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Explaining the Recent Fish Oil Trial "Failures"

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Introduction

Omega-3 fatty acids, from fish and supplements, have been shown to reduce the risk of Cardiovascular Diseases (CVD) and all-cause mortality in several epidemiologic studies and Randomized Controlled Trials (RCTs), which has formed the basis of the recommendation of the American Heart Association (AHA) to consume an increased amount of fish by those at risk of CVD [1-3]. Several large studies have supported the role of omega-3 fatty acids in the prevention of CVD. The Gruppo Italiano per lo Studio della Sopravvivenza2 nell'Infarto Miocardico (GISSI)–Prevention trial was a randomized that enrolled 11,324 patients with a history of Myocardial Infarction (MI) that showed that supplementation with omega-3 fatty acids in leads to a significant decrease in all-cause mortality (relative risk reduction [RRR] 14% [95% CI 3-24] two-way, RRR 20% [6-33] four-way) and mortality due to CVD (RRR 14% [3-24] two-way, RRR 20% [6-33] four-way, p = 0.0242) and Coronary Heart Disease (CHD;p =0.0226) [4]. The trial also showed a significant decrease in the risk of fatal and non-fatal CHD events (p = 0.024) and Sudden Cardiac Death (SCD) (p = 0.010). The first combined primary endpoint of death, non-fatal MI, and non-fatal stroke showed a significant reduction in both analyses (10% relative decrease in the two-way factorial analysis, [95% CI 1-18, p = 0.048] and 15% relative decrease in the four-way factorial analysis [95% CI 2-26, p = 0.023]). The other combined primary endpoint of CVD death, non-fatal MI, and non-fatal stroke showed an insignificant reduction (11% in the two-way factorial analysis [95% CI 1-20, p =0.053]) and a significant 20% reduction in the four-way factorial analysis (95% CI 5-32, p = 0.008) [4]. Another study – the DART trial – like the GISSI-Prevention trial was a large RCT conducted on 2,033 men who had suffered a previous MI to assess the effects of inclusion of fatty fish or fish oil in their diet [5]. Results of this study showed a clinically significant reduction in all-cause mortality in patients with a previous history of MI (RR = 0.71 [0.54-0.92]). The effect still remained significant after adjustment for all potential confounding factors (RR = 0.71 [0.54-0.93]) [5]. A very large randomized trial – The Japan Eicosapentaenoic Acid Lipid Intervention Study (JELIS) trial – was conducted in 18,645 hypercholesterolaemic patients who were randomized to statin therapy with or without omega-3 fatty acids (1.8 grams of eicosapentaenoic acid). The omega-3 fatty acid supplement was effective in further reducing the risk of major CHD events [6]. The JELIS trial showed that the addition of omega-3 fatty acids to the diet of hypercholesterolaemic patients taking statin drugs leads to a significant further decrease in the incidence of major CHD events (19%, p = 0.011) and that the mechanism of this positive effect is not through the reduction of low density lipoprotein (LDL) cholesterol. Therefore, the beneficial effects of omega-3 fatty acids may be additive to those conferred by statin drugs. However, the doses of statins used in this trial were relatively low. A sub-analysis of the JELIS trial also showed a clinically significant reduction (20%, Hazard Ratio [HR] = 0.80 [0.64-0.997]) in the incidence of recurrent stroke in the secondary prevention cohort of the JELIS trial [7].

The positive effects of omega-3 fatty acids are also observed in patients with heart failure (HF). The GISSI–HF was a large RCT conducted in 6,975 patients with chronic HF to assess the additional effects of omega-3 fatty acids in patients already receiving optimum clinical care for HF [8]. It was shown that the patients receiving long term omega-3 fatty acids had a lower incidence of death or hospitalizations due to CV causes (adjusted HR = 0.92 [99% CI 0.849-0.999], p = 0.009) and a reduced all-cause mortality absolute rate (1.8% [0.3-3.9], adjusted HR = 0.91 [95.5% CI 0.833-0.998], p = 0.041) without any adverse effects. The beneficial effect of omega-3 fatty acid supplementation for reducing the number of fatal CHD events (HR = 0.51, [0.27-0.97]) and arrhythmia-related events (HR = 0.51, [0.24-1.11]) has also been shown to be valid for diabetics [9]. The beneficial effects of omega-3 fatty acids are also validated by various meta-analyses. A recent meta-analysis conducted on RCTs assessing the effects of omega-3 fatty acids in patients with CHD showed a decrease in the overall risk of non-fatal MI (RR = 0.8 [0.5-1.2], p = 0.16), fatal MI (RR = 0.7 [0.6-0.8], p < 0.001), overall death (RR = 0.8 [0.7-0.9], p < 0.001), and SCD (RR = 0.7 [0.6-0.9], p < 0.01) [10]. Another meta-analysis demonstrated a moderate but clinically significant reduction (RR = 0.88 [0.84-0.93]) in the incidence of cerebrovascular diseases in patients with a higher intake of fish as compared to those with a lower intake [11]. Recently, however, some studies have showed a lack of the inverse relationship between fish oil intake and CVD risk. This editorial discusses the possible factors leading to some of the conflicting results seen in the studies on fish oil and risk factor for CVD.

