

## **Omega-3 fatty acids and cardiovascular outcomes : an update**

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Cardiovascular risk factors, cardiovascular health and cardiovascular outcomes are probably the most intensively and extensively researched parts of the omega-3 (n-3) fatty acid story, with much of this research focussing on the marine n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [1-5]. This activity continues and 2016, 2017 and 2018 saw the publication of important new cohort studies (e.g. [6]), pooled data from cohort studies (e.g. [7,8]), randomised controlled trials (RCTs) [9-11], meta-analyses [12-17] and statements regarding clinical practice [18]. This article will describe and discuss these recent publications, placing them in the context of the already existing literature.

Less than ten years ago, the notion that the marine n-3 fatty acids EPA and DHA had an important role in both prevention and treatment of cardiovascular disease (CVD), particularly coronary heart disease (CHD), was largely undisputed [1-3]. The role in prevention was based upon protective associations seen in several large cohort studies (e.g. [19,20]) while the role in treatment (e.g. post-myocardial infarction (MI); in heart failure) was based upon a small number of large trials that reported reduced mortality in patients receiving marine n-3 fatty acids compared to control [21-23]. These latter findings were supported by meta-analyses that also included data from smaller trials [24-28]. In 2010, the conclusion that marine n-3 fatty acids reduce mortality in at-risk patients was challenged by three large RCTs [29-31]. As discussed elsewhere [4,32], these trials used lower doses of EPA and DHA than previous successful trials, were of shorter duration and typically had low event rates limiting their power to identify an effect. While some meta-analyses published in 2012 that included these trials reported no effect of marine n-3 fatty acids on mortality outcomes [33-35], other meta-analyses favouring a mortality benefit of EPA and DHA were published around that time [36,37]. Of great relevance, Poole et al. [38] performed a retrospective analysis of almost 2,500 patients who had been prescribed approximately 900 mg EPA plus DHA as ethyl esters daily in the 90 days after their first MI; these patients were compared with about 10,000 matched post-MI patients who had not been prescribed marine n-3 fatty acids. Patients were receiving other contemporary medications. All-cause mortality was lower in patients prescribed marine n-3 fatty acids (adjusted hazard ratio 0.78).

In 2012 and 2013 results of two large RCTs investigating the effects of marine n-3 fatty acids on cardiovascular mortality were published [39,40]. The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial [39] randomized over 12,500 patients with high risk for cardiovascular events and with elevated fasting glucose, impaired glucose tolerance or diabetes to approximately 900 mg/day of EPA and DHA as ethyl esters or to placebo and to insulin glargine or standard care. Median follow-up time was 6.2 years. There was no effect of marine n-3 fatty acids on cardiovascular mortality, the primary outcome, or on cardiovascular events. The second trial (the Risk and Prevention Study) was a randomized controlled trial of approximately 900 mg/day of EPA and DHA as ethyl esters or placebo conducted in 12,500 adults with multiple cardiovascular risk factors or with diagnosed atherosclerosis, but who had not had an MI [40]. The stated primary outcome of this study was the composite of death, non-fatal MI and non-fatal stroke. However, after 1 year, the event rate was lower than anticipated and so the primary outcome was changed to hospitalization or death from cardiovascular causes. Median follow-up time was 5 years. There was no difference between groups in either the revised primary outcome or in most of the secondary outcomes. However, there were significantly fewer admissions for heart failure in the marine n-3 fatty acid group and a pre-specified subgroup analysis showed that the primary outcome was significantly less likely among women in the marine n-3 fatty acid group than among women in the placebo group.

