Omega-3 Index and Cardiovascular Health

Clemens von Schacky 1,2

1 Preventive Cardiology, Medical Clinic and Poli-Clinic I, Ludwig Maximilians-University Munich, Ziemssenstr. 1, Munich 80336, Germany; E-Mail: Clemens.vonschacky@med.uni-muenchen.de; Tel.: +49-89-5506-3007
2 Omegametrix, Am Klopferspitz 19, Martinsried 82152, Germany; E-Mail: c.vonschacky@omegametrix.eu

Received: 20 January 2014; in revised form: 12 February 2014 / Accepted: 13 February 2014 / Published: 21 February 2014

Abstract: Recent large trials with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in the cardiovascular field did not demonstrate a beneficial effect in terms of reductions of clinical endpoints like total mortality, sudden cardiac arrest or other major adverse cardiac events. Pertinent guidelines do not uniformly recommend EPA + DHA for cardiac patients. In contrast, in epidemiologic findings, higher blood levels of EPA + DHA were consistently associated with a lower risk for the endpoints mentioned. Because of low biological and analytical variability, a standardized analytical procedure, a large database and for other reasons, blood levels of EPA + DHA are frequently assessed in erythrocytes, using the HS-Omega-3 Index® methodology. A low Omega-3 Index fulfills the current criteria for a novel cardiovascular risk factor. Neutral results of intervention trials can be explained by issues of bioavailability and trial design that surfaced after the trials were initiated. In the future, incorporating the Omega-3 Index into trial designs by recruiting participants with a low Omega-3 Index and treating them within a pre-specified target range (e.g., 8%–11%), will make more efficient trials possible and provide clearer answers to the questions asked than previously possible.

Keywords: cardiovascular disease; eicosapentaenoic acid; docosahexaenoic acid; omega-3 index; cardiovascular prevention
1. Introduction

Fish, marine oils, and their concentrates all serve as sources of the two marine omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), as do some products from algae. To demonstrate an effect of EPA + DHA on heart health, a number of randomized, controlled intervention studies with clinical endpoints like overall mortality or a combination of adverse cardiac events were conducted in populations with elevated cardiovascular risk. One early intervention study with oily fish, rich in EPA + DHA, and some early studies with fish oil or fish oil concentrate or even purified EPA at doses ranging between 0.9 and 1.8 g/day indeed demonstrated effects in terms of fewer sudden cardiac deaths, fatal or non-fatal myocardial infarctions, or a combination of adverse cardiac events [1–6]. More recent trials did not demonstrate such effects [7–12]. Recent meta-analyses found no significant benefits on total mortality, cardiovascular mortality, and other adverse cardiac or cardiovascular events [13–18]. This is in contrast to findings in epidemiologic studies, where intake of EPA + DHA had been found to correlate generally with an up to 50% lower incidence of adverse cardiac events [18,19], and in even sharper contrast to epidemiologic studies based on levels of EPA + DHA, demonstrating e.g., a 10-fold lower incidence of sudden cardiac death associated with high levels of the fatty acids, as compared to low levels [20,21]. This seemingly contradictory evidence has led the American Heart Association to recommend “omega-3 fatty acids from fish or fish oil capsules (1 g/day) for cardiovascular disease risk reduction” for secondary prevention, whereas the European Society for Cardiology recommends “Fish at least twice a week, one of which to be oily fish”, but no supplements for cardiovascular prevention [22,23]. The more recent guidelines on treating patients with stable ischemic heart disease or patients after a myocardial infarction, targeting similar patient populations, do not recommend EPA + DHA [24,25]. At least in Europe, cardiologists do not routinely use EPA + DHA to reduce cardiovascular risk.

A similar picture emerges for atrial fibrillation: In epidemiologic studies, consumption of EPA + DHA or higher levels of EPA + DHA were associated with lower risk for developing atrial fibrillation, while intervention studies found no effect [26–28]. Pertinent guidelines do not mention EPA + DHA [29]. A similar picture also emerges for severe ventricular rhythm disturbances [20,21,30,31].

Why is it that trial results are at odds with results from epidemiology? What needs to be done to better translate the epidemiologic findings into trial results? The current review will try to shed some light on this issue, with a special consideration of the Omega-3 Index.

2. The Omega-3 Index as a Cardiovascular Risk Factor

At least some nutritional surveys do not provide valid data [32]. This may explain, why the relation of EPA + DHA in the diet to clinical events has been found to be looser than the relation of levels of EPA + DHA measured in blood to clinical events (e.g., [20,33]). A detailed discussion of the pros and cons of the various fatty acid compartments in which levels of omega-3 fatty acids (whole blood, whole plasma, plasma phospholipids, and others) should be measured is outside the scope of this review and can be found elsewhere [34]. The following points argue for the use of erythrocytes: erythrocyte fatty acid composition has a low biological variability, erythrocyte fat consists almost exclusively of phospholipids, erythrocyte fatty acid composition reflects tissue fatty acid composition, pre-analytical stability, and other points [34–38]. In 2004, EPA + DHA in erythrocyte fatty acids were defined as the
Omega-3 Index and suggested as a risk factor for sudden cardiac death [39]. Integral to the definition was a specific and standardized analytical procedure, conforming the quality management routinely implemented in the field of clinical chemistry [39]. In fatty acid analysis, methods have a large impact on results: when one sample was sent to five different laboratories offering determination of an Omega-3 Index, results differed by a factor of 3.5 [34]. While results may be internally valid in one laboratory, a difference by a factor of 3.5 makes it impossible to compare results among laboratories. Therefore, the Omega-3 Index was renamed HS-Omega-3 Index®. In contrast, the laboratories adhering to the HS-Omega-3 Index methodology perform regular proficiency testing, as mandated in routine Clinical Chemistry labs [34]. So far, the HS-Omega-3 Index is the only analytical procedure used in several laboratories. A standardized analytical procedure is a prerequisite to generate the data base necessary to transport a laboratory parameter from research into clinical routine. Moreover, standardization of the analytical procedure is the first important criterion for establishing a new biomarker for cardiovascular risk set forth by the American Heart Association and the US Preventive Services Task Force [40,41].

