Federazione Italiana di Cardiologia
Italian Federation of Cardiology

Cardiovascular risk and the omega-3 index

Clemens von Schacky[a] and William S. Harris[b]

A reliable risk factor for sudden cardiac death (SCD) for the general population remains to be defined. We propose the omega-3 index, defined as the combined percentage of eicosapentaenoic (EPA) and docosahexaenoic acids (DHA) in red blood cell membranes. It reflects the EPA + DHA status of a given individual. It can be determined by a standardised and reproducible laboratory procedure. Several lines of evidence support the omega-3 index as a risk factor for SCD: in epidemiological studies, a steep dependence of risk for SCD and the omega-3 index has been observed between 6.5% (risk 0.1) and 3.3% (risk 1.0). EPA + DHA are antiarrhythmic on the supraventricular and ventricular levels. Dietary EPA + DHA reduce the incidence of SCD. Cardiac societies recommend EPA + DHA for prevention of SCD. The omega-3 index can assess risk for SCD and monitor therapy with EPA + DHA. Moreover, it compares very favourably with other risk factors for SCD. *J Cardiovasc Med* **8 (suppl 1):S46–S49 © 2007 Italian Federation of Cardiology.**

Journal of Cardiovascular Medicine 2007, **8 (suppl 1)**:S46–S49

Keywords: coronary artery disease, docosahexaenoic acid, eicosapentaenoic acid, omega-3 index, risk factors, sudden cardiac death

[a]Preventive Cardiology, Medizinische Klinik und Poliklinik Innenstadt, Ludwig Maximilians-Universität München, Munich, Germany and [b]Sanford Research/USD, Sanford School of Medicine, University of South Dakota, Sioux Falls, South Dakota, USA

Correspondence to Prof Clemens von Schacky, Preventive Cardiology, Medizinische Klinik und Poliklinik Innenstadt, Ziemssenstr. 1, 80336 Munich, Germany
Fax: +49 89 51602194; e-mail: Clemens.vonschacky@med.uni-muenchen.de

Acknowledgements: Clemens von Schacky's original research was supported by Bundesministerium für Bildung und Forschung, Deutsche Forschungsgesellschaft, Wilhelm Sander Stiftung, National Institutes of Health, USA, and various pharmaceutical companies. Clemens von Schacky owns Omegametrix, Europe, a company that offers measuring the omega-3 index. William S. Harris' original research was supported by National Institutes of Health, USA, and the Saint Luke's Hospital Foundation of Kansas City, USA.

Introduction

An individual's risk for coronary artery disease can be reliably assessed using current algorithms [1]. However, assessing the risk for sudden cardiac death (SCD) has remained elusive. Compared to the total numbers of SCDs in the population, the numbers of SCDs occurring in persons who can presently be identified as being at high risk is small, and prevention by implantable cardioverter-defibrillators (ICDs) is costly (Table 1) [2–6]. The majority of SCDs occur in the general population (e.g., >300 000/year in the United States), in persons unaware of their risk [2]. We suggest a new risk factor for SCD, the omega-3 index [7]. The present article defines the omega-3 index, describes the rationale behind it, reviews the literature pertinent to it, and discusses its merits and possible applications.

Definition of the omega-3 index

The omega-3 index is the combined percentage of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) of total fatty acids in red blood cell membranes [7]. Other omega-3 biomarkers that are highly correlated with the omega-3 index include the concentration of total long-chain omega-3 fatty acids (EPA + docosapentaenoic acid [DPA] + DHA) in whole blood [3], of EPA + DHA in plasma phospholipids [5], and of EPA in serum cholesterol esters [8].

For the omega-3 index to be of practical use, the laboratory methods for its measurement must be standardised. The omega-3 index is analysed by direct methylation of packed red blood cells using boron trifluoride in methanol. Fatty acid methyl esters thus generated are analysed by capillary gas chromatography using a 100-m SP2560 column as described previously [7,9]. Sample handling, standards (external and internal), and fatty acids to be included in the analysis must be carefully defined, with a rigorous system of quality management. Use of this standardised approach reduces the necessary sample volume (~0.2 ml EDTA blood). Owing to pre-analytical instability, analyses must be started within 7 days of blood sampling, or samples must be stored at −80°C. In experienced laboratories, the measurement of the omega-3 index is highly reproducible (coefficient of variation 5%; unpublished data), and values can be determined within several hours.

The omega-3 index may also be an independent risk factor compared with estimated dietary intake of omega-3 fatty acids [10]. This may be due to error in the assessment of estimated dietary EPA + DHA intake (e.g., due to fish containing varying amounts of EPA + DHA) or to individual differences related to incorporation, metabolism, or genetic variability [7,9].

The rationale behind the omega-3 index

Epidemiology

Fish consumption is generally associated with a reduced risk for SCD and coronary heart disease death [4]. This association is strongest for types of fish (dark meat or oily fish) that contain higher levels of omega-3 fatty acids [4].

1558-2027

Table 1 Incidence of sudden cardiac death per 100 000 person-years [2–6]

MADIT-II, post-MI, 2003	
Ejection fraction <30%	~10 000
Europe, post-MI, 1980s	
No omega-3 fatty acids	5697
Treated with omega-3 fatty acids	3842
Europe, post-MI, 1990s (two-way analysis)	
No omega-3 fatty acids	828
Treated with omega-3 fatty acids	615
Europe, apparently healthy	122
United States, physicians	91
Japan	
Hyperlipidaemic ± cardiovascular disease	40
Healthy	7.8

MI, myocardial infarction.

When considering biomarkers of omega-3 fatty acids and risk of SCD, a steep inverse dependence between concentration and risk is observed. In a population-based case-control study of out-of-hospital SCDs, persons with an omega-3 index of 6.5% had a 90% lower risk for SCD (odds ratio 0.1, 95% confidence interval 0.1–0.4) compared to persons with an omega-3 index of 3.3%, after adjustment for other risk factors [10]. Similar results were seen in the Physicians' Health Study [3]. Physicians with 6.87% total long-chain omega-3 fatty acids in whole blood, equivalent to an omega-3 index of 6.53% (based upon laboratory tests comparing the omega-3 index to whole blood EPA + DPA + DHA as described in [7]), had a 90% lower risk for SCD (odds ratio 0.10, 95% confidence interval 0.02–0.48), as compared to physicians with 3.58% total long-chain omega-3 fatty acids (equivalent to an omega-3 index of 3.75%), after adjustment for other risk factors [3]. In both studies, risk was ~50% lower at approximately 4.5% omega-3 fatty acids and ~80% lower at approximately 5.3% omega-3 fatty acids. Thus, the proportion of omega-3 fatty acids in red blood cells or in whole blood was strongly related to the incidence of SCD. Similar (but slightly less pronounced) results were seen for omega-3 fatty acids measured in serum cholesterol esters [8]. In keeping with this, in the Cardiovascular Health Study, higher levels of EPA + DHA in plasma phospholipid fatty acids were strongly associated with a lower risk of fatal ischaemic heart disease (odds ratio 0.32, 95% confidence interval 0.13–0.78, $P = 0.01$) [5].

These observations are corroborated by ecologic (cross-population) studies (Table 1). In Europe (a region with relatively lower concentrations of omega-3 fatty acids in blood, e.g., Belfast), the incidence of SCD in apparently healthy persons is 122/100 000 person-years [4]. In contrast, in Japan (a population with very high intake of omega-3 fatty acids), the incidence of SCD is 7.8/100 000 person-years, or 94% lower than in Europe [4].

Antiarrhythmic mechanisms

Omega-3 fatty acids have antiarrhythmic effects at both the supraventricular and ventricular levels that have been reviewed elsewhere and in this issue [4,11]. Omega-3 fatty acids decrease resting heart rate, improve heart rate recovery and variability; each of these parameters are associated with risk for SCD. At the ventricular level, infusion of omega-3 fatty acids reduced inducibility of sustained ventricular tachycardia (4).

Three randomised, double-blind intervention trials in patients with ICDs and reduced ejection fractions investigated whether recurrent ventricular tachyarrhythmias could be prevented by omega-3 fatty acids. Two of these trials demonstrated no significant changes in the primary endpoint [12,13]. In the third trial, 402 patients received 2.6 g/day EPA + DHA or placebo for 12 months [14]. Red blood cell EPA + DHA rose from 3.4% to 7.6% in the intervention group and did not change in the control group. A strong trend was seen towards a 28% lower risk of the primary endpoint (time to ventricular tachycardia, ventricular fibrillation, or death) in the intervention group ($P = 0.057$).

Differences in the omega-3 index may explain the differences in the results of these trials. In the observational studies of SCD mentioned above, individuals with an omega-3 index of 4.7% had a 50% lower risk of SCD, compared to individuals with an omega-3 index of 3.3% [10]. The omega-3 index in the control group of Raitt *et al.* [12] (null result) was 4.7%, whereas it was 3.4% in the control group of Leaf *et al.* [14] (positive result). During one year, roughly half as many episodes of ventricular tachycardia/fibrillation occurred in the control group of Raitt *et al.* [12], as compared to the control group of Leaf *et al.* [14]. Therefore, the null result of Raitt *et al.* [12] trial may have been due to a lower background risk in the control group secondary to higher tissue levels of EPA + DHA. The third ICD trial did not measure the omega-3 index, but only the EPA in serum cholesterol esters, making an omega-3 index-based evaluation impossible [13].

Other potential mechanisms of action

In a randomised, placebo-controlled trial of 223 patients with angiographically proven coronary artery disease, 1.65 g/day EPA + DHA increased the omega-3 index from 3.4% to 8.3% and reduced the progression of coronary lesions [9]. This may be ascribed to plaque stabilisation by EPA + DHA [6]. These findings suggest that increasing the omega-3 index to levels above 8% mitigates the course of coronary atherosclerosis and may produce fewer unstable plaques. Such effects, at these levels of the omega-3 index, may reduce the risk of myocardial infarction and contribute to a reduction in SCD.

Trials documenting a reduction in sudden cardiac death

Four randomised trials of fish or fish oil consumption (DART, GISSI-Prevenzione, DART2, and JELIS) are reviewed elsewhere and in this issue [4,11]. DART and

GISSI-Prevenzione, but not DART2 or JELIS, demonstrated reductions in SCD by EPA + DHA. Previously, we estimated the omega-3 index to have been well above 8% in the intervention groups of DART and GISSI-Prevenzione [7]. DART2 was severely underfunded with serious limitations in design and study implementation, so that no valid conclusions can be drawn from its findings. In JELIS, conducted in a population with a very low arachidonic acid to EPA ratio, indicative of a very high omega-3 index, the incidence of SCD was so low in the control group that a further reduction could not be expected. Together with the epidemiological data and experimental studies demonstrating antiarrhythmic and other effects, the results of these intervention trials indicate a clear inverse correlation between the tissue concentration of EPA + DHA (in red blood cells, the omega-3 index) and the occurrence of SCD.

Other risk factors for sudden cardiac death

A number of risk factors for SCD have been proposed [2,15]. Many of these risk factors are either not highly discriminative (e.g., signs for left ventricular hypertrophy on the electrocardiogram) or apply to only a small fraction of the population (e.g., Brugada syndrome). Other putative risk factors for SCD (e.g., hypercholesterolaemia, hypertension, diabetes) are actually risk factors for coronary artery disease, and thus lack appropriate specificity. An important aspect of a risk factor is its incremental prognostic value, a question as yet unresolved for many proposed risk factors (e.g., coronary calcium scores [16,17]). Other risk factors (e.g., homocysteine) may not play a causative role [18]. Several others (e.g., age, gender) cannot be modified.

These limitations do not apply to the omega-3 index (Table 2). It is valid, reproducible, easily measured, and highly discriminative. Importantly, it is modifiable, and this modification lowers the risk of SCD. The incremental prognostic value of the omega-3 index remains to be defined prospectively, but because it is independent of other known risk factors, the incremental prognostic value is likely to be substantial. Siscovick *et al.* [10] observed that the inverse association between estimated dietary consumption of omega-3 fatty acids and risk of SCD was mitigated after adjustment for the omega-3 index, whereas the opposite was not true. Thus, the biomarker was more powerfully associated with risk than the estimated dietary intake, likely related to greater error in the assessment of dietary intake and/or effects related to fatty acid incorporation or metabolism that would be captured by the biomarker.

