

Cardiovascular effects of marine omega-3 fatty acids



Palaniappan Saravanan, Neil C Davidson, Erik B Schmidt, Philip C Calder

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 uncertainty 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 studies⁵⁻⁸ reported that high fish consumption was associated with a lowered mortality from coronary artery disease. These findings 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 study¹³ 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 study¹⁶ (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 study¹⁷

Published Online
July 16, 2010
DOI:10.1016/S0140-6736(10)60445-X

Cardiovascular Research Group, Manchester Academic Health Sciences Centre, University of Manchester, Manchester, UK (P Saravanan MD); University Hospital of South Manchester NHS Foundation Trust, Manchester, UK (P Saravanan, N C Davidson MD); Department of Cardiology, Centre for Cardiovascular Research, Aalborg Hospital, Aarhus University Hospital, Aalborg, Denmark (Prof E B Schmidt MD); and Institute of Human Nutrition, School of Medicine, University of Southampton, Southampton, UK (Prof P C Calder DPhil)

Correspondence to:
Dr Palaniappan Saravanan, Cardiovascular Research Group, 3rd floor, Core Technology Facility, 46 Grafton Street, University of Manchester, Manchester M13 9NT, UK
drplsuk@yahoo.co.uk

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 studies¹⁸ for patients who underwent percutaneous coronary revascularisation procedures with conventional balloon angioplasty showed

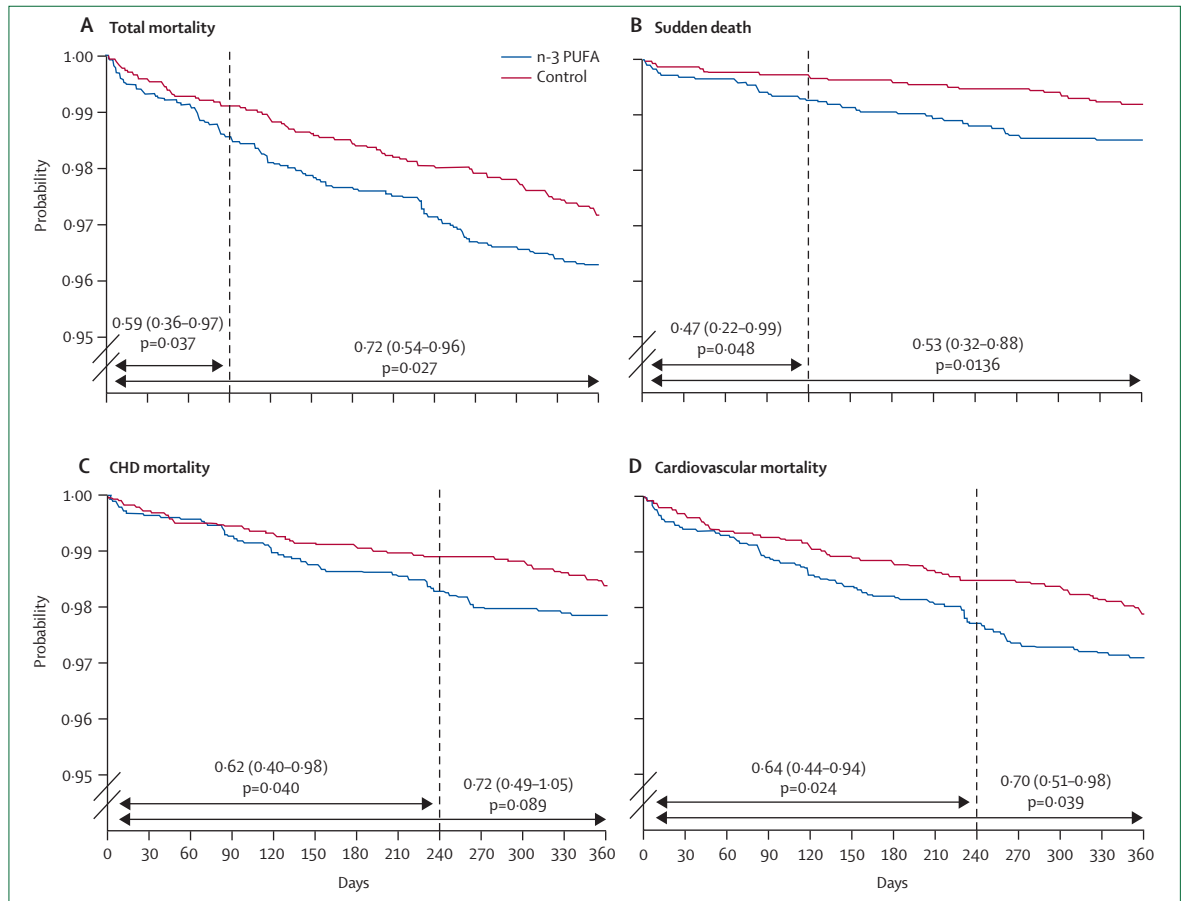


Figure 1: Early protection from mortality with n-3PUFA supplementation in GISSI-Prevenzione study¹²—a time course analysis
 Data are hazard ratio (95% CI). n-3 PUFA=omega-3 polyunsaturated fatty acid. CHD=coronary heart disease. Reproduced from reference 12 with permission of Wolters Kluwer Health.

