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Nicholls SJ, Lincoff AM, Garcia M, Bash D, Ballantyne CM, Barter PJ, et al. Effect of High-Dose Omega-3 Fatty Acids vs Corn Oil on Major Adverse Cardiovascular Events in Patients at High Cardiovascular Risk - The STRENGTH Randomized Clinical Trial. JAMA [Internet]. 2020;44195:1–13.

What We Know, Think We Know, or Are Starting to Know

Back in August, in a previous Deepdive digging into the effect of the omega-3 fatty acids eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA] and heart health, I wrote: *"Cumulatively, the weight of the data is shifting back to a more clear benefit to omega-3 supplementation in people at risk of cardiovascular disease, which may benefit additionally to current pharmacotherapy."*

Yet fast forward a short 3 months later to November 2020, and the headlines are suggesting the shift is going back the other way [again], and fish oil supplementation is - again - declared to of little use for cardiovascular disease risk. How this particular research question can swing from one end of the pendulum of what we know, or think we know, to the other end within the same year.

And, as we know, the pendulum swings in nutrition are extreme. A major Cochrane review in 2018 concluded that omega-3 supplementation has no effect on coronary heart disease, following exclusion of 2 trials which had resulted in a statistically significant 7% risk reduction in the initial analysis [(1).] The trials included in these studies encompassed a range of doses, of varying EPA/DHA levels, of varying durations - a range of factors which could all influence any effect of omega-3 supplementation.

In the Italian GISSI-Prevenzione trial [(2)], supplementation with 850–882mg EPA+DHA in addition to routine treatment in participants who had recently suffered a heart attack [i.e., secondary prevention] resulted in a 20% reduction in risk for cardiovascular death over 3.5yrs compared to a control of routine treatment only. In GISSI, the omega-3 supplement was in the form of ethyl esters*, and used a 1:2 ratio of EPA:DHA. In the JELIS trial in Japan [(3)], supplementation with 1,800mg EPA ethyl ester alone [no DHA] plus a statin resulted in a 19% reduction in heart disease risk over 4.6yrs compared to statins alone. In JELIS, the greatest difference in risk factors in the study was in relation to triglycerides - the change in LDL was similar due to the effect of statins in both groups - with the greatest reduction in risk of 53% in participants with triglyceride levels >1.7mmol/L [150mg/dL] at baseline.

Mechanistically, the pronounced effect of omega-3 fatty acids on triglycerides has been robustly established [(4,5)]. In January 2019, the REDUCE-IT trial was published, in which 4g per day of EPA, again as a purified ethyl ester, additional to statin therapy resulted in a 25% reduction in risk for a cardiovascular events in participants in secondary prevention [(6)]. This was followed up with a meta-analysis published in 2019 of omega-3 supplement trials, which found a dose-response such that each 1g per day greater EPA/DHA intake was associated with a 17% reduced risk for CVD [(7)].