As exemplified by Table 1, the HS-Omega-3 Index has been measured in many populations. Of note, a lower HS-Omega-3 Index was always associated with a poorer clinical condition (Table 1).

| Population | HS-Omega-3 Index |
|------------|------------------|
| **Western countries (high incidence of coronary heart disease)** |                   |
| Germany    |                   |
| Unselected Individuals (n = 5000) | 7.15 (±2.19)% |
| Patients with atherosclerosis [42], (n = 190) | 5.94 (±1.41)% |
| Patients with hyperlipidemia [43], (n = 47) | 7.00 (±1.90)% |
| Pregnant women, week 24 (n = 103) | 7.66 (±1.83)% |
| Patients with congestive heart failure (n = 895) | 3.47 (±1.20)% |
| Patients with major depression [44], (n = 90) | 3.93 (±1.50)% |
| Spain      |                   |
| Individuals with high risk for, but without cardiovascular disease [45], (n = 198) (SD not reported) | 7.10% |
| Norway     |                   |
| Patients with myocardial infarction [46] (SD not reported) | |
| With ventricular fibrillation (n = 10) | 4.88% |
| Without ventricular fibrillation (n = 185) | 6.08% |
| Europe     |                   |
| Unselected data from routine determinations, n = 10,000 | 6.96 (±2.15)% |
| USA        |                   |
| Healthy in Kansas City [47], (n = 163) | 4.90 (±2.10)% |
| Framingham-Offspring [48], (n = 3196) | 5.60 (±1.70)% |
| Patients with stable coronary heart disease [49], (n = 956) (SD not reported) | 4.60% |
| Patients with major depression [50], (n = 118) | 2.90 (±1.50)% |
| Adolescents with major depression [51], (n = 150) (SD not reported) | 3.46% |
All levels of fatty acids are determined by the balance of substance entering the body and those leaving the body. Neither a recent meal, even if rich in EPA + DHA, nor severe cardiac events altered the HS-Omega-3 Index [38,58–61]. However, while long-term intake of EPA + DHA, e.g., as assessed with food questionnaires, was the main predictor of the HS-Omega-3 Index, long-term intake explained only 12%–25% of its variability [46,62,63]. A hereditary component of 24% exists [64]. A number of other factors correlated positively (+) or negatively (−), like age (+), body mass index (−), socioeconomic status (+), smoking (−), but no other conventional cardiac risk factors [47,64–71]. More factors determining the level of the HS-Omega-3 Index, especially regarding efflux remain to be defined. Therefore, it is impossible to predict the HS-Omega-3 Index in an individual, as it is impossible to predict the increase in the HS-Omega-3 Index in an individual in response to a given dose of EPA + DHA [42,46,62,63]. In Table 2, current evidence is presented on the relation of the HS-Omega-3 Index to cardiovascular events.

This evidence is supported by measurements of EPA + DHA in other fatty acid compartments, as discussed in more detail elsewhere [72,73]. Within the framework of “Heart and Soul” and “Triumph”, it was investigated whether determination of the HS-Omega-3 Index added to the information obtained by assessing cardiovascular risk with a conventional scoring system, like the Framingham or GRACE scores for predicting fatal events. The HS-Omega-3 Index provided additional information, as demonstrated by larger areas under the curves in various c-statistics for fatal [74] and non-fatal events [53,75]. Taken together, the HS-Omega-3 Index predicts risk, appears largely independent of conventional risk factors, and adds to the information obtained by conventional risk scoring, thus fulfilling the second criterion for establishing a new biomarker for cardiovascular risk set forth by the American Heart Association and the US Preventive Services Task Force [40,41].

| Patients with severe obstructive sleep apnea [52], (n = 52) (SD not reported) | 4.00% |
|---------------------------------------------------------------|-------|
| **Saudi Arabia**                                              |       |
| Individuals, most with diabetes (n = 69)                      | 3.47 (±1.20) % |
| **Asian countries (low incidence of coronary heart disease)** |       |
| **Korea**                                                     |       |
| Healthy controls [53], (n = 50) (SD not reported)             | 11.81% |
| Healthy control [54], (n = 40)                                | 10.55 (±0.48)% |
| Patients with myocardial infarction [53], (n = 50)           | 9.57% |
| Patients with hemorrhagic brain infarction [54], (n = 40)    | 8.55 (±0.41)% |
| Patients with ischemic brain infarction [54], (n = 40)       | 8.19 (±0.64)% |
| Hemodialysis-patients without calcification on plain chest radiograph [55], (n = 11) | 9.82 (±2.37)% |
| Hemodialysis-patients with calcification on plain chest radiograph [55], (n = 20) | 9.23 (±2.34)% |
| Peritoneal Dialysis Patients [56], (n = 14)                  | 12.83 (±3.30)% |
| Patients with a kidney transplant [57], (n = 49)             | 9.70 (±1.85)% |
| **Japan**                                                     |       |
| Unselected men (n = 262), (SD not reported)                   | 9.58% |
Table 2. Summary of epidemiologic studies relating the Omega-3 Index to cardiovascular events.

| Acronym [reference] | Design | Disease   | n     | Years | Criterion                  | Comparison                  | Result                                      |
|---------------------|--------|-----------|-------|-------|----------------------------|-----------------------------|---------------------------------------------|
| **Total mortality** |        |           |       |       |                            |                             |                                             |
| Heart & Soul [49]   | cohort | stable CAD| 956   | 5.9   | total mortality           | HS-Omega-3 Index            | HR 0.73; 95% CI, 0.56–0.94                  |
|                     |        |           |       |       |                            | EPA < 0.25% total mortality 26%, 0.25 < EPA < 0.8% total mortality 13%, EPA > 0.80% total mortality 7% |
| Triumph [74]        | cohort | recent MI | 1144  | 2     | total mortality           | EPA in red cells tertiles   |                                             |
|                     |        |           |       |       |                            |                             |                                             |
| Triumph [76]        | cohort | recent MI | 1424  | 1     | total mortality           | HS-Omega-3 Index < 4% vs. >4.0% | HR 2.0; 95% CI 1.2–3.3                      |
| Racs * [77]         | cohort | recent ACS| 460   | 2     | total mortality           | HS-Omega-3 Index in quartiles| not significant.                            |
| **Sudden cardiac death** |       |           |       |       |                            |                             |                                             |
| [20]                | case-control | SCD | 82/108 cases/controls | SCD | red cell EPA + DHA in quartiles | OR 1.0–0.1 (95% CI 0.1–0.4) |
| Phys Health [21]    | case-control | SCD | 84/182 cases/controls | SCD | whole blood EPA + DHA in quartiles | OR 1.0–0.1 (95% CI 0.02–0.48) across quartiles |
| **Cardiac morbidity** |       |           |       |       |                            |                             |                                             |
| [78]                | case-control | ACS | 94/94 cases/controls | ACS | whole blood EPA + DHA in quintiles | OR 1.0–0.2 (95% CI not reported), 0.67 (95% CI 0.46 to 0.98) per, 1 standard deviation increase EPA + DHA |
| [79]                | case-control | ACS | 768/768 cases/controls | ACS | HS-Omega-3 Index in tertiles | OR 1.0–0.31 (95% CI 0.14–0.67) across tertiles |
| [53]                | case-control | ACS | 50/50 cases/controls | ACS | HS-Omega-3 Index in tertiles | OR 1.0–0.08 (95% CI 0.02–0.38) across tertiles |
| no acronym [80]     | case-control | ACS | 24/68 cases/controls | STEMI | HS-Omega-3 Index in tertiles | OR 6.38 (95% CI 1.02–39.85)–1.0 across tertiles |

