-MI with supplements) | Treatment with n-3 PUFA lowered risk of overall of cardiovascular disease and SCD |
| Burr et al[24] (DART-2 study) | Clinical trial (stable CAD with dietary advice) | Men advised to eat oily fish, and especially those supplied with fish-oil capsules had a raised risk of cardiac death, especially of SCD |
| Svensson et al[13] | Clinical trial (secondary prevention in haemodialysis, supplements) | Treatment with n-3 PUFAs did not reduce total number of cardiovascular events and death in a high-risk population but substantially reduced the number of MIs as a secondary outcome |
| Yokoyama et al[16] (JELIS study) | Clinical trial (primary prevention with supplements) | Treatment with n-3 PUFA had no benefit on major coronary events in the primary prevention group, but in the secondary prevention subgroup a reduction in non-fatal coronary events but not in cardiovascular mortality were reported |
| GISSI-HF Investigators[25] | Clinical trial (heart failure with supplements) | Treatment with n-3 PUFA reduced all-cause mortality but not SCD; a substantial reduction in death due to presumed arrhythmias |
| Bucher et al[26] | Meta-analysis | Dietary and non-dietary intake of n-3 PUFA reduces overall mortality, mortality due to MI, and SCD in patients with CHD |
| León et al[27] | Systematic review | n-3 PUFA supplementation associated with reduction in deaths from cardiac causes but no effect on arrhythmias or all-cause mortality |
| Zhao et al[28] | Systematic review | n-3 PUFA has a beneficial effect on prevention of SCD in patients with previous MI but not in patients who have angina |

CHD=coronary heart disease. SCD=sudden cardiac death. n-3 PUFA=omega-3 polyunsaturated fatty acid. MI=myocardial infarction. CAD=coronary artery disease.

***Table 1:*** **Evidence for the effect of n-3 PUFA on SCD and cardiovascular mortality**

some promising results for reduced risk of restenosis, but in several large studies[19] undertaken subsequently, no benefit was reported. All available evidence for this patient group was obtained in the pre-stent era, and is less relevant to present clinical practice than prevtiously, because stent insertion is now used for almost every coronary angioplasty procedure. In the only study[20] to investigate graft-vessel patency after surgical coronary revascularisation, investigators reported a substantial reduction in angiographic vein-graft occlusion after 1 year of supplementation with 3·4 g per day of n-3 PUFAs.

Information about the role of n-3 PUFA intake or supplementation in primary prevention of coronary artery disease is scarce, but the available evidence suggests that those with hyperlipidaemia and diabetes might benefit most. The main benefit reported for the secondary prevention relates to the reduction in occurrence of sudden cardiac death, leading to much interest in the role of n-3 PUFAs in prevention of sudden cardiac death and their anti-arrhythmic potential.

## Sudden cardiac death and ventricular arrhythmias

Several observational and interventional studies reported that high intakes of n-3 PUFAs reduced risk of cardiovascular mortality and sudden cardiac death, especially in patients with previous myocardial infarction (table 1). The most convincing evidence for a protective role of n-3 PUFAs against sudden cardiac death comes from a subanalysis of the GISSI-Prevenzione study[12] showing a significant reduction (p=0·048) within 4 months after a myocardial infarction. The presumed mechanism of such benefit would be a reduction in life-threatening ventricular arrhythmias—the most common cause of sudden cardiac death in the early stages after a myocardial infarction.

The role of n-3 PUFA in reduction of risk of sudden cardiac death in patients with non-ischaemic cardiac disease is unknown, and very little investigation has been done in this area. Investigators of a study[29] in a small number of patients with dilated cardiomyopathy reported beneficial alterations in known risk indicators for sudden cardiac death. In the GISSI Heart Failure study,[25] in which half of participants had heart failure attributable to non-ischaemic causes, sudden cardiac death was not greatly reduced. However, the greatest proportion of reduction in the primary endpoints of total mortality and hospital admission was attributed to a reduction in such events because of a presumed arrhythmic cause.

Anti-arrhythmic potential of n-3 PUFAs was tested in patients with an automatic implantable cardioverter

| | Mode of n-3 PUFA administration | Electrophysiological effect | Triggered activity | Re-entry |
|---|---|---|---|---|
| Xiao et al,[37,38] Leifert et al[39] | Acutely applied (compare circulating levels) | Inhibition of sodium channel | Decreased | Increased |
| Verkerk et al[35] | Supplemented in feeds (incorporated) | Shortening of action potential | Decreased | Increased |
| Dhein et al[36] | Acute infusion (compare circulating levels) | Slowing of ventricular conduction | Decreased | Increased |

n-3 PUFA=omega-3 polyunsaturated fatty acid.