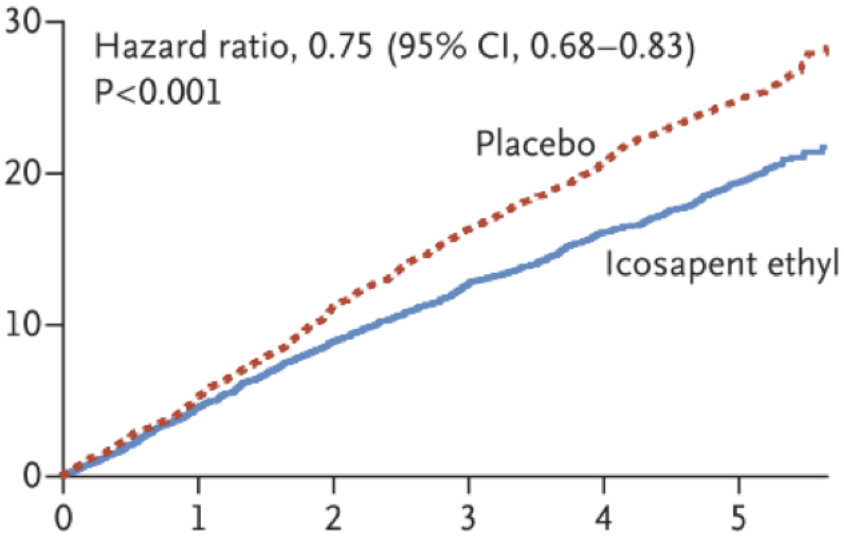

Figure *from the REDUCE-IT trial (**R**) demonstrating the reduction in risk for cardiovascular disease events over 5yrs in the intervention group (**blue line**) consuming 4g/d icosapent ethyl - which is purified EPA ethyl ester - compared to the placebo group (**red dotted line**). There was a 25% relative risk reduction in the intervention group, compared to the placebo control group.*

These lines of evidence appeared to be tipping what we thought we know towards favouring higher dose omega-3 supplementation, specifically EPA ethyl ester, in a specific population subgroup: individuals with high triglycerides, in secondary prevention. The STRENGTH study, an acronym reflecting the impressively verbose title 'Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia', published this past week November 2020, has challenged this view.

*Geek Box: Esters and Carboxylic Acids

In order to understand the differences in the type of omega-3 fatty acids used in these studies, it is important to a have a very brief chemistry rundown. For example, the REDUCE-IT trial used an EPA ethyl ester. Most fats that we consumed through the diet, or even within supplements, are in the form of triglycerides, i.e., three fatty acids bound to a glycerol (which is a sugar alcohol) backbone, which may also be known as 'esters', as the reaction that condenses the fatty acids and glycerol together is known as 'esterification'. For example, you may often see the term 'free fatty acids' [FFA] referred to as 'NEFA', i.e., 'non-esterified fatty acids'. All fats and oils are therefore esters of fatty acids and glycerol. An ethyl is a chemical group derived from ethanol, an alcohol. Therefore, an 'ethyl ester' form of omega-3 fish oils is formed when the long-chain fatty acids EPA and DHA are bound (esterified) to ethanol (rather than glycerol, which would form a triglyceride instead). An ethyl ester form of omega-3 supplement results in a more concentrated level of EPA and DHA than a triglyceride form supplement, which most commercially available fish oils are. The absorption of ethyl esters is similar to long-chain fatty acids, i.e., intestinal absorption and subsequent breakdown into free fatty acids. Consequently, their absorption is influenced by dietary fat content, and is lower on an empty stomach or with very low-fat meals. As a result of the additional processing required, ethyl ester EPA and/or DHA is more expensive, and pharmaceutical-grade products agents that are not generally available. Carboxylic acids are something you're likely familiar with - the acid in vinegar or vitamin C in oranges are carboxylic acids. Any fatty acid structure ends with a carboxyl group - carboxylic acid formulations of omega-3 are free fatty acid forms of EPA and DHA, i.e., they are not bound to either glycerol (triglycerides) or ethanol (ethyl esters). This means they are absorbed with greater efficiency, and have significantly higher bioavailability than ethyl ester forms of omega-3. This higher bioavailability has been assumed to mean that carboxylic acid forms of omega-3's are "better",

The Study

The STRENGTH study was a randomised, double-blind, placebo-controlled trial comparing the effects of 4g per day of a carboxylic acid* formulation of EPA and DHA against a control group of 4g per day corn oil, in participants at high-risk of cardiovascular disease. 50% of participants were required to be in secondary prevention, i.e., had established cardiovascular disease.

All patients were required to be on statins for a minimum of 4-weeks prior to the study, and have achieved a low LDL-cholesterol of <2.5mmol/L [<100mg/dL]. However, participants were required to have high triglycerides of >2.0mmol/L [180mmol/L], and low HDL-cholesterol of <1.0 or 1.2mmol/L [42 or 47mg/dL] for men or women, respectively.

Results: 13,078 participants were randomised, across 22 countries - 6,539 each in the intervention and control group. The trial was stopped early after a median 3yrs, due to a pre-specified number of patients in the intervention group experiencing a primary endpoint, i.e., there was a low probability of demonstrating a clinical benefit to the intervention by that stage.

