Omega-3 Fatty Acids, Acute Coronary Syndrome, and Sudden Death

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Omega-3 fatty acids (FAs) are currently recommended to reduce the risk of cardiovascular diseases. These recommendations are based on randomized trials, prospective cohort studies, and case-control data and are supported by experimental studies in humans, animals, and isolated cells. Raising tissue levels of omega-3 FAs reduces the risk of sudden cardiac death, most likely due to reduced susceptibility to fatal arrhythmias, but the effect of these FAs on the risk of myocardial infarction per se is less clear. Reductions in nonfatal events have not typically been seen in randomized trials, but case-control and prospective cohort studies support such an effect. Future studies should assess tissue levels of omega-3 FAs to more precisely estimate exposure and to more clearly define the relations between omega-3 status and the risk of fatal or nonfatal cardiovascular diseases.

Introduction

Omega-3 fatty acids (FAs) are currently recommended by the American Heart Association [1], American College of Cardiology [2], European Society of Cardiology [3], and a number of national scientific societies for reducing the risk of coronary heart disease (CHD) and as a treatment after myocardial infarction (MI) [1,4]. Epidemiologic evidence, mechanistic evidence, and clinical trials support the view that eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) reduce the risk of cardiovascular death [5], particularly sudden cardiac death [6]. However, effects on nonfatal cardiac events are less clear. This article reviews the pertinent clinical evidence, summarizes the data for nonfatal end points, and discusses potential mechanisms of action.

Omega-3 FA in Randomized Controlled Trials with CHD End Points

Four large (> 1000 subjects) randomized controlled trials have tested the hypothesis that increasing the intake of omega-3 FA (EPA alone or EPA and DHA), whether from oily fish or capsules, will reduce cardiovascular risk. Two of the studies advised increased intake of oily fish. In the Diet and Reinfarction Trial (DART), 2033 male survivors of a recent first MI were randomized into two groups: those advised to eat fish and a control group that was given advice on "sensible eating" [7]. The former were instructed to increase their intake of oily fish (salmon, mackerel, herring, sardines) by 300 g/wk or, if this was disagreeable, to take three fish oil capsules provided by the study. After 2 years, all-cause mortality was reduced by 29% and mortality from ischemic heart disease by 32%. Total ischemic heart disease events were not significantly different between groups; there was a small but nonsignificant increase in nonfatal events in the group advised to eat fish. This presumably does not mean that eating fish increased the risk of nonfatal events but, rather, that some events that would otherwise have been lethal were not. A similar randomized trial was conducted by the same group several years later in men with angina [8]. However, execution of the study and other factors were so problematic that valid conclusions cannot be drawn [9].

Building on the DART study, a large cardiovascular research group in Italy conducted the GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico)–Prevenzione study [10]. This trial enrolled 11,234 patients fewer than 3 months after MI and randomly assigned them to 0.85 g/d of EPA and DHA ethyl esters (1 g Lovasa; GlaxoSmithKline, Philadelphia, PA]) for 3.5 years. Treatment resulted in a total mortality benefit of 21% ($P < 0.01$) and a 45% decrease in sudden death ($P < 0.001$). These differences became statistically significant after only 3 months of treatment for total mortality and after 4 months for sudden death. Due to this rapid onset of benefit, an anti-arrhythmic mechanism was hypothesized. In contrast, there was no significant change in the risk of nonfatal MI (0.91; 95% CI, 0.70–1.18) and

nonfatal stroke (1.22; 95% CI, 0.75–1.97). However, the combined end point of CHD death and nonfatal MI was significantly reduced (0.78; 95% CI, 0.65–0.94; $P < 0.01$), indicating that omega-3 FA treatment lowered the total CHD event rate.

GISSI was a landmark trial for several reasons. First, it was the first to show significant CHD benefit from supplementation with EPA and DHA alone, not from oily fish. Thus, the beneficial component of fish was defined in this end-point study. The benefits also were seen in addition to standard cardiovascular pharmacotherapy (including statins, aspirin, angiotensin-converting enzyme [ACE] inhibitors, and β-blockers, as individually indicated). In Italy, a "Mediterranean diet" is more commonly followed than in the United States, but the effects of EPA and DHA supplementation were unaffected by this background diet [11]. Finally, GISSI was the first study to document a marked sudden death benefit from supplementation with omega-3 FAs. The study's weaknesses included an open-label design and a 70% compliance rate.

