

Review

Cardiovascular benefits of omega-3 fatty acids

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Abstract

Cardiac societies recommend the intake of 1 g/day of the two omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) for cardiovascular disease prevention, treatment after a myocardial infarction, prevention of sudden death, and secondary prevention of cardiovascular disease. These recommendations are based on a body of scientific evidence that encompasses literally thousands of publications. Of four large scale intervention studies three also support the recommendations of these cardiac societies. One methodologically questionable study with a negative result led a Cochrane meta-analysis to a null conclusion. This null conclusion, however, has not swayed the recommendations of the cardiac societies mentioned, and has been refuted with good reason by scientific societies.

Based on the scientific evidence just mentioned, we propose a **new risk factor to be considered for sudden cardiac death, the omega-3 index**. It is measured in red blood cells, and is expressed as a **percentage of EPA + DHA of total fatty acids**. **An omega-3 index of >8% is associated with 90% less risk for sudden cardiac death, as compared to an omega-3 index of <4%**. The omega-3 index as a risk factor for sudden cardiac death has striking similarities to LDL as a risk factor for coronary artery disease. Moreover, the omega-3 index reflects the omega-3 fatty acid status of a given individual (analogous to HbA1c reflecting glucose homeostasis). The omega-3 index can therefore be used as a goal for treatment with EPA and DHA. As is the case now for LDL, in the future, the cardiac societies might very well recommend treatment with EPA and DHA to become goal oriented (e.g. an omega-3 index >8%).

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1. Introduction

In their most recent recommendations, the American Heart Association/American College of Cardiology, the European Society for Cardiology, and national cardiac societies recommend the intake of 1 g/day of the two marine omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) for secondary prevention, cardiovascular prevention, treatment post-myocardial infarction and prevention of sudden cardiac death [1–5]. These

recommendations were published in spite of a null result of a systematic Cochrane analysis on the “risks and benefits of omega-3 fats for mortality, cardiovascular disease and cancer” [6]. This is an irritating situation. The background and the reasons for the unified positions of these major cardiac societies will be the focus of the present review, as will be a discussion of the Cochrane analysis. A new risk factor for sudden cardiac death, the omega-3 index, will also be discussed.

2. Epidemiologic studies

Consumption of fish is generally associated with a reduced risk for sudden cardiac death and for cardiac disease [7,8]. In most studies, this association becomes stronger, as soon as the omega-3 fatty acid content in the fish consumed is factored in

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[7,8]. However, when considering biomarkers of omega-3 fatty acids, a steep concentration-risk dependence is observed: Persons with 6.5% omega-3 fatty acids in red blood cell membranes have 90% less risk for sudden cardiac death as compared to persons with 3.3% [9]. These data are from a case-control study in Seattle, performed in victims of sudden cardiac death and matched controls [9]. In the Physicians' health study, similar results have been seen [10]: Physicians with 6.87% omega-3 fatty acids in their whole blood had 90% less risk for sudden cardiac death, as compared to physicians with 3.58%, after adjustment for confounders [10]. Less pronounced, but similar results were obtained after determination of the content of omega-3 fatty acids of serum cholesteryl esters [11]. Other studies have reported a lower heart rate and a lower incidence of atrial fibrillation in persons with high intakes of omega-3 fatty acids [12,13].

In other areas of the vasculature, omega-3 fatty acids are also associated with reduced risk: In women ingesting fish 5 or more times a week, the risk of stroke was 0.48 (95% confidence interval 0.21–1.06), whereas it was 1.0 in women ingesting fish less than once per month [14]. These results were mostly driven by fewer thrombotic strokes, whereas no relation was observed with respect to hemorrhagic stroke [14]. Less clear-cut results have been seen with respect to peripheral arterial disease [15].

3. Mechanisms of action, animal models and studies with surrogate and intermediate endpoints

In thousands of publications, mechanisms potentially responsible for these effects have been examined [7,8,16]. This attests to the fact that, like other fatty acids, EPA and DHA form part of the cell membrane, replacing other mostly unsaturated fatty acids upon incorporation, and thereby modulating cellular function. Therefore, a number of changes of cell function can be observed upon incorporation of EPA and DHA into the cell membrane. Among them are the modulation of the eicosanoid system towards vasodilatation and less proinflammation, a lowering of blood triglycerides, antiarrhythmic effects, reductions in pro-atherogenic cytokines and growth factors and others [7,8,16]. In animal models, in dogs, swine and primates, but not in rodents, beneficial effects have been observed in models of vasoocclusion and atherosclerosis [7,8,16].

Antiarrhythmic effects of EPA and DHA have been demonstrated in various ways: as a reduced heart rate, a faster return to resting heart rate after exercise, an increase of heart rate variability, all after ingestion of EPA and DHA [13,17,18]. In patients undergoing coronary bypass grafting, EPA and DHA suppress the onset of new atrial fibrillation [19]. Moreover, fewer ventricular tachycardias were inducible after acute infusion of EPA and DHA in carriers of an implanted cardioverter/defibrillator [20]. More importantly, however, in carriers of an implanted cardioverter/defibrillator, EPA and DHA prolonged the time to first event for ventricular tachycardia or fibrillation, as recorded by the device [21–23].

Vascular patency is improved by ingestion of EPA and DHA. In a randomized controlled trial in patients waiting for surgical carotid endarterectomy, unstable plaques were stabilized [24]. Plaque morphology was assessed histologically, and fewer thin capped fibrous plaques and no signs of inflammations were found in the specimens from the patients treated with EPA and DHA, vs. those treated with sunflower oil (rich in omega-6 fatty acids) or the controls [24]. It can therefore be assumed that ingestion of EPA and DHA stabilizes plaques in the coronary circulation as well. In keeping with this finding, in a trial assessing coronary angiograms, more regression and less progression of lesions were seen in the patients treated with EPA and DHA, than in the control patients [25]. Venous coronary bypass grafts had a higher patency rate in patients treated with EPA and DHA than in the controls [26].

Other effects of EPA and DHA. They dose-dependently lower triglyceride levels in the fasting and post-prandial state, and do so reliably and effectively [7,8,27]. Combination with a statin thus far appeared safe [7,8,27]. The use of EPA and DHA to lower triglycerides is recommended by the cardiac societies [1–5]. LDL-levels are slightly increased probably due to higher levels of the more buoyant, fast-floating LDL-subclasses increase, while the denser, slow-floating LDL-subclasses decrease [27]. This effect appears to be due to DHA, but not EPA [27]. The effects on other serum lipids, like total cholesterol or HDL are less clear cut [27].

Improvements in endothelial function have been described after EPA and DHA, whether studied by using ultrasound or plethysmographically [7,8,27,28]. In large doses, EPA and DHA reduce blood pressure [7,8]. Interestingly, the active compound appears to be DHA, at least when given at 4 g/day [27]. However, the reduction of blood pressure brought about by 1 g/day of EPA and DHA, the most common dose, does not seem to be of clinical importance. EPA and DHA both slightly inhibit platelet aggregability, with DHA being more effective, and have a slight anticoagulatory effect [27]. These effects, however, are probably negligible in patients treated with aspirin or other pharmacologic platelet inhibitors [29]. In a number of studies, the effects of EPA and/or DHA on glucose homeostasis have been investigated in patients with diabetes mellitus, and essentially none were found [27].

4. Studies with clinical endpoints

Four trials with clinical endpoints have been reported.

- DART (the Diet and Reinfarction Trial) randomized 2033 men on average of 42 days after their first myocardial infarction to receive or not receive advice to increase their intake of oily fish to twice a week. After two years of follow-up with repeated dietary advice, the fish advice resulted in a 29% reduction in total mortality, mostly driven by a 32% decrease in fatal myocardial reinfarction [30]. The authors estimated that the fatty fish intake resulted in an intake of EPA of 2.5 g/week, i.e. 357 mg/

day [30]. Based on the assumption that EPA contributes about 40% of the total EPA + DHA in oily fish, daily intake of EPA + DHA was about 900 mg. In a follow-up study, the differences in eating habits and mortality were found to wane outside the formal research setting in the subsequent years [31].

- GISSI-Prevenzione was a randomized, open-label 3.5 year study performed in Italy in 11,323 persons having survived a myocardial infarction for a median of 16 days [32,33]. In a factorial design the addition of 850 mg/day EPA and DHA and 300 mg/day vitamin E was tested, the latter showing no effect. The primary endpoint, a combination of death, non-fatal myocardial infarction, and stroke was reduced by 10% or 15% ($p=0.048$ or $p=0.008$ respectively), depending on the analysis (two-way or four-way). Importantly, a reduction of total mortality, mostly driven by a reduction in sudden cardiac death, by ingestion of 0.85 g/day EPA + DHA was demonstrated by the GISSI-Prevenzione study [32,33]. Time course analyses of the occurrence of the clinical endpoints demonstrated diverging curves, all favoring the intervention [33]. Treatment effects could be discerned early, e.g. in the case of total mortality after 90 days ($p=0.037$, confidence interval 0.59–0.97), or in the case of sudden cardiac death after 120 days ($p=0.048$, confidence interval 0.22–0.99).
- DART-2 [34,35]: This randomized dietary trial with clinical endpoints was designed to test the effects on total mortality of either giving advice to eat fish or providing fish oil capsules to men with angina (a symptom, not a disease). Surprisingly, while total mortality was not statistically different in the two groups, there was less sudden death in the control group than in the intervention group. Although reasonably well-designed, it was seriously under-funded and thus not properly conducted or reported. For example, only a rudimentary set of baseline parameters are presented for all participants, while the rest of the data refer to small subgroups at a subset of time points. Compliance by analysis of blood fatty acid levels was checked in only 2% of the cohort and only at 6 months. Neither long-term compliance with the advice nor how concomitant medications and health behaviours may have changed are known. The authors offered several possible explanations for their admittedly aberrant findings [34,35].
- The design of a trial with the acronym “JELIS” (Japan EPA Lipid Intervention Study) has been published, and the results have been reported as a late breaking clinical trial at the American Heart Association Scientific Sessions in November 2005 [36]. A total of 18,645 patients with hyperlipidemia, of which 3664 had already established coronary artery disease, were openly randomized to receive 1.8 g/day EPA or to serve as a control. Hyperlipidemia was treated in all patients with either 5 mg simvastatin or 10 mg pravastatin. Average follow-up was 4.6 years. The primary endpoint was “major coronary

events” a composite of sudden cardiac death, fatal and non-fatal myocardial infarction, unstable angina, events of angioplasty/stenting or coronary bypass grafting. This primary endpoint was reduced by 19 relative percent ($p=0.011$) by 1.8 g EPA/day [36]. Of note, conventional risk factors like hypertension (35%), diabetes (16%) or smoking (19%) were as prevalent as in similar trials like HOPE or EUROPA [37,38]. The incidence of the primary endpoint in JELIS was among 1% per year, whereas in HOPE or EUROPA it was at least threefold higher [37,38].

5. The Cochrane analysis

A Cochrane meta-analysis has been published in the British Medical Journal, which came to the conclusion that “long chain and shorter chain omega-3 fats do not have a clear effect on total mortality, combined cardiovascular events, or cancer” [6].

With respect to cardiovascular mortality and morbidity, the null conclusion of the Cochrane report rests entirely upon inclusion of one trial, DART-2 [34,35]. However, according to a number of criteria, the results of DART-2 have the characteristics of an outlier, as reflected by a positive test for heterogeneity which disappeared after the authors of the Cochrane analysis removed DART-2 [6]. As just discussed above, the results of DART-2 were generated with inadequate methodology. Upon excluding DART-2, the Cochrane analysis demonstrated a positive effect of omega-3 fatty acids (relative risk 0.83, confidence intervals 0.75 to 0.91, p not given, Ref. [6]). In the overall conclusions, however, this was not considered.

Even as it stands, the Cochrane analysis suggests a 16–17% reduction in total mortality by ingestion of omega-3 fatty acids, an effect size that is even larger than that of statins [39]. That the confidence intervals overlap by 1.0 indicates that further studies were needed to improve precision of the estimate, not that the estimate is wrong. A number of large omega-3 and CHD studies (both epidemiological and interventional) are currently underway [e.g. 40], and these will provide a much clearer picture of the extent to which cardiovascular morbidity and mortality are reduced by omega-3 fatty acids.

Other concerns with the Cochrane report encompass, but are not limited to the following facts (as documented in a series of letters to the editors of the British Medical Journal, Ref. [41]):

- Biomarker studies were excluded (biomarkers of omega-3 fatty acids reflect best the endogenous levels \pm dietary intake).
- Omission of several relevant cohort studies.
- Inclusion of a study with questionable scientific integrity
- Contradictory search criteria
- Uncritical combination of studies conducted in vastly different populations.

Taken together, overall results and conclusions arrived at of the Cochrane analysis with respect to total mortality and combined cardiovascular events are subject to disagreement. The International Society for the Study of Fatty Acids and Lipids (ISSFAL) has therefore formally refuted the conclusions of this Cochrane analysis [42].

6. A new development: the omega-3 index

Since higher blood levels of omega-3 fatty acids have been shown to be associated with lower risk for cardiovascular events, especially sudden cardiac death, the possibility that an omega-3 biomarker might have clinical prognostic utility, must be considered. The authors have recently proposed that “the omega-3 index” may serve as a new risk factor for sudden cardiac death [43].

The omega-3 index is defined as the percentage of EPA and DHA in the red cell membrane, with the remaining fatty acids building up to 100% [43]. The omega-3 index correlates well with other biomarkers of omega-3 fatty acids, like determining EPA + docosapentaenoic acid + DHA in whole blood, fatty acid composition of cardiac samples, serum EPA and DHA and others [44]. It does however, have a half life 4–6 times longer than serum EPA and DHA, and therefore reflects the integral of intake of omega-3 fatty acids analogous to levels of HbA1c reflecting the glucose metabolism in a diabetic. In the authors’ laboratories, the omega-3 index is determined according to a standardized method under rigorous quality control.