Cohort studies are valuable because they can suggest associations (or not) between dietary intake or nutrient status markers and disease outcomes after a medium or long-term follow-up period, generally much longer than used in RCTs. There are of course limitations of data from cohort studies and findings from these studies do not demonstrate cause and effect. Nevertheless, consistent findings over many cohort studies would suggest a level of robustness in the association that is identified. In 2014 Chowdhury et al. [41] published a meta-analysis bringing together data from prospective cohort studies examining the association of dietary or circulating fatty acids, including marine n-3 fatty acids, with risk of “coronary outcomes”. The aggregation of data from 16 studies involving over 422,000 individuals showed a relative risk (RR) of 0.87 (95% CI 0.78 - 0.97) for those in the top third of dietary EPA plus DHA intake compared with those in the lower third of intake. The aggregation of data from 13 studies involving over 20,000 individuals showed RR of 0.78 (95%

CI 0.65 - 0.94), 0.79 (95% CI 0.67 - 0.93), and 0.75 (95% CI 0.62 - 0.89) for those in the top third of circulating EPA, DHA, and EPA plus DHA, respectively, compared with those in the lower third [41]. In 2017 Alexander et al. [12] published a meta-analysis bringing together data from prospective cohort studies examining the association of dietary marine n-3 fatty acid intake and risk of various coronary outcomes. The aggregation of data from 17 studies showed a RR of 0.82 (95% CI 0.74 - 0.92) for any CHD event for those with higher dietary intake of EPA plus DHA compared to those with lower intake. There were also significant reductions in RR for fatal coronary events (RR 0.77), coronary death (RR 0.82), and sudden cardiac death (RR 0.53). Several relevant studies have been published since this 2016 meta-analysis [6-8,13]

Del Gobbo et al.[7] pooled data from 19 studies involving over 45,000 individuals that investigated the association between EPA or DHA concentration in a body compartment like plasma, serum, red blood cells, or adipose tissue and risk of future CHD in adults who were healthy at study entry. DHA was associated with a lower risk of fatal CHD, with a RR of 0.90 (95% CI 0.84 – 0.96) for each one standard deviation increase in content. Omega-3 index is EPA+DHA as a proportion of total fatty acids in red blood cells [42]; it is a marker of both long term dietary intake of these fatty acids and their tissue levels. Further, it is suggested to be a marker of CHD risk [42]. To explore this further, Harris et al. [8] used data from 10 cohort studies to examine the association between omega-3 index and risk of fatal CHD. They identified a hazard ratio of 0.85 (95% CI 0.80 - 0.91) for each one standard deviation increase in omega-3 index. It was estimated that risk of fatal CHD would be reduced by ~30% moving from an omega-3 index of 4% to 8% [8]. Chen et al. [13] meta-analysed data from eleven prospective cohort studies involving over 370,000 individuals and identified the RR for all-cause mortality was 0.91 (95%CI 0.84 - 0.98) for high versus low intake of marine n-3 fatty acids. For EPA and DHA individually the RRs were 0.83 (95% CI 0.75 - 0.92) and 0.81 (95% CI 0.74 - 0.95), respectively. It was estimated that each 300 mg/day increment in intake of marine n-3 fatty acids would be associated with a 6% lower risk of all-cause mortality. Furthermore, each 1% increment in blood EPA or DHA would be associated with a 20% (for EPA) and 21% (for DHA) decreased risk of all-cause mortality. Recently, Zhang et al. [6] examined the association between marine n-3 fatty acid intake and total and cause-specific mortality among over 421,000 individuals in the US. Higher intake of marine n-3 fatty acids

