GOED OMEGA-3

GLOBAL ORGANIZATION FOR EPA AND DHA OMEGA-3

Omega-3 Science Update: Adding ASCEND, VITAL and REDUCE-IT to the Body of Evidence

November 15: In the last three months, the results of VITamin D and OmegA-3 TriaL (VITAL)[1], Reduction of Cardiovascular Events With EPA – Intervention Trial (REDUCE-IT)[2] and A Study of Cardiovascular Events in Diabetes (ASCEND)[3] have been published, marking the first important new interventional studies on cardiovascular outcomes to be published in several years. It's now important to draw some conclusions about what this research is telling us. This discussion attempts to identify what we have learned, which conclusions of the trials are strengthened by prior knowledge and the results of the other trials, and which results were unexpected and open important new avenues of research.

These three trials are all large, well-designed, long-term studies whose primary outcome is the effect of long-chain omega-3s on the risk of major cardiovascular events. As a summary:

- ASCEND (A Study of Cardiovascular Events in Diabetes): 15,480 diabetics without any sign of existing cardiovascular disease were randomly assigned to receive a daily 1 g capsule of omega-3 fatty acids (840 mg of EPA+DHA) or a placebo. Participants were followed for an average of 7.4 years, and as a primary outcome, the study found no difference between the two groups in the rate of major cardiovascular events, but there was a statistically significant 19% reduction in the risk of vascular death. Diabetics are at a much higher risk of cardiovascular events than the general population, and this study is the first interventional trial to evaluate the effect of omega-3s on this high-risk population.

- VITAL (Vitamin D and Omega-3 Trial): 25,871 healthy participants received either a daily 1g capsule of omega-3 fatty acids (840 mg of EPA+DHA) or a placebo. This is the first study of the effects of long-chain omega-3s on cardiovascular risk ever conducted on a healthy population, and it provides the first insights on the effect of these nutrients in a low-risk population. VITAL found that treatment reduced the risk of major coronary heart disease events by about 8%, but this was not statistically significant. It also found that the risk of MI (myocardial infarction/heart attack) was reduced by 28%, which did reach statistical significance.

- REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl – Intervention Trial): 8,179 participants, all with either established cardiovascular disease or diabetes or other risk factors. All participants had high blood triglycerides, and they were undergoing successful statin therapy. Participants were randomly assigned to receive 4g/day of EPA or placebo, and they were followed for a median of 4.9 years. REDUCE-IT found that the treatment lowered the risk of major cardiovascular events by 25%, and that the risk of other cardiovascular outcomes (like stroke, or myocardial infarction) were reduced by a similar factor.

Outcomes of Interest

Of particular interest from these three studies are two particular outcomes: the risk of coronary heart disease (CHD) events, and the risk of non-fatal MI, for the following reasons:

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- CHD events: In general, the strongest evidence to date shows a clear reduction in the risk of cardiac mortality, and GOED commissioned a meta-analysis on this outcome last year[4]. But for CHD events, the evidence has remained mixed, and this is the most commonly cited effect of omega-3 intake, so it is important to see whether these new studies bring any clarity to this issue.

- Non-fatal MI: The VITAL researchers report an important reduction in the risk of myocardial infarction (a reduction of 41%, which is unexpectedly high). If confirmed, this finding would be of major significance in the prevention of CHD, but this result has already been the subject of significant discussion and controversy. The VITAL researchers conclude that because it was a strong protective effect in a common event, and because the statistics supporting it are strong, then this should be considered a robust result, and one of clinical importance. Critics observe that because this was not the primary outcome of interest in the trial, any findings should be considered as preliminary, and confirmed by subsequent studies. Both positions are reasonable, but they ignore that there is already a significant body of research on this outcome.

CHD Events

The outcome of CHD events was studied by the 2018 meta-analysis by Abdelhamid et al[5], also known as the Cochrane analysis. Based on 28 trials, and over 84,000 participants (and 5,469 events), the meta-analysis found a statistically significant reduction of 7% (RR = 0.93; [0.88 – 0.97]). But rather than reporting this as a positive finding, the authors chose to focus on a smaller list of studies that they determined to be of better quality ("low overall risk of bias," in the language of the article). These studies showed a smaller, 2%, risk reduction (0.98; [0.91 – 1.05]), and the authors concluded that the risk reduction observed in the totality of the evidence was probably driven by a few lower quality studies, so a positive finding was not warranted.