The risk of sudden cardiac death associated with an omega-3 index of 3.3% is 10 times the risk of sudden cardiac death associated with an omega-3 index of around 7%, with a concentration-dependent gradient in risk in-between [9]. Sudden cardiac death is virtually unknown in healthy Japanese with an incidence of 7.8/100,000 [45]. In Japan, high levels of omega-3 fatty acids are measured, although the omega-3 index remains to be determined [36,46]. In contrast, in Europe, in an area, where the omega-3 index is among 3.3%, the incidence of sudden cardiac death in a healthy population is 122/100,000, a 15.5 fold difference in comparison with Japan [47]. In JELIS (just mentioned above), conducted in Japan in hyperlipidemic patients of whom 20% had established coronary disease, the risk for sudden cardiac death of the study population was 40/100,000 [36]. In HOPE, a roughly comparable study conducted in a Western population, the risk was 207/100,000 [37]. Therefore, levels above 7% might offer further protection from sudden cardiac death. In keeping, the risk indicated by the omega-3 index may very well vary more than 15 fold, which makes the omega-3 index a highly discriminative risk factor.

The omega-3 index reflects the omega-3 fatty acid status in a given individual [44]. Data to date indicate that the omega-3 index is not influenced by other risk factors for sudden cardiac death, like presence of coronary artery disease (or risk factors for it), NYHA functional class, ejection fraction, previous cardiac arrest, etc. Therefore, the incremental information to be gleaned from determining the

omega-3 index is substantial, although it remains to be precisely determined for specific populations.

The omega-3 index can be considered a modifiable risk factor — strikingly similar to LDL [44]. As is the case with LDL, levels of the omega-3 index are determined by diet and probably also by a genetic component. Both LDL and the omega-3 index can be measured in different individuals, and results can be expected to reflect the diet followed, amount of omega-3 fatty acids present in the diet, and other factors, like pregnancy or energy expenditure. Moreover, changes in the omega-3 index can be expected in a given individual after a change in diet, during treatment with omega-3 fatty acids and a change in another factor. While clear treatment goals have been defined for LDL in the guidelines of the cardiac societies, as yet these societies recommend a standard dose of omega-3 fatty acids. Upon further validation of the omega-3 index, treatment with omega-3 fatty acids is also likely to become goal oriented. At present, we suggest a goal of 8% for prevention of sudden cardiac death [44]. This goal, however, might very well be different for other diseases amenable for treatment with omega-3 fatty acids, like chronic polyarthritis, or, maybe, in the future, depression [48,49]. The goal of 8% might change and be further refined, with the development of the literature. This has also been the case with the treatment goals for LDL.

Clearly, when designing intervention studies with omega-3 fatty acids, the baseline status should be an inclusion criterion, as it is unlikely that an effect of the intervention with omega-3 fatty acids will be seen in a person with high levels. The omega-3 fatty acid status should also be known in both intervention and control groups throughout the study, since non-compliance can occur in the intervention group (by not taking study medication) as well as in the control group (increased intake of omega-3 fatty acids from other sources). These points have important bearing on study size, duration, and outcome also outside the cardiovascular field.

7. What source of omega-3 fatty acids?

Reductions in cardiovascular events have been demonstrated in endpoint studies with two servings of fatty fish per week, 1 g/day of a 85% EPA + DHA concentrate in the form of an ethyl ester, and 1.8 g/day of EPA as an ethyl ester [30,32,36]. Comparative studies with clinical endpoints have not been performed. However, in some fish, and in some fish oils, contaminants like methyl-mercury or organic compounds have been detected, which appeared to set off the positive effect of EPA + DHA in epidemiologic studies [7]. Thus, these contaminants should be avoided. A further firm recommendation as to what source of omega-3 fatty acids is preferable or whether EPA should be preferred to DHA cannot be given, and is not given in the guidelines from cardiac societies.

8. Conclusion

As expected, guidelines of cardiac societies are well founded in the current literature, not just on a small number

of intervention trials with clinical endpoints, demonstrating clearly cardiovascular benefits of omega-3 fatty acids. These benefits are derived primarily from prevention of sudden cardiac death and reduction in major adverse cardiac events. Apparently, the current literature rather served as a foundation for the treatment guidelines than the results of a Cochrane analysis.

We think that the omega-3 index is a highly discriminative risk factor for sudden cardiac death. This risk factor can be modified by intake of EPA and DHA. The standard dose of 1 g/day EPA and DHA recommended by the cardiac societies, however, is probably far from ideal for everybody, since not only this standard dose, but also diet, individual genetic background, body mass index, intake and disposal of calories, and other factors all taken together probably determine the omega-3 fatty acid status of a given person. We suggest therefore that the omega-3 index acts not only as a risk factor for sudden cardiac death, but at present also, at above 8%, as a treatment goal for treatment with EPA and DHA.

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