Abbreviations: n: number of individuals studied; Coronary artery disease: CAD; HR: hazard ratio; MI: myocardial infarction; EPA: eicosapentaenoic acid; ACS: acute coronary syndrome; SCD: sudden cardiac death; DHA: docosahexaenoic acid; OR: odds ratio; STEMI: ST-elevation myocardial infarction. * No case estimate was reported in Racs. Therefore, by definition, it is unclear, whether the discriminatory power of the HS-Omega-3 Index was too small, or the study was too small to detect the discriminatory power.
Moreover, the HS-Omega-3 Index has made it possible to reclassify individuals from intermediate cardiovascular risk into the respective high risk and low risk strata [74,75], the third criterion for establishing a new biomarker for cardiovascular risk [40,41].

Increasing the HS-Omega-3 Index by increased intake of EPA + DHA in randomized controlled trials improved a number of surrogate parameters for cardiovascular risk: heart rate was reduced, heart rate variability was increased, blood pressure was reduced, platelet reactivity was reduced, triglycerides were reduced, large buoyant low-density lipoprotein (LDL)-particles were increased and small dense LDL-particles were reduced, large buoyant high-density lipoproteins (HDL)2 were increased, very low-density lipoprotein (VLDL1 + 2 was reduced, pro-inflammatory cytokines (e.g., tumor necrosis factor alpha, interleukin-1β, interleukins-6,8,10 and monocyte chemoattractant protein-1) were reduced, anti-inflammatory oxylipins were increased [43,81–94]. Importantly, in a two-year randomized double-blind angiographic intervention trial, increased erythrocyte EPA + DHA reduced progression and increased regression of coronary lesions, an intermediate parameter [95]. Taken together, increasing the HS-Omega-3 Index improved surrogate and intermediate parameters for cardiovascular events. A large intervention trial with clinical endpoints based on the HS-Omega-3 Index remains to be conducted. Therefore, the fourth criterion, proof of therapeutic consequence of determining the HS-Omega-3 Index, is only partially fulfilled [40,41].

3. Discussion of Neutral Results of Large Intervention Trials

Why is it that a low HS-Omega-3 Index can be a cardiovascular risk factor, and yet the results of the large trials testing EPA + DHA on clinical endpoints were neutral?

3.1. Bioavailability Issues

According to personal information from the respective first authors, participants of recent large intervention trials were advised to take their supplements, frequently an encapsulated EPA + DHA ethyl-ester with breakfast—in many countries a low-fat meal [7–11]. As discussed in more detail in a recent review, bioavailability of EPA + DHA depends on the chemical form in which they are bound (phospholipids > recombined triglycerides > triglycerides > free fatty acids > ethyl-esters) [96,97], on matrix effects (capsule ingestion with concomitant intake of food, fat content in food) or galenic form (i.e., microencapsulation, emulsification). The chemical binding form impacts on bioavailability roughly with a factor of two, whereas matrix effects can impact bioavailability up to a factor of 13, and the galenic form up to a factor of 21 [96–99]. When the large trials mentioned here were designed, the bioavailability issues just mentioned were unknown. Thus, involuntarily, the combination used in many of the large trials—An unemulsified ethyl-ester or triglyceride with a low fat meal—guaranteed a very low bioavailability of EPA + DHA.

3.2. Issues in Trial Design

In all large intervention trials conducted so far, study participants were recruited based on clinical conditions, but irrespective of their baseline omega-3 fatty acid status [1–12]. In all populations studied so far, the HS-Omega-3 Index had a statistically normal distribution (Table 1). Thus, the proportion of
the study population with high levels was not prone to the effects of EPA + DHA, if any. In order to recruit a study population, in which an effect of EPA + DHA can be demonstrated, recruiting study participants with a low HS-Omega-3 Index is a logical choice.

In all large intervention trials conducted so far, study participants were exposed to a trial-specific, but fixed dose of EPA + DHA or placebo [1–12]. The inter-individual variability in response to a fixed dose of EPA + DHA has been found to be large, i.e., vary up to a factor of 13 [42,61]. This fact alone suggests individualizing the dose given in a trial, in order to reach a predefined target range of the HS-Omega-3 Index, e.g., 8%–11%. The statistically normal distribution of the baseline HS-Omega-3 Index further complicates this problem: A large overlap of omega-3 levels in the EPA + DHA group and placebo or control group can be expected, and has been seen in at least one large trial (Mühlhäuser, B., personal communication) [100]. With levels of omega-3 fatty acids not differing between intervention and placebo or control groups, a difference in study outcome cannot be expected, even if the condition studied would be susceptible to treatment with EPA + DHA. It is worth noting that when a neutral intervention trial was analyzed in a cross-sectional way, EPA + DHA levels directly related to study outcome and less to treatment allocation [101].

Conversely, if a trial reports a positive result, it is likely to have been conducted in a study population with low baseline levels of EPA and DHA, like congestive heart failure: a positive result of a large trial was reported [6], and we found a low mean HS-Omega-3 Index in patients with congestive heart failure (unpublished data, Table 1). A similar case can be made for major depression (Table 1, references [44,50,51,84]).

In the future, recruiting study participants with a low baseline HS-Omega-3 Index and treating them within a predefined target range will allow clearer trial results to be a distinct possibility. Dose adjustments will need to be performed in the placebo group. Since a larger treatment effect can be assumed in the study size estimation, it can be expected that study sizes will be smaller and thus studies less expensive. Clearly, these thoughts are not restricted to trials with patients with cardiovascular risk, atrial fibrillation or ventricular arrhythmia, but can be extended to all areas of omega-3 fatty acid research. This will facilitate scientific progress and lead to a faster recognition of the effects of EPA + DHA.

4. Conclusions

In an inconsistent manner, EPA and DHA are either recommended or not included in guidelines of cardiac scientific societies. The use of EPA and DHA is not supported by results of recent intervention trials or their meta-analyses. However, epidemiologic data based on assessments of diet and, even more so, data based on levels of EPA + DHA measured in humans, clearly demonstrate that EPA + DHA are associated with a low risk for total mortality, sudden cardiac arrest, and fatal and non-fatal myocardial infarctions. For a number of reasons, like a standardized analytical procedure and a large data base, levels of EPA + DHA are best assessed with the HS-Omega-3 Index. According to current criteria of the American Heart Association and others, the HS-Omega-3 Index is a novel cardiovascular risk factor. Moreover, the HS-Omega-3 Index has led to a fresh look at the field of omega-3 fatty acids and has made it possible to identify issues of bioavailability and study design, explaining at least in part the neutral
results of previous intervention trials. In the future, more efficient intervention studies can be conducted based on the HS-Omega-3 Index, thus providing a clearer picture of the effects of EPA + DHA.