was associated with lower total mortality and cardiovascular mortality amongst both men and women (hazard ratio for highest versus lowest quintile of intake 0.89 (CI 0.85 - 0.92) and 0.85 (95% CI 0.80 - 0.90) for men and 0.90 (95% CI 0.86 - 0.94) and 0.82 (95% CI 0.75 - 0.90) for women, respectively). These new publications [6-8,13] provide good support for a role for EPA and DHA in primary prevention of CHD, and perhaps more widely, of CVD. EPA and DHA could act to reduce risk of developing CVD through beneficial modification of risk factors. This has been the subject of much research over the several decades. In 2018, AbuMweis et al. [14] published a comprehensive meta-analysis of RCTs of marine n-3 fatty acids and risk factors for CVD. They identified significant effects of marine n-3 fatty acids on blood triglycerides (110 studies; effect size -0.37 (95% CI -0.43 - -0.31) mmol/L), HDL-cholesterol (110 studies; effect size 0.039 (95% CI 0.024 - 0.054) mmol/L), systolic blood pressure (50 studies; effect size -2.2 (95% CI -3.2 - -1.32) mm Hg), diastolic blood pressure (50 studies; effect size -1.1 (95% CI -2.4 - -0.33) mm Hg), the inflammatory marker C-reactive protein (20 studies; effect size -0.34 (95% CI -0.45 - -0.23) mg/L) and heart rate (26 studies; effect size -1.4 (95% CI -2.4 - -0.3) bpm). This broad range of effects, some of them modest, may account for the association with reduced risk of CVD seen in cohort studies. One effect of marine n-3 fatty acids that is not modest is triglyceride lowering. In 2017 a meta-analysis of 53 RCTs involving over 7,000 participants evaluating the effect of marine n-3 fatty acids on blood triglyceride concentrations was published [15]. The meta-analysis identified a mean reduction of 38.6 (95% CI -47.2 - -30.2) mg/dL. This mean reduction is about 0.43mmol/L, similar to the 0.37 mmol/L reported by AbuMweis et al. [14]. The triglyceride-lowering effect was related to dose of marine n-3 fatty acids used and was greater in those starting with higher fasting triglyceride concentrations [15]. In an interesting analysis using estimated associations between intake of marine n-3 fatty acids and disease and data from the US National Health and Nutrition Examination Surveys, Micha et al. [43] estimated that insufficient intake of EPA and DHA resulted in over 54,000 deaths from cardiometabolic diseases (CHD, stroke, type-2 diabetes) in the US in 2012; this figure represented 7.8% of adult mortality.

During 2017 and 2018 new meta-analyses of RCTs using marine n-3 fatty acids in patients with CVD were published [12,16,17]. Alexander et al. [12] explored a number of coronary outcomes, aggregating data from primary prevention, mixed primary and secondary

prevention, and purely secondary prevention trials. Using data from secondary prevention trials (n = 10) or from all trials (n = 18), there was no overall significant effect of marine n-3 fatty acids on any CHD event. However, sub-group analysis revealed that patients with elevated fasting triglycerides (> 150 mg/dL) had fewer CHD events when given marine n-3 fatty acids compared with control (relative risk 0.84 (95% CI 0.72 – 0.98)). Aung et al. [16] combined data from 10 RCTs involving almost 78,000 patients; trials had to have involved at least 500 participants and to have been of at least one year duration to be included. Marine n-3 fatty acids had no significant effect on CHD death (relative risk 0.93 (99% CI 0.83 – 1.03)), non-fatal MI (relative risk 0.97 (99% CI 0.87 – 1.08)), any CHD event (relative risk 0.96 (99% CI 0.90 – 1.01)) or major vascular events (relative risk 0.97 (99% CI 0.93 – 1.01)). Most recently, a Cochrane meta-analysis included 79 RCTs involving over 112,000 participants that lasted at least 12 months and compared supplementation and/or advice to increase plant or marine n-3 fatty acids [17]. Trials were of 12 to 72 months duration and included adults at varying cardiovascular risk. Most trials assessed marine n-3 fatty acid supplements. The meta-analysis suggested little or no effect of increasing intake of marine n-3 fatty acids on all-cause mortality (39 trials; RR 0.98 (95% CI 0.90 - 1.03)), cardiovascular mortality (25 trials; RR 0.95 (95% CI 0.87 - 1.03)), cardiovascular events (38 trials; RR 0.99 (95% CI 0.94 - 1.04)), CHD mortality (21 trials; RR 0.93 (95% CI 0.79 - 1.09)), stroke, or arrhythmia. However, there was a suggestion that marine n-3 fatty acids reduced CHD events (28 trials; RR 0.93 (95% CI 0.88 - 0.97)). The authors concluded that increasing intake of EPA and DHA has little or no effect on mortality or cardiovascular health. However, both the cohort studies described earlier and some recently reported RCTs (see below) challenge this conclusion.