The Japan EPA Lipid Intervention Study (JELIS) was the largest randomized controlled omega-3 FA study with clinical CHD end points [12••]. JELIS tested the hypothesis that adding 1.8 g/d of pure EPA (without DHA) will reduce the incidence of major cardiovascular events in hypercholesterolemic patients on background statin therapy. JELIS randomized 14,981 high-risk primary prevention patients and 3,664 secondary prevention patients to EPA or usual care in a prospective open-label, blinded end-point trial and followed them for 4.6 years. All patients continued on their usual diets, averaging about 900 mg/d of EPA and DHA [13•]. EPA treatment reduced the primary end point (incidence of major adverse coronary events, including nonfatal MI, death related to coronary artery disease, unstable angina, and revascularization procedures) by 19% ($P = 0.011$). The incidence of unstable angina and nonfatal coronary events was significantly reduced (14% [$P = 0.014$] and 19% [$P = 0.015$, respectively). Only 26 sudden cardiac deaths occurred in the 4.6-year study in the secondary prevention arm of JELIS, which was 81% less than in GISSI's control group (154 vs 828 events per 100,000 person-years); therefore, a major reduction in sudden death could not be expected in JELIS. Risk of major cardiac events was reduced by about 19% in the primary and secondary prevention cohorts but was statistically significant only for the latter; there were too few events in the former group to achieve significance ($P = 0.13$). There were no lipid or lipoprotein changes with EPA treatment except for a minor (5%) decrease in triglycerides, a change unlikely to materially contribute to the observed risk reduction.

JELIS is important for several reasons:

1. Even with a high background intake of omega-3 FAs (800–1000 mg/d), additional EPA can further reduce risk of cardiac events.
2. EPA can reduce risk without altering lipoprotein levels.
3. The effects of EPA are additive to those of statins.
4. The effects on nonfatal events and unstable angina suggest that EPA improved plaque stability, as suggested by Thies et al. [14].
5. As in GISSI, the effects manifested very soon after initiation of therapy.
6. Women (who constituted about 70% of the JELIS population) and men appear to derive equal benefits from EPA.
7. The intervention was safe.
8. The effects were of essentially the same magnitude in secondary and primary prevention settings.

Thus, the JELIS trial provides continued support for the increased intake of omega-3 FAs for reducing the risk of CHD, even with substantial background dietary intakes.

The Omega-3 Index and Sudden Cardiac Death

In an attempt to define exposure to omega-3 FAs more precisely, we recently proposed the omega-3 index as a biomarker for an individual's omega-3 FA status. Moreover, we suggested the omega-3 index to be considered as a possible new risk factor for sudden cardiac death [15]. The omega-3 index is the combined EPA and DHA content of erythrocyte membranes given as a percentage of total FAs. Based on a synthesis of studies from the literature, we further suggested that cut points of 4% or below, 4.1% to 7.9%, and 8% or more might define high-, intermediate-, and low-risk categories, respectively. Persons with a 6.5% omega-3 index had a risk of sudden cardiac death of 0.1 (95% CI, 0.14–0.37) relative to that of individuals with an omega-3 index of 3.3% in a case-control study [16]. Similar results have been derived from the Physicians' Health Study: physicians with 6.9% omega-3 FAs in whole blood (equivalent to an omega-3 index of about 6.5% [17]) had a relative risk of sudden cardiac death of 0.1 (95% CI, 0.02–0.48) compared with physicians with an omega-3 index of about 3.8% after adjustment of confounders [6]. In both studies, risk was 0.5 at roughly 4.5% and was 0.2 at 5.3%. Thus, risk of sudden cardiac death and the omega-3 index appear to be strongly inversely related. The relation of oily fish consumption to sudden cardiac death is less steep [16]. JELIS did not measure the omega-3 index but did measure plasma EPA levels. They increased from 2.9% to 4.9% in the intervention group but remained constant at 2.9% in the control group. In comparison, plasma EPA levels in Western countries are approximately 0.3% [18]. Although direct extrapolation to the omega-3 index is not possible,

these differences in serum EPA levels suggest that tissue EPA and DHA are markedly higher in Japan than in the West. This may explain why the incidence of sudden cardiac death was so low in the JELIS population (40/100,000 participant-years), especially considering that all of these patients were at increased risk for CHD and most would qualify for cardiovascular prevention, including complete pharmacotherapy. This is corroborated by epidemiologic studies: in Europe, an area in which an omega-3 index of 4% or below is common (eg, in Belfast or Munich), the incidence of sudden cardiac death in the general population is 146/100,000 person-years [19]. However, in the general population in Japan it is 7.8/100,000 person-years, or 94% lower than in Europe [13•]. Thus, the incidence of sudden cardiac death is increased fivefold in the high-risk population in JELIS as compared with the Japanese general population. The risk of sudden cardiac death in the general population in Germany, however, is 3.6-fold higher than that in the high-risk JELIS population. Based on these observations, an individual's omega-3 FA status, best assessed as the omega-3 index [17], appears to be a better predictor of sudden cardiac death than the presence or absence of cardiovascular disease. Although an omega-3 index of 8% or more confers substantial protection from sudden cardiac death [17], optimal levels may be higher but remain to be defined. In addition, because no international standardization system exists for the laboratory measurement of erythrocyte omega-3 FA content, values from different laboratories may not be comparable, and thus the cut points discussed here must be considered tentative. The value of the omega-3 index as a risk marker will be markedly enhanced after such a standardization program has been established.