Conflicts of Interest

CvS operates Omegametrix, a laboratory for fatty acid analyses. Speaker honoraria were received from Reckitt-Benckiser and the Portuguese National Fisheries.

Acknowledgments

Research grants were provided by several government agencies, AkerBiomarine, Neptune, and Fresenius Kabi. The cost of travel to the AAOCS meeting was provided by Sanofi Consumer Health Care.

References

1. Burr, M.L.; Fehily, A.M.; Gilbert, J.F.; Rogers, S.; Holliday, R.M.; Sweetnam, P.M.; Elwood, P.C.; Deadman, N.M. Effects of changes in fat, fish, and fibre intakes on death and myocardial infarction: Diet and reinfarction trial (DART). *Lancet* 1989, 2, 757–761.
2. GISSI Prevenzione Investigators. Dietary supplementation with $n$-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: Results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico. *Lancet* 1999, 354, 447–455.
3. Marchioli, R.; Barzi, F.; Bomba. E.; Chieffo, C.; di Gregorio, D.D.M.R.; Franzosi, M.G.; Geraci, E.; Levatesi, G.; Maggioni, A.P.; Mantini, L.; et al. Early protection against sudden death by $n$-3 polyunsaturated fatty acids after myocardial infarction. Time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardio (GISSI)-Prevenzione. *Circulation* 2002, 105, 1897–1903.
4. Svensson, M.; Schmidt, E.B.; Jørgensen, K.A.; Christensen, J.H.; OPACH Study Group. $n$-3 Fatty acids as secondary prevention against cardiovascular events in patients who undergo chronic haemodialysis: A randomized, placebo-controlled intervention trial. *Clin. J. Am. Soc. Nephrol.* 2006, 1, 780–786.
5. Yokoyama, M.; Origasa, H.; Matsuzaki, M.; Matsuzawa, Y.; Saito, Y.; Ishikawa, Y.; Oikawa, S.; Sasaki, J.; Hishida, H.; Itakura, H.; et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): A randomised open-label, blinded endpoint analysis. *Lancet* 2007, 369, 1090–1098.
6. Gissi-HF Investigators; Tavazzi, L.; Maggioni, A.P.; Marchioli, R.; Barlera, S.; Franzosi, M.G.; Latini, R.; Lucci, D.; Nicolosi, G.L.; Porcu, M.; et al. Effect of $n$-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): A randomised, double-blind, placebo-controlled trial. *Lancet* 2008, 372, 1223–1230.
7. Galan, P.; Kesse-Guyot, E.; Czernichow, S.; Briancon, S.; Blacher, J.; Hercberg, S.; SU.FOL.OM3 Collaborative Group. Effects of B vitamins and omega 3 fatty acids on cardiovascular diseases: A randomised placebo controlled trial. *Br. Med. J.* 2010, 341, c6273.
8. Rauch, B.; Schiele, R.; Schneider, S.; Diller, F.; Victor, N.; Gohlke, H.; Gottwik, M.; Steinbeck, G.; del Castillo, U.; Sack, R.; et al. OMEGA, a randomized, placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. *Circulation* **2010**, *122*, 2152–2159.

9. Einvik, G.; Klemsdal, T.O.; Sandvik, L.; Hjerkinn, E.M. A randomized clinical trial on n-3 polyunsaturated fatty acids supplementation and all-cause mortality in elderly men at high cardiovascular risk. *Eur. J. Cardiovasc. Prev. Rehabil.* **2010**, *17*, 588–592.

10. Kromhout, D.; Giltay, E.J.; Geleijse, J.M.; Alpha Omega Trial Group. n-3 Fatty acids and cardiovascular events after myocardial infarction. *N. Engl. J. Med.* **2010**, *363*, 2015–2026.

11. ORIGIN Trial Investigators; Bosch, J.; Gerstein, H.C.; Dagenais, G.R.; Diaz, R.; Dyal, L.; Jung, H.; Maggioni, A.P.; Probstfield, J.; Ramachandran, A.; et al. n-3 Fatty acids and cardiovascular outcomes in patients with dysglycemia. *N. Engl. J. Med.* **2011**, *367*, 319–328.

12. Risk and Prevention Study Collaborative Group; Roncaglioni, M.C.; Tombesi, M.; Avanzini, F.; Barlera, S.; Caimi, V.; Longoni, P.; Marzona, I.; Milani, V.; Silletta, M.G.; et al. n-3 Fatty acids in patients with multiple cardiovascular risk factors. *N. Engl. J. Med.* **2013**, *368*, 1800–1808.

13. Chowdhury, R.; Stevens, S.; Gorman, D.; Pan, A.; Warnakula, S.; Chowdhury, S.; Ward, H.; Johnson, L.; Crowe, F.; Hu, F.B.; et al. Association between fish consumption, long chain omega 3 fatty acids, and risk of cerebrovascular disease: Systematic review and meta-analysis. *Br. Med. J.* **2012**, *345*, e6698.

14. Kotwal, S.; Jun, M.; Sullivan, D.; Perkovic, V.; Neal, B. Omega 3 fatty acids and cardiovascular outcomes: Systematic review and meta-analysis. *Circ. Cardiovasc. Qual. Outcomes* **2012**, *5*, 808–818.

15. Rizos, E.C.; Ntzani, E.E.; Bika, E.; Kostapanos, M.S.; Elisaf, M.S. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: A systematic review and meta-analysis. *J. Am. Med. Assoc.* **2012**, *308*, 1024–1033.

16. Kwak, S.M.; Myung, S.K.; Lee, Y.J.; Seo, H.G.; Korean Meta-analysis Study Group. Efficacy of omega-3 fatty acid supplements (eicosapentaenoic acid and docosahexaenoic acid) in the secondary prevention of cardiovascular disease: A meta-analysis of randomized, double-blind, placebo-controlled trials. *Arch. Intern. Med.* **2012**, *172*, 686–694.

17. Delgado-Lista, J.; Perez-Martinez, P.; Lopez-Miranda, J.; Perez-Jimenez, F. Long chain omega-3 fatty acids and cardiovascular disease: A systematic review. *Br. J. Nutr.* **2012**, *107*, S201–S213.

18. Mozaffarian, D.; Rimm, E.B. Fish intake, contaminants, and human health: Evaluating the risks and the benefits. *J. Am. Med. Assoc.* **2006**, *296*, 1885–1899.