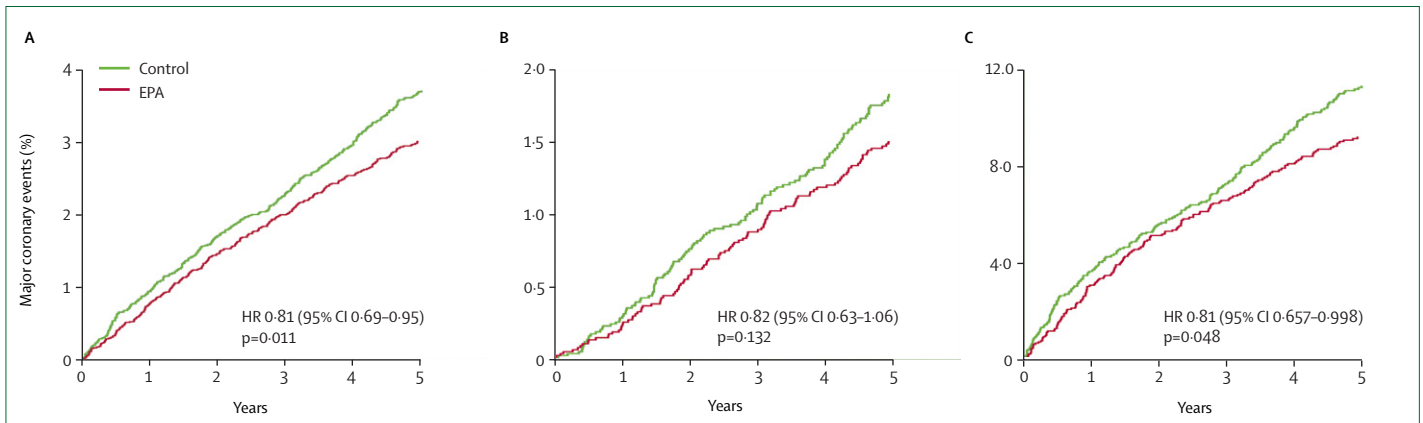


Figure 2: Kaplan-Meier estimates of incidence of coronary events in JELIS study¹⁶
 Total study population (A); primary prevention group (B); secondary prevention group (C). EPA=eicosapentaenoic acid. HR=hazard ratio. Reprinted from reference 16 with permission from Elsevier.

	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 ²¹	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 ¹⁶	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 ¹⁷	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 ¹⁸	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 studies¹⁹ 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 previously, because stent insertion is now used for almost every coronary angioplasty procedure. In the only study²⁰ 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 study¹² showing a significant reduction ($p=0\cdot048$) 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 study²⁹ 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 third³² 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-analysis³³ 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 study²⁴ 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 duration³⁵ 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 data³⁷ 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 study⁶³ 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=docosahexaenoic 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 study⁶⁷ 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 ⁶⁰	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 study⁶⁸ 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 study⁷⁰ 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 studies⁷² 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 Investigators⁷⁵ 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 Investigators²⁵ 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 trial⁷⁹ 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

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 review⁸² 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 A₂, 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 consumed⁸⁷ could help to explain at least