Late 2018 saw the publication of three large important RCTs of marine n-3 fatty acids [9-11]. The A Study of Cardiovascular Events in Diabetes (ASCEND) trial [9] randomized 15,480 patients with diabetes but without evidence of CVD to approximately 900 mg/day of EPA and DHA as ethyl esters or to placebo. Mean follow-up time was 7.4 years. There was no effect of marine n-3 fatty acids on the composite primary outcome, the “first serious vascular event” (non-fatal MI, stroke, transient ischemic attack or vascular death), on the secondary outcome which was the composite of any serious vascular event or any arterial revascularization procedure, or on all-cause mortality. The primary outcome occurred in

about 9% of patients. Within the components of the primary and secondary outcomes, there was no effect of marine n-3 fatty acids on non-fatal MI, non-fatal ischemic stroke, transient ischemic attack, or revascularisation but there was a reduction in vascular death (rate ratio 0.91 (95% CI 0.67 – 0.99)). There was a trend towards a reduction in coronary death (rate ratio 0.79 (95% CI 0.61 – 1.02)). A post-hoc power calculation indicates that ASCEND had 90% power to detect a between group difference of 15% in the primary outcome.

The Vitamin D and omega-3 Trial (VITAL) [10] randomized 25,871 men (aged > 50 years) and women (aged > 55 years) without CVD to vitamin D or marine n-3 fatty acids (approximately 900 mg/day of EPA and DHA as ethyl esters) or placebo in a 2 x 2 factorial design. Median follow-up time was 5.3 years. The primary cardiovascular outcome (a major cardiovascular event) was a composite of MI, stroke, or death from cardiovascular causes. Secondary outcomes were the individual components of the primary outcome and the composite primary outcome plus coronary revascularisation (termed cardiovascular events). Being a primary prevention study, the incidence of the primary outcome was low (cumulative incidence about 0.03 over the full follow-up period). Risk of a major cardiovascular event (the primary outcome) was 0.92 (95% CI 0.80 – 1.06) with marine n-3 fatty acids compared to placebo. Among the components of the primary outcome, the hazard ratio for MI was 0.72 (95% CI 0.59 – 0.90), while amongst other outcomes the hazard ratio for fatal MI was 0.50 (95% CI 0.26 – 0.97) and for total CHD it was 0.83 (95% CI 0.71 – 0.97). It would appear that these three outcomes were significantly reduced by marine n-3 fatty acids compared with placebo. Indeed, the paper includes the statements “the lower incidence of MI in the n-3 group persisted [beyond two years of follow-up]”, “analysis of components of the primary composite cardiovascular end point suggested that the risk of MI was lower in the n-3 group than in the placebo group” and “the finding of lower risk of coronary events with n-3 fatty acids than with placebo in our trial ...”. A sub-group analysis according to fish consumption found that in those who ate < 1.5 servings of fish per week n-3 fatty acids significantly decreased the primary outcome compared to control (hazard ratio 0.81 (95% CI 0.67 – 0.98)); this effect of n-3 fatty acids was not seen in those who ate > 1.5 servings of fish per week. This finding suggests true benefit of marine n-3 fatty acids on major cardiovascular events in those who eat less fish than recommended.

The Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) [11] randomized 8,179 patients with established CVD or with diabetes and other risk factors, who had been receiving statin therapy and with fasting triglycerides between 135 and 499 mg/dL (1.52 to 5.63 mmol/L) to 4 g/day EPA as an ethyl ester or to placebo. About 70% of patients had established CVD, while about 30% had diabetes and other risk factors. Follow-up was for a median of 4.9 years. While most studies investigating the ability of n-3 fatty acids to lower blood triglycerides have used combinations of EPA and DHA, it is known that both EPA and DHA are triglyceride lowering [5]. In REDUCE-IT, fasting triglycerides were decreased by a mean of 39 mg/dL (or 0.44 mmol/L) in the EPA group after one year, consistent with the effect size reported in recent meta-analyses [14,15]. The primary outcome was a composite of cardiovascular death, non-fatal MI, non-fatal stroke, coronary revascularisation, or unstable angina. These being at risk patients, the incidence of the primary outcome was about 20%. The main secondary outcome was a composite of cardiovascular death, non-fatal MI, or non-fatal stroke. The hazard ratio for the primary outcome was 0.75 (95% CI 0.68 – 0.83) in the EPA group compared to the placebo group. For the main secondary outcome the hazard ratio was 0.74 (95% CI 0.65 – 0.83). Amongst the other outcomes, EPA significantly decreased cardiovascular death (hazard ratio 0.80 (95% CI 0.66 – 0.98)), fatal or non-fatal MI (hazard ratio 0.69 (95% CI 0.58 – 0.81)), hospitalisation for unstable angina (hazard ratio 0.68 (95% CI 0.53 – 0.87)), fatal or non-fatal stroke (hazard ratio 0.72 (95% CI 0.55 – 0.93)), sudden cardiac death (hazard ratio 0.69 (95% CI 0.50 – 0.96)) and cardiac arrest (hazard ratio 0.52 (95% CI 0.31 – 0.86)).