***Table 2:*** **Potential effect of n-3 PUFAs on mechanisms of arrhythmia initiation**

defibrillator. Results of such studies have reported inconsistent results, with one study showing marginal benefit,[30] another no effect,[31] and a third[32] suggesting a possibility of increased risk of ventricular arrhythmic episodes in patients whose qualifying arrhythmia was ventricular tachycardia rather than ventricular fibrillation. An absence of overall effect was also reported in a meta-analysis[33] of these studies and in a systematic review of studies on mortality and arrhythmias, including a study of an appropriate implantable cardioverter defibrillator therapy as a marker of arrhythmic burden.[27] Moreover, one clinical study[24] reported that patients with coronary artery disease without previous myocardial infarction could have a heightened risk of sudden cardiac death with a high n-3 PUFA intake. Although this study had methodological limitations, evidence from studies in laboratory animals showed that n-3 PUFAs in the presence of coronary ischaemia, without previous myocardial infarction, might predispose to an increased risk of ventricular arrhythmias.[34] The conflicting finding and the apparent absence of benefit in studies designed to assess a direct anti-arrhythmic effect could be attributable to differences in the mechanisms of arrhythmia initiation in subsets within these study populations.

The two common mechanisms of initiation of life-threatening ventricular arrhythmias are triggered activity and re-entry. Of the cellular electrophysiological effects of n-3 PUFAs, shortening of action potential duration[35] and slowing of impulse conduction,[36] which would affect triggered activity with a favourable outcome, could promote re-entry in a susceptible substrate (table 2). Thus, a given patient could have either a lowered or raised risk of serious ventricular arrhythmias on the basis of the mechanism of initiation of the arrhythmia.[40] Thus, patients who have had a recent myocardial infarction and heart failure, with triggered activity as the predominant mechanism of arrhythmia initiation, would have a beneficial reduction in arrhythmias, whereas those with ischaemic heart disease in the absence of previous myocardial infarction and any other clinical situation in which the predominant mechanism of arrhythmia initiation is re-entry could be expected to have heightened arrhythmic risk. This finding is especially important because it suggests that patient selection could be a crucial issue before starting therapy with n-3 PUFAs.

In experimental studies, mostly done in laboratory animals, researchers have reported that n-3 PUFAs have several potential anti-arrhythmic effects[40,41]—most notably a direct effect on cardiac ion channels. Initial data[37] from single-cell experiments with isolated cardiomyocytes showed that acute application of purified n-3 PUFAs had a profound inhibitory effect on sodium channels, reducing the peak sodium current by more than 50% and shifting the steady-state inactivation towards negative potentials, thus reducing excitability. This finding was supported by other similar studies,[38,39] leading to the hypothesis that n-3 PUFAs exert their predominant anti-arrhythmic effect by their inhibitory action on sodium channels. However, when cardiac cells with high membrane incorporation of n-3 PUFA, which was obtained from animals fed a diet fortified with fish oil, were studied, this effect was not consistently reported. Further studies in laboratory animals revealed that n-3 PUFAs have a diverse range of effects on other ion channels, such as potassium channels, L-type calcium channels, sodium-calcium exchanger proteins, and calcium-handling proteins (table 3). n-3 PUFAs have also been shown to alter membrane fluidity,[56] with consequent effects on ion transport. Thus, we would expect that the net effect would be derived from the sum of all these effects, on the basis of the relative concentrations and potencies of circulating free and incorporated n-3 PUFAs, along with the state of excitability of the substrate and mechanism of arrhythmia initiation.

