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The cardiovascular implications of omega-3 fatty acids

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Abstract

Nutrition is an important factor in the primary and secondary prevention of cardiovascular disease. Cardiovascular disease is the leading cause of death in North America and the world. Observational studies have generally favoured a beneficial role of n-3 fatty acids in the prevention of heart disease, especially in the prevention of sudden cardiac death. The results of more recent randomised controlled studies, however, have made conclusions regarding the benefit more controversial, with the suggestion of possible harm with fish oil supplementation to those with diagnosed cardiovascular disease.

We provide an overview of the results of studies to date and introduce the controversial topics of the omega-6/omega-3 ratio, the public's concerns regarding ingestion of mercury from marine n-3 sources and the potential role of highly bioactive n-3 metabolites in the process of atherosclerosis. We also provide some general guidelines for the ingestion of n-3 fatty acids that may help clinicians and patients make informed decisions. (Folia Cardiol. 2006; 13: 557–569)

Key words: omega-3 fatty acids, omega-6 fatty acids, n-6/n-3 ratio, omacor, omega-3 index

Introduction

Omega-3 fatty acids (n-3s) are essential components of human nutrition as they cannot be internally synthesised in amounts sufficient for health [1]. Omega-3 fatty acids are a group of polyunsaturated fats in the human diet with the first double bond at the 3rd carbon–carbon bond from the terminal methyl end (ω) of the carbon chain, from which is derived their nomenclature designation as "n-3" fatty acids. These fatty acids concentrate in high amounts in metabolically active tissues, including the myocardium, brain, retina, and testes. Alpha-linolenic acid (ALA) is found in plant sources, whereas the important long chain omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are found in the tissues of marine animals. Alpha-linolenic acid [ALA (18 3n-3)] is the omega-3 fatty acid ingested in the greatest amount in a typical diet, given its prevalence in commonly consumed plant oils, including canola (rapeseed) and flax seed. ALA has demonstrated conversion into eicosapentaenoic acid [EPA (20 5n-3)] and docosahexaenoic acid [DHA (22 6n-3)], although evidence suggests that this pathway may not produce amounts adequate for attaining optimal health [1]. The fish-derived n-3 fatty acids are of greatest interest as they have been correlated with cardiovascular disease more consistently than has ALA.

Cardiovascular disease is the leading cause of death among adults in the United States, with an estimated 910,000 individuals dying from this

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disease in 2003 [2]. Heart disease is predicted to grow in importance with respect to public health as medical advances allow individuals to live much longer than they did just 30 years ago. Attempts to reduce the public health burden of heart disease have enlisted numerous methods, including lifestyle modifications, medications and a variety of expensive technologies. Nutritional modifications that alter the risk of cardiovascular disease have been a major focus of intervention efforts, as reflected in numerous studies and expert consensus panel recommendations. Saturated fat and cholesterol have been of particular interest owing to their wide prevalence in modern western diets and well documented roles in the process of atherosclerosis. Omega-3 fatty acids, particularly those derived from marine sources, have also been of great interest because of their unique biochemical and physiological properties. Although many of the benefits of omega-3 fatty acids for cardiovascular health remain controversial, new information about how they affect arterial endothelial function, haemodynamics (cardiac mechanics) and cardiac myocyte function (including anti-arrhythmic effects), have improved our understanding of their possible mechanisms of action. The omega-6 (n-6) class of fatty acids, on the other hand, compose a counteracting branch in the fatty acid pathway that compete with the n-3 anti-inflammatory compounds in the enzymatic pathway necessary to create biologically active molecules [3]. It has been suggested that a lower ratio of dietary n-6 to n-3 fatty acids promotes health and that this ratio in the human diet has significantly increased over the millennia [3, 4]. Controversies have arisen regarding the relative benefits of omega-6 *vs.* omega-3 fatty acids (the omega-6/omega-3 ratio) as well as the safety of fish and fish oil supplement consumption. At the same time, metabolites of omega-3 fatty acids are now being considered as possible anti-inflammatory mediators in the process of protecting against atherosclerosis.

Possible mechanisms of action

Effects on lipid metabolism

N-3 fatty acids can reduce fasting and postprandial triglyceride concentrations by 20–35% by accelerating chylomicron triglyceride clearance and suppressing hepatic very low-density lipoprotein (VLDL)-triglyceride production [5]. Evidence suggests that they also modulate the susceptibility of VLDL to lipolysis [6, 7]. Concerns have been expressed regarding the fact that omega-3 fatty acids tend to raise low-density lipoprotein (LDL) and may predispose to lipid oxidation. These concerns, however, appear to be outweighed by evidence in support of a cardioprotective effect of n-3 fatty acids [5, 8, 9]. Current evidence reveals that omega-3 fatty acids tend to raise high-density lipoprotein (HDL) slightly in most individuals, but n-3 effects on HDL are not felt to play a significant role in cardiovascular risk reduction [10].

Anti-inflammatory effects

The anti-inflammatory effects of omega-3 fatty acids on the cardiovascular system are controversial [11]. Data from the Diet and N-3 Intervention Trial (DOIT) revealed that a three-year diet and/or n-3 supplementation period in elderly males (mean age 70 years) with hyperlipidaemia did not consistently improve several markers of endothelial activation including soluble vascular adhesion molecule and von Willebrand's factor [12]. Fish intake has also not correlated well with C-reactive protein, intercellular adhesion molecules and interleukin-6 [13]. Other studies have added to the controversy by either revealing a direct effect [14] or no effect on inflammatory markers [15]. The specific effects of inflammation on the risk of ventricular tachycardia/ventricular fibrillation and sudden cardiac death are unclear.

Inhibition of thrombosis

Inhibition of thrombosis is a mechanism by which n-3 fatty acids appear to exert a protective effect within the cardiovascular system. EPA inhibits the formation of the prothrombotic eicosanoid thromboxane A_2 by competing with arachidonic acid for the cyclo-oxygenase enzyme [16]. N-3 fatty acids also inhibit platelet adhesion, platelet aggregation, and the formation of thromboxane B_2, another prothrombotic cytokine. In the Thrombogenic Factors and Recurrent Coronary Events (THROMBO) study [17], of six haemostatic factors, 7 lipid measures, and insulin, D-dimer, apoA and apoB were identified as independently predicting recurrent ischaemic events. Although omega-3 fatty acid supplementation has been associated with lower D-dimer levels in subjects without heart disease [18], no consistent relationship has been demonstrated for n-3 effects on these two other prothrombotic variables.

Attenuation of tissue hypertrophy and fibrosis

N-3 fatty acids appear to attenuate tissue hypertrophy and fibrosis within the cardiovascular system. They have, for example, been demonstrated

to inhibit the adverse effects of angiotensin II on vascular smooth muscle [19]. If similar metabolic effects occur in myocardial tissue, the hypertrophic effects of angiotensin II may be inhibited [20]. The benefits of inhibiting angiotensin II has been demonstrated through the ability of ACE inhibitors to inhibit fibrotic hypertrophy and improve survival in affected individuals [21–25].

Anti-arrhythmic effects

Since the mid-1970s an anti-arrhythmic effect of n-3 fatty acids has been investigated, with evidence that ALA increased the arrhythmia threshold [26, 27]. A variety of animal model studies have revealed a reduction in arrhythmic events, including important investigations conducted by Billman et al. [28]. In these studies, exercise-induced ventricular fibrillation in an ischaemic heart disease dog model was prevented in animals infused with an emulsion of n-3 fatty acids. A variety of *in vitro* and animal experiments have revealed that omega-3 fatty acids may exert anti-arrhythmic effects by directly modulating potassium, sodium, and calcium channels [29]. These fatty acids also incorporate into the phospholipids of cell membranes, modulating the excitation-coupling that can result in arrhythmia [30] and can affect the intracellular enzymes which control the contraction and relaxation cycles of myocytes [31]. N-3 fatty acids also tend to inhibit ventricular arrhythmias by blocking the effects of catecholamines on the myocardium, similar to beta-blockade [32]. They apparently accomplish this by affecting the adrenoceptors, which are membrane proteins that allow the neuroendocrine messages of catecholamines to transmit to the myocardium.

Modulating arterial compliance, heart rate variability, and ventricular function

N-3 fatty acids have been shown to improve arterial compliance in response to physiological stressors [33]. Omega-3 fatty acids have also been demonstrated to improve baseline arterial compliance [34]. Heart rate variability (HRV) is an accepted measure of cardiovascular health as normal HRV reflects increased parasympathetic tone [35]. Optimal HRV can subsequently increase the ventricular fibrillation threshold and thus protect the myocardium from ventricular arrhythmias. Notable is the fact that beta-blockers and angiotensin-converting enzyme inhibitors, which improve long term survival in those with heart failure, also improve heart rate variability [36]. At least two studies, one involving a post-myocardial infarction cohort, have revealed improved heart rate variability in subjects exposed to supplemental sources of n-3 fatty acids, with one also demonstrating improved ventricular compliance [37, 38]. A higher dietary fish intake has also been independently associated with lower heart rates, reduced systemic vascular resistance, left ventricular mass and greater stroke volume [39].

Primary prevention

Investigations of the role of omega-3 fatty acids in primary prevention studies have been limited to epidemiological and observational studies (Table 1). Three early prospective observational studies reported that men consuming at least some fish every week had a lower mortality rate from coronary artery disease (CHD) than those men who ate no fish weekly [40]. More recently, the Chicago Western Electric Study found that men who

Table 1. Major primary prevention/observational studies.