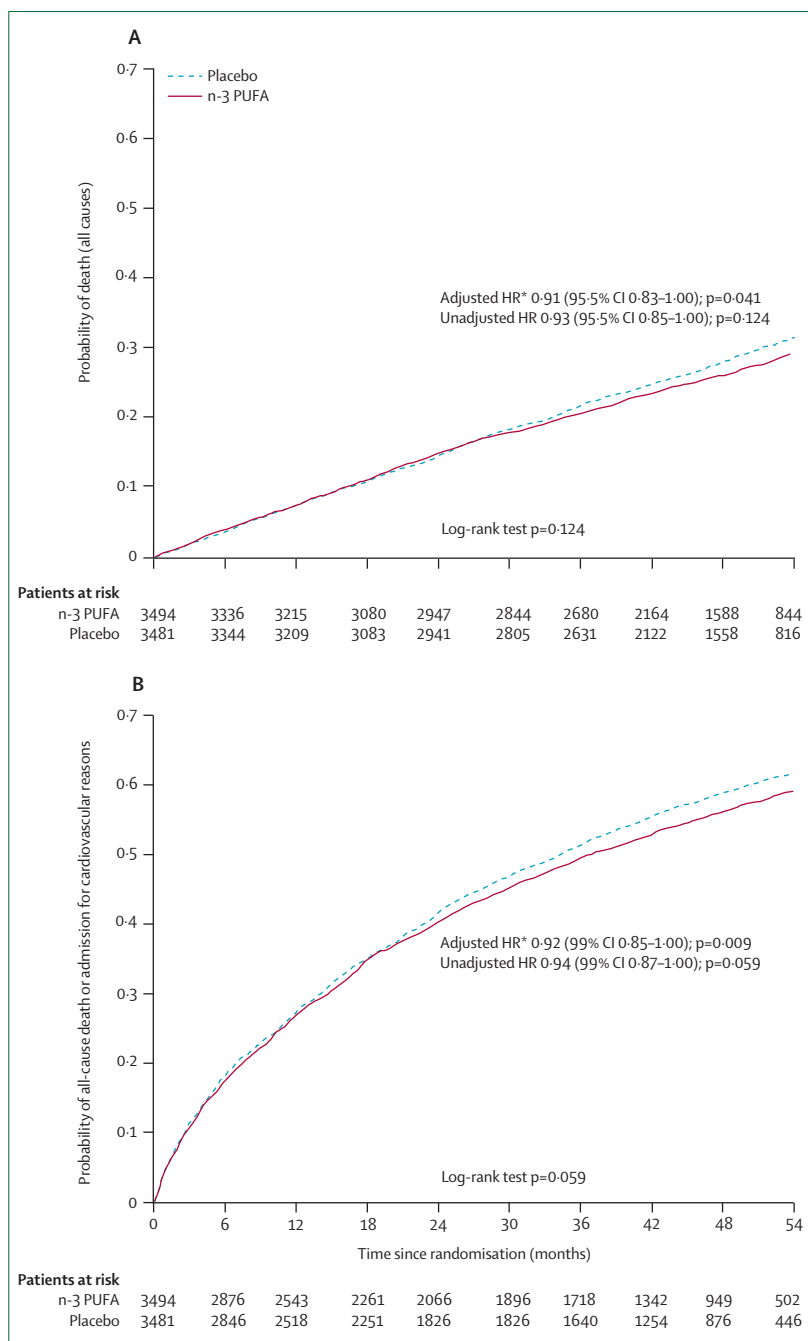


Figure 3: Kaplan-Meier curves for time to all-cause mortality (A) and all-cause mortality or admission to hospital for cardiovascular reasons (B) in GISSI-HF study²⁵

n-3 PUFA=omega-3 polyunsaturated fatty acid. HR=hazard ratio. Reprinted from reference 25 with permission from Elsevier.

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 reported⁹¹ 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 A₂⁹⁸ 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 fish¹⁰²—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 Schacky¹⁰⁴ 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 Association 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.

Acknowledgments

PS is supported by a fellowship from the British Heart Foundation, UK.