The authors claim that their focusing on only "good quality" studies is one of the strengths of their analysis, but in fact it is a significant departure from well-established practice and it deserves more scrutiny. GOED has already written extensively about the issue[6].

When the results of the three new trials are added to this meta-analysis, the estimated risk reduction changes slightly. In 31 trials, and almost 134,000 participants, the estimated effect of omega-3 fatty acids on CHD events is now a statistically significant 9% reduction (RR: 0.91 [0.81 – 0.95]).

As mentioned previously, all three trials are well-designed, large-scale studies, and while this needs independent corroboration, we believe that they would be found to be of good quality under the definition used by Abdelhamid et al. When these new trials are added to just the 'good quality' trials in Abdelhamid's analysis, the result is a statistically significant 8% risk reduction (RR: 0.92; [0.85 – 0.99]). This estimate is basically the same as that which is obtained by examining all trials, and with the addition of these three trials, most of the evidence in favor of a protective effect against CHD events now comes from 'high quality' trials, eliminating the objections raised by the Cochrane authors' controversial interpretation.

Non-Fatal Myocardial Infarction (MI)

Non-fatal myocardial infarction was meta-analyzed by Rizos et al[7] in 2012. It was also covered in a more recent analysis by Aung et al[8], published in 2018, but this article only covers the results of 10 large clinical trials, chosen based on the availability of individual patient data, rather than on a systematic search of all existing evidence. While recognizing the fact that Rizos' analysis may have missed some recent trials, it includes all trials included by Aung.

Based on 14 trials and almost 54,000 participants, Rizos finds a non-statistically-significant risk reduction of 11% (RR: 0.89; [0.76 – 1.04]). The correct conclusion was that the existing evidence did not support the conclusion that omega-3 supplementation reduced the risk of this outcome.

Including the three recent large studies changes this conclusion. On the evidence of 17 trials that include over 103,000 participants, the updated estimate is a statistically significant 14% risk reduction (RR: 0.86; [0.76 – 0.97]). The inclusion of the newer trials does not change the estimate by much (from 11% to 14%), but almost doubling the number of participants included yields much more precise estimates.

Most trials included in this analysis reported a decrease in the risk of non-fatal myocardial infarction, and the pooled evidence confirms that this is a real, large, robust effect. The conclusion reached by the VITAL researchers that omega-3 supplementation does reduce the risk of this outcome (and that this reduction is of importance to clinical practice) is strongly supported by prior evidence. But the results are heterogeneous – there are larger than expected differences among studies in how big this protective effect is. While omega-3s reduce the risk of non-fatal myocardial infarction, it is possible that some groups of people may benefit more than others from this intervention, and a more careful analysis of the existing evidence and probably more clinical trials will be necessary to identify those groups.

One Final Comment

Amarin, the sponsor of REDUCE-IT, claims that their product is so different from other omega-3 formulations that the results of REDUCE-IT cannot be generalized to long-chain omega-3s. Their opinion is also that, for the same reason, these results should not be combined with the results of existing research. It is certainly true that EPA and DHA have different biological activities, and probably different roles in cardiovascular prevention, and that more research is needed to better understand the effects of different combinations of these nutrients. It is also true that the protective effects reported for REDUCE-IT are larger than those observed in most other studies, but this can more easily be explained by differences in dosage than by the uniqueness of the product's formulation. Most clinical research on omega-3s has been conducted using around 840 mg of EPA+DHA per day, while REDUCE-IT used 4,000 mg per day, and it should come as no surprise that increasing dosage by a factor of 5 would lead to stronger outcomes. GOED believes that for cardiovascular protection the dosage and the consistency with which omega-3s are used are more important than the exact formulation.

Moreover, and perhaps more importantly, the results of REDUCE-IT are consistent with the results of existing research (which strengthens the conclusions of that study), but their inclusion in this analysis does not change our estimates or their statistical significance in any meaningful way.

References:

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