Where do these new publications leave us? New data from cohort studies either individually [6] or when pooled [7,8,12,13] continue to support that marine n-3 fatty acids play an important role in reducing the risk of CHD and, more broadly, CVD. This protective role probably relates to an improvement of the risk factor profile with marine n-3 fatty acids, as confirmed by recent meta-analyses [14,15]. However, the lack of genuine long-term primary prevention trials has been a limitation creating uncertainty despite the consistent findings from prospective cohort studies. ASCEND was essentially a primary prevention trial in diabetics while VITAL was a primary prevention trial. Both used 900 mg EPA plus DHA per day. Although most outcomes in ASCEND were not affected by marine n-3 fatty acids, there



was a reduction in vascular death and a trend towards less coronary death. In VITAL, one component of the primary outcome (MI) was decreased by marine n-3 fatty acids and several other outcomes (e.g. fatal MI, total CHD) were decreased. Furthermore, in those participants who ate < 1.5 servings of fish per week marine n-3 fatty acids decreased the primary outcome compared to control. Hence, despite the moderate dose of marine n-3 fatty acids used and the low event rates of these primary prevention studies, there is evidence of benefit from the combination of EPA and DHA in both ASCEND and VITAL. ASCEND and VITAL were published after the recent meta-analyses of RCTs, which mainly dealt with high-risk patients and often in the secondary prevention setting. These meta-analyses fail to provide strong evidence of an impact of marine n-3 fatty acids on CVD outcomes and mortality, although there is a suggestion that some outcomes may be improved and that certain sub-groups may benefit more from marine n-3 fatty acids than others [12,16,17]. Consistent with this, the American Heart Association Advisory published in late 2017 [18] remains supportive of the use of marine n-3 fatty acids. The Advisory concludes “Although recent RCT evidence has raised questions about the benefits of omega-3 supplementation to prevent clinical CVD events, the recommendation for patients with prevalent CHD such as a recent MI remains essentially unchanged: Treatment with omega-3 PUFA supplements is reasonable for these patients. Even a potential modest reduction in CHD mortality (10%) in this clinical population would justify treatment with a relatively safe therapy. We now recommend treatment for patients with prevalent heart failure without preserved left ventricular function to reduce mortality and hospitalizations (9%) on the basis of a single, large RCT.” REDUCE-IT [11] was a combination of primary and secondary prevention enrolling patients with established CVD or with diabetes; the former predominated. Patients were on statins and had fasting triglyceride concentrations between 135 and 499 mg/dL. Importantly, and in contrast to other recent RCTs, REDUCE-IT used a high dose of EPA alone (4 g/day). Both primary and secondary outcomes were improved by EPA, with a reduction in risk of about 25%, as were several other relevant outcomes. REDUCE-IT tells us that marine n-3 fatty acids (or at least EPA) can be effective in contemporary secondary prevention settings. The comparison of the clear findings from REDUCE-IT [11] with the less clear findings from ASCEND [9] and VITAL [10], and from ORIGIN [39] and the Risk and Prevention Study [40] earlier on, indicates that a dose of marine n-3 fatty acids of 900 mg/day as used in each of those studies may be insufficient to

have significant benefit in at-risk patients in the contemporary setting. More studies using higher doses of marine n-3 fatty acids are needed. Other questions raised by REDUCE-IT are whether EPA is sufficient to get maximal cardiovascular benefit, whether DHA alone would be equally as effective and whether a specific combination of EPA and DHA at high dose would be even more effective than either fatty acid alone. More research is needed ....