In addition to a direct anti-arrhythmic effect, other mechanisms that could explain some or all of the observed benefits from large clinical trials have been reported. These mechanisms are: beneficial modulation of the autonomic tone shown as improved heart rate variability;[57–59] reduction in basal heart rate,[60] probably due to an inhibitory effect on the pacemaker current (the funny current-$I_f$) in the sinus node cells;[61] and nutritional preconditioning similar to ischaemic preconditioning, restricting infarct size and reducing reperfusion-induced arrhythmias.[62]

However, in the OMEGA multicentre study[63] in Germany, no significant reduction in sudden cardiac death or coronary events were reported in a cohort of patients who had an optimum use of conventional therapy, such as β blockers, statins, and angiotensin-converting enzyme inhibitors with a high rate of revascularisation procedures, which are used in standard clinical practice. Even though this study had a low power to detect such events, the possibility that n-3 PUFAs might not confer additional benefits to those treated with optimum conventional medical therapy needs to be

| | Study type | Main findings |
|---|---|---|
| McLennan et al[42] | Dietary supplementation in a whole animal model (rat) | n-3 PUFAs (tuna fish oil) reduced vulnerability to both ischaemic and reperfusion arrhythmias |
| McLennan et al[43] | Dietary supplementation in a whole animal model (rat) | n-3 PUFAs reduced reperfusion arrhythmias; fatal VF was reduced in the n-3 PUFA group compared with the saturated fat group |
| McLennan et al[44] | Dietary supplementation in a whole animal model (marmoset monkey) | n-3 PUFA reduced vulnerability of normal or ischaemic myocardium to arrhythmias (measured as VF threshold) in a non-human primate |
| Billman et al[45] | Intravenous administration in a whole animal model (dog) | Intravenous administration of EPA or DHA prevented fatal ischaemia-induced arrhythmias in an infarct model |
| Macleod et al[46] | Acute application in ventricular myocytes (rat and guineapig) | Acute application of EPA shortened action potential and increased refractory period |
| Verkerk et al[35] | Dietary supplementation; incorporation in ventricular myocytes (pig) | n-3 PUFA shortened action potential duration, inhibited L-type calcium current, reduced re-opening of calcium channels at plateau potentials, which could prevent triggered activity; no effect on transient outward current but an increase in Ik1 and IkS potassium currents and inhibition of sodium-calcium exchanger |
| Dhein et al[36] | Acute application in whole heart preparation (rabbit) | Threshold for elicitation of a ventricular extrasystole was enhanced by DHA and EPA; DHA dose-dependently reduced longitudinal and transverse propagation velocity |
| Xiao et al[37] | Acute application in isolated ventricular myocytes (neonatal rats) | EPA reduced (51%) peak sodium current |
| Leifert et al[39] | Acute application in isolated ventricular myocytes (adult rats) | EPA and DHA shifted the voltage dependence of activation of the sodium channel to more positive potentials, and this effect correlated with increase in membrane fluidity |
| Leifert et al[47] | Dietary supplementation; incorporation in ventricular myocytes (adult rat) | Incorporated n-3 PUFA had no effect on peak sodium current or the voltage dependent activation of sodium channels |
| Ferrier et al[48] | Acute application in isolated ventricular myocytes (guineapig) | DHA suppressed L-type calcium current while preserving myocardial function |
| Bogdanov et al[49] | Acute application in isolated ventricular myocytes (adult rat) | At low concentrations, EPA and DHA inhibited transient outward potassium current and prolonged action potential |
| Xiao et al[50] | Acute application in cultured myocytes | EPA inhibited outward and inward sodium-calcium exchanger current |
| Swan et al[51] | Acute application in isolated ventricular myocytes (adult rat) | EPA reduced frequency of spontaneous waves of calcium release, decreased diastolic calcium concentrations, and increased calcium wave amplitudes and propagation |
| Berecki et al[52] | Dietary supplementation; incorporation in ventricular myocytes (pig) | Myocytes from n-3 PUFA-treated pigs displayed decreased SR calcium content, reduced L-type calcium current, and less recruitment of the sodium-calcium exchange current in response to noradrenalin |
| Dujardin et al[53] | Dietary supplementation; incorporation into Langendorff-perfused hearts (rabbit) | DHA inhibited ultra-fast sodium current and reduced dofetilide-induced changes in triangulation, reverse use-dependence, instability, and dispersion of cardiac action potential |
| Xiao et al[54] | Acute application in vivo; pericardial administration (pig) | Pericardial infusion of DHA reduced malignant arrhythmias and infarct sizes in a porcine infarct model |
| Den Ruijter et al[55] | Acute application in isolated ventricular myocytes; heart failure (human beings and rabbits) | n-3 PUFAs (EPA and DHA) abolished triggered activity, reduced delayed after depolarisations and calcium after transients, reduced action potential shortening and intracellular calcium elevation in response to noradrenalin |
| Coronel et al[34] | Dietary supplementation; incorporation in ventricular myocytes (pig) | More episodes of ischaemia-induced VT/VF in n-3 PUFA group; myocardial excitability reduced during the early phase of arrhythmogenesis in n-3 PUFA group, but in the late phase excitability was more reduced in the control group than in n-3 PUFA group |

n-3 PUFA=omega-3 polyunsaturated fatty acid. VF=ventricular fibrillation. EPA=eicosapentaenoic acid. DHA=docosahaexaenoic acid. SR=sarcoplasmic reticulum. VT=ventricular tachycardia.

