Fish oil's long voyage may culminate with the incorporation into standard of care together with statins for managing atherosclerotic vascular disease.

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Editorial Board, Journal of Excipients and Food Chemicals

Editorial

KEY WORDS: Atherosclerotic vascular disease, omega-3, fish oil, vascepa, Icosapent ethyl, eicosapentaenoic acid, docosahexaenoic acid, hypertriglyceridemia, alpha tocopherol, Inclisiran, PCSK9 inhibitors, statins

Fish tales have been around much longer than the perceived benefits of fish oil, the former conveying a greater degree of exaggeration, than the latter. In the 1970s', Bang and Dyerberg observed that the Inuit of Greenland had a low rate of heart disease. The authors attributed this to their 'Eskimo diet', which contained large amounts of fish and marine animals. This spawned a multi-million-dollar food supplement, functional food, and nutraceuticals market in fish-oil, mostly in the developed world, that still flourishes; despite a plethora of subsequent clinical trials whose ambiguous or negative results repudiated the initial euphoria regarding the cardioprotective effects of fish oil supplements. In fact, until a few months ago, there was not a single large placebo-controlled omega-3 clinical trial that reached clinical significance concerning atherosclerotic vascular disease (ASCVD) outcomes. The FDA has approved a qualified health claim for conventional foods and dietary supplements that contain eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA), the main omega-3 acids in fish oil supplements. It states, "Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease."

The failure of previous studies to reach significance for managing ASCVD has been variously attributed to one or a combination of several factors. Some trials excluded patients with high triglyceride levels, others used relatively low doses of omega-3 fatty acids leading to less discernible, and statistically insignificant, defined end-point differences. Other trials used natural fish oil or a mixture of omega-3 fatty acids containing both EPA and DHA. These two specific fatty acids are known to have differential effects on circulating blood triglycerides and cholesterol. In particular, DHA increases LDL-C levels. Such effects may have offset or blunted their otherwise individual clinical advantages. Still, other studies designated soft non-composite study endpoints such as unstable angina or biomarker changes that could not be directly translated into cardiovascular risk reduction. Clinical studies were poorly designed to report only a basket of composite endpoints such as heart attacks, strokes, and cardiovascular mortality together, without the option of reporting individual components as primary endpoints. It turns out that some individual components did reach significance in these studies, however, the decided upon bundled composite end-point did not. Some clinical trials excluded patients with multiple vascular risk factors other than ASCVD or diabetes, thereby reducing

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the number of differential cardiac events that might have occurred in this expanded population. Some studies only included narrow geographical patient populations whose background diet additionally already incorporated a sufficient amount of omega-3, such that any additional increase above this threshold offered little or no additional cardiovascular benefit. Still, other studies were not placebo-controlled or lacked statistical rigor.

Fish oil or its purified constituent(s) have been approved as medications to reduce hypertriglyceridemia where plasma triglyceride (TG) levels are > 500 mg/dL. Among these drugs are Lovaza®, Epanova®, Omtryg®, and Vascepa®. The market for this indication is relatively small; at < 5 million patients in the USA. Since epidemiological data suggest that elevated TG levels are associated with an increased risk of ASCVD, it seems a logical clinical and economic progression to expand the label claim of these drugs and concomitantly expand the patient population; to include decreased risk of ASCVD and to >70 million patients in the USA respectively. Amarin Corporation PLC designed a randomized, placebo-controlled, double-blind phase III clinical study designated the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT), to demonstrate a significant cardiovascular benefit from adding Vascepa® to statin treatment for high-risk patients with elevated TG levels. More than 8,000 patients were enrolled between 2011 and 2016 and followed for a median duration of 4.9 years.

By all accounts, the study design was well-thought-out. First, if successful, it could legitimately differentiate over-the-counter nutraceuticals or supplements containing a multitude of omega-3 fatty acids, from the approved product, due to the latter being a purified one-molecule ester *viz.* Icosapent ethyl (Vascepa®). Such a differentiation, especially in light of multiple natural fish-oil clinical trial failures, would discourage the continuation of off-label use of fish-oil supplements and encourage adoption of the approved product into prescription SoC protocols as an add-on alongside statin therapy for the management of ASCVD. In addition, differentiation over competitors would be achieved, many of whom were using the free acids or mixtures of EPA and DHA in their own clinical trials. Second, the global study used a higher dose of Icosapent ethyl (up to 4 g/day, which is 4 times that used in several previous studies) thereby increasing the chances of event reduction in patients with an omega-3 intake less than, or even moderately greater than, the recommended daily average (RDA). Additionally, the plasma EPA level with this dose would be equivalent to that observed with another country-specific clinical study in which a significantly lower risk of ischemic events was observed with the combination of EPA plus statin when compared to statin alone. Third, the study included patients with a broad range of triglycerides; those with a slightly elevated (>135 mg/dL) to patients with significantly elevated (<500 mg/dL) levels. Since the action mechanism of omega-3 has not been unequivocally established, the inclusion of this broad a range of TG maximized the chances of cardiovascular risk reduction (and of label expansion), because it was invariant of whether or not the mechanism of action was specific to this particular biomarker pathway. Further, due to intraindividual variability in TG levels, patients with a 10% lower level than the target TG lower limit of 150 mg/dL were enrolled, effectively favorably locking in statistical variability in the selection criteria. Fourth, although the primary efficacy endpoint was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina in a time-to-event analysis, individual endpoints could be reported and statistically analyzed as well. Such a design increased the probability of attaining statistical significance in at least one of the many individual events that made up the composite endpoint thereby keeping the case for an incremental label expansion open, rather than an all-or-nothing endeavor.

REDUCE-IT reached its primary endpoint, with a 25% reduction in major ischemic events including cardiovascular death ($p < 0.001$) among patients who had elevated triglyceride levels despite the use of statins. Cardiovascular risk reduction was independent of an observed significant decrease in TG levels. Subgroup

analysis was consistent with the whole cohort, with a favorable safety profile. In November, an FDA advisory committee voted unanimously to recommend approval of Vascapa® capsules to reduce cardiovascular risk in patients on statin therapy, with a December 28th PDUFA date.

Since baseline triglyceride levels did not influence the primary or key secondary efficacy endpoints, at least some of the effect of icosapent ethyl that resulted in a lower risk of ischemic events may have been the result of metabolic alteration. Administration of EPA was shown to decrease the serum HDL_3 level, resulting in an increase in the HDL_2/HDL_3 ratio and hence regulating HDL particle size. It is also speculated that EPA may decrease the lipolysis of chylomicrons and/or VLDL particles, thereby decreasing the formation of the so-called atherogenic "remnant-like particles." These remnant-like particles; when circulating in excess can enter the arterial wall and be taken up by macrophages in the vasculature, leading to the formation of foam cells and the progression of plaques. Hence EPA may stabilize or cause regression of coronary plaque. It is also possible that the difference in the high-sensitivity C-reactive protein level observed in the REDUCE-IT study could have contributed to the benefit.

There was some concern that the mineral oil placebo used in the REDUCE-IT study may have contributed to raising LDL-C levels in the placebo group thereby magnifying the cardioprotective effect of Icosapent ethyl. Previous studies used a placebo containing corn oil. 4 g of corn oil contains approximately 0.8% of the dose of omega-3 fatty acids as in 4 g of Icosapent-ethyl. All of the hypertriglyceridemic drugs also contain the antioxidant excipient, α-tocopherol. A Patