ALINEA

NUTRITION

AUGUST 2020

www.alineanutrition.com

TABLE OF

CONTENTS

What We Know, Think We Know, or Are Starting to Know 03

The Study 04

Geek Box: Meta-analysis 04

Results 05

The Critical Breakdown 05

Key Characteristic 06

Interesting Finding 06

Geek Box: Sensitivity Analysis 07

Relevance 07

Application to Practice 08

References 09

Hu Y, Hu FB, Manson JAE. Marine Omega-3 Supplementation and Cardiovascular Disease: An Updated Meta-Analysis of 13 Randomized Controlled Trials Involving 127 477 Participants. J Am Heart Assoc. 2019;8(19).

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

The story of what we know or think we know with the marine omega-3 fatty acids, eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA] and cardiovascular health could be a bedtime story, from explorers and Inuits to scientists and laboratories.

In the 1970' s, two Danish physicians, Hans Olaf Bang and Jorn Dyerberg, travelled to Greenland to investigate a anecdotal reports of low rates of coronary heart disease [CHD] amongst the Inuit in a town named Umanak, whom were reported to eat large amounts of seal and whale blubber [(1)]. Their conclusion was that high levels of long-chain omega-3 fatty acids explained the heart-health benefits, despite eating pure blubber. This study entered into nutritional lore of sorts, but it is important to note that it was based on a tiny town some 500km north of the Arctic Circle, and the physician pair did not examine cardiovascular health, but based their analysis on medical records.

However, even earlier than the work by Bang and Dyerberg, in the 1940' s Danish doctors in Greenland had published findings highlighting frequent incidence of CHD in the Greenland Inuit population [(2)]. This may have been the truth all along: a recent study indicated that prevalence of CHD in the Inuit was as high as 'Western' populations, with evidence of excessive mortality due to cerebrovascular stroke, and average life expectancy 10yrs shorted than age-matched controls [(2)].

Nonetheless, interest in the role of EPA/DHA in cardiovascular health has remained, but a 2018 Cochrane Review [(3)] found no effect of omega-3 supplementation on CHD. The "fish oils are useless" bells rang out. But then, REDUCE-IT [Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial] was published, finding that a high-dose EPA supplement given to patients in secondary prevention [i.e., they had already suffered a cardiovascular event] led to a 25% reduction in risk for a further cardiovascular event [(4)]. The present study updated the evidence in a meta-analysis.

The Study

The investigators conducted a meta-analysis* of randomised controlled clinical trials, including 3 recent large studies, and applying the following inclusion criteria:

- Omega-3 supplementation compared to placebo/open label control [an open label placebo is where the placebo group are told they are in the placebo group or getting no active treatment, to try and minimise the "placebo effect"]
- Minimum sample size of >500 participants
- Follow-up duration of >1yr
- Cardiovascular disease and coronary heart disease events and mortality as endpoints

As REDUCE-IT had used a dose of 4g/d purified EPA, meta-analysis was conducted with and without this trial included. An analysis was also conducted restricted to studies in which a minimum of 840mg/d total EPA/DHA was administered, over 2yrs, with >1,000 participants. Dose-responses between total EPA/DHA and the endpoints of interest were also examined.

In total, 13 RCTs were included with a total 127,477 participants, 59.7% male / 40.3% female, with a mean age of 64.3yo at baseline.

*Geek Box: Meta-analysis

The term 'meta-analysis' first entered scientific terminology in 1976 in a paper by psychologist Gene Glass. The intended outcome of a meta-analysis is quantitative precision; to obtain a strong statistical summary of the effect size for a given exposure and outcome. Meta-analysis can also be used to compare and contrast results from different studies, examining the reason for divergent effect sizes, and also to identify patterns between studies, for example whether there is effects at specific doses, but not others. The first aim - to obtain a statistically precise overall summary of effect - is effective when certain assumptions are met in included studies: precise independent effects, specialised population group, clearly defined intervention, similar effect size measures. This tends to reflect the desired aim within evidence-based medicine for a meta-analysis to include evidence from RCTs, with similar methodology, looking at the same exposure-outcome relationship, for example statins and heart disease. This is reflected in the position of meta-analysis at the top of the pyramid hierarchy of evidence, with the implication that if RCTs are to be considered the 'gold standard' of evidence, meta-analysis are widely considered the 'platinum standard'. Indeed this may be the case when the exposure is a drug. However, the conceptual basis and underlying assumptions favour biomedical RCTs, and applying this methodology to nutrition - either interventions or prospective cohort studies - without consideration of these factors may often yield misleading answers. In biomedical sciences, we may see a meta-analysis of a specific drug, like the example of statins and heart disease. But imagine doing a meta-analysis on heart disease risk and including studies on statins, niacin, aspirin, blood pressure medications, beta-blockers, fish oils, CETP-inhibitors, and assuming they were all equivocal: this is exactly the kind of "distortive lumping" that is all too typical among nutrition meta-analysis. Studies may differ in the foods or supplement used, the dose, the duration of the intervention relative to the time-course of the disease, the population group, or the outcome measures. So, with nutrition meta-analysis, we need to take extra caution in analysing their findings, and not merely assume that because of their position on the hierarchy of evidence, that they are somehow infallible.

