Commentary: New meta-analysis confirms the long established triacylglycerol-lowering effect of omega-3 fatty acids given in supplemental form

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In this issue of *European Journal of Lipid Science and Technology*, Nam et al. [1] present the findings of a new meta-analysis of the impact of omega-3 supplements (eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA)) on blood lipids; much of the focus of the paper is on the effect on blood triacylglycerol (TG) concentrations. Quite rightly, the analysis uses data from randomised, double blind, placebo controlled trials. In total, data from 53 such trials involving over 7000 participants are used to evaluate the effect on blood TG concentrations, 54, 55 and 50 trials are used to evaluate the effect on blood total cholesterol, high density lipoprotein (HDL)-

cholesterol and low density lipoprotein (LDL)-cholesterol concentrations, respectively. This seems a robust database from which to draw firm conclusions and the meta-analysis appears to be well performed. Overall, it is identified that supplemental omega-3 fatty acids lower blood TG concentrations by an average of 38.6 mg/dL [1]. Although no value for *p* is provided, it is evident from the 95% confidence intervals (CI; -47.2 - -30.2 mg/dL) that the TG lowering effect of omega-3 fatty acids is highly statistically significant. There was no overall effect of omega-3 fatty acids on total cholesterol concentration, but both HDL-cholesterol and LDL-cholesterol concentrations were increased. For HDL-cholesterol the increase was 1.6 mg/dL (95% CI 0.9 - 2.3 mg/dL), while for LDL-cholesterol it was 3.1 mg/dL (95% CI 1.1 - 5.0 mg/dL). The authors present a number of sub-group analyses that are very important in understanding the nature of the evidence base around supplemental omega-3 fatty acids and blood TG lowering. The two most important sub-group analyses are regarding the dose of supplemental omega-3 fatty acids used and the starting (i.e. baseline) blood TG concentration. First, it is demonstrated that low doses of supplemental omega-3 fatty acids have a smaller effect than higher doses [1]. This identification of a dose-dependent effect of omega-3 fatty acids provides a biological plausibility to the findings. Importantly, the meta-analysis identifies that more than one g per day of EPA and/or DHA is required to have a significant impact on blood TGs [1]. Secondly, the effect of omega-3 fatty acids is shown to be greater if the starting blood TG concentration is higher; this finding provides a strong clinical rationale for use of supplemental omega-3 fatty acids in those with hypertriacylglycerolemia. Other subgroup analyses identified no difference in the effect of omega-3 fatty acids on blood TG according to whether the pharmaceutical industry provided the omega-3 supplements or not; to whether the pharmaceutical industry or an independent organisation funded the trial; to which continent the trial was conducted on; or to the duration of supplementation [1]. These findings give confidence to the conclusion that supplemental omega-3 fatty acids can be used to lower blood TG concentrations.

The findings of this new meta-analysis are entirely consistent with the existing literature. In fact, the TG lowering effect of EPA and DHA has been known for decades. As long ago as 1996, Harris [2] identified 72 placebo-controlled human trials of at least 2 wk duration and providing ≤ 7 g of omega-3 fatty acids a day. In normolipidemic subjects (TGs < 2.0 mmol/L or 177 mg/dL), mean TG concentrations decreased by 25%, while total cholesterol increased by 2% due to the combined increases in LDL-cholesterol of 4% and in HDL-cholesterol of 3%. In hypertriacylglycerolemic patients (TGs ≥ 2.0 mmol/L), mean TG concentrations decreased by 28% [2]. Combining data from several studies, Roche [3] clearly identified that the TG-lowering effect of omega-3 fatty acids is dose dependent. A number of meta-analyses confirming the effects of TG lowering effects of omega-3 fatty acids been published, including several recently (e.g., [4]). In a very recent meta-analysis, AbuMweis et al. [5] aggregated data from 110 randomised, placebo-controlled trials of omega-3 fatty acids and blood TG concentrations and identified a mean decrease of 0.37 mmol/L (95% CI -0.43 - -0.31 mmol/L).

Given the strength of the findings, the biological plausibility evidenced by a dose dependent effect of omega-3 fatty acids, and the existing evidence base, including a number of earlier meta-analyses with which their findings are entirely consistent, the conclusions of Nam et al. [1] are perplexing. They conclude that “there is no sufficient clinical evidence for the use of omega-3 fatty acid supplements in the management of dyslipidemia, especially hypertriglyceridemia”. It is not clear how the identified reduction of 59 mg/dL (95% CI -77.2 - -40.9 mg/dL) in fasting TGs in a person with starting TGs of 200 to 499 mg/dL cannot be viewed as clinically meaningful. This effect was seen when findings from 20 studies fulfilling the rigorous inclusion criteria were aggregated [1]. Furthermore, albeit with a much smaller number of included studies, a reduction of 393 mg/dL (95% CI -729.6 - -58.1 mg/dL) was identified in those individuals with a starting

blood TG concentration of ≥ 500 mg/dL [1]. Overall, the findings of Nam et al. [1] suggest that supplemental omega-3 fatty acids have an important role in the control of blood TGs, especially in those with hypertriacylglycerolemia.