Study	Year	Subjects	Results (with higher fish intake)
Health Professionals Follow-Up	1995	44,895 men	No reduction in fatal CHD, non-fatal MI, SCD, CABG, PTCA
Seven Countries	1996	12,763 men	No reduction in CHD death
Western Electric	1997	1,822 men	Reduced total CHD and non-sudden CHD death
US Physicians' Health	1998	20,551 men	Reduced total mortality and SCD. No reduction in non-sudden CHD death, CHD mortality or total MI
Nurses' Health	2002	84,688 women	Reduced risk of CHD and CHD mortality. No reduction in non-fatal MI
EUROASPIRE	2003	415 (285 men, 130 women)	Reduced total and CHD mortality

CHD — coronary heart disease, MI — myocardial infarction, SCD — sudden cardiac death, CABG — coronary artery bypass grafting, PTCA — percutaneous transluminal coronary angioplasty

consumed 35 g of fish or more daily had a relative risk of CHD death of 0.62 and a relative risk of non-sudden death from myocardial infarction (MI) of 0.33 compared with men who consumed no fish [41]. An ecological study including data from 36 countries found that fish consumption was associated with a reduced risk of ischaemic heart disease, stroke and all-cause mortality [42]. A recent analysis focusing on women's health within the Nurses' Health Study documented an inverse correlation between fish intake and omega-3 fatty acids and CHD death [43]. In that study, women consuming fish from once to three times per month, once per week, from two to four times per week and > five times per week had a risk for CHD death that was 21%, 29%, 31%, and 34% lower respectively than women who ate fish less than once per month.

Other observational studies have not demonstrated reduced CHD mortality associated with fish consumption. In the US Physicians' Health Study, no significant association was observed between fish intake (or omega-3 intake consumption) and a reduced risk of non-sudden cardiac death, total cardiovascular mortality or total MI [44]. In this study fish consumption was associated with total mortality, however. Similarly, in the Health Professionals' Follow-up Study, risk of any CHD (non-fatal MI, coronary artery bypass grafting, angioplasty or fatal coronary disease, including sudden cardiac death) was not associated with fish consumption (and omega-3 fatty acids) [45]. In the Seven Countries Study, despite the presence of an inverse relationship between fish consumption and 25-year mortality from CHD across several populations, this association was not significant when the relationship was adjusted for the effects of flavonoids, smoking and saturated fat [46].

Biomarkers of fatty acid intake, including adipose tissue and plasma levels, have inconsistently been associated with the risk of coronary heart events. Several case-control and cohort studies have demonstrated that high levels of n-3 fatty acids are associated with a reduced risk of acute MI [47–50], primary cardiac arrest [51] and sudden cardiac death [52]. No association between biomarkers of n-3 polyunsaturated fatty acids (PUFA) and acute coronary syndromes has been found in other studies, however [53–56].

A variety of explanations for the conflicting observational data have been proposed [1]. These include variability in the end points studied, study populations, how fish intake was estimated or the experimental design, confounding of reference groups who had an unhealthy lifestyle, and differences in sudden cardiac death definitions. Only studies that included a large population of non-fish-eating individuals have reported an inverse correlation of fish consumption with coronary disease mortality. Other explanations considered are that only eating fatty fish can provide the levels of omega-3 fatty acids required to provide protection and that only those populations at high risk benefit from a reduction in CHD mortality.

The evidence of benefit in reducing risk of sudden cardiac death is more consistent. A report from the US Physicians' Health Study found that the relative risk of sudden death in men without a history of cardiovascular disease (CVD) was significantly reduced in men with omega-3 blood levels in the third quartile (RR = 0.28) and fourth quartile (RR = 0.19) when compared to men with blood levels in the lowest quartile [52]. A prior analysis within the same cohort demonstrated that men consuming fish at least once each week had a relative risk of sudden death of 0.48 ($p = 0.04$) compared to men consuming fish less than once each month [44]. Finally, in another nested, case-control population-based study fish consumption equivalent to two fatty fish meals each week was associated with a 50% reduction in risk for primary cardiac arrest [51].