***Table 3:*** **Studies in animal models on the effect of n-3 PUFA on ventricular arrhythmogenesis**

addressed, because previous studies were done in patients with suboptimum use of these agents (table 4).

## Atrial arrhythmias

Atrial fibrillation is the most common cardiac arrhythmia reported in clinical practice. Drug treatments for this disorder are restricted by pro-arrhythmic effects on the ventricles, and a need exists to identify effective drugs that can be used to treat atrial arrhythmias with a minimum risk of ventricular arrhythmia. In the absence of coronary ischaemia, n-3 PUFAs are unlikely to increase risk of ventricular arrhythmias, and might have the potential to be useful in management of atrial fibrillation. However, evidence for the effect of n-3 PUFAs on the incidence of atrial fibrillation seems to be inconsistent.

In large epidemiological studies[64,65] investigating the effect of fish intake on the risk of development of atrial fibrillation, researchers reported an absence of benefit, but in a prospective population-based study of adults 65 years and older investigators reported that risk of this disorder was lowered with consumption of grilled or baked fish,[66] with a possible dose-response effect that was confirmed by measurements of plasma concentrations of eicosapentaenoic acid and docosahexaenoic acid. In another observational study[67] in men older than 42 years, high serum concentrations of docosahexaenoic acid had a protective effect against atrial fibrillation during a follow-up of 17 years.

Data for the role of therapeutic supplementation of n-3 PUFAs in management of atrial fibrillation are restricted to few studies with relatively small sample sizes

| | Antiplatelet drugs (%) | Cholesterol-lowering agents (%) | Cholesterol-lowering agents (%) | ACEI/ARB (%) | Relative risk reduction in CV mortality (%) |
|---|---|---|---|---|---|
| DART[10] | 10·2% | NA | NA | NA | 31·0% |
| GISSI-Prevenzione[11]* | 87·9% | 28·6% | 28·6% | 40·9% | 17·7% |
| OMEGA[63] | 95·0% | 94·0% | 94·0% | 83·0% | No difference |

Data are percentage of study population. ACEI=angiotensin-converting enzyme inhibitor. ARB=angiotensin receptor blocker. CV=cardiovascular. n-3 PUFA=omega-3 polyunsaturated fatty acid. NA=not applicable. *All data derived from values at 6 months' follow-up, when reduction in CV mortality was significant. †Trials were included if the full set of data for concomitant drug therapy were available.

*Table 4:* **Comparison of concomitant drug therapy and cardiovascular mortality in clinical trials with n-3 PUFA†**

that were undertaken in patients undergoing cardiac surgery. Of these, one study[68] reported a significant reduction (p=0·013) in occurrence of postoperative atrial fibrillation after coronary artery bypass graft surgery in patients who were supplemented with 2 g per day of n-3 PUFA for as few as 5 days before surgery. In another,[69] investigators used high concentrations of n-3 PUFAs (100 mg/kg bodyweight per day) as an intravenous infusion for a short period (24–72 h) in the perioperative phase and reported similar benefits, but another study[70] showed that these fatty acids do not reduce risk of atrial fibrillation after this surgery, with a possible increase in risk. Postoperative atrial fibrillation, however, might not be an appropriate model to study the effectiveness of an agent in management of common clinical forms of atrial fibrillation, because the cause and pathology of postoperative atrial fibrillation differs substantially from those of this disorder in the general population.