Human evidence for an anti-arrhythmic effect of omega-3 FAs

In a small pilot study involving 10 patients with repeated episodes of documented sustained ventricular tachycardia (VT), Schrepf et al. [20] demonstrated in electrophysiologic studies that intravenous infusion of 3.8 g of omega-3 FAs reduced susceptibility to induction of sustained VT in five of the seven patients with inducible VT at baseline. For three of the ten patients, VT could not be induced even at baseline and, interestingly, these patients had a higher mean plasma phospholipid omega-3 FA content than those with inducible arrhythmia (6.2% vs 4.8%). The same inverse relationship between FA content and incidence of malignant ventricular arrhythmias was demonstrated by Christensen et al. [21] in 98 patients with ischemic heart disease and implantable cardioverter defibrillators (ICDs). During 1-year follow-up, those with the lowest level of omega-3 FAs in serum phospholipids (mean, 5.5%) had more ventricular arrhythmias than those with the highest concentrations (mean, 13.0%). A trend toward protection was also evident in an intervention study by Leaf et al. [22•]. After 12 months of supplementation with 2.6 g/d of omega-3 FAs, which increased the erythrocyte content of combined EPA and DHA from 3.4% to 7.6%, a 28% reduction of risk of the combined end point of ICD-treated VT/ventricular fibrillation (VF) or all-cause mortality was strongly suggested ($P = 0.057$). However, two other studies involving ICDs were not able to confirm this protective effect of omega-3 FAs [23•,24•]. One of the studies found a trend toward increased susceptibility to ventricular arrhythmia in patients with VT as the qualifying arrhythmia who received supplementation with omega-3 FAs [24•].

One reason for the divergent results from studies involving ICDs might be different mechanisms of arrhythmia in different patients. During an acute ischemic event, a gradient of depolarization occurs in the myocardium as a consequence of impaired oxygen supply and lack of energy for maintenance of the membrane potential. The theoretical mechanism of action of omega-3 FAs as antiarrhythmic agents is based on an indirect effect on sodium and calcium ion channels through their incorporation into cellular membranes [25]. This shifts the resting membrane potential toward a more hyperpolarized state and thereby prolongs the refractory period of the cardiac cycle, making it less likely for a partial depolarization to elicit a ventricular arrhythmia. In nonischemic myocardium, the effect on the resting membrane potential will not be as dramatic as in the ischemic zone, and ventricular arrhythmias based on nonischemic mechanisms therefore might not be affected by omega-3 FAs to the same extent. According to this hypothesis, a protective effect against VF and VT would probably only be expected in ICD patients in whom intermittent ischemia caused their arrhythmias. Risk of arrhythmias originating from myocardial scaring and heart failure might not be reduced by omega-3 FA treatment. In fact, the only study without a trend toward protection from omega-3 FAs was performed in ICD patients with documented sustained ventricular arrhythmia not induced by an ischemic event [24•].

Omega-3 FA treatment has been shown to lower heart rate in epidemiologic [26] and interventional studies [27]. Heart rate variability also has been reported to be directly related to tissue omega-3 FA levels [28] and, in some [27,29,30] but not all [31] studies, to increase with omega-3 treatment. Subjects who reported eating higher amounts of nonfried fish had electrocardiographic evidence of slower atrioventricular conduction [32], possibly due to ion channel effects in the atrioventricular node. Such an effect would be consistent with the observation that even in cardiac transplantation patients (denervated hearts), supplementation with about 1 g of combined EPA and DHA can reduce heart rate [33]. A higher likelihood of prolonged QTc (which is associated with an increased risk of sudden cardiac death [34]) was also seen in elderly subjects reporting lower intakes of oily fish [35,36].