Recent fish oil trials

The US Physicians' Health Study, a prospective cohort study conducted on a large number of US physicians, showed a significantly reduced risk of SCD (RR = 0.48 [0.24-0.96], p = 0.04) and all-cause mortality (RR = 0.70 [0.55-0.89], p = 0.02) in physicians who ate fish at least once a week [12]. However the study showed no reductions in the risk of MI (RR = 0.99 [0.64-1.54], 0.67), non-SCD (RR = 1.19 [0.42-3.35], p = 0.33), total CVD mortality (RR = 0.79 [0.51-1.23], p = 0.50), or all-cause mortality (RR = 0.71 [0.55-0.91], p = 0.45). The study, also noted by the authors, had several striking limitations. The participants with a higher intake of fish were more likely to be suffering from hypertension, hypercholesterolemia, and have a family history of heart diseases. On the other hand, most of the participants under observation were consuming at least some amount of fish and therefore may have

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already been benefiting, therefore any further decrease may be difficult to demonstrate. Fish consumption by the participants was conducted only once and the possibility that the amount of fish intake changing over time was not accounted for. These limitations may account for the apparent lack of association between fish oil and CVD risk factors.

The FISH study was conducted to assess the effect of fish oil on patients with end stage chronic kidney disease having synthetic arteriovenous hemodialysis grafts [13]. This trial showed that daily fish oil reduced graft failure (incidence rate ratio = 0.58 [0.44-0.75], p < 0.001), reduced the rates of thrombosis (IRR = 0.50 [0.35-0.72], p <0.001), and decreased the risk of further corrective interventions (IRR = 0.59 [0.44-0.78], p <0.001). Fish oil also reduced the incidence of CVD (HR = 0.43 [0.19-0.96], p = 0.04) and improved blood pressure (mean systolic blood pressure difference = -8.10 [-15.4 to -0.85], p = 0.01). These findings were associated with a significant positive clinical effect. However the study did not find an improvement in the loss of graft native patency (RR = 0.78 [0.60-1.03], p = 0.06), which, according to the authors, may have been due to a slightly smaller number of patients enrolled in the study than that required for the statistical power to detect such an effect. A similar study [14] showed even more strikingly significant effects of fish oil supplementation; an improved 12-month graft patency, decrease in the blood pressure, prevention of thrombosis, attenuation of development of venous stenosis, and reduced intimal hyperplasia. Improvement in the 12-month graft patency in this study supports a further trial to evaluate the effect of omega-3 fatty acids on graft patency.

The OMEGA trial was conducted to test the effects of omega-3 fatty acids on the incidence of SCD, non-fatal CVD events, and all-cause mortality in patients with a previous MI [15]. Omega-3 fatty acids therapy was not shown to lower the rates of SCD (OR = 0.95 [0.56-1.60], p = 0.84), total mortality (OR = 1.25 [0.90-1.72], p = 0.18), or major CVD and cerebrovascular events (p = 0.1) in the study population. It should be noted, that the participants of this study were receiving treatment for MI according to the current guidelines along with the omega-3 fatty acids. The rates of fatal and non-fatal clinical events was already quite low during the follow-up of this study, probably due to the participants receiving guideline treatment for their condition, which could have masked any clinically significant positive effect of omega-3 supplementation. In addition, the study was of a relatively short duration (one year), did not use an appropriate placebo (the placebo used was olive oil), had a high baseline level of fish intake and used a smaller amount of omega-3 fatty acids (1 g/day) as compared to other studies, and did not have enough power to show a positive effect.

Another recent trial, Alpha Omega, failed to detect any significant reduction in CVD risk with n-3 fatty acids [9]. This trial was carried out in patients with a previous MI who were already receiving anti-hypertensive, anti-thrombotic, and lipid-modifying therapy, which may have masked any of the beneficial effects of omega-3 fatty acids. In support of this argument, the authors also mentioned that it is relatively higher number of patients receiving statins in this study as compared to some of the previous ones. Lastly, a large proportion of the participants in this trial were older males and therefore the sample population used for this study is not indicative of the general population. Despite these limitations of the study, there was evidence for a significant positive effect of omega-3 fatty acids on the incidence of fatal CHD events (HR = 0.51, [0.27-0.97]) and arrhythmia-related events (HR = 0.51, [0.24-1.11]) in diabetics. Moreover, in statin non-users (n = 413) omega-3 plus alpha linoleic acid showed a borderline significant reduction in CVD events (9% vs. 18%, respectively, adjusted HR = 0.46; 95% CI; 0.21-2.02; p = 0.051) [16].