### **Conflicts of interest**

PCC advises BASF AS, DSM, Smartfish, Cargill and Fresenius-Kabi and has research funding from BASF AS.

### **References**

1. Calder PC. N-3 fatty acids and cardiovascular disease: evidence explained and mechanisms explored. *Clin Sci* 2004; 107:1–11.
2. Saravanan P, Davidson NC, Schmidt EB, Calder PC. Cardiovascular effects of marine omega-3 fatty acids. *Lancet* 2010; 376:540–550.
3. De Caterina R. N-3 fatty acids in cardiovascular disease. *N Engl J Med* 2011; 364:2439-2450.
4. Calder PC, Deckelbaum R. Dietary fatty acids in health and disease: greater controversy, greater interest. *Curr Opin Clin Nutr Metab Care* 2014; 17:111-1115.
5. Innes JK, Calder PC. The differential effects of eicosapentaenoic acid and docosahexaenoic acid on cardiometabolic risk factors: A systematic review. *Int J Mol Sci* 2018;19:532.
6. Zhang Y, Zhuang P, He W, et al. Association of fish and long-chain omega-3 fatty acids intakes with total and cause-specific mortality: prospective analysis of 421 309 individuals. *J Intern Med* 2018; 284:399-417.
7. Del Gobbo LC, Imamura F, Aslibekyan S, et al.  $\omega$ -3 Polyunsaturated fatty acid biomarkers and coronary heart disease: Pooling project of 19 cohort studies. *JAMA Intern Med* 2016; 176:1155-1166.
8. Harris WS, Del Gobbo L, Tintle NL. The omega-3 index and relative risk for coronary heart disease mortality: Estimation from 10 cohort studies. *Atherosclerosis* 2017; 262:51-54.
9. The ASCEND Study Collaborative Group. Effects of n-3 Fatty Acid Supplements in Diabetes Mellitus. *N Engl J Med* 2018; 379:1540-1550.

10. Manson JE, Cook NR, Lee IM, et al. Marine n-3 fatty acids and prevention of cardiovascular disease and cancer. *N Engl J Med* 2018; in press.
11. Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med* 2018; in press
12. Alexander DD, Miller PE, Van Elswyk ME, Kuratko CN, Bylsma LC. A meta-analysis of randomized controlled trials and prospective cohort studies of eicosapentaenoic and docosahexaenoic long-chain omega-3 fatty acids and coronary heart disease risk. *Mayo Clin Proc* 2017; 92:15-29.
13. Chen GC, Yang J, Eggersdorfer M, Zhang W, Qin LQ. N-3 long-chain polyunsaturated fatty acids and risk of all-cause mortality among general populations: a meta-analysis. *Sci Rep* 2016; 6:28165.
14. AbuMweis S, Jew S, Tayyem R, Agraib L. Eicosapentaenoic acid and docosahexaenoic acid containing supplements modulate risk factors for cardiovascular disease: a meta-analysis of randomised placebo-control human clinical trials. *J Hum Nutr Diet* 2018; 31:67-84.
15. Nam GE, Myung SK, Choi YJ. Use of omega-3 fatty acid supplements has insufficient clinical evidence for treatment of hypertriglyceridemia: A meta-analysis of randomized, double-blind, placebo-controlled trials. *Eur J Lipid Sci Technol* 2017; 119:170011.
16. Aung T, Halsey J, Kromhout D, et al. Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: Meta-analysis of 10 trials involving 77 917 individuals. *JAMA Cardiol* 2018; 3:225-234.
17. Abdelhamid AS, Brown TJ, Brainard JS, et al. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2018; 7:CD003177.
18. Siscovick DS, Barringer TA, Fretts AM, et al. Omega-3 polyunsaturated fatty acid (fish oil) supplementation and the prevention of clinical cardiovascular disease: A science advisory from the American Heart Association. *Circulation* 2017; 135:e867-e884.
19. Hu FB, Bronner L, Willett WC, et al. Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. *JAMA* 2002; 287:1815-1821.
20. Albert CM, Campos H, Stampfer MJ, 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.
21. Anonymous. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI Prevenzione trial. *Lancet* 1999; 354:447-455.