Atrial fibrillation is a heterogeneous disease that affects various age groups. Often young patients (≤35 years) have lone atrial fibrillation in the absence of structural heart disease, whereas older individuals (typically ≥65 years) have underlying cardiovascular disorders that result in structural remodelling of the atrium, predisposing to atrial fibrillation. Therefore, on the basis of available evidence, we can postulate that n-3 PUFAs might have a beneficial effect on the structural remodelling of the atrium but a lessened effect on electrical remodelling, underpinning maintenance of atrial fibrillation in lone atrial fibrillation. This view is supported by the observation that n-3 PUFAs do not have a great effect on the atrial electrical properties in an atrially paced model of atrial fibrillation, whereas they have substantial benefits in a ventricular-paced (heart failure) model of this disorder.[71] These issues can be addressed by further research in patients with atrial fibrillation with and without underlying structural heart disease.

## Heart failure

Findings from epidemiological studies[72] have shown an inverse association between consumption of fish and risk of heart failure. In a large observational study with 60 000 participants who were followed up for 13 years, investigators reported a reduction in death attributable to heart failure with increased fish intake.[73] The Atherosclerosis Risk in Communities (ARIC) study,[74] a prospective study of 3592 white men and women, reported for 14·2 years of follow-up that raised serum concentrations of n-3 PUFAs, especially docosahexaenoic acid, were associated with a lowered incidence of heart failure in women. The GISSI Prevenzione Investigators[75] reported that the observed reduction in sudden cardiac death in patients who had had myocardial infarction was most pronounced in those with evidence of systolic left-ventricular dysfunction. In a large randomised study, GISSI HF Investigators[25] reported substantial reductions in overall mortality and admissions in patients with New York Heart Association class II–IV heart failure with 1 g per day of eicosapentaenoic and docosahexaenoic acid (figure 3). Even though the observed benefit was modest, the fact that the benefits seen were incremental to optimum standard therapy lends support to use of n-3 PUFAs in management of heart failure.

## Atherosclerosis and stroke

Researchers for observational studies[76,77] have reported less atherosclerotic plaque burden in native Japanese people compared with Japanese people living in other developed countries and with white people. This finding has been attributed to the high intake of n-3 PUFAs consumed in the traditional Japanese diet. Usually, this traditional diet contains eight to 15 times more n-3 PUFAs than does a typical non-Japanese diet.[78] Although other factors are present in the Japanese diet that could have contributed to the observed reduction in plaque burden, these studies showed that the low atherosclerotic plaque burden was no longer present when adjusted for serum n-3 PUFA content, thus suggesting that the high serum n-3 PUFA content is the most likely explanation for the low plaque burden reported in native Japanese people.

Researchers for a randomised, double blind, placebo-controlled clinical trial[79] with patients with symptomatic carotid atherosclerotic disease undergoing carotid endarterectomy have reported that n-3 PUFAs incorporation into the atherosclerotic plaque could have a plaque-stabilising effect. This study showed that n-3 PUFAs are readily incorporated into advanced atherosclerotic plaques during a short period of supplementation (median 42 days), and this supplementation was associated with a reduced number of macrophages in the plaque, and a plaque morphology suggestive of increased stability. A thin plaque cap with heavy infiltration of inflammatory cells (macrophages and foam cells) increases the likelihood of rupture of the