Secondary prevention

The majority of investigations of the role of n-3 fatty acids in secondary prevention of heart disease have been randomised controlled trials (Table 2). In the Diet and Reinfarction Trial (DART), men after an MI were randomised to increased dietary intake of fish (200–400 g of fatty fish per week, correlating with 500–800 mg/d of omega-3 fatty acids) and showed a 29% reduced incidence of all-cause mortality [4]. The benefits were largest in the prevention of fatal MIs, leading to a hypothesis that n-3 fatty acids protect the myocardium from the adverse consequences of ischaemic stress. In the Lyon Heart Study post-MI individuals advised to eat a diet high in alpha-linolenic acid had a greatly reduced incidence of cardiovascular mortality, total mortality, recurrent MI, stroke, unstable angina and heart failure [57]. The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocarico (GISSI)-Prevention Study was the largest trial testing the efficacy of omega-3 fatty acids for secondary prevention [58]. This study of individuals with a recent MI (< 3 months) demonstrated that 850 mg/d of omega-3 supplementation reduced all-cause mortality after a MI, with a 15% reduction in the primary end

Table 2. Major secondary prevention/intervention studies.

Study	Year	Subjects	Intervention	Outcome (with higher n-3 intake)
DART	1989	2033 men	Dietary fish	Reduced total mortality and fatal MI
Lyon Heart Study	1994	605 men and women	High-ALA Mediterranean diet	Reduced CHD, total mortality, recurrent MI, stroke, unstable angina and CHF
GISSI	1999	11,323 men and women	n-3 supplement	Reduced total mortality, combined end point of non-fatal MI, non-fatal stroke and death
Nilsen et al.	2001	300	n-3 supplement	No reduction in MI, SCD or non-SCD, unstable angina
DART-2	2003	3114 men	Dietary fish or n-3 supplement	Increased risk of SCD
Raitt et al.	2005	200 men and women	n-3 supplement	No significant change in ventricular arrhythmias
FAAT	2005	402 men and women	n-3 supplement	Marginal reduction in ventricular arrhythmias or total death
SOFA	2006	546 men and women	n-3 supplement	No change in ventricular arrhythmias or total mortality

MI — myocardial infarction, CHD — coronary heart disease, CHF — coronary heart failure, SCD — sudden cardiac death

point of non-fatal MI, non-fatal stroke and death ($p < 0.001$). A 20% reduction in all-cause mortality ($p = 0.01$) and a 45% reduction in sudden death ($p < 0.001$) occurred in comparison with the control group. An analysis of follow-up data from GISSI revealed that the survival curves for those randomised to take or not take omega-3 supplements diverged at only three months [59]. Although this was a very large trial in which patients received routine post-MI care, a limitation is that it was not placebo-controlled.

Some recent studies have not shown a benefit for omega-3 fatty acids in the realm of secondary prevention. In DART-2 men with stable angina pectoris were randomised to a recommendation to eat two fatty fish meals each week or no change in diet [60]. Those who could not consume this much fish were supplemented with 3 g of fish oil per day. The risk of sudden cardiac death, interestingly, was increased in those randomised to increased n-3 intake (hazard ratio = 1.54), particularly in those recommended to take supplements (hazard ratio = 1.84).

In another trial 300 patients after an acute MI were randomised to either 3.5 g of EPA + DHA or corn oil and followed for an average of 1.5 years [61]. No significant difference was demonstrated in single or combined events of unstable angina, recurrent MI, resuscitation or cardiac death. As this study was conducted in western Norway, its authors speculated that the high habitual fish consumption in the region may have already provided a benefit in those with the lowest levels of omega-3 fatty acid consumption, minimising the presence of a dose-dependent effect.

In the EUROASPIRE study of 285 men and 130 women with established CHD the relative risks for death, adjusted for CHD risk factors, for those with the highest tertile of serum omega-3 fatty acids, were 0.33 for ALA, 0.33 for EPA and 0.31 for DHA [62]. A high proportion of EPA was associated with a reduced risk of CHD death and, compared with no omega-3 fatty acid consumption, fish intake tended to be associated with a lower risk of death (p for trend = 0.059). In the large international case-control EURAMIC Study adipose tissue DHA (a measure of long-term fish intake) was not associated with risk of MI [53].

The benefits of n-3 fatty acids in reducing angiographic progression are controversial. Sacks et al. [63] randomised patients with angiographically documented CHD and normal plasma lipid levels to receive either 6 g of n-3 fatty acids (n = 31), or olive oil (n = 28) for a mean duration of 28 months. Fish oil lowered triglyceride levels 30% ($p = 0.007$), had no effects on other plasma lipoprotein levels and did not promote major favourable changes in the diameter of atherosclerotic coronary arteries ($p = 0.8$). Von Schacky et al. [64] randomised 223 patients with angiographically documented coronary artery disease to fish oil concentrate or placebo with a fat composition resembling that of the average European diet for a total of 24 months. At the end of treatment a significant difference in the number of vessels with documented change in luminal diameter was noted

between the fish oil and placebo groups (p = 0.041). Losses in minimal luminal diameter were somewhat less in the fish oil group (p > 0.1) and fish oil recipients had fewer cardiovascular events (p = 0.10); other clinical variables did not differ between the study groups [64]. Eritsland et al. [65] randomised 610 patients undergoing coronary artery bypass grafting to either 4 g/d of fish oil concentrate per day or to a control group. The primary end point was one-year graft patency, assessed angiographically, and vein graft occlusion rates were 27% in the fish oil group and 33% in the control group (odds ratio = = 0.77, p = 0.034). In the fish oil group fewer subjects had > or = 1 occluded vein graft(s) compared with the control group (odds ratio = 0.72, p = 0.05). Most importantly, a significant trend of fewer patients with vein graft occlusions with increasing relative change in serum phospholipid n-3 fatty acids existed (p for linear trend = 0.0037).

Arrhythmia prevention in those with cardiomyopathy

The anti-arrhythmic effects of omega-3 fatty acids in individuals with cardiomyopathy are unclear. In a recently published trial by Raitt et al. [66] subjects with cardiomyopathy, an implantable cardioverter defibrillator (AICD) and a recent episode of ventricular tachycardia or ventricular defibrillation were randomised to 1.3 g/d of omega-3 fats or placebo. The supplements did not prevent arrhythmias and actually demonstrated a decrease in time to recurrent VT/VF in those with a history of ventricular tachycardia. This increase was not, however, statistically significant. Total and cardiac mortality were, however, lower in the fish oil compared to the placebo group, although this difference was not statistically significant. In subgroup analyses subjects with ventricular fibrillation at entry and those with non-ischaemic cardiomyopathy had, in comparison with those with ischaemic disease, a longer shock-free interval with omega-3 fatty acid supplementation. The average left ventricular ejection fraction (LVEF) in this study was 35%, significantly better than 23% in the Multi-center Automatic Implantable Defibrillator Trial-II, where LVEF was shown to be associated with AICD activation and post-enrolment heart failure [67]. The improved LVEF in the Raitt study [66] may have limited the effects of omega-3 fatty acids on ventricular arrhythmias. Notable also is the fact that the "survival" curves of time-to-AICD activation for the supplemented and non-supplemented groups converged ~650 days after randomisation in those at higher risk of sudden cardiac death (LVEF < 40%), whereas they remained quite disparate in those with an LVEF > 40%. A limitation of this study is the fact that there was only 70% power to detect the anticipated differential in the rate of VT/VF between the two groups owing to the lack of events. The findings could, therefore, have been related to chance alone or to an undetected risk modifier. Leaf et al. [68], in the Fatty Acid Anti-arrhythmic Trial (FAAT), randomised subjects with an AICD to either 4 g per day of fish oil supplement or an olive oil placebo and recorded the number of therapeutic discharges or fatal arrhythmias. Eligible patients for this study were those with an AICD implanted for a prior episode of cardiac arrest from VF or sustained VT, or for syncope with inducible sustained VT or VF. Assignment to treatment with fish oil showed a trend to a prolonged time to the first AICD event (VT or VF) or to death from any aetiology (RR = 0.72, p = 0.057). When AICD therapies for probable events were included, the reduction in risk became statistically significant (RR = 0.69, p = 0.033). For those with confirmed events the anti-arrhythmic benefits of fish oil were improved if the subject remained on the protocol for at least 11 months. The Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA) has been the most recent to investigate the effects of omega-3 fatty acids in preventing arrhythmia in those with an AICD [69]. In SOFA patients with an AICD and a prior documented episode of ventricular fibrillation or malignant ventricular tachycardia were randomly assigned to take 2 g/d of fish oil or placebo. The main end point of appropriate AICD intervention for VT or VF or all-cause mortality did not differ significantly between the groups. This lack of benefit from omega-3 supplementation was also noted in subgroups of patients with a prior MI or those who had experienced VT within the year before the study.

The Raitt et al., FAAT, and SOFA studies do not suggest a consistent benefit from omega-3 fatty acids in the prevention of ventricular arrhythmias and sudden cardiac death in those with cardiomyopathy. A dose effect may be present, however, as these trials generally used high dose and pharmacological-grade (up to 4 g/d) omega-3 supplements, whereas consumption of less than 1 g/d has been demonstrated to reduce the risk of fatal coronary events [70]. These studies were also essentially secondary sudden death prevention trials, as they studied subjects with prior sudden cardiac death, documented spontaneous VT/VF or syncope with inducible VT/VF. Note that prior trials revealing an improved outcome were in the realm of primary malignant arrhythmia prevention. These

more recent trials also used arrhythmia as the end point, whereas experimental studies have used ischaemic VF as the end point, and clinical trial and cohort studies have used sudden death as the outcome of interest [66]. Prior trials, in addition, have also focused on individuals with a recent MI and relatively preserved LVEF, whereas these three recent studies have investigated n-3 effects in those without recent MI, on average a reduced LVEF and documented VT/VF. The contrast of these studies with prior investigations may thus be due to differences in the pathophysiology and severity of heart disease amongst different study populations. The major secondary prevention studies are detailed in Table 2.

Meta-analyses

A recent systematic review assessing the effects of omega-3 fatty acids on cardiovascular disease suggests that omega-3 fatty acids may not have consistent cardioprotective effects. In this meta-analysis Hooper et al. [71] evaluated 48 randomised controlled trials that assessed outcome after at least six months of omega-3 supplementation and 41 cohort studies that determined outcome after follow-up of at least six months. The pooled results of the trials were inconsistent but with no reduction in total mortality or cardiovascular events. For those studies at low risk of bias no reduction in total mortality or cardiovascular events was found. When analysis was isolated to studies assessing only long-chain fatty acids, no reduction in the same events was noted either.

The safety of fish and omega-3 supplements

Formal recommendations have been made by the American Heart Association advocating that all adults eat oily fish as least twice each week and that patients with documented coronary heart disease consume approximately 1 g of the two fish-derived omega-3 fatty acids, eicosapentaenoic acid and docosahexaenoic acid, each day [1]. The U.S. government has recommended that non-pregnant adults consume fish for its nutritional benefits [72]. Concerns regarding the potential adverse health effects of methylmercury and polychlorinated biphenyl (PCB) ingestion from fish, however, have prompted investigations into whether these concerns are warranted. Fish is a leading source of exposure to methylmercury and some evidence suggests that mercury may reduce the beneficial effects of n-3 PUFAs on CHD risk [73]. The Harvard Center for Risk Analysis recently convened an expert panel to investigate the aggregate impacts of hypothetical shifts in fish consumption resulting from these concerns [72]. This panel concluded that if non-pregnant adults inappropriately and mistakenly reduce their fish consumption, the net impact on public health would be negative. The panel's findings, instead, suggested that the public should focus on eating low-mercury fish that tend to be lower on the food chain. The health benefits of eating salmon in fact, based on human data and doses typically consumed, are estimated to be at least 100-fold greater than the estimates of harm. Although this analysis only included the effects of methylmercury (not PCBs), the potential health effects of PCBs are considered to be unlikely to be important in comparison with those of mercury. Willett [74], in an accompanying editorial article on the fact that fish consumption has decreased in the U.S. owing to health concerns, notes that this panel's analysis "highlights concerns that educational messages and the implementation of policies must be carefully crafted to avoid unintended consequences".

Omacor^{R} is the only pharmaceutical-grade, FDA approved, omega-3 fatty acid supplement available in the United States [75, 76]. It is available only by prescription, 90% composed of the omega-3 ethyl esters EPA and DHA and sold by Reliant Pharmaceuticals. It is approved at a dose of 4 g/d, for the treatment of triglyceride levels ≥ 500 mg/dl in conjunction with lifestyle modification. Through its patented process Reliant and the FDA have ensured that levels of mercury and other pollutants are not a concern. With regard to over-the-counter supplements, the FDA has determined that intakes of marine omega-3 fatty acids up to 3 g/d are GRAS (Generally Regarded As Safe) [77] and has approved a qualified health claim for DHA and EPA as dietary supplements [78]. The ruling on safety included specific consideration of the effects of omega-3 fatty acids in raising LDL cholesterol levels slightly and of their having no demonstrated adverse effect on glycaemic control in patients with diabetes.

The relevance of the omega-6/omega-3 ratio

The ratio of n-6 to n-3 fatty acids has intellectual appeal as a predictor for coronary artery events, given that the ratio of these fatty acids in the human diet is estimated to have increased over the millennia from approximately 1:1 to 20–25:1 [79] and the fact that these two classes of fatty acids

compete for the same metabolic pathways. Part of the concern over this metric is the fact that a ratio can be altered with relative changes in the numerator or the denominator, whereas the total level of n-6 and n-3 fatty acids may be more important. Furthermore, the ratio includes all n-6 and n-3 fatty acids and thus does not take into account the fact that long-chain fatty acids have different physiological properties from their shorter-chain counterparts.

Epidemiological evidence does not tend to support an increased risk with a higher n-6/n-3 ratio. Within the National Heart, Lung, and Blood Institute's Family Heart Study the relationship between dietary linolenic (n-3) and linoleic (n-6) and the prevalence of atherosclerotic heart disease was evaluated in 4,584 subjects [80]. In this study levels of both linolenic and linoleic fatty acids, increasing from the lowest to the highest quintiles, were associated with a reduction in risk (with p values for trend = 0.014 for men and 0.012 for women, respectively for linolenic acid). The combined beneficial effect of linoleic and linolenic acids was, in fact, stronger than the effects of each fatty acid individually. This suggests that a ratio of fatty acids that are both beneficial may not be relevant. Within the Health Professionals Follow-Up Study [81] the relationship of fatty acid intake to the incidence of CHD events was evaluated. The authors specifically investigated whether levels of n-6 fatty acids attenuated the benefits of n-3 fatty acids. Levels of intake of both long-chain (EPA, DPA, and DHA) and intermediate chain n-3 fatty acids (ALA) ≥ the median were associated with a reduction in risk of a CHD event, whether n-6 fatty acid consumption was above or below the median.