References

- Kris-Etherton PM, Harris WS, Appel LJ, for the Nutrition Committee. AHA scientific statement—fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation* 2002; **106**: 2747–57.
- NICE. Secondary prevention in primary and secondary care for patients following a myocardial infarction. NICE clinical guideline 48, 2007. London: National Institute for Health and Clinical Excellence, 2007.
- Bang HO, Dyerberg J. Lipid metabolism and ischemic heart disease in Greenland Eskimos. In: Draper H, ed. *Advances in Nutrition Research*. New York, NY: Plenum Press, 1980: 1–22.
- Kagawa Y, Nishizawa M, Suzuki M. Eicosapolyenoic acids of serum lipids of Japanese islanders with low incidence of cardiovascular diseases. *J Nutr Sci Vitaminol (Tokyo)* 1982; **28**: 441–53.
- Kromhout D, Bosschieter EB, de Lezenne Coulander C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. *N Engl J Med* 1985; **312**: 1205–09.
- Kromhout D, Feskens EJ, Bowles CH. The protective effect of a small amount of fish on coronary heart disease mortality in an elderly population. *Int J Epidemiol* 1995; **24**: 340–45.
- Dolecek TA, Granditis G. Dietary polyunsaturated fatty acids and mortality in the Multiple Risk Factor Intervention Trial (MRFIT). *World Rev Nutr Diet* 1991; **66**: 205–16.
- Albert CM, Hennekens CH, O'Donnell CJ, et al. Fish consumption and risk of sudden cardiac death. *JAMA* 1998; **279**: 23–28.
- Dyerberg J, Bang HO, Stoffersen E, Moncada S, Vane JR. Eicosapentaenoic acid and prevention of thrombosis and atherosclerosis? *Lancet* 1978; **2**: 117–19.
- Burr ML, Gilbert JF, Holliday RM, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet* 1989; **344**: 757–61.
- GISSI-Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico). Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet* 1999; **354**: 447–55.
- Marchioli R, Barzi F, Bomba E, et al, for the GISSI-Prevenzione Investigators. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. *Circulation* 2002; **105**: 1897–903.
- Svensson M, Schmidt EB, Jørgensen KA, Christensen JH; OPACH Study Group. N-3 fatty acids as secondary prevention against cardiovascular events in patients who undergo chronic hemodialysis: a randomized, placebo-controlled intervention trial. *Clin J Am Soc Nephrol* 2006; **1**: 780–86.
- Guallar E, Aro A, Jiménez FJ, et al. Omega-3 fatty acids in adipose tissue and risk of myocardial infarction: the EURAMIC study. *Arterioscler Thromb Vasc Biol* 1999; **19**: 1111–18.
- Kromhout D, Bloembergen BP, Feskens EJ, Hertog MG, Menotti A, Blackburn H. Alcohol, fish, fibre and antioxidant vitamins intake do not explain population differences in coronary heart disease mortality. *Int J Epidemiol* 1996; **25**: 753–59.
- Yokoyama M, Origasa H, Matsuzaki M, et al, for the Japan EPA lipid intervention study (JELIS) Investigators. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet* 2007; **369**: 1090–98.
- Bjerregaard LJ, Joensen AM, Dethlefsen C, et al. Fish intake and acute coronary syndrome. *Eur Heart J* 2010; **31**: 29–34.
- Gapinski JP, VanRuiswyk JV, Heudebert GR, Schectman GS. Preventing restenosis with fish oils following coronary angioplasty. A meta-analysis. *Arch Intern Med* 1993; **153**: 1595–601.
- Arnesen H. n-3 fatty acids and revascularization procedures. *Lipids* 2001; **36** (suppl): 103–06.
- Eritsland J, Arnesen H, Grønseth K, Fjeld NB, Abdelnoor M. Effect of dietary supplementation with n-3 fatty acids on coronary artery bypass graft patency. *Am J Cardiol* 1996; **77**: 31–36.
- Albert CM, Campos H, Stampfer MJ, et al. Blood levels of long-chain n-3 fatty acids and the risk of sudden death. *N Engl J Med* 2002; **346**: 1113–18.
- Lemaitre RN, King IB, Mozaffarian D, Kuller LH, Tracy RP, Siscovick DS. n-3 Polyunsaturated fatty acids, fatal ischemic heart disease, and nonfatal myocardial infarction in older adults: the Cardiovascular Health Study. *Am J Clin Nutr* 2003; **77**: 319–25.
- Streppel MT, Ocké MC, Boshuizen HC, Kok FJ, Kromhout D. Long-term fish consumption and n-3 fatty acid intake in relation to (sudden) coronary heart disease death: the Zutphen study. *Eur Heart J* 2008; **29**: 2024–30.
- Burr ML, Ashfield-Watt PA, Dunstan FD, et al. Lack of benefit of dietary advice to men with angina: results of a controlled trial. *Eur J Clin Nutr* 2003; **57**: 193–200.

- 25 GISSI-HF Investigators. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008; **372**: 1223–30.
- 26 Bucher HC, Hengstler P, Schindler C, Meier G. N-3 polyunsaturated fatty acids in coronary heart disease: a meta-analysis of randomized controlled trials. *Am J Med* 2002; **112**: 298–304.
- 27 León H, Shibata MC, Sivakumaran S, Dorgan M, Chatterley T, Tsuyuki RT. Effect of fish oil on arrhythmias and mortality: systematic review. *BMJ* 2008; **337**: 2931.
- 28 Zhao YT, Shao L, Teng LL, et al. Effects of n-3 polyunsaturated fatty acid therapy on plasma inflammatory markers and N-terminal pro-brain natriuretic peptide in elderly patients with chronic heart failure. *J Int Med Res* 2009; **37**: 1831–41.
- 29 Nodari S, Metra M, Milesi G, et al. The role of n-3 PUFAs in preventing the arrhythmic risk in patients with idiopathic dilated cardiomyopathy. *Cardiovasc Drugs Ther* 2009; **23**: 5–15.
- 30 Leaf A, Albert CM, Josephson M, et al, for the Fatty Acid Antiarrhythmia Trial Investigators. Prevention of fatal arrhythmias in high-risk subjects by fish oil n-3 fatty acid intake. *Circulation* 2005; **112**: 2762–68.
- 31 Brouwer IA, Zock PL, Camm AJ, et al, for the SOFA Study Group. Effect of fish oil on ventricular tachyarrhythmia and death in patients with implantable cardioverter defibrillators: the Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA) randomized trial. *JAMA* 2006; **295**: 2613–19.
- 32 Raitt MH, Connor WE, Morris C, et al. Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implantable defibrillators: a randomized controlled trial. *JAMA* 2005; **293**: 2884–91.
- 33 Brouwer IA, Raitt MH, Dullemeijer C, et al. Effect of fish oil on ventricular tachyarrhythmia in three studies in patients with implantable cardioverter defibrillators. *Eur Heart J* 2009; **30**: 820–26.
- 34 Coronel R, Wilms-Schopman FJ, Den Ruijter HM, et al. Dietary n-3 fatty acids promote arrhythmias during acute regional myocardial ischemia in isolated pig hearts. *Cardiovasc Res* 2007; **73**: 386–94.
- 35 Verkerk AO, van Ginneken ACG, Berecki G, et al. Incorporated sarcolemmal fish oil fatty acids shorten pig ventricular action potentials. *Cardiovasc Res* 2006; **70**: 509–20.
- 36 Dhein S, Michaelis B, Mohr FW. Antiarrhythmic and electrophysiological effects of long-chain omega-3 polyunsaturated fatty acids. *Naunyn-Schmiedeberg's Arch Pharmacol* 2005; **371**: 202–11.
- 37 Xiao YF, Kang JX, Morgan JP, Leaf A. Blocking effects of polyunsaturated fatty acids on Na⁺ channels in neonatal rat ventricular myocytes. *Proc Natl Acad Sci* 1995; **92**: 11000–04.
- 38 Xiao YF, Wright SN, Wang GK, Morgan JP, Leaf A. Fatty acids suppress voltage-gated Na⁺ currents in HEK293t cells transfected with the alpha subunit of the human cardiac sodium channel. *Proc Natl Acad Sci* 1998; **95**: 2680–85.
- 39 Leifert WR, McMurchie EJ, Saint DA. Inhibition of cardiac sodium currents in adult rat myocytes by n-3 polyunsaturated fatty acids. *J Physiol* 1999; **520**: 671–79.
- 40 Den Ruijter HM, Berecki G, Opthof T, Verkerk AO, Zock PL, Coronel R. Pro- and antiarrhythmic properties of a diet rich in fish oil. *Cardiovasc Res* 2007; **73**: 316–25.
- 41 London B, Albert C, Anderson ME, et al. Omega-3 fatty acids and cardiac arrhythmias: prior studies and recommendations for future research: a report from the National Heart, Lung, and Blood Institute and Office Of Dietary Supplements Omega-3 Fatty Acids and their Role in Cardiac Arrhythmogenesis Workshop. *Circulation* 2007; **116**: e320–35.
- 42 McLennan PL, Abeywardena MY, Charnock JS. Dietary fish oil prevents ventricular fibrillation following coronary artery occlusion and reperfusion. *Am Heart J* 1988; **116**: 709–17.
- 43 McLennan PL. Relative effects of dietary saturated, monounsaturated, and polyunsaturated fatty acids on cardiac arrhythmias in rats. *Am J Clin Nutr* 1993; **57**: 207–12.
- 44 McLennan PL, Bridle TM, Abeywardena MY, Charnock JS. Comparative efficacy of n-3 and n-6 polyunsaturated fatty acids in modulating ventricular fibrillation threshold in marmoset monkeys. *Am J Clin Nutr* 1993; **58**: 666–69.
- 45 Billman GE, Kang JX, Leaf A. Prevention of sudden cardiac death by dietary pure omega-3 polyunsaturated fatty acids in dogs. *Circulation* 1999; **99**: 2452–57.
- 46 Macleod JC, Macknight AD, Rodrigo GC. The electrical and mechanical response of adult guinea pig and rat ventricular myocytes to omega3 polyunsaturated fatty acids. *Eur J Pharmacol* 1998; **356**: 261–70.