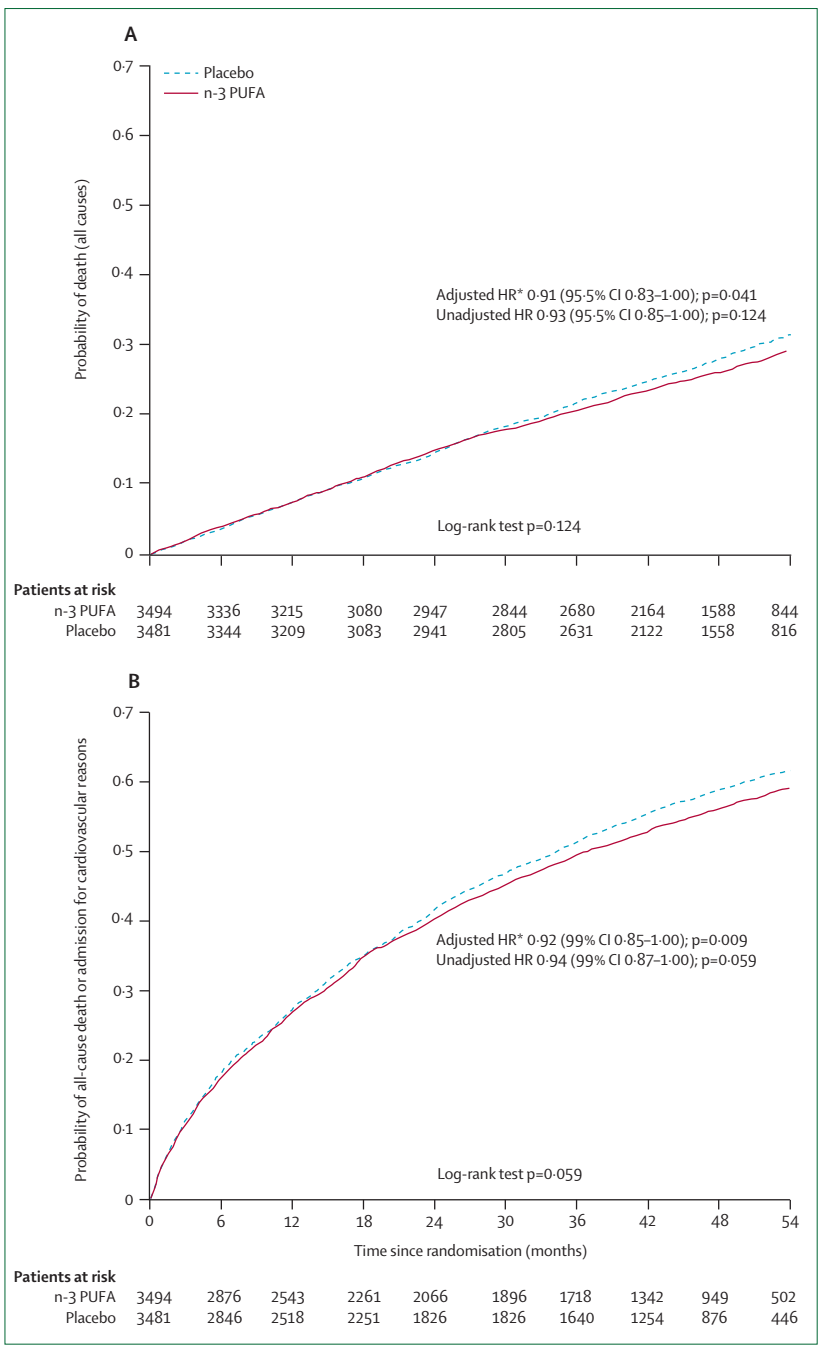


***Figure 3:*** **Kaplan-Meier curves for time to all-cause mortality (A) and all-cause mortality or admission to hospital for cardiovascular reasons (B) in GISSI-HF study[25]**
n-3 PUFA=omega-3 polyunsaturated fatty acid. HR=hazard ratio. Reprinted from reference 25 with permission from Elsevier.

plaque,[80] and the instability of a plaque has been shown to be related to the number or function of the macrophages and foam cells in the plaque.[80] Hence, the findings of this study,[79] if confirmed in other trials, possibly represent an important mechanism by which n-3 PUFAs could reduce ischaemic cardiovascular events. So far, no data are available for the effects of n-3 PUFA supplementation in reduction of risk of stroke in symptomatic patients with atherosclerotic carotid arterial disease.

## Dyslipidaemia, diabetes, and hypertension

A consistent effect of n-3 PUFAs is a lowering of plasma triglyceride concentrations.[1] This effect is achieved by a combination of a reduction in hepatic synthesis of triglycerides and an increased clearance of circulating triglycerides.[81] This effect can be used therapeutically in people in whom diet and lifestyle measures have not led to appropriate concentrations of triglycerides. For this purpose, doses of 2–4 g of n-3 PUFAs are usually needed, and these doses will lower triglyceride concentrations by about 30%. Such an intake of n-3 PUFAs cannot be easily obtained by diet alone and needs to be achieved from supplements. Pharmaceutical preparations of n-3 PUFAs are registered for this indication in some countries.