One important clinical rationale for considering an intervention to lower blood TGs is that fasting TGs are an independent risk factor for cardiovascular disease [6-8]. The effect size reported for supplemental omega-3 fatty acids and blood TG concentrations [1-5], indicates that TG lowering is likely to one component, and an important one at that, contributing to the cardioprotective effects of EPA and DHA [9]. However, again, Nam et al. [1] dismiss a role for omega-3 fatty acids, focussing on the limited of evidence from secondary prevention trials conducted in patients who had already had a cardiovascular event like a myocardial infarction. Those individuals are likely to already have a significant burden of atherosclerosis. The more important role of risk factor management with omega-3 fatty acids is likely to be in primary prevention, that is, in slowing the buildup of atherosclerotic plaques over a period of decades. Indeed, as discussed elsewhere [10], there is good evidence that omega-3 fatty acids in the form of EPA and DHA have an important role in primary prevention of coronary heart disease (CHD). This is evident from several recent publications [11,12]. For example, Choudhury et al. [11] conducted a systematic review and meta-analysis bringing together prospective studies examining the association of dietary or circulating fatty acids, including omega-3 fatty acids, with risk of coronary outcomes. The aggregation of data from 16 studies involving over 422,000 individuals showed a risk reduction (RR) of 0.87 (95% CI 0.78 – 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 – 0.94), 0.79 (95% CI 0.67 – 0.93) and 0.75 (95% CI 0.62 – 0.89) for those in the top third of circulating EPA, DHA, and EPA plus DHA, respectively, compared with those in the

lower third [11]. In a more recent study, Del Gobbo et al. [12] pooled data from 19 studies 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. EPA and DHA were each associated with a lower risk of fatal CHD, with a RR of 0.91 (95% CI 0.21 – 1.00) for EPA and of 0.90 (95% CI 0.85 – 0.96) for DHA [12]. These analyses [11, 12] support a clear role for EPA and DHA in primary prevention of CHD, and perhaps more widely, of cardiovascular disease. The ability of EPA and DHA to lower blood TG concentrations is likely to one of the several mechanisms involved [9].

Nam et al. [1] fail to acknowledge a role for TG lowering by supplemental omega-3 fatty acids in primary prevention of CHD. They also do not adequately discuss their findings on LDL- and HDL-cholesterol, which are in line with previous analyses (e.g. [2]). An elevation in HDL-cholesterol concentration could be a beneficial effect of omega-3 fatty acids, since HDL particles are cardioprotective. However, it must be acknowledged that the effect of EPA and DHA on HDL-cholesterol concentration is small. The LDL-cholesterol raising effect of supplemental omega-3 fatty acids is widely acknowledged and seems not to be harmful or, if harmful, to be offset by other beneficial effects, for example TG lowering. One reason why the increased LDL-cholesterol concentration may not be harmful is that it is related to an increase in size of the LDL particle, making it less atherogenic [13]. Thus, an omega-3 fatty acid-induced elevation in LDL-cholesterol concentration could actually indicate a further benefit.

In 2002 the American Heart Association (AHA) published recommendations for use of supplemental EPA and DHA in people with existing CHD and for patients with elevated TG concentrations [14]. Nam et al. [1] call for the American Heart Association recommendations “to be considered to be revised based on the findings of [their] meta-analysis”. Nam et al. [1]

seemed unaware that the AHA was in the process of publishing undated recommendations [15]. The AHA review of the evidence base was limited to randomised controlled trials. It concluded that "the recommendation for patients with prevalent CHD such as a recent myocardial infarction remains essentially unchanged [from 2002]" and that "treatment with omega-3 fatty acid supplements is reasonable for the secondary prevention of CHD death" [15]. Because the AHA only considered evidence from randomised controlled trials they stated "because there are no reported randomised controlled trials related to primary prevention of CHD … we were not able to make recommendations for these" [15]. The AHA has not revised its 2002 recommendation of "2 to 4 g of EPA + DHA per day provided as capsules under physician's care" for patients needing TG lowering [14].

