



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]), randomized 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 10 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 2500 patients who had been prescribed approximately 900 mg EPA in addition to DHA as ethyl esters daily in the 90 days after their

first MI; these patients were compared with about 10000 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 12500 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 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 12500 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, nonfatal MI and nonfatal 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

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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 prespecified 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 to 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 to 0.94), 0.79 (95% CI 0.67 to 0.93) and 0.75 (95% CI 0.62 to 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 an RR of 0.82 (95% CI 0.74 to 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 an RR of 0.90 (95% CI 0.84 to 0.96) for each one standard deviation increase in content. The omega-3 index reports 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. Furthermore, 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 to 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 4–8% [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 to 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 to 0.92) and 0.81 (95% CI 0.74 to 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 United States. Higher intake of marine n-3 fatty acids was associated with lower total mortality and cardiovascular mortality among both men and women [hazard ratio for highest versus lowest quintile of intake 0.89 (CI 0.85 to 0.92) and 0.85 (95% CI 0.80 to 0.90) for men and 0.90 (95% CI 0.86 to 0.94) and 0.82 (95% CI 0.75 to 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 to -0.31) mmol/l], HDL-cholesterol [110 studies; effect size 0.039 (95% CI 0.024 to 0.054) mmol/l], SBP [50 studies; effect size -2.2 (95% CI -3.2 to -1.32) mm Hg], DBP [50 studies; effect size -1.1 (95% CI -2.4 to -0.33) mm Hg], the inflammatory marker C-reactive protein [20 studies; effect size -0.34 (95% CI -0.45 to -0.23) mg/l] and heart rate (26 studies; effect size -1.4 (95% CI -2.4 to -0.3) bpm]. This broad range of effects, some of them modest, may account for the association with reduced risk of CVD seen in

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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 7000 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 to -30.2) mg/dl. This mean reduction is about 0.43 mmol/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 United States 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 [RR 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 1 year duration to be included. Marine n-3 fatty acids had no significant effect on CHD death [RR 0.93 (99% CI 0.83 to 1.03)], nonfatal MI [RR 0.97 (99% CI 0.87 to 1.08)], any CHD event [RR 0.96 (99% CI 0.90 to 1.01)] or major vascular events [RR 0.97 (99% CI 0.93 to 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 12–72 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 to 1.03)], cardiovascular mortality [25 trials; RR 0.95 (95% CI 0.87 to 1.03)], cardiovascular events [38 trials; RR 0.99 (95% CI

0.94 to 1.04)], CHD mortality [21 trials; RR 0.93 (95% CI 0.79 to 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 to 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' (nonfatal 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 nonfatal MI, nonfatal ischemic stroke, transient ischemic attack, or revascularization but there was a reduction in vascular death [RR 0.91 (95% CI 0.67 to 0.99)]. There was a trend towards a reduction in coronary death [RR 0.79 (95% CI 0.61 to 1.02)]. A posthoc 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 2×2 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 revascularization (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 to 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 to 0.90), while among other outcomes the

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hazard ratio for fatal MI was 0.50 (95% CI 0.26 to 0.97) and for total CHD it was 0.83 (95% CI 0.71 to 0.97). It would appear that these three outcomes were significantly reduced by marine n-3 fatty acids compared with placebo. Indeed, the article 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 less than 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 to 0.98)]; this effect of n-3 fatty acids was not seen in those who ate more than 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 8179 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 (1.52–5.63 mmol/l) to 4 g/day EPA as an ethyl ester or to placebo. About 70% of patients had established CVD, whereas 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 1 year, consistent with the effect size reported in recent meta-analyses [14,15]. The primary outcome was a composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, 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, nonfatal MI, or nonfatal stroke. The hazard ratio for the primary outcome was 0.75 (95% CI 0.68 to 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 to 0.83). Among the other outcomes, EPA significantly decreased cardiovascular death [hazard ratio 0.80 (95% CI 0.66 to 0.98)], fatal or nonfatal MI [hazard ratio 0.69 (95% CI 0.58 to 0.81)], hospitalization for unstable angina [hazard ratio 0.68 (95% CI 0.53 to 0.87)], fatal or nonfatal stroke [hazard ratio 0.72 (95% CI 0.55 to 0.93)],

sudden cardiac death [hazard ratio 0.69 (95% CI 0.50 to 0.96)] and cardiac arrest [hazard ratio 0.52 (95% CI 0.31 to 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 diabetic individuals while VITAL was a primary prevention trial in a study population with few diabetics. Both used 900 mg EPA in addition to 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 less than 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 paper by Maki and Dicklin in this issue [44] raises the question of how differences in bioavailability of EPA and DHA from different omega-3 supplements could contribute to confounding outcomes in recent trials. As well, we have previously written on how multiple other factors can contribute to differences in trial outcomes [45]. 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 . . .

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Conflicts of interest

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