19. Hu, F.B.; Bronner, L.; Willett, W.C.; Stampfer, M.J.; Rexrode, K.M.; Albert, C.M.; Hunter, D.; Manson, J.E. Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. *J. Am. Med. Assoc.* **2002**, *287*, 1815–1821.

20. Siscovick, D.S.; Raghunathan, T.E.; King, I.; Weinmann, S.; Wicklund, K.G.; Albright, J.; Bovbjerg, V.; Arbogast, P.; Smith, H.; Kushi, L.H. Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. *J. Am. Med. Assoc.* **1995**, *275*, 836–837.
21. Albert, C.M.; Campos, H.; Stampfer, M.J.; Ridker, P.M.; Manson, J.E.; Willett, W.C.; Ma, J. Blood levels of long-chain $n$-3 fatty acids and the risk of sudden death. *N. Engl. J. Med.* **2002**, *346*, 1113–1118.

22. Smith, S.C., Jr.; Benjamin, E.J.; Bonow, R.O.; Braun, L.T.; Creager, M.A.; Franklin, B.A.; Gibbons, R.J.; Grundy, S.M.; Hiratzka, L.F.; Jones, D.W.; *et al.* AHA/ACC primary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: A guideline from the american heart association and american college of cardiology foundation. *Circulation* **2011**, *124*, 2458–2473.

23. Perk, J.; de Backer, G.; Gohlke, H.; Graham, I.; Reiner, Z.; Verschuren, M.; Albus, C.; Benlian, P.; Boysen, G.; Cifkova, R.; *et al.* European guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur. Heart J.* **2012**, *33*, 1635–1701.

24. Fihn, S.D.; Gardin, J.M.; Abrams, J.; Berra, K.; Blankenship, J.C.; Dallas, A.P.; Douglas, P.S.; Foody, J.M.; Gerber, T.C.; Hinderliter, A.L.; *et al.* 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: A report of the American college of cardiology foundation/american heart association task force on practice guidelines, and the american college of physicians, american association for thoracic surgery, preventive cardiovascular nurses association, society for cardiovascular angiography and interventions, and society of thoracic surgeons. *Circulation* **2012**, *126*, e354–e471.

25. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC); Steg, P.G.; James, S.K.; Atar, D.; Badano, L.P.; Blömstrom-Lundqvist, C.; Borger, M.A.; di Mario, C.; Dickstein, K.; Ducro eq, G.; *et al.* ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur. Heart J.* **2012**, *33*, 2569–2619.

26. Mozaffarian, D.; Psaty, B.M.; Rimm, E.B.; Lemaitre, R.N.; Burke, G.L.; Lyles, M.F.; Lefkowitz, D.; Siscovick, D.S. Fish intake and risk of incident atrial fibrillation. *Circulation* **2004**, *110*, 368–373.

27. Wu, J.H.; Lemaitre, R.N.; King, I.B.; Song, X.; Sacks, F.M.; Rimm, E.B.; Heckbert, S.R.; Siscovick, D.S.; Mozaffarian, D. Association of plasma phospholipid long-chain $\omega$-3 fatty acids with incident atrial fibrillation in older adults: The cardiovascular health study. *Circulation* **2012**, *125*, 1084–1093.

28. Mozaffarian, D.; Wu, J.H.; de Oliveira Otto, M.C.; Sandesara, C.M.; Metcalf, R.G.; Latini, R.; Libby, P.; Lombardi, F.; O’Gara, P.T.; Page, R.L.; *et al.* Fish oil and post-operative atrial fibrillation: A meta-analysis of randomized controlled trials. *J. Am. Coll. Cardiol.* **2013**, *61*, 2194–2196.

29. European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery; Camm, A.J.; Kirchhof, P.; Lip, G.Y.; Schotten, U.; Savelieva, I.; Ernst, S.; can Gelder, I.C.; Al-Attar, N.; *et al.* Guidelines for the management of atrial fibrillation: The task force for the management of atrial fibrillation of the european society of cardiology (ESC). *Eur. Heart J.* **2010**, *31*, 2369–2429.
30. Brouwer, I.A.; Raitt, M.H.; Dullemeijer, C.; Kraemer, D.F.; Zock, P.L.; Morris, C.; Katan, M.B.; Connor, W.E.; Camm, J.A.; Schouten, E.G.; et al. Effect of fish oil on ventricular tachyarrhythmia in three studies in patients with implantable cardioverter defibrillators. *Eur. Heart J.* 2009, 30, 820–826.

31. Zipes, D.P.; Camm, A.J.; Borggrefe, M.; Buxton, A.E.; Chaitman, B.; Fromer, M.; Gregoratos, G.; Klein, G.; Moss, A.J.; Myerburg, R.J.; 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 of 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.

32. Archer, E.; Hand, G.A.; Blair, S.N. Validity of U. S. nutritional surveillance: National Health and Nutrition Examination Survey caloric energy intake data, 1971–2010. *PLoS One* 2013, 8, e76632.

33. De Oliveira Otto, M.C.; Wu, J.H.; Baylin, A.; Vaidya, D.; Rich, S.S.; Tsai, M.Y.; Jacobs, D.R.; Mozaffarian, D. Circulating and dietary omega-3 and omega-6 polyunsaturated fatty acids and incidence of CVD in the multi-ethnic study of atherosclerosis. *J. Am. Heart Assoc.* 2013, 2, e000506.

34. Harris, W.S.; von Schacky, C.; Park, Y. Standardizing Methods for Assessing Omega-3 Biostatus. In *The Omega-3 Deficiency Syndrome*; McNamara, R.K., Ed.; Nova Publishers: Hauppauge, NY, USA, 2013; pp. 385–398.

35. Von Schacky, C.; Fischer, S.; Weber, P.C. Long term effects of dietary marine omega-3 fatty acids upon plasma- and cellular lipids, platelet function and eicosanoid formation in humans. *J. Clin. Investig.* 1985, 76, 1626–1631.

36. Harris, W.S.; Sands, S.A.; Windsor, S.L.; Ali, H.A.; Stevens, T.L.; Magalski, A.; Porter, C.B.; Borkon, A.M. Omega-3 fatty acid levels in transplanted human hearts: Effect of supplementation and comparison with erythrocytes. *Circulation* 2004, 110, 1645–1649.

37. Arnold, C.; Markovic, M.; Blossey, K.; Wallukat, G.; Fischer, R.; Dechend, R.; Konkel, A.; von Schacky, C.; Luft, F.C.; Muller, D.N.; *et al.* Arachidonic acid-metabolizing cytochrome P-450 enzymes are targets of omega-3 fatty acids. *J. Biol. Chem.* 2010, 285, 32720–32733.