Results: The results are presented for the overall analysis, including REDUCE-IT [more under ***Key Characteristic***, below]. The overallstatistically significant effects are presented for the major endpoint, as follows:

- ***Total CHD:*** 7% reduction in risk [HR 0.93, 95% CI 0.89-0.96]
- ***CHD Death:*** 8% reduction in risk [HR 0.92, 95% CI 0.86-0.98]
- ***Total CVD:*** 5% reduction in risk [HR 0.95, 95% CI 0.92-0.98]
- ***CVD Death:*** 8% reduction in risk [HR 0.92, 95% CI 0.88-0.97]
- ***Myocardial Infarction [MI]:*** 12% reduction in risk [HR 0.88, 95% CI 0.83-0.94]
- ***Major vascular events:*** 5% reduction in risk [HR 0.95, 95% CI 0.93-0.98]

For the dose-response analysis, each 1g/d of EPA/DHA supplementation resulted in the following:

- ***CVD death:*** 17% reduction in risk [HR 0.92, 95% CI 0.88-0.97]
- ***Total CVD:*** 5% reduction in risk [HR 0.95, 95% CI 0.92-0.98]
- ***Total CHD:*** 7% reduction in risk [HR 0.93, 95% CI 0.87-1.00]
- ***[MI]:*** 9% reduction in risk [HR 0.91, 95% CI 0.85-0.98]

The Critical Breakdown

Pros: Including 3 major recent trials increased the overall sample size of the included studies by 64%. Only a single included study had 1yr follow-up, the remainder had a minimum of >3yrs, which may be important to observe effects from omega-3 supplementation. All but 3 studies had omega-3 doses >800mg/d, which may also be an important factor regarding dose. The relative similarity of the trials in terms of intervention, population characteristics, and outcomes, lends confidence to the pooling of results in meta-analysis.

Cons: The dose-response analysis is not quite a 'dose response', given that the dose in REDUCE-IT was so high [4g/d], the next largest dose was 1.8g/d. EPA and the JELIS trial also used EPA only, and the remaining studies had varying ratios of EPA/DHA; thus, whether these factors are relevant for outcomes remains to be fully elucidated. Subgroup analysis based on factors like age, sex, medications, etc., was not possible to conduct.

Key Characteristic

Conducting the analysis both with and without REDUCE-IT allowed for the significant effects of this particular trial on the overall results to be fully examined.

This is important: REDUCE-IT wasn't any omega-3 intervention, but was in a specific population of patients who had already achieved low LDL-cholesterol levels from statin therapy, but who had residual risk from elevated triglycerides. The intervention wasn't a plain omega-3 supplement, but a a highly purified and stable EPA form, which have been shown at doses of 3-4g [REDUCE-IT used 4g/d] to reliably and predictably reduce triglyceride levels.

A trial like this, with large effects, could have a major bearing on the results of the meta-analysis. For example, the risk reduction for MI in the analysis excluding REDUCE-IT was an 8% reduction in risk; REDUCE-IT alone resulted in an 30% reduction in risk [the overall analysis was a 12% reduction in risk]. The key point is that even without REDUCE-IT, the results were statistically significant in favour of omega-3 supplementation; adding REDUCE-IT increased the strength of the reduction in risk.

Interesting Finding

One of the sensitivity analysis* conducted examined the effects of omega-3 supplementation after exclusion of both the GISSI-P and JELIS trials. This is interesting because in the 2018 Cochrane Review of omega-3 supplementation which concluded no effect on CVD risk, the initial analysis including both these trials resulted in a statistically significant 7% [HR 0.93, 95% CI 0.88-0.97] reduction in risk for coronary heart disease events [(3)]. However, the final conclusion was based on off a sensitivity analysis which excluded both the GISSI-P and JELIS trials, which together constituted 24.3% of the overall statistical weight, due to Cochrane Review criteria deeming these trials 'high risk of bias' due to lack of placebo blinding.

But here is the thing: both the GISSI-P and JELIS trials were open-label studies, which means that both the researchers and the participants know what intervention the participants are receiving, conducted in high-risk CVD patients. GISSI-P in particular was a heralded study, designed as a pragmatic RCT in patients in secondary prevention following a previous MI, and found significant benefits to omega-3 supplementation. In the present study, which included the most recent 3 large RCTs, excluding the GISSI-P and JELIS trials did not change the estimates of effect for nearly all CVD endpoints, except CHD mortality [which remained significantly but the effect size was reduced]. This may indicate that in the previous meta-analysis, once GISSI-P and JELIS trials were removed, the remaining studies were not sufficient robust to hold up the significant reduction in risk. It also reflects a methodological challenge for nutrition interventions, highlighting the limitations of applying drug-trial RCT criteria to trial inclusion for meta-analysis, in circumstances where the research question more appropriately relates to effectiveness [i.e., "does this work"] rather than efficacy ["how does this work"].

*Geek Box: Sensitivity Analysis

When reading research papers, you will inevitably come across the term 'sensitivity analysis' in the methods section, so it is helpful to understand what this means. A sensitivity analysis is an important method of assessing the reliability of findings from an overall analysis, by examining the extent to which the overall results may have been influenced by different methods used in a study, for example the duration of a study, or different factors within the study, like the sex or age of the participants. The aim of a sensitivity analysis is to identify results that may be dependent on unreliable inputs. For example, in the present study, the investigators conducted a sensitivity analysis by excluding trials that had small sample sizes [the DOIT trial], low doses of omega-3s [the SU.FO-L.OM3 and Alpha.Omega trials], and short duration [the OMEGA trial], to examine whether these factors [size, duration, dose] influenced the overall analysis. The result was that the association between omega-3 supplementation and the major CVD endpoints became stronger, including trials with minimum of >3yrs follow-up, minimum of 800mg/d dose, and >1,000 participants in the sensitivity analysis. They also conducted another sensitivity analysis excluding the GISSI-P and JELIS trials because these trials were open-label, so in this case it was this factor - open-label design - which the sensitivity analysis was examining to see if their removal influenced the overall results. You can also see types of sensitivity analysis in intervention studies, for example Intention-to-Treat analysis, where data from participants who dropped out of the study is included based on their last data point, to see if the imbalance between study groups from dropouts may have influenced the results.

Relevance

From the whale blubber fantasy to supplemental intervention studies, the effects of omega-3' s on heart health have been the subject of much hyperbole coupled with inconsistent findings in research. Part of the reason is that, like many studies in nutrition, trials may use different doses, formulations, or be too short to see a true effect. In addition, previous meta-analysis excluding trials with positive findings due to risk of bias may have missed true associations between supplementation and CVD/CHD outcomes.

The present study navigates many of these issues, indicating that minimum doses of ~850mg/d EPA+DHA significantly reduces risk of CVD and CHD events and mortality. EPA/DHA supplementation in controlled trials has been shown to improve plaque stability in the arteries, and reduce atherosclerotic plaque inflammation [5,6]. A recent exploratory study suggested that higher EPA/DHA levels may be associated with reduced coronary artery calcification, a marker of calcified lesions that occur in the artery which is correlated with the extent of atherosclerosis [7]. The well-established triglyceride-lowering effect of omega-3' s were recently confirmed in REDUCE-IT, where triglycerides were reduced by 18.3% over 1yr, and the effect of the high-dose EPA intervention was greatest in participants with higher baseline triglycerides [4].

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.

Application to Practice

It is important to note that the present study included studies of patients in treatment for CVD/CHD risk, with a mean age of 64yo. Thus, any preventative effect of omega-3 supplementation cannot be extrapolated from this study, but prospective studies indicate that ~250g fish per week may significantly reduce risk of CHD and MI [8], and this range corresponds to the 2 servings per week which form current public health recommendations.

References

1. Bang H, Dyerberg J, Hjome N. Investigation of Blood Lipids and Composition of Food of Greenlandic Eskimos. Nutrition Today. 1974;9(6):15.
2. Fodor J, Helis E, Yazdekhasti N, Vohnout B. "Fishing" for the Origins of the "Eskimos and Heart Disease" Story: Facts or Wishful Thinking?. Canadian Journal of Cardiology. 2014;30(8):864-868.
3. Abdelhamid A, Brown T, Brainard J, Biswas P, Thorpe G, Moore H et al. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews. 2018;.
4. Bhatt D, Steg P, Miller M, Brinton E, Jacobson T, Ketchum S et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia: REDUCE-IT. New England Journal of Medicine. 2019;380(1):11-22.
5. Calder P. The role of marine omega-3 (n-3) fatty acids in inflammatory processes, atherosclerosis and plaque stability. Molecular Nutrition & Food Research. 2012;56(7):1073-1080.
6. Thies F, Garry J, Yaqoob P, Rerkasem K, Williams J, Shearman C et al. Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomised controlled trial. The Lancet. 2003;361(9356):477-485.
7. Bittner D, Goeller M, Zopf Y, Achenbach S, Marwan M. Early-onset coronary atherosclerosis in patients with low levels of omega-3 fatty acids. European Journal of Clinical Nutrition. 2020;74(4):651-656.
8. Kris-Etherton P, Harris W, Appel L. Fish Consumption, Fish Oil, Omega-3 Fatty Acids, and Cardiovascular Disease. Arteriosclerosis, Thrombosis, and Vascular Biology. 2003;23(2).