Table 2 Advantages of the omega-3 index as a risk factor for sudden cardiac death (SCD)

Validly and reproducibly expresses a given individual's omega-3 status.
Highly discriminative for SCD, predicting a 10-fold difference in risk.
Independent of other known risk factors for SCD.
Easily measured, requiring only a blood sample (fasting or non-fasting).
Modifiable, by means of fish consumption or fish oil supplements.
Modification has been demonstrated to reduce the risk of SCD in intervention trials.

Conclusion

The omega-3 index, as a risk factor for SCD, is similar to (if not more discriminative than) low-density lipoprotein cholesterol as a risk factor for coronary artery disease [1,19]. The omega-3 index can identify persons at risk for SCD in the general population and among patients with established coronary artery disease. It is more easily measured and discriminative than most other risk factors thus far proposed. Whether the omega-3 index might serve as a risk factor for nonfatal cardiac events is currently being investigated. The American Heart Association, American College of Cardiology, and European Society of Cardiology recommend EPA + DHA consumption for prevention of SCD [2]. The omega-3 index can identify individuals at risk and guide therapy with omega-3 fatty acids.

References

1 De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, *et al.* European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Eur Heart J* 2003; **24**:1601–1610.

2 Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, *et al.* ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death – executive summary: a report of the American College of Cardiology/American Heart Association Task Force and the European Society for Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Eur Heart J* 2006; **27**:2099–2140.

3 Albert CM, Campos H, Stampfer MJ, Ridker PM, Manson JE, Willett WC, *et al.* Blood levels of long-chain n-3 fatty acids and the risk of sudden death. *N Engl J Med* 2002; **346**:1113–1118.

4 von Schacky C, Harris WS. Cardiovascular benefits of omega-3 fatty acids. *Cardiovasc Res* 2007; **73**:310–315.

5 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**:319–325.

6 Thies F, Garry JM, Yaqoob P, Rerkasem K, Williams J, Shearman CP, *et al.* Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomised controlled trial. *Lancet* 2003; **361**:477–485.

7 Harris WS, von Schacky C. The omega-3 index: a new risk factor for death from coronary heart disease? *Prev Med* 2004; **39**:212–220.

8 Erkkila AT, Lehto S, Pyorala K, Uusitupa MI. n-3 Fatty acids and 5-y risks of death and cardiovascular disease events in patients with coronary artery disease. *Am J Clin Nutr* 2003; **78**:65–71.

9 von Schacky C, Angerer P, Kothny W, Theisen K, Mudra H. The effect of dietary omega-3 fatty acids on coronary atherosclerosis. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1999; **130**:554–562.

10 Siscovick DS, Raghunathan TE, King I, Weinmann S, Wicklund KG, Albright J, *et al.* Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. *JAMA* 1995; **274**:1363–1367.

11 Leaf A. Prevention of sudden cardiac death by n-3 polyunsaturated fatty acids. *J Cardiovasc Med* 2007; **8**:000–000.

12 Raitt MH, Connor WE, Morris C, Kron J, Halperin B, Chugh SS, *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**:2884–2891.

13 Effect of fish oil on ventricular tachyarrhythmia and death in patients with implantable cardioverter defibrillators: Brouwer IA, Zock PL, Camm AJ, Böcker D, Hauer RN, Wever EF, *et al*; SOFA Study Group. The Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA) randomized trial. *J Am Med Assoc* 2006; **295**:2613–2619.
14 Leaf A, Albert CM, Josephson M, Steinhaus D, Kluger J, Kang JX, *et al*., on behalf of 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**:2762–2768.
15 Podrid PJ, Myerburg RJ. Epidemiology and stratification of risk for sudden cardiac death. *Clin Cardiol* 2005; **28 (Suppl 1)**:I3–I11.
16 Clouse ME. How useful is computed tomography for screening for coronary artery disease? Noninvasive screening for coronary artery disease with computed tomography is useful. *Circulation* 2006; **113**:125–137.
17 Chen J, Krumholz HM. How useful is computed tomography for screening for coronary artery disease? Screening for coronary artery disease with electron-beam computed tomography is not useful. *Circulation* 2006; **113**:137–146.
18 Bonaa KH, Njolstad I, Ueland PM, Schirmer H, Tverdal A, Steigen T, *et al*., on behalf of the NORVIT Trial Investigators. Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N Engl J Med* 2006; **354**:1578–1588.
19 Smith SC, Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC, *et al*. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update. *Circulation* 2006; **113**:2363–2372.