38. Harris, W.S.; Thomas, R.M. Biological variability of blood omega-3 biomarkers. *Clin. Biochem.* 2010, 43, 338–340.

39. Harris, W.S.; von Schacky, C. The omega-3 index: A new risk factor for death from CHD? *Prev. Med.* 2004, 39, 212–220.

40. Hlatky, M.A.; Greenland, P.; Arnett, D.K.; Ballantyne, C.M.; Criqui, M.H.; Elkind, M.S.; Go, A.S.; Harrell, F.E., Jr.; Hong, Y.; Howard, B.V.; *et al.* American heart association expert panel on subclinical atherosclerotic diseases and emerging risk factors and the stroke council. *Circulation* 2009, 119, 2408–2416.

41. Helfand, M.; Buckley, D.I.; Freeman, M.; Fu, R.; Rogers, K.; Fleming, C.; Humphrey, L.L. Emerging risk factors for coronary heart disease: A summary of systematic reviews conducted for the U.S. preventive services task force. *Ann. Intern. Med.* 2009, 151, 496–507.
42. Köhler, A.; Bittner, D.; Löw, A.; von Schacky, C. Effects of a convenience drink fortified with n-3 fatty acids on the n-3 index. *Br. J. Nutr.* 2010, 104, 729–736.

43. Neubronner, J.; Schuchardt, J.P.; Kressel, G.; Merkel, M.; von Schacky, C.; Hahn, A. Enhanced increase of omega-3 index in response to long-term n-3 fatty acid supplementation from triacylglycerides vs. ethyl esters. *Eur. J. Clin. Nutr.* 2011, 65, 247–254.

44. Baghai, T.C.; Varallo-Bedarida, G.; Born, C.; Häfner, S.; Schüle, C.; Eser, D.; Rupprecht, R.; Bondy, B.; von Schacky, C. Major depression is associated with cardiovascular risk factors and low Omega-3 Index. *J. Clin. Psychiatry* 2011, 72, 1242–1247.

45. Sala-Vila, A.; Harris, W.S.; Cofán, M.; Pérez-Heras, A.M.; Pintó, X.; Lamuela-Raventós, R.M.; Covas, M.I.; Estruch, R.; Ros, E. Determinants of the omega-3 index in a Mediterranean population at increased risk for CHD. *Br. J. Nutr.* 2011, 106, 425–431.

46. Aarsetoey, H.; Pönitz, V.; Nilsen, O.B.; Grundt, H.; Harris, W.S.; Nilsen, D.W. Low levels of cellular omega-3 increases the risk of ventricular fibrillation during the acute ischaemic phase of a myocardial infarction. *Resuscitation* 2008, 78, 258–264.

47. Sands, S.A.; Reid, K.J.; Windsor, S.L.; Harris, W.S. The impact of age, body mass index, and fish intake on the EPA and DHA content of human erythrocytes. *Lipids* 2005, 40, 343–347.

48. Harris, W.S.; Pottala, J.V.; Vasan, R.S.; Larson, M.G.; Robins, S.J. Changes in erythrocyte membrane trans and marine fatty acids between 1999 and 2006 in older Americans. *J. Nutr.* 2012, 142, 1297–1303.

49. Pottala, J.V.; Garg, S.; Cohen, B.E.; Whooley, M.A.; Harris, W.S. Blood eicosapentaenoic and docosahexaenoic acids predict all-cause mortality in patients with stable coronary heart disease: The heart and soul study. *Circ. Cardiovasc. Qual. Outcomes* 2010, 3, 406–412.

50. Amin, A.A.; Menon, R.A.; Reid, K.J.; Harris, W.S.; Spertus, J.A. Acute coronary syndrome patients with depression have low blood cell membrane omega-3 fatty acid levels. *Psychosom. Med.* 2008, 70, 856–862.

51. Pottala, J.V.; Churchill, S.W.; Talley, J.A.; Lynch, D.A.; von Schacky, C.; Harris, W.S. Red blood cell fatty acids are associated with depression in a case-control study of adolescents. *Prostaglandins Leukot. Essent. Fatty Acids* 2012, 86, 161–165.

52. Ladesich, J.B.; Pottala, J.V.; Romaker, A.; Harris, W.S.; Membrane levels of omega-3 docosahexaenoic acid is associated with obstructive sleep apnea. *J. Clin. Sleep Med.* 2011, 7, 391–396.

53. Park, Y.; Lim, J.; Lee, J.; Kim, S.G. Erythrocyte fatty acid profiles can predict acute non-fatal myocardial infarction. *Br. J. Nutr.* 2009, 102, 1355–1356.

54. Park, Y.; Park, S.; Yi, H.; Kim, H.Y.; Kang, S.J.; Kim, J.; Ahn, H. Low level of n-3 polyunsaturated fatty acids in erythrocytes is a risk factor for both acute ischemic and hemorrhagic stroke in Koreans. *Nutr. Res.* 2009, 29, 825–830.

55. Son, Y.K.; Lee, S.M.; Kim, S.E.; Kim, K.H.; Lee, S.Y.; Bae, H.R.; Han, J.Y.; Park, Y.; An, W.S. Association between vascular calcification scores on plain radiographs and fatty acid contents of erythrocyte membrane in hemodialysis patients. *J. Ren. Nutr.* 2012, 22, 58–66.

56. An, W.S.; Kim, S.E.; Kim, K.H.; Lee, S.; Park, Y.; Kim, H.J.; Vaziri, N.D. Comparison of fatty acid contents of erythrocyte membrane in hemodialysis and peritoneal dialysis patients. *J. Ren. Nutr.* 2009, 19, 267–274.
57. Oh, J.S.; Kim, S.M.; Sin, Y.H.; Kim, J.K.; Park, Y.; Bae, H.R.; Son, Y.K.; Nam, H.K.; Kang, H.J.; An, W.S. Comparison of erythrocyte membrane fatty acid contents in renal transplant recipients and dialysis patients. *Transplant. Proc.* **2012**, *44*, 2932–2935.

58. Harris, W.S.; Varvel, S.A.; Pottala, J.V.; Warnick, G.R.; McConnell, J.P. The comparative effects of an acute dose of fish oil on omega-3 fatty acid levels in red blood cells versus plasma: Implications for clinical utility. *J. Clin. Lipidol.* **2013**, *7*, 433–440.

59. Shearer, G.C.; Chen, J.; Chen, Y.; Harris, W.S. Myocardial infarction does not affect fatty acid profiles in rats. *Prostaglandins Leukot. Essent. Fatty Acids* **2009**, *81*, 411–416.

60. Aarsetøy, H.; Aarsetøy, R.; Lindner, T.; Staines, H.; Harris, W.S.; Nilsen, D.W.T. Low levels of the omega-3 index are associated with sudden cardiac arrest and remain stable in survivors in the subacute phase. *Lipids* **2011**, *46*, 151–161.