22. Yokoyama M, Origasa H, Matsuzaki M, 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.
23. Tavazzi L, Maggioni AP, Marchioli R, 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.
24. Bucher HC, Hengstler P, Schindler C, Meier G. N-3 polyunsaturated fatty acids in coronary heart disease: a meta-analysis of randomized controlled trials. *Am J Med* 2002; 112:298-304.
25. Studer M, Briel M, Leimenstoll B, et al. Effect of different antilipidemic agents and diets on mortality: a systematic review. *Arch Intern Med* 2005; 165:725-730.
26. Filion KB, El Khoury F, Bielinski M, Schiller I, Dendukuri N, Brophy JM. Omega-3 fatty acids in high-risk cardiovascular patients: a meta-analysis of randomized controlled trials. *BMC Cardiovasc Disord* 2010; 10:24.
27. Marik PE, Varon J. Omega-3 dietary supplements and the risk of cardiovascular events: a systematic review. *Clin Cardiol* 2009;32: 365-372.
28. Zhao YT, Chen Q, Sun YX, Li XB, Zhang P, Xu Y, Guo JH. Prevention of sudden cardiac death with omega-3 fatty acids in patients with coronary heart disease: a meta-analysis of randomized controlled trials. *Ann Med* 2009; 41:301-310.
29. Galan P, Kesse-Guyot E, Czernichow S, et al. Effects of B vitamins and omega 3 fatty acids on cardiovascular diseases: a randomised placebo controlled trial. *Br Med J* 2010; 341:c6273.
30. Kromhout D, Giltay EJ, Geleijnse JM, for the Alpha Omega Trial Group. n-3 fatty acids and cardiovascular events after myocardial infarction. *N Engl J Med* 2010; 363:2015-2026.
31. Rauch B, Schiele R, Schneider S, et al., OMEGA Study Group. 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.
32. Calder PC, Yaqoob P. Marine omega-3 fatty acids and coronary heart disease. *Curr Opin Cardiol* 2012; 27:412-419.
33. Kwak SM, Myung SK, Lee YJ, Seo HG, Korean Meta-analysis Study Group. Efficacy of omega-3 fatty acid supplements (eicosapentaenoic acid and docosahexaenoic acid) in

- secondary prevention of cardiovascular disease: a meta-analysis of randomized, double-blind, placebo-controlled trials. *Arch Intern Med* 2012; 172:686-694.
34. Rizos EC, Ntzani EE, Bika E, et al. 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.
35. 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.
36. Casula M, Soranna D, Catapano AL, Corrao G. Long-term effect of high dose omega-3 fatty acid supplementation for secondary prevention of cardiovascular outcomes: A meta-analysis of randomized, placebo controlled trials. *Atheroscler Suppl* 2013; 14:243-251.
37. Chen Q, Cheng LQ, Xiao TH, et al. Effects of omega-3 fatty acid for sudden cardiac death prevention in patients with cardiovascular disease: a contemporary meta-analysis of randomized, controlled trials. *Cardiovasc Drugs Ther* 2011; 25:259-265.
38. Poole CD, Halcox JP, Jenkins-Jones S, et al. Omega-3 Fatty acids and mortality outcome in patients with and without type 2 diabetes after myocardial infarction: a retrospective, matched-cohort study. *Clin Ther* 2013; 35:40-51.
39. ORIGIN Trial Investigators. Bosch J, Gerstein HC, Dagenais GR, et al. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. *N Engl J Med* 2012; 367:309-318.
40. Risk Prevention Study Collaborative Group. Roncaglioni MC, Tombesi M, Avanzini F, et al. n-3 fatty acids in patients with multiple cardiovascular risk factors. *N Engl J Med* 2013; 368:1800-1808.
41. Chowdhury R, Warnakula S, Kunutsor S, et al. Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. *Ann Intern Med* 2014; 160:398-406.
42. 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.
43. Micha R, Peñalvo JL, Cudhea F, Imamura F, Rehm CD, Mozaffarian D. Association between dietary factors and mortality from heart disease, stroke, and type 2 diabetes in the United States. *JAMA* 2017; 317:912-924.