Goyens et al. [82] examined the relationship of dietary ALA and linoleic acid (LA) on serum lipoprotein subclass distributions and particle sizes in 54 healthy subjects. Each subject consumed a control diet providing 0.4% of energy (En%) as ALA and 7 En% as LA during a four-week run-in period. During a six-week intervention each of 18 subjects consumed the control diet, a low-LA diet (3 En% LA, 0.4 En% ALA), or a high-ALA diet (7 En% LA, 1.1 En% ALA). The ALA:LA ratio for the control diet was 1:19 and was a constant 1:7 for the other two diets. Compared with that of the control group LDL cholesterol decreased significantly in the high-ALA group (–0.32 mmol/L, p = 0.024), as did total cholesterol, apolipoprotein (apo) B and the total: HDL cholesterol ratio. In this study, therefore, it was the total level of ALA, not the ratio of ALA to LA, which was associated with changes in lipid levels. In the Nurses' Health Study and the Health Professionals Follow-Up Study, Pischon et al., evaluated the correlation of fatty acid intake and levels of serum inflammatory markers [83]. After adjusting for other predictors of inflammation, intake of the n-3 fatty acids EPA and DHA was inversely associated with levels of tumour necrosis factor ($p < 0.05$) and somewhat less so for C-reactive protein ($p = 0.08$). Little if any association of n-3 fatty acid (EPA + + DHA) intake with tumour necrosis factor receptors was found among participants with low intake of n-6 but a strong inverse association was noted amongst those with a high n-6 intake ($p = 0.04$). These data suggest that n-6 fatty acids do not inhibit the beneficial effects of n-3 fatty acids and that, in fact, a combination of both types of fatty acid may be associated with the lowest risk of cardiovascular disease.

The omega-3 index

Sudden cardiac death (SCD) is one of the leading causes of death in developed nations [84]. In the United States the Centers for Disease Control and Prevention estimates an annual incidence of 450,000 sudden deaths, with a survival rate of 5%. Despite a reduction in total cardiac mortality from 1989 to 1999, the proportion attributed to SCD increased from 38% to 47%. In absolute terms, SCD accounts for more annual deaths than breast cancer, lung cancer, stroke and AIDS combined. It is the first presentation of heart disease in 33% to 50% of patients and is three times more common in men than women. The ability of n-3 blood level quantification to predict cardiovascular events has been of interest, given that predicting sudden cardiac death can be quite challenging. Two authors have explored the potential benefits of measuring red blood cell phospholipid membrane n-3 levels as a proportion of total fatty acids (an omega-3 index) as a predictor of death from cardiovascular disease [85]. They conducted laboratory and clinical experiments to produce the data required to validate the omega-3 index as a CHD predictor. The correlation of this putative marker with risk for CHD death, particularly SCD, was subsequently investigated in several published primary and secondary prevention studies. Their results demonstrated an inverse association with CHD death, particularly a dose-response reduction in risk for SCD that was superior to that for CRP, homocysteine, total cholesterol, LDL, HDL, triglycerides and the total cholesterol/HDL ratio. These data suggest that the omega-3 index may be an easily modifiable, independent, graded and novel risk factor for sudden cardiac death and total CHD mortality.