The Supplementation en Folates et Omega-3 (SU.FOL.OM3) trial was conducted to assess whether B vitamins or omega 3 fatty acids have any effect in preventing CVD events [17]. The participants in this group were divided into four groups: vitamin B, omega-3 fatty acids, both, or placebo. This trial also showed an apparent lack of a positive effect of omega-3 fatty acids on major CVD events (HR= 1.08 [0.79-1.47], p = 0.64). It has been suggested that B-vitamins may be associated with an increased rate of CVD events [18] and all- cause mortality [19]. Thus, the effects of omega-3s may have been muted by the detrimental ones of B-vitamins excluding the participants who received both B-vitamins and omega-3, leaves only 633 patients in fish oil only group. Thus, the power of this trial is very small to detect any positive effect of omega-3. The authors also note that the actual number of major vascular CVD was 15% lower than initially expected, which adversely affected statistical power to detect a 10% difference in major CVD events (approximately 20% power to detect a 25% benefit of omega-3s). Therefore, the authors conclude that there is a possibility that the duration of supplements and follow-up was insufficient. The compliance of the group was self-reported without any objective measure. Thus, the study is prone to bias. Moreover, in the GISSI-P trial, the average time from the CVD event to start of omega-3s was 16 days, whereas it was six times longer (101 days) in SU.FOL.OM3, and since most of the benefits of omega-3s in the GISSI-P trial were seen in the early period of treatment, we can safely assume that much of the benefits of omega-3s would have been missed in SU.FOL.OM3 trial. The baseline characteristics of participants of the trial showed a higher use of angiotensin coverting enzyme inhibitors and angiotensin II receptor blockers in the placebo group than in the omega-3 group (thus biasing the results in favor of placebo). There were also a greater number of patients with a history of MI and current smoker status in omega-3 group when compared with the placebo group. There were also a much lower number of patients with complete follow-up in the groups with placebo and B-vitamins when compared to the omega-3 group, (n = 561, 542 vs. 572, respectively). Considering the fact that adverse events would go largely undetected if the study participants were not followed up, this biases the results in favor of the placebo and B-vitamins. A worst-case scenario (if every extra person lost in follow-up on B-vitamins and placebo had an event) would indicate 30 extra events in B-vitamin group and 19 extra events in the placebo group. Considering all of these factors, the apparent lack of a positive effect of omega-3 supplementation in this trial, may be explained by other factors. Lastly, only 380 mg of EPA/DHA was used in this trial, despite other post-MI trials (JELIS and GISSI-P) using 1 g and 1.8 g respectively, and despite Japanese patients having a very high baseline omega-3 fatty acid intake.

The ORIGIN trial was a large study conducted on patients with a high risk of CVD and impaired glucose tolerance or diabetes taking n-3 fatty acids [20]. This study failed to demonstrate any benefits of supplementation with n-3 fatty acids on the incidence of major CVD events (HR = 1.01 [0.93-1.10], p = 0.81), SCD (HR = 1.10 [0.93-1.30], p = 0.26), CVD mortality (HR = 0.98 [0.87-1.10], p = 0.72), or overall mortality (HR = 0.98 [0.89-1.07], p = 0.63) in patients with diabetes or impaired glucose tolerance. These findings may in part be explained due to the high background intake of n-3 fatty acids (median: 210 mg/day) in the participants of this trial. Such a high background intake of n-3 fatty acids may have muted any benefit seen from additional omega-3 supplementation. The third National Health and Nutrition Examination Survey (NHANES III) and the Continuing Food Survey of Intakes by Individuals (CSFII) indicates a median Eicosapentaenoic acid (EPA) + Docosahexaenoic acid (DHA) intake of 0 and 46 mg/day, respectively, which is considerably less than that seen in the ORIGIN

trial (210 mg/day) [21]. Thus, background EPA + DHA intake was higher in ORIGIN compared to that of the general US population. Furthermore, Mozaffarian and colleagues have shown a probable threshold effect at 250 mg/day of EPA + DHA [22]. That is, the greatest risk reduction in primary prevention for CHD death and SCD occurs at doses at or above 250 mg/day EPA + DHA. The high baseline use of EPA + DHA in the ORIGIN trial could have potentially partly nullified the benefits of omega-3 supplementation. The participants of this trial were also more likely to be using cardioprotective therapies, which might have contributed to masking any beneficial effects of n-3 supplementation. It is noteworthy that methylmercury, a contaminant found in fish in certain geographic areas, may antagonize the effects of fish or fish oil supplements, if not appropriately filtered out in the manufacturing process, therefore potentially contributing to the conflicting results seen in different studies [1].