61. Flock, M.R.; Skulas-Ray, A.C.; Harris, W.S.; Etherton, T.D.; Fleming, J.A.; Kris-Etherton, P.M. Determinants of erythrocyte omega-3 fatty acid content in response to fish oil supplementation: A dose-response randomized controlled trial. *J. Am. Heart Assoc.* **2013**, *2*, e000513.

62. Ebbesson, S.O.; Devereux, R.B.; Cole, S.; Ebbesson, L.O.; Fabsitz, R.R.; Haack, K.; Harris, W.S.; Howard, W.J.; Laston, S.; Lopez-Alvarenga, J.C.; et al. Heart rate is associated with red blood cell fatty acid concentration: The Genetics of Coronary Artery Disease in Alaska Natives (GOCADAN) Study. *Am. Heart J.* **2010**, *159*, 1020–1025.

63. Harris, W.S.; Pottala, J.V.; Lacey, S.M.; Vasan, R.S.; Larson, M.G.; Robins, S.J. Clinical correlates and heritability of erythrocyte eicosapentaenoic and docosahexaenoic acid content in the Framingham Heart Study. *Atherosclerosis* **2012**, *225*, 425–431.

64. Cohen, B.E.; Garg, S.K.; Ali, S.; Harris, W.S.; Whooley, M.A. Red blood cell EPA and DHA concentrations are positively associated with socioeconomic status in patients with established coronary artery disease: Data from the Heart and Soul Study. *J. Nutr.* **2008**, *138*, 1135–1140.

65. Block, R.C.; Harris, W.S.; Pottala, J.V. Determinants of blood cell omega-3 fatty acid content. *Open Biomark. J.* **2008**, *1*, 1–6.

66. Farzaneh-Far, R.; Harris, W.S.; Garg, S.; Na, B.; Whooley, M.A. Inverse association of erythrocyte n-3 fatty acid levels with inflammatory biomarkers in stable coronary artery disease: The Heart and Soul Study. *Atherosclerosis* **2009**, *205*, 538–543.

67. An, W.S.; Son, Y.K.; Kim, S.E.; Kim, K.H.; Bae, H.R.; Lee, S.; Park, Y.; Kim, H.J.; Vaziri, N.D. Association of adiponectin and leptin with serum lipids and erythrocyte omega-3 and omega-6 fatty acids in dialysis patients. *Clin. Nephrol.* **2011**, *75*, 195–203.

68. Salisbury, A.C.; Amin, A.P.; Harris, W.S.; Chan, P.S.; Gosch, K.L.; Rich, M.W.; O’Keefe, J.H., Jr.; Spertus, J.A. Predictors of omega-3 index in patients with acute myocardial infarction. *Mayo Clin. Proc.* **2011**, *86*, 626–632.

69. Jo, S.; An, W.S.; Park Y. Erythrocyte n-3 polyunsaturated fatty acids and the risk of type 2 diabetes in Koreans: A case-control study. *Ann. Nutr. Metab.* **2013**, *63*, 283–290.

70. Park, Y.; Kim, M. Serum 25-hydroxyvitamin D concentrations are associated with erythrocyte levels of n-3 PUFA but not risk of CVD. *Br. J. Nutr.* **2011**, *106*, 1529–1534.
71. Grenon, S.M.; Conte, M.S.; Nosova, E.; Alley, H.; Chong, K.; Harris, W.S.; Vittinghoff, E.; Owens, C.D. Association between n-3 polyunsaturated fatty acid content of red blood cells and inflammatory biomarkers in patients with peripheral artery disease. *J. Vasc. Surg.* **2013**, *58*, 1283–1290.

72. Harris, W.S.; Poston, W.C.; Haddock, C.K. Tissue n-3 and n-6 fatty acids and risk for coronary heart disease events. *Atherosclerosis* **2007**, *193*, 1–10.

73. Superko, H.R.; Superko, S.M.; Nasir, K.; Agatston, A.; Garrett, B.C. Omega-3 fatty acid blood levels: Clinical significance and controversy. *Circulation* **2013**, *128*, 2154–2161.

74. Harris, W.S.; Kennedy, K.F.; O’Keefe, J.H., Jr.; Spertus, J.A. Red blood cell fatty acid levels improve GRACE score prediction of 2-year mortality in patients with myocardial infarction. *Int. J. Cardiol.* **2013**, *168*, 53–59.

75. Shearer, G.C.; Pottala, J.V.; Spertus, J.A.; Harris, W.S. Red blood cell fatty acid patterns and acute coronary syndrome. *PLoS One* **2009**, *4*, e5444.

76. Abuannadi, M.; O’Keefe, J.H.; Spertus, J.A.; Kennedy, K.F.; Harris, W.S. Omega-3 Index: An Independent Predictor of 1 Year All Cause Mortality in Myocardial Infarction (MI) Patients. Poster 174, AHA QCOR Meeting, 19–21 May 2010. Available online: http://my.americanheart.org/idc/groups/ahamah-public/@wcm/@sop/@scon/documents/downloadable/ucm_319392.pdf (accessed on 15 January 2014).

77. Aarsetoey, H.; Pönitz, V.; Grundt, H.; Staines, H.; Harris, W.S.; Nilsen, D.W. (n-3) Fatty acid content of red blood cells does not predict risk of future cardiovascular events following an acute coronary syndrome. *J. Nutr.* **2009**, *139*, 507–513.

78. Harris, W.S.; Reid, K.J.; Sands, S.A.; Spertus, J.A. Blood omega-3 and trans fatty acids in middle-aged acute coronary syndrome patients. *Am. J. Cardiol.* **2007**, *99*, 154–158.

79. Block, R.C.; Harris, W.S.; Reid, K.J.; Sands, S.A.; Spertus, J.A. EPA and DHA in blood cell membranes from acute coronary syndrome patients and controls. *Atherosclerosis* **2008**, *197*, 821–828.

80. Kim, Y.J.; Jeong, D.W.; Lee, J.G.; Lee, H.C.; Lee, S.Y.; Kim, Y.J.; Yi, Y.H.; Park, Y.S.; Cho, Y.H.; Bae, M.J.; *et al.* Omega-3 index and smoking in patients with acute ST-elevation myocardial infarction taking statins: A case-control study in Korea. *Lipids Health Dis.* **2012**, *11*, 43.

81. Harris, W.S.; Gonzales, M.; Laney, N.; Sastre, A.; Borkon, A.M. Effects of omega-3 fatty acids on heart rate in cardiac transplant recipients. *Am. J. Cardiol.* **2006**, *98*, 1393–1395.

82. Harris, W.S.; Pottala, J.V.; Sands, S.A.; Jones, P.G. Comparison of the effects of fish and fish oil capsules on the n-3 fatty acid content of blood cells and plasma phospholipids. *Am. J. Clin. Nutr.* **2007**, *86*, 1621–1625.