- 47 Leifert WR, Jahangiri A, Saint DA, McMurchie EJ. Effects of dietary n-3 fatty acids on contractility, Na⁺ and K⁺ currents in a rat cardiomyocyte model of arrhythmia. *J Nutr Biochem* 2000; **11**: 382–92.
- 48 Ferrier GR, Redondo I, Zhu J, Murphy MG. Differential effects of docosahexaenoic acid on contractions and L-type Ca²⁺ current in adult cardiac myocytes. *Cardiovasc Res* 2002; **54**: 601–10.
- 49 Bogdanov KY, Spurgeon HA, Vinogradova TM, Lakatta EG. Modulation of the transient outward current in adult rat ventricular myocytes by polyunsaturated fatty acids. *Am J Physiol* 1998; **274**: H571–79.
- 50 Xiao YF, Ke Q, Chen Y, Morgan JP, Leaf A. Inhibitory effect of n-3 fish oil fatty acids on cardiac Na⁺/Ca²⁺ exchange currents in HEK293t cells. *Biochem Biophys Res Commun* 2004; **321**: 116–23.
- 51 Swan JS, Dibb K, Negretti N, O'Neill SC, Sitsapesan R. Effects of eicosapentaenoic acid on cardiac SR Ca(2+)-release and ryanodine receptor function. *Cardiovasc Res* 2003; **60**: 337–46.
- 52 Berecki G, Den Ruijter HM, Verkerk AO, et al. Dietary fish oil reduces the incidence of triggered arrhythmias in pig ventricular myocytes. *Heart Rhythm* 2000; **4**: 1452–60.
- 53 Dujardin KS, Dumotier B, David M, Guizy M, Valenzuela C, Hondeghem LM. Ultrafast sodium channel block by dietary fish oil prevents dofetilide-induced ventricular arrhythmias in rabbit hearts. *Am J Physiol Heart Circ Physiol* 2008; **295**: H1414–21.
- 54 Xiao YF, Sigg DC, Ujhelyi MR, Wilhelm JJ, Richardson ES, Iuzzo PA. Pericardial delivery of omega-3 fatty acid: a novel approach to reducing myocardial infarct sizes and arrhythmias. *Am J Physiol Heart Circ Physiol* 2008; **294**: H2212–18.
- 55 Den Ruijter HM, Berecki G, Verkerk AO, et al. Acute administration of fish oil inhibits triggered activity in isolated myocytes from rabbits and patients with heart failure. *Circulation* 2008; **117**: 536–44.
- 56 Leifert WR, Jahangiri A, McMurchie EJ. Membrane fluidity changes are associated with the antiarrhythmic effects of docosahexaenoic acid in adult rat cardiomyocytes. *J Nutr Biochem* 2000; **11**: 38–44.
- 57 Mozaffarian D, Stein PK, Prineas RJ, Siscovick DS. Dietary fish and omega-3 fatty acid consumption and heart rate variability in US adults. *Circulation* 2008; **117**: 1130–37.
- 58 Christensen JH, Gustenhoff P, Korup E, et al. Effect of fish oil on heart rate variability in survivors of myocardial infarction: a double blind randomized controlled trial. *BMJ* 1996; **31**: 677–78.
- 59 O'Keefe JH Jr, Abuissa H, Sastre A, Steinhaus DM, Harris WS. Effects of omega-3 fatty acids on resting heart rate, heart rate recovery after exercise and heart rate variability in men with healed myocardial infarctions and depressed ejection fractions. *Am J Cardiol* 2006; **97**: 1127–30.
- 60 Mozaffarian D, Geelen A, Brouwer IA, Geleijnse JM, Zock PL, Katan MB. Effect of fish oil on heart rate in humans: a meta-analysis of randomized controlled trials. *Circulation* 2005; **112**: 1945–52.
- 61 Verkerk AO, den Ruijter HM, Bourrier J, et al. Dietary fish oil reduces pacemaker current and heart rate in rabbit. *Heart Rhythm* 2009; **6**: 1485–92.
- 62 Abdukeyum GG, Owen AJ, McLennan PL. Dietary (n-3) long-chain polyunsaturated fatty acids inhibit ischemia and reperfusion arrhythmias and infarction in rat heart not enhanced by ischemic preconditioning. *J Nutr* 2008; **138**: 1902–09.
- 63 Senges S, for the OMEGA Study group. Randomised trial of omega-3 fatty acids on top of modern therapy after acute myocardial infarction: the OMEGA trial. Oral presentation at the Annual Scientific Sessions of the American College of Cardiology; Orlando, FL, March 2009.
- 64 Brouwer IA, Heeringa J, Geleijnse JM, Zock PL, Witteman JC. Intake of very long-chain n-3 fatty acids from fish and incidence of atrial fibrillation. The Rotterdam Study. *Am Heart J* 2006; **151**: 857–62.
- 65 Frost L, Vestergaard P. n-3 Fatty acids consumed from fish and risk of atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study. *Am J Clin Nutr* 2005; **81**: 50–54.
- 66 Mozaffarian D, Psaty BM, Rimm EB, et al. Fish intake and risk of incident atrial fibrillation. *Circulation* 2004; **110**: 368–73.
- 67 Virtanen JK, Mursu J, Voutilainen S, Tuomainen TP. Serum long-chain n-3 polyunsaturated fatty acids and risk of hospital diagnosis of atrial fibrillation in men. *Circulation* 2009; **120**: 2315–21.