Negative meta-analyses

A recently published meta-analysis on the association of omega-3 fatty acid supplements and CVD concluded that there is insufficient evidence of a protective effect of these supplements on CVD events [23]. The meta-analysis did not find any association between omega-3 fatty acids and the risk of CVD events (RR = 0.99 [0.89-1.09]). However, this meta-analysis did not consider two very large studies, both of which showed significant inverse association of fish oil with CVD events [4,6] and had enrolled 11,324 and 18,645 patients, respectively. On the other hand, the meta-analysis included 14 RCTs comprising only of 50 to 550 patients with a total of 20,485 patients and a follow-up of only two years or less. As can be seen from the numbers, the inclusion of the two studies in this meta-analysis would be expected to have a very significant effect on its results. In support of this argument, previous meta-analyses supporting the role of fish oil in preventing CVD had considered these two studies in their calculations. In addition to excluding two very important studies, the meta-analysis was based only on studies of short duration and with a small number of participants. Both of these factors weaken the calculations of the meta-analysis.

Another meta-analysis conducted on this topic concluded that omega-3 fatty acids may protect against CVD (RR = 0.86 [0.75–0.99], p = 0.03). However, the magnitude of the positive effects was not as great as was suggested by the older studies [24]. No statistically significant effect could be demonstrated on the incidence of CHD events (RR = 0.86 [0.67–1.11], p = 0.24), arrhythmias (RR = 0.99 [0.85–1.16], p = 0.92), cerebrovascular events (RR = 1.03 [0.92–1.16], p = 0.59), CVD events (RR = 0.96 [0.90–1.03], p = 0.24) or on all-cause mortality (RR = 0.95 [0.86–1.04], p = 0.28). This meta-analysis was significantly flawed because of the heterogeneity of the studies included. An attempt had been made by the authors to combine all of the studies on fish oil and combine all clinically relevant outcomes in this meta-analysis. The authors also noted that this heterogeneity may have contributed to the apparent absence of positive effects in this meta-analysis. A more sensible approach would have been to either conduct separate meta-analyses for each of the clinically relevant outcomes or perform a systematic review without a meta-analysis. Meta-analyses conducted on studies with substantial heterogeneity may lead to misleading results and this may well have been the case.

A similar meta-analysis on the association of omega-3 fatty acid supplementation and the risk of CVD events was recently published and concluded no beneficial effects on all-cause mortality (RR = 0.96 [0.91 to 1.02], absolute RR [RD] = −0.004 [−0.01 to 0.02]), CVD death (RR = 0.91 [0.85 to 0.98], RD = −0.01 [−0.02 to 0.00]), SCD (RR = 0.87 [0.75 to 1.01], RD = −0.003 [−0.012 to 0.006]), MI (RR = 0.89 [0.76 to 1.04], RD = −0.002 [−0.007 to 0.002]), and stroke (RR = 1.05 [0.93 to 1.18], RD = 0.001 [−0.002 to 0.004]) [25]. This meta-analysis used a much stricter p value for a threshold of significance (p value = 0.0063). Despite the strict threshold of significance, the CVD mortality was decreased, but after the values were readjusted for potential confounding factors, the decrease in the mortality rate was no longer significant. The reduction in the rate of SCD and all-cause mortality was quite large, however, but was not significant according to the strict criteria of the meta-analysis. Since omega-3 fatty acids are inexpensive, safe and natural, the use of an unusually strict level of statistical significance was inappropriate, thus potentially making the reductions in mortality and SCD "almost significant", and the reduction in CVD death "significant".

Conclusion

Many flaws in the recent fish oil trials may explain their "failures". Many of the trials were underpowered, used in very low-risk populations, or had used low doses of omega-3s (in the SU.FOL.OM3). Meta-analyses based on these newer, somewhat flawed studies, therefore, might have been unable to demonstrate any significant benefits of the fish oil use. In an era of optimal medical therapy, it is harder to show any benefit of omega-3 fatty acids because of a low background level of adverse CVD events. However, considering that omega-3 fatty acids are safe, natural, and inexpensive, and the guidelines suggest supplementing omega-3 in addition to optimum medical therapy, the same level of evidence is not required for incorporation of omega-3 fatty acids as a part of multi-factorial prevention programs as would have been the case for expensive or potentially dangerous treatment options, such as invasive procedures or devices. Assuming the worst-case scenario, that there is no evidence of any potential health benefits of fish intake or omega-3 fatty acid supplementation, we still do not have sufficient evidence to recommend that people stop taking them. Better, high-quality research trials need to be conducted to strengthen the evidence base for a firmer, more evidence-based conclusion.

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