In the intervention group, 12% [785 of 6,539] of participants experienced a CVD event, compared to 12.2% [795 of 6,539] in the control group. There was therefore no significant difference between groups [HR 0.99, 95% CI 0.90-1.09]. There was also no significant difference between the intervention and control groups in any of the individual endpoints [i.e., myocardial infarction or non-fatal stroke, etc.].

Triglycerides decreased by 19% in the intervention group [from an average of 240mg/dL to 191mg/dL], compared to no significant change in the placebo control group.

There was no relationship between plasma or red blood cell content of either EPA or DHA, and any CVD outcomes.

The Critical Breakdown

Pros: The trial had a 'gold standard' design, and randomisation, concealment of allocation from the researchers, and a clearly defined intervention and control group, were all achieved. The sample size was very large, and follow-up was of sufficient duration to detect effects [even with the trial stopping early]. The trial was conducted across over 600 research centres in 22 countries, allowing for a broader inclusion of regional and race/ethnicity groups in the study.

Cons: There was a significant increase in certain adverse events in the intervention group, in particular atrial fibrillation, and gastrointestinal upset. There was no dietary assessment to quantify habitual fish consumption, which may have influenced the outcomes, e.g., if the placebo group consumed more oily fish than the intervention group. While this would have cost implications, given the discrepancies in the literature it could have been highly informative [and potentially avoided the need for additional expensive studies] to have compared the carboxylic acid to another group of EPA ethyl ester, against the placebo.

Key Characteristic

The use of a carboxylic acid, i.e., free fatty acid form of EPA and DHA supplementation, distinguishes this study from previous large-scale interventions finding a benefit to isolated EPA ethyl esters. The two studies to first tested carboxylic acid omega-3 supplements - the EVOLVE and ESPIRIT trials - examined intermediate risk factors, specifically triglycerides and cholesterol levels. In these studies, 4g of carboxylic acid omega-3 supplementation - the same dose used in the present study - were shown to reduce triglycerides by 20-30% [8,9].

However, these studies did not investigate 'hard' endpoints, i.e., CVD events. The present study was therefore the first large intervention to investigate the effects of carboxylic acid omega-3 supplementation on incidence of CVD events. In the present study, triglycerides were reduced by 19%, however, there was no significant reduction in incidence of CVD events compared to the control group.

This invites us to think beyond the purported effect of omega-3 fish oils reducing CVD by reducing triglycerides alone. It is crucial to bear in mind that there remains no identifiable mechanism of action explaining why omega-3 fatty acids reduce triglycerides. We still don' t really know. Thus, we' re not fully in a position to reconcile why one study may result in a decrease in triglycerides and a reduction in CVD events [REDUCE-IT] while another may decrease triglycerides and not reduce CVD events [STRENGTH]. Given the multiplicity of effects of omega-3 fatty acids, and differential effects of EPA and DHA respectively, it may be that the effect of the type of supplement - carboxylic acid or ethyl ester - is through pathways other than, and/or in addition to, triglyceride reduction.

Interesting Finding

Plasma EPA concentrations increased to 89mg/L in this study, despite the 4g per day dose of mixed EPA and DHA. The enthusiasm for carboxylic acid forms of EPA/DHA appears to based on two factors:

- a) their absorption, which doesn' t require a full stomach or a fat-containing meal and is therefore more flexible for participants to take, and;
- b) the greater bioavailability compared to ethyl ester forms.

Let' s think about the bioavailability aspect. In the EVOLVE study [8], plasma EPA levels increased to 170mg/L, while in the ESPIRIT study [9] plasma EPA increased to to 105mg/L. All of these studies used the same dose of 4g carboxylic acid omega-3' s. The reason for this discrepancy is not clear.

In two of the interventions using 4g EPA ethyl esters, plasma EPA levels increased to 169mg/L in JELIS [3], and 144mg/L in REDUCE-IT [6]. In REDUCE-IT, plasma EPA levels strongly correlated with reduced risk of CVD events; in the present STRENGTH study, there was no such correlation. Again, the reason for such discrepancy is unclear - it could be that a greater magnitude of increase is required, as the achieved level in REDUCE-IT was substantially higher than the present study.