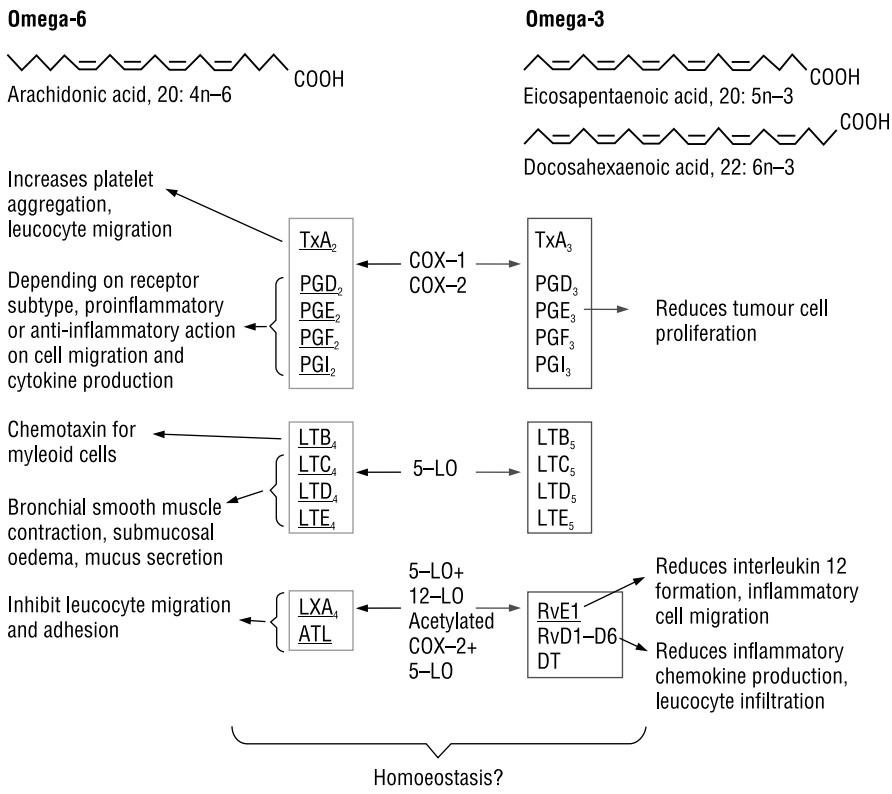

Figure 1. Omega-3 and omega-6 metabolites. Omega-3 and omega-6 essential fatty acids and some of their metabolites and biological effects. COX — cyclo-oxygenases, LO — lipoxygenases. Prostaglandins (PG), thromboxanes (Tx), leukotrienes (LT), lipoxins (LX), resolvins (Rv), docosatrienes (DT) and aspirin-triggered lipoxins (ATL) are shown with their respective abbreviations. Underlined are those mediators for which specific receptors have been identified. From [86].

Omega-3 fatty acid metabolites

Weylandt and Kang [86] commented in "The Lancet" in 2005 that "to fully understand the relative contributions of omega-3 and omega-6 fatty acids in lipid-mediator cascades, several steps are now necessary: more mediators derived from omega-3 fatty acids need to be identified and characterised; the synthesis pathways for these mediators and their regulation need to be analysed; the molecular targets of the mediators need to be understood; and the effects of non-steroidal anti-inflammatory drugs and others on these pathways need to be analysed" (Fig. 1) [3]. Serhan et al. [87] have discovered that EPA and DHA are the precursors to potent bioactive mediators which possess both protective and anti-inflammatory properties. These mediators have been termed resolvins, protectins and docosatrienes. Resolvins have been identified during the resolution phase of acute inflammation and are synthesised by human cells via cell-to-cell interactions. Aspirin affects the pathways identified as contributing to the synthesis of these fatty acid metabolites by triggering the formation of their epimers. Although the clinical implications of these newly identified compounds are yet to be determined, their anti-inflammatory and protective properties may have widespread implications.

Conclusions

The evidence supports the recommendations of the US government and the American Heart Association that non-pregnant adults consume oily fish as part of a well-balanced diet, and should substitute fish relatively low in harmful contaminants, such as salmon and chunk light tuna, for those high in contaminants, including king mackerel, shark, and tilefish. For those individuals without cardiovascular disease the benefits of consuming fish outweigh the potential harm and may significantly reduce the risk of sudden cardiac death. For those with diagnosed CVD the evidence is less consistent, but, overall, suggests that the American Heart

Table 3. Suggestions for omega-3 intake.

Eating ≥ 2 servings of oily fish/wk for all adults with and without CVD appears healthy
Fish oil supplements for CVD prevention in those with or without CVD are controversial and may be harmful for some patients with CVD
No data supports the use of fish oil supplements for preventing ventricular arrhythmias in those with cardiomyopathy
Measuring RBC n-3 levels (known as the Omega-3 Index) may be useful as a clinical predictor of CVD events, particularly sudden cardiac death
No evidence supports the measurement of the n-6/n-3 ratio in clinical decision-making
4 g/d of Omacor^{R} is a treatment option for triglycerides ≥ 500 mg/dl. OTC fish oil supplements are an alternative

CVD — cardiovascular disease, OTC — over the counter

Association's recommendation to consume 1 g of EPA and DHA each day may be beneficial. The evidence from DART-2, however, is cause for concern and suggests that further research is needed to understand the factors that determine benefit for those with CVD. For patients at high risk of malignant ventricular arrhythmias further research will also be required to understand why n-3 fatty acids demonstrate an anti-arrhythmic effect in experimental studies but not in individuals with cardiomyopathy, who often have comorbidities and take several medications. The challenge may be to define the roles of highly bioactive fatty acid metabolites, often formed in the presence of aspirin, in the process of atherosclerosis and in determining clinical outcomes. Our conclusions regarding n-3 intake made on the basis of current data are set out in Table 3.

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