In the past, concerns have been raised that n-3 PUFAs in high doses might lead to deterioration of diabetic control, but a systematic review[82] on the effect of n-3 PUFAs on glycaemic control and cholesterol concentrations identified no adverse effect on glycaemic control, with a substantial reduction in triglyceride concentrations. n-3 PUFAs could have several beneficial effects in patients with diabetes,[83] and this factor, in addition to the subgroup analysis of the JELIS study showing a substantial reduction in cardiac events in patients with impaired glucose tolerance,[84] suggests that n-3 PUFAs might confer a significant benefit in terms of cardiovascular risk reduction in patients with type-2 diabetes. Large prospective studies in diabetic patients assessing the role of these fatty acids in reduction of risk of cardiovascular events are underway.[85,86]

Hypertension is another important risk factor for cardiac disease, and several studies have indicated that sufficiently high doses of n-3 PUFAs are associated with modest reductions in systemic blood pressure.[87] This effect seems to be more pronounced in people with hypertension and those who are older (≥45 years) than in other groups, and seems to need doses of more than 3 g per day of n-3 PUFAs.[88] Mechanisms proposed to explain this effect include reduced production of the vasoconstrictor thromboxane $A_2$, increased synthesis of the vasodilator nitric oxide, improved vascular reactivity and compliance, and an effect on autonomic nerve function.[89] The slight reduction in blood pressure of 0·66 mm Hg systolic and 0·35 mm Hg diastolic per g of n-3 PUFA consumed[87] could help to explain at least some of the beneficial effects of n-3 PUFAs on cardiac disease. However, in view of the practical difficulty in achievement of such high concentrations by dietary intake alone, and the availability of several effective and well tolerated drugs to treat hypertension, this treatment is unlikely to have a place in mainline therapy of hypertension.

## Anti-inflammatory and immunomodulatory effects

Increased consumption of marine n-3 PUFAs results in their dose-dependent incorporation into cell phospholipids,[90] and is partly at the expense of arachidonic acid. A decrease in arachidonic-acid content means a decreased amount of substrate available for synthesis of the classic pro-inflammatory eicosanoids. In keeping with this finding, increased intake of n-3 PUFA in animals and human beings has been reported[91] to decrease production of a range of pro-inflammatory eicosanoids. This effect seems to be evident with an eicosapentaenoic acid intake of more than 2 g per day.[90] Eicosapentaenoic acid also gives rise to alternative eicosanoid families, with less inflammatory potential than from analogues of arachidonic acid.[91] Although a reduction in production of arachidonic acid metabolites is thought to be the classic anti-inflammatory mechanism, researchers have identified a novel group of mediators derived from eicosapentaenoic acid and docosahexaenoic acid—E-series and D-series resolvins, respectively. These mediators seem to exert potent anti-inflammatory and immunomodulatory actions on neutrophils, macrophages, dendritic cells, and T cells.[92,93] Metabolism of docosahexaenoic acid also generates a derivative called neuroprotectin D1, which has also been reported to have potent suppressive effects on neutrophils, macrophages, T cells, and microglia.[94,95]

Thus, it seems that n-3 PUFAs exert an anti-inflammatory or immunomodulatory action through several mechanisms. A combination of all these effects might be beneficial in various clinical cardiac disorders in which inflammation (eg, acute coronary syndrome) and excessive immune activation (eg, post-cardiac transplant allograft rejection) account for poor outcomes. No clinical trial evidence is yet available to support use of n-3 PUFAs as an immunomodulator after cardiac transplant, but studies in laboratory animals have shown encouraging results.[96,97] This area needs further research before experimental findings can be translated into clinical benefit.

## Adverse effects and drug interactions

n-3 PUFAs have been reported to reduce synthesis of the platelet agonist thromboxane A2[98] and might also affect platelet reactivity by other mechanisms.[99] This finding raises the possibility of a potential increase in the risk of bleeding when n-3 PUFAs are combined with other oral antiplatelet drugs or anticoagulants. However, clinical studies have reported that supplementation at doses less than 4 g per day, when coprescribed with antiplatelet and anticoagulant drugs, are not associated with increased risk of major or minor bleeding episodes.[100,101] Because many cardiovascular benefits of n-3 PUFAs are observed within this dose range, they can be safely used in this patient population. There is some concern about ingestion of mercury when fish are eaten, because some species (eg, sharks and swordfish) have a high mercury content in their muscles. However, commonly consumed oily fish such as most types of tuna, trout, sardines, mackerel, and salmon do not contain high levels of mercury. Purified fish oils used in pharmaceutical grade capsules have negligible amounts.