In addition, as noted above, the magnitude of triglyceride reduction is in a similar range in all of these studies, whether a reduction in CVD events has been demonstrated or not, and with varying degrees of increases in plasma EPA. One clue could be the recent EVAPORATE trial [10] published this year, in which 4g EPA ethyl esters resulted in a significant reduction in arterial plaque progression, without significantly altering triglycerides. It could it be that trials finding a benefit to EPA ethyl ester, although demonstrating a reduction in triglycerides, are exerting a primary benefit through direct effects on atherosclerotic plaque. It may also be that the greater bioavailability of carboxylic acid omega-3 supplements is not a relevant factor in their effects of CVD.

Relevance

The evidential conundrum of the effect of omega-3 fatty acids EPA and DHA on cardiovascular disease continues. Reconciling this body of evidence is going to require further research, as currently there are many variables which could be relevant. For example:

- ***Supplement Form***: EPA ethyl ester vs. Mixed EPA/DHA carboxylic acid
- ***Dose***: 4g/d EPA alone vs. 4g mixed EPA/DHA
- ***Choice of Placebo***: Mineral oil vs. Corn oil
- ***Participant Health Status***: Secondary prevention vs. Primary prevention
- ***Mechanism of Action***: Triglyceride reduction? Plaque stabilisation? Anti-inflammatory effects? Anti-thrombotic effects?
- ***Oily Fish Intake***: Could diet influence the effect of the intervention vs. control?

So, can we make sense of it? I' m going to lay out my current position, based on the totality of evidence. The first is that the most consistent effect to date has been demonstrated with EPA ethyl ester in the JELIS [3], REDUCE-IT [6], and EVAPORATE [10] trials: the present study used a carboxylic acid formula. Secondly, the dose of 4g EPA ethyl ester is >96% purified EPA, and it does not appear that mixed EPA/DHA supplements have the same effect: the present study used a mixed EPA/DHA formula. Third, it appears that the most consistent effect is in participants in secondary prevention [2,3,6,7,10]. Even in the present study, although the finding was not statistically significant, there was a trend toward a reduction in risk in patients with established CVD at baseline.

Fourthly, the mechanism of action may have more to do with the action of EPA on arterial plaque, and not specifically on the reduction in triglycerides [although this likely also benefits]: these mechanisms were not investigated in the present study. In EVAPORATE, regression of arterial plaque thickness was observed with the addition of 4g/d EPA ethyl ester to statin therapy. Plaque in arteries readily incorporates EPA, and a number of interventions have demonstrated that EPA, and increased incorporation of EPA into arterial plaque, is associated with reduced plaque inflammation, decreased foam cells [macrophages containing cholesterol which form plaque], and increased plaque stability [11,12]. There are also a number of vascular effects, anti-inflammatory effects, and other pathways through which EPA may have a more important role than DHA, as it relates to CVD risk [13].