- 68 Calò L, Bianconi L, Colivicchi F, et al. N-3 Fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a randomized, controlled trial. *J Am Coll Cardiol* 2005; **45**: 1723–28.
- 69 Heidt MC, Vician M, Stracke SK, et al. Beneficial effects of intravenously administered N-3 fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a prospective randomized study. *Thorac Cardiovasc Surg* 2009; **57**: 276–80.
- 70 Saravanan P, Bridgewater B, West AL, O'Neill SC, Calder PC, Davidson NC. Omega-3 fatty acid supplementation does not reduce risk of atrial fibrillation after coronary artery bypass surgery: a randomized, double-blind, placebo-controlled clinical trial. *Circ Arrhythm Electrophysiol* 2010; **3**: 46–53.
- 71 Sakabe M, Shiroshita-Takeshita A, Maguy A, et al. Omega-3 polyunsaturated fatty acids prevent atrial fibrillation associated with heart failure but not atrial tachycardia remodeling. *Circulation* 2007; **116**: 2101–09.
- 72 Mozaffarian D, Bryson CL, Lemaitre RN, Burke GL, Siscovick DS. Fish intake and risk of incident heart failure. *J Am Coll Cardiol* 2005; **45**: 2015–21.
- 73 Yamagishi K, Iso H, Date C, et al, for the Japan Collaborative Cohort Study for Evaluation of Cancer Risk Study Group. Fish, omega-3 polyunsaturated fatty acids, and mortality from cardiovascular diseases in a nationwide community-based cohort of Japanese men and women the JACC (Japan Collaborative Cohort Study for Evaluation of Cancer Risk) Study. *J Am Coll Cardiol* 2008; **52**: 988–96.
- 74 Yamagishi K, Nettleton JA, Folsom AR; ARIC Study Investigators. Plasma fatty acid composition and incident heart failure in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J* 2008; **156**: 965–74.
- 75 Macchia A, Levantesi G, Franzosi MG, et al; GISSI-Prevenzione Investigators. Left ventricular systolic dysfunction, total mortality, and sudden death in patients with myocardial infarction treated with n-3 polyunsaturated fatty acids. *Eur J Heart Fail* 2005; **7**: 904–09.
- 76 Sekikawa A, Ueshima H, Kadowaki T, et al. Less subclinical atherosclerosis in Japanese men in Japan than in White men in the United States in the post-World War II birth cohort. *Am J Epidemiol* 2007; **165**: 617–24.
- 77 Sekikawa A, Curb JD, Ueshima H, et al. Marine-derived n-3 fatty acids and atherosclerosis in Japanese, Japanese-American, and white men: a cross-sectional study. *J Am Coll Cardiol* 2008; **52**: 417–424.
- 78 Iso H, Kobayashi M, Ishihara J, et al, for the JPHC Study Group. Intake of fish and n3 fatty acids and risk of coronary heart disease among Japanese: the Japan Public Health Center-Based (JPHC) Study Cohort I. *Circulation* 2006; **113**: 195–202.
- 79 Thies F, Garry JM, Yaqoob P, et al. Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomised controlled trial. *Lancet* 2003; **361**: 477–85.
- 80 Plutzky J. Atherosclerotic plaque rupture: emerging insights and opportunities. *Am J Cardiol* 1999; **84**: 15–20.
- 81 Harris WS, Miller M, Tighe AP, Davidson MH, Schaefer EJ. Omega-3 fatty acids and coronary heart disease risk: clinical and mechanistic perspectives. *Atherosclerosis* 2008; **197**: 12–24.
- 82 Hartweg J, Perera R, Montori V, Dinneen S, Neil HA, Farmer A. Omega-3 polyunsaturated fatty acids (PUFA) for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2008; CD003205.
- 83 De Caterina R, Madonna R, Bertolotto A, Schmidt EB. n-3 fatty acids in the treatment of diabetic patients: biological rationale and clinical data. *Diabetes Care* 2007; **30**: 1012–26.
- 84 Oikawa S, Yokoyama M, Origasa H, et al, for the JELIS Investigators, Japan. Suppressive effect of EPA on the incidence of coronary events in hypercholesterolemia with impaired glucose metabolism: Sub-analysis of the Japan EPA Lipid Intervention Study (JELIS). *Atherosclerosis* 2008; **200**: 135–40.
- 85 A Study of Cardiovascular Events in Diabetes (ASCEND)—A Randomized 2x2 Factorial Study of Aspirin Versus Placebo, and of Omega-3 Fatty Acid Supplementation Versus Placebo, for Primary Prevention of Cardiovascular Events in People With Diabetes (Clinicaltrials.gov identifier NCT00135226).
- 86 Origin Trial Investigators, Gerstein H, Yusuf S, Riddle MC, Ryden L, Bosch J. Rationale, design, and baseline characteristics for a large international trial of cardiovascular disease prevention in people with dysglycemia: the ORIGIN Trial (Outcome Reduction with an Initial Glargine Intervention). *Am Heart J* 2008; **155**: 26–32.