## Dietary intake versus therapeutic supplements

Dietary intake of fish is the most desirable way to increase marine n-3 PUFA intake, but 1 g per day of a n-3 PUFA (eicosapentaenoic acid and docosahexaenoic acid) supplement is equivalent to the fish oil present in about 55–85 g of fresh tuna, sardines, salmon, or trout, and 652 g of Atlantic cod fish[102]—high intakes that are difficult to achieve in most parts of the world. This finding was documented in a study by the EUROACTION study group.[103] In this study, despite the fact that the active interventional approaches more than doubled the number of patients consuming recommended levels of oily fish (8% *vs* 17%), increase of long-term changes in diet was poor despite household re-education. Additionally, the n-3 PUFA intakes needed to reduce triglyceride concentrations, coronary events (as shown in the JELIS trial), blood pressure, inflammation, and various other indications probably cannot be achieved by diet alone. Hence, an argument could be made for prescribing supplements in all patients for whom reliable increases in n-3 PUFA intake is indicated.

A new approach suggested by Harris and von Schacky[104] is to measure the content of eicosapentaenoic acid and docosahexaenoic acid in red blood cells, termed the omega-3 index, as an indicator of n-3 PUFA intake, and target dietary modification or supplementation to achieve optimum values of this index. An omega-3 index of 8% or higher has been reported to be associated with the greatest cardioprotection, whereas an index of 4% or less gives the least cardioprotection.[104] This approach, if validated in prospective clinical trials, would be a novel and potentially modifiable risk factor for death due to coronary artery disease.

## Guidelines and further recommendations

The joint American College of Cardiology and American Heart Assoication statement on n-3 PUFA use recommends an intake of at least two fish meals per week in patients with coronary artery disease, and supplemental therapy for 1 year with 1 g per day of n-3 PUFA ethyl esters for those who have had a myocardial infarction.[1] Recommendations for dietary intake in coronary artery disease are lent support by results of many observational studies, but in patients who have had a myocardial infarction, this evidence is derived solely from one study.[11] In this study, use of conventional medical therapy such as β blockers and rate of coronary revascularisation were low, both of which have been shown to reduce mortality after myocardial infarction. Whether n-3 PUFAs in this setting would confer additional survival benefits is unknown, and further large-scale investigations in this patient group are needed to justify continued use of these agents in this setting.

In patients with high triglyceride concentrations, present guidelines recommend n-3 PUFA supplementation at a dose approaching 4 g per day. Although clinical studies[105,106] have reported substantial reductions in concentrations of triglycerides with n-3 PUFA supplementation, no data for hard clinical endpoints are available to lend support to this recommendation—further investigation is needed for this area. Use of n-3 PUFA supplements in heart failure is supported by findings of the GISSI HF trial,[25] possibly making a case to incorporate this indication in the present guidelines. In other cardiovascular disorders, such as hypertension and atherosclerotic vascular disease, n-3 PUFA supplementation is restricted by a small effect size, but could be an attractive option as an adjunct to standard therapy.

## Conclusions

Marine n-3 PUFAs act as pleiotropic agents on the cardiovascular system with a diverse range of effects, most of which are beneficial. So far, the most important effect seems to be related to reduction in mortality after a myocardial infarction. Although findings from several studies have suggested a mechanistic possibility of an anti-arrhythmic effect, those from clinical studies have not convincingly supported this mode of action. The overall effect of n-3 PUFAs in patients with coronary ischaemia without previous myocardial infarction is not established, with a potential benefit in the reduction of ischaemic coronary events set against an ongoing controversy over a possible rise in the risk of arrhythmic events. The anti-inflammatory, anti-atherosclerotic, and anti-immunomodulatory effects have not yet been proven to translate into clinical benefits, and further focused studies are needed to explore these properties. Assessment of effectiveness of these agents in the setting of optimum conventional drug therapy and elucidation of the mechanisms of the perceived benefits also need to be established.

**Contributors**

All authors contributed to this work. PS did the literature search and drafted the initial report. NCD, EBS, and PCC provided intellectual input in refining the report to its final form.

**Conflicts of interest**

EBS has received research funding from Pronova Biocare—manufacturer of Omacor. PCC has received speaking fees from Solvay Healthcare (UK) and Solvay Pharmaceuticals (Germany), both suppliers of Omacor, and has previously received research funding from Pronova Biocare. As an employee of the University of Southampton, PCC was named as an inventor on patent application 0210212.7 ("Effects of dietary n-3 and n-6 PUFA intake on atheromatous plaque stability") filed in 2002 and licensed to Pronova Biocare in 2003. PS and NCD declare that they have no conflicts of interest.

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