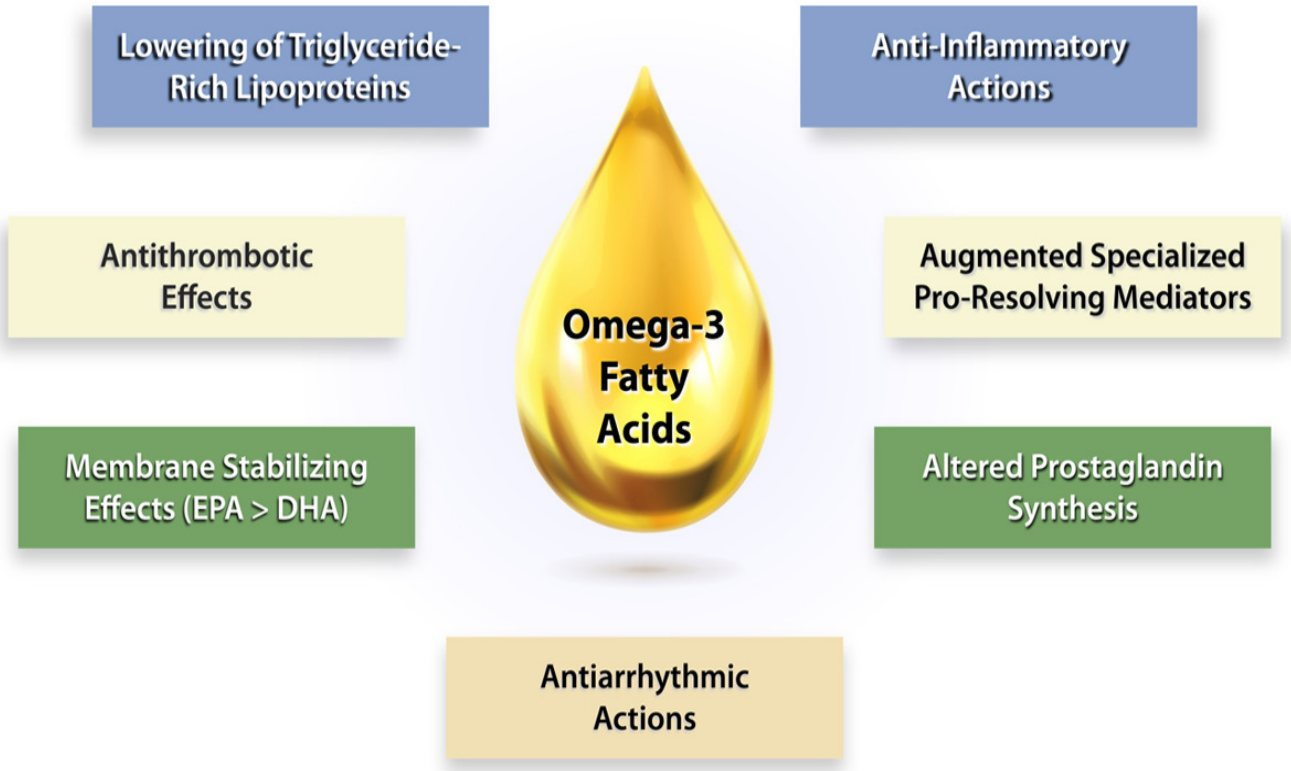

Figure *from [13] illustrating the multiple mechanisms of action of omega-3 fatty acids, EPA and DHA. The respective contribution of these pathways to reduced cardiovascular disease risk remains to be fully determined, however, it does appear that for many of these mechanisms, EPA has a greater effect than DHA: membrane stabilising, anti-inflammatory effects, anti-thrombotic effects, pro-resolving mediators, and altered prostaglandins synthesis. This may explain a greater efficacy to high dose, purified, EPA ethyl ester over other omega-3 formulations.*

Finally, let' s discuss some minor additional considerations. In relation to the placebo/control choice, there was a suggestion that the use of mineral oil as the in REDUCE-IT may have increased CVD risk in the control group, i.e., inflated the effect of the intervention. However, a review of the data indicated that the effect of the mineral oil placebo did not materially change the outcome [14], while the EVAPORATE trial - which also used a mineral oil control - deliberately examined this and found no effect on plaque progression [10]. This argument, which emerged after REDUCE-IT was published, does not appear to have much weight. The very last factor to consider is that these studies are more appropriately considered pharmaceutical interventions [the supplements used are all classified as pharmaceutical drugs], and background fish intake is seldom assessed.

So with that headache somewhat throbbing, let me conclude more succinctly: based on the current evidence, I am of the opinion that high doses of 4g/d EPA ethyl ester form may reduce CVD risk in individuals in secondary prevention of CVD, when administered adjuvant to lipid-lowering therapy [i.e., statins], with the primary mechanism being improved atherosclerotic plaque characteristics. This view may change given better evidence.

Application to Practice

This study provides a robust example of why 'null' findings are so important to the overall evidence base. There is little direct application to practice, beyond the importance that the study serves as an additional data point in the omega-3/heart health scientific literature. The pharmaceutical grade omega-3 supplements used in these interventions are beyond the reach of most practitioners. Perhaps the real-world application is reflected in the fact that in 2019 the omega-3 fatty acid supplement market was worth $4.1billion. As most are low-dose triglyceride forms of mixed EPA/DHA, advising your client not to contribute to this market may be money well saved.

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