- 87 Morris MC, Sacks F, Rosner B. Does fish oil lower blood pressure? A meta-analysis of controlled trials. *Circulation* 1993; **88**: 523–33.
- 88 Geleijnse JM, Giltay EJ, Grobbee DE, Donders AR, Kok FJ. Blood pressure response to fish oil supplementation: meta-regression analysis of randomized trials. *J Hypertens* 2002; **20**: 1493–99.
- 89 Mori TA, Woodman RJ. The independent effects of eicosapentaenoic acid and docosahexaenoic acid on cardiovascular risk factors in humans. *Curr Opin Clin Nutr Metab Care* 2006; **9**: 95–104.
- 90 Rees D, Miles EA, Banerjee T. Dose-related effects of eicosapentaenoic acid on innate immune function in healthy humans: a comparison of young and older men. *Am J Clin Nutr* 2006; **83**: 331–42.
- 91 Calder PC. Polyunsaturated fatty acids and inflammatory processes: new twists in an old tale. *Biochimie* 2009; **91**: 791–95.
- 92 Serhan CN, Clish CB, Brannon J, Colgan SP, Gronert K, Chiang N. Anti-microinflammatory lipid signals generated from dietary N-3 fatty acids via cyclooxygenase-2 and transcellular processing: a novel mechanism for NSAID and N-3 PUFA therapeutic actions. *J Physiol Pharmacol* 2000; **51**: 643–54.
- 93 Serhan CN, Clish CB, Brannon J, Colgan SP, Chiang N, Gronert K. Novel functional sets of lipid-derived mediators with antiinflammatory actions generated from omega-3 fatty acids via cyclooxygenase 2-nonsteroidal anti-inflammatory drugs and transcellular processing. *J Exp Med* 2000; **192**: 1197–204.
- 94 Serhan CN, Chiang N, Van Dyke TE. Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. *Nat Rev Immunol* 2008; **8**: 349–61.
- 95 Mukherjee PK, Marcheselli VL, Serhan CN, Bazan NG. Neuroprotectin D1: a docosahexaenoic acid-derived docosatriene protects human retinal pigment epithelial cells from oxidative stress. *Proc Natl Acad Sci USA* 2004; **101**: 8491–96.
- 96 Yin R, Huang H, Zhang J, Zhu J, Jing H, Li Z. Dietary n-3 fatty acids attenuate cardiac allograft vasculopathy via activating peroxisome proliferator-activated receptor-gamma. *Pediatr Transplant* 2008; **12**: 550–56.
- 97 Alexander JW, Valente JF, Greenberg NA, et al. Dietary omega-3 and omega-9 fatty acids uniquely enhance allograft survival in cyclosporine-treated and donor-specific transfusion-treated rats. *Transplantation* 1998; **65**: 1304–09.
- 98 Knapp HR, Reilly IA, Alessandrini P, Fitzgerald GA. In vivo indexes of platelet and vascular function during fish-oil administration in patients with atherosclerosis. *N Engl J Med* 1986; **314**: 937–42.
- 99 Kristensen SD, Iversen AM, Schmidt EB. n-3 polyunsaturated fatty acids and coronary thrombosis. *Lipids* 2001; **36** (suppl): 79–82.
- 100 Eritsland J, Arnesen H, Seljeflot I, Kierulf P. Long-term effects of n-3 polyunsaturated fatty acids on haemostatic variables and bleeding episodes in patients with coronary artery disease. *Blood Coagul Fibrinolysis* 1995; **6**: 17–22.
- 101 Watson PD, Joy PS, Nkonde C, Hessen SE, Karalis DG. Comparison of bleeding complications with omega-3 fatty acids + aspirin + clopidogrel—versus— aspirin + clopidogrel in patients with cardiovascular disease. *Am J Cardiol* 2009; **104**: 1052–54.
- 102 Harris WS. Fish oil supplementation: evidence for health benefits. *Cleve Clin J Med* 2004; **71**: 208–10.
- 103 Wood DA, Kotseva K, Connolly S, et al, on behalf of the EUROACTION Study Group. Nurse-coordinated multidisciplinary, family-based cardiovascular disease prevention programme (EUROACTION) for patients with coronary heart disease and asymptomatic individuals at high risk of cardiovascular disease: a paired, cluster-randomised controlled trial. *Lancet* 2008; **371**: 1999–2012.
- 104 Harris WS, Von Schacky C. The Omega-3 Index: a new risk factor for death from coronary heart disease? *Prev Med* 2004; **39**: 212–20.
- 105 Balk EM, Lichtenstein AH, Chung M, Kupelnick B, Chew P, Lau J. Effects of omega-3 fatty acids on serum markers of cardiovascular disease risk: a systematic review. *Atherosclerosis* 2006; **189**: 19–30.
- 106 McKenney JM, Sica D. Role of prescription omega-3 fatty acids in the treatment of hypertriglyceridemia. *Pharmacotherapy* 2007; **27**: 715–28.