83. Larson, M.K.; Ashmore, J.H.; Harris, K.A.; Vogelaar, J.L.; Pottala, J.V.; Sprehe, M.; Harris, W.S. Effects of omega-3 acid ethyl esters and aspirin, alone and in combination, on platelet function in healthy subjects. *Thromb. Haemost.* **2008**, *100*, 634–641.

84. Carney, R.M.; Freedland, K.E.; Stein, P.K.; Steinmeyer, B.C.; Harris, W.S.; Rubin, E.H.; Krone, R.J.; Rich, M.W. Effect of omega-3 fatty acids on heart rate variability in depressed patients with coronary heart disease. *Psychosom. Med.* **2010**, *72*, 748–754.
85. Skulas-Ray, A.C.; Kris-Etherton, P.M.; Harris, W.S.; Vanden Heuvel, J.P.; Wagner, P.R.; West, S.G. Dose response effects of omega-3 fatty acids on triglycerides, inflammation, and endothelial function in healthy people with moderate hypertriglyceridemia. *Am. J. Clin. Nutr.* 2011, 93, 243–252.

86. Schuchardt, J.P.; Neubronner, J.; Kressel, G.; Merkel, A.; von Schacky, C.; Hahn, A. Moderate doses of EPA and DHA from re-esterified triacylglycerols but not from ethyl-esters lower fasting serum triacylglycerols in statin-treated dyslipidemic subjects: Results from a six month randomized controlled trial. *Prostaglandins Leukot. Essent. Fatty Acids* 2011, 85, 381–386.

87. Dewell, A.; Marvasti, F.F.; Harris, W.S.; Tsao, P.; Gardner, C.D. Dose-dependent effects of plant and marine omega-3 fatty acids on inflammatory markers in insulin resistant adults. A randomized controlled trial. *J. Nutr.* 2011, 141, 2166–2171.

88. Maki, K.C.; Bays, H.E.; Dicklin, M.R.; Johnson, S.L.; Shabbout, M. Effects of prescription omega-3-acid ethyl esters, coadministered with atorvastatin, on circulating levels of lipoprotein particles, apolipoprotein CIII, and lipoprotein-associated phospholipase A2 mass in men and women with mixed dyslipidemia. *J. Clin. Lipidol.* 2011, 5, 483–492.

89. Krul, E.S.; Lenke, S.L.; Mukherjea, R.; Taylor, M.L.; Goldstein, D.A.; Su, H.; Liu, P.; Lawless, A.; Harris, W.S.; Maki, K.C. Effects of duration of treatment and dosage of eicosapentaenoic acid and stearidonic acid on red blood cell eicosapentaenoic acid content. *Prostaglandins Leukot. Essent. Fatty Acids* 2012, 86, 51–59.

90. An, W.S.; Lee, S.M.; Son, Y.K.; Kim, S.E.; Kim, K.H.; Han, J.Y.; Bae, H.R.; Park, Y. Effect of omega-3 fatty acids on the modification of erythrocyte membrane fatty acid content including oleic acid in peritoneal dialysis patients. *Prostaglandins Leukot. Essent. Fatty Acids* 2012, 86, 29–34.

91. Shearer, G.C.; Pottala, J.V.; Hansen, S.N.; Brandenburg, V.; Harris, W.S. Effects of prescription niacin and omega-3 fatty acids on lipids and vascular function in metabolic syndrome: A randomized controlled trial. *J. Lipid Res.* 2012, 53, 2429–2435.

92. Skulas-Ray, A.C.; Kris-Etherton, P.M.; Harris, W.S.; West, S.G. Effects of marine-derived omega-3 fatty acids on systemic hemodynamics at rest and during stress: A dose-response study. *Ann. Behav. Med.* 2012, 44, 301–308.

93. Keenan, A.H.; Pedersen, T.L.; Fillaus, K.; Larson, M.K.; Shearer, G.C.; Newman, J.W. Basal omega-3 fatty acid status affects fatty acid and oxylipin responses to high-dose n-3-HUFA in healthy volunteers. *J. Lipid Res.* 2012, 53, 1662–1669.

94. Block, R.C.; Dier, U.; Calderonartero, P.; Shearer, G.C.; Kakinami, L.; Larson, M.K.; Harris, W.S.; Georas, S.; Mousa, S.A. The effects of EPA + DHA and aspirin on inflammatory cytokines and angiogenesis factors. *World J. Cardiovasc. Dis.* 2012, 2, 14–19.

95. 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. Int. Med.* 1999, 130, 554–562.

96. Schuchardt, J.P.; Hahn, A. Bioavailability of long-chain omega-3 fatty acids. *Prostaglandins Leukot. Essent. Fatty Acids* 2013, 89, 1–8.

97. Dyerberg, J.; Madsen, P.; Moller, J.M.; Aardestrup, I.; Schmidt, E.B. Bioavailability of marine n-3 fatty acid formulations. *Prostaglandins Leukot. Essent. Fatty Acids* 2010, 83, 137–41.
98. Davidson, M.H.; Johnson, J.; Rooney, M.W.; Kyle, M.L.; Kling, D.F. A novel omega-3 free fatty acid formulation has dramatically improved bioavailability during a low-fat diet compared with omega-3-acid ethyl esters: The ECLIPSE (Epanova® compared to Lovaza® in a pharmacokinetic single-dose evaluation) study. *J. Clin. Lipidol.* 2012, 6, 573–584.

99. Hussey, E.K.; Portelli, S.; Fossler, M.J.; Gao, F.; Harris, W.S.; Blum, R.A.; Lates, C.D.; Gould, E.; Abu-Baker, O.; Johnson, S.; et al. Relative bioavailability of an emulsion formulation for omega-3-acid ethyl esters compared to the commercially available formulation: A randomized, parallel-group, single-dose study followed by repeat dosing in healthy volunteers. *Clin. Pharm. Drug Dev.* 2012, 1, 14–23.

100. Makrides, M.; Gibson, R.A.; McPhee, A.J.; Yelland, L.; Quinlivan, J.; Ryan, P. DOMInO Investigative Team. Effect of DHA supplementation during pregnancy on maternal depression and neurodevelopment of young children: A randomized controlled trial. *J. Am. Med. Assoc.* 2010, 304, 1675–1683.

101. Montgomery, P.; Burton, J.R.; Sewell, R.P.; Spreckelsen, T.F.; Richardson, A.J. Low blood long chain omega-3 fatty acids in UK children are associated with poor cognitive performance and behavior: A cross-sectional analysis from the DOLAB study. *PLoS One* 2013, 8, e66697.

© 2014 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license (http://creativecommons.org/licenses/by/3.0/).