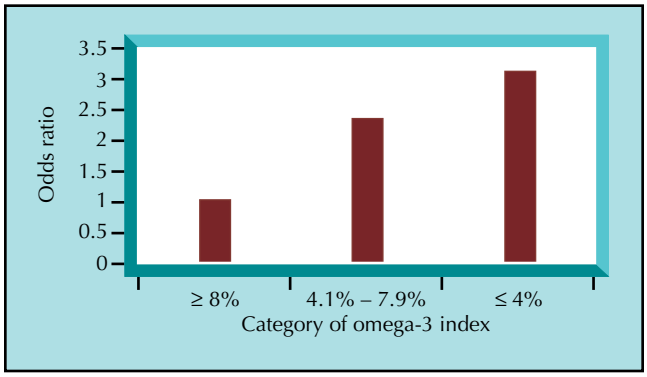

Figure 1. Odds ratios for acute coronary syndrome case status by omega-3 index risk category. Low-, intermediate-, and high-risk omega-3 index categories *(left to right)* are given as a percentage of total erythrocyte membrane fatty acids. Odds are adjusted for age, race, sex, diabetes, hypertension, family history of coronary artery disease, history of myocardial infarction, and serum lipids (low-density lipoproteins, high-density lipoproteins, log triglycerides). The odds ratio was lower in the highest omega-3 index category than the intermediate category ($P = 0.017$) ($P < 0.0001$ for trend). (*Adapted from* Block et al. [44].)

The Omega-3 Index and Nonfatal Cardiac Events

Although there is reasonable consensus that omega-3 FAs lower the risk of fatal end points, the association between these FAs and the risk of nonfatal cardiac events (ie, MI, unstable angina) remains less clear. Such a benefit was observed in JELIS [12••] but not in DART [7] or GISSI [10]. However, the cumulative rate of major coronary events (the primary end point, largely nonfatal events) in the 5-year period was much lower in JELIS than in comparable studies in Western populations with much lower levels of omega-3 FAs. In the total 5-year JELIS study period, major coronary events occurred in 2.8% of the EPA group and 3.5% of controls. The 5-year cumulative incidence of comparable events in the treated groups was 14% with ACE inhibitors [37] and 20% with statins in the Heart Protection Study [38]. Importantly, the use of secondary prevention drugs known to prolong life and reduce major adverse cardiac events (antiplatelet agents, β-blockers, and ACE inhibitors) was much higher in the Heart Outcomes Prevention Evaluation (HOPE) study than in JELIS.

Fish intake (an imperfect surrogate for EPA and DHA intake) and MI risk were not consistently related in epidemiologic studies [39,40]. Inconsistent findings were also reported in biomarker-based epidemiologic studies [41–43]. Thus, despite extensive inquiry about the association between omega-3 FAs and nonfatal coronary events, significant controversy regarding the association remains.

Blood cell membrane omega-3 FA levels from 768 patients with acute coronary syndrome (ACS) were recently compared with those in 768 age-, gender-, and race-matched controls [44]. Associations of omega-3 FAs with ACS status were assessed using multivariable models adjusting for the matching variables and for smoking status, alcohol use, diabetes, body mass index, serum lipids, education, family history of coronary artery disease, and personal histories of MI, hypertension, and dyslipidemia. The omega-3 index was 21% lower in cases than controls (3.4% ± 1.6% vs 4.3% ± 2.0%, $P < 0.001$). The multivariable-adjusted odds ratio for case status was 0.77 (95% CI, 0.70–0.85) for a one-unit increase in the omega-3 index in a model that included serum lipids and other covariates. Compared with the odds for case status in the lowest omega-3 index group (≤ 4%), odds were 0.75 (95% CI, 0.58–0.98) in the intermediate group (4.1%–7.9%) and 0.32 in the highest group (95% CI, 0.17–0.63) (≥ 8%; P for trend < 0.0001) (Fig. 1). Hence, in this study, one of the largest published, odds for ACS case status increased incrementally as the omega-3 index decreased. Although cross-sectional, these data do support the view that a low omega-3 index is a risk factor for nonfatal ACS.

Overall, it seems that in persons with a low omega-3 index (≤ 4%), a marginal increase (eg, to about 5%) appears to reduce risk of sudden cardiac death by about 50%. An omega-3 index of 8% or more is associated with a reduction of sudden cardiac death of 90%. Optimal levels may be higher but remain to be defined. If sudden cardiac death is less of an issue (patients with ACS living to reach the hospital or persons with a high omega-3 index), nonfatal cardiovascular events appear to occur less frequently [14,45–50].

Conclusions

Because the risk of sudden cardiac death appears to be significantly mitigated by increasing tissue levels of EPA and DHA, assessing a marker of omega-3 status such as the omega-3 index may help identify high-risk patients. Interventions to raise omega-3 FA tissue levels (diet or supplementation) could then be instituted to achieve cardioprotective levels. This is a safe and inexpensive approach to reducing the risk of sudden cardiac death. The omega-3 index also may serve as a risk marker for ACS and other nonfatal cardiovascular events, but further research is needed to determine the extent to which altering the index by diet or supplementation will lower risk.

Disclosures

Dr. von Schacky owns OmegaMetrix Europe, a company that offers testing of blood fatty acid.

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