In ignoring the main findings of their own meta-analysis and in calling for the AHA to revise its recommendations, Nam et al. [1] also miss the reality of treating the patient with hyperlipidemia. Although the evidence base for recommendations and guidelines that govern practice may come from large cohort studies, randomised controlled trials, systematic reviews and meta-analyses, physicians treat their patients individually, not as members of a cohort in a trial. Thus, a patient identified through a blood test to have hypercholesterolemia may be treated with a statin and will return for a repeat blood test after a period of time to see if, and how well, the statin worked. If the result is to the physician's satisfaction, the treatment is likely to continue; however if the result is not as expected, the dose and/or type of statin used may be changed. Again how well that works will be monitored at an individual level through repeat blood testing. Thus, a physician becomes aware through dealing with real patients whether a drug that is being prescribed for risk factor management works well or not. The same is true of the use of supplemental omega-3 fatty acids used to treat hypertriacylglycerolemia. How well the omega-3 fatty acids work will be evaluated by the physician at the individual patient level. Pharmaceutical

grade preparations of omega-3 fatty acids have been widely used for TG lowering over many years and it seems unlikely that this would be the case if physicians did not see evidence that this approach worked in their patients.

In summary, this well conducted systematic review and meta-analysis [1] confirms that supplemental EPA and/or DHA are effective at lowering blood TG concentrations. Further, it confirms that the effect is dose-dependent and demonstrates that it is greater in those with higher starting TG concentrations. A TG-lowering effect of omega-3 fatty acids would be expected to contribute to reduced risk of CHD.

Conflicts of interest. PCC is an advisor to DSM, Pronova BioPharma (pat of BASF), Cargill, and FrieslandCampinas and has research funding from Pronova BioPharma.

References

[1] Nam, G. E., Myung, S-K., Choi, Y-J., Use of omega-3 fatty acid supplements has insufficient clinical evidence for treatment of hypertriglyceridemia: a meta-analysis of randomised, double-blind, placebo-controlled trials. *Eur. J. Lipid Sci. Technol.* 2017, in press.

[2] Harris, W. S., N-3 fatty acids and lipoproteins: comparison of results from human and animal studies. *Lipids* 31, 243-52.

[3] Roche, H. M., Unsaturated fatty acids. *Proc. Nutr. Soc*. 1999, 58, 397-401

[4] Leslie, M. A., Cohen, D. J., Liddle, D. M., Robinson, L. E., Ma, D. W., A review of the effect of omega-3 polyunsaturated fatty acids on blood triacylglycerol levels in normolipidemic and borderline hyperlipidemic individuals. *Lipids Health Dis* 2015, 14, 53.

[5] AbuMweis, S., Jew, S., Tayyem, R., Agraib, L., Eicosapentaenoic acid and docosahexaenoic acid containing supplements modulate risk factors for cardiovascular disease: a meta-analysis of randomised placebo-control human clinical trials. *J. Hum. Nutr. Diet.* 2017, in press.

[6] Hokanson, J. E., Austin, M. A., Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J. Cardiovasc. Risk* 1996, 3, 213-219.

[7] Liu, J., Zeng, F. F., Liu, Z. M., Zhang, C. X., Ling, W. H., Chen, Y. M. Effects of blood triglycerides on cardiovascular and all-cause mortality: a systematic review and meta-analysis of 61 prospective studies. *Lipids Health Dis.* 2013, 12, 159.

[8] Austin, M. A., Plasma triglyceride as a risk factor for cardiovascular disease. *Can. J. Cardiol.* 1998, 14(Suppl B), 14B-17B.

[9] Calder, P. C., N-3 Fatty acids and cardiovascular disease: evidence explained and mechanisms explored. *Clin. Sci. (Lond.)* 2004, 107, 1-11.

[10] Calder, P. C., New evidence that omega-3 fatty acids have a role in primary prevention of coronary heart disease. *J Pub Health Emerg*. 2017, 1, 35

[11] Chowdhury, R., Warnakula, S., Kunutsor, S., Crowe, F., Ward, H. A., Johnson, L., *et al*., Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. *Ann. Intern. Med.* 2014, 160, 398-406.

[12] Del Gobbo, L. C., Imamura, F., Aslibekyan, S., Marklund, M., Virtanen, J. K., Wennberg, M., *et al*., ω-3 Polyunsaturated fatty acid biomarkers and coronary heart disease: pooling project of 19 cohort studies. *JAMA Intern. Med*. 2016, 176, 1155-1166.

[13] Bays, H., Clinical overview of Omacor: a concentrated formulation of omega-3 polyunsaturated fatty acids. *Am. J. Cardiol*. 2006, 98, 71i-76i.

[14] Kris-Etherton, P. M., Harris, W. S., Appel, L. J., AHA Scientific Statement: Fish

consumption, fish oil, omega-3 fatty acids and cardiovascular disease. *Circulation* 2002, 106, 2747-2757.

[15] Siscovick, D. S., Barringer, T. A., Fretts, A. M., Wu, J. H., Lichtenstein, A. H., Costello, R. B., *et al*., Omega-3 polyunsaturated fatty acid (fish oil) supplementation and the prevention of clinical cardiovascular disease: A science advisory from the American Heart Association. *Circulation* 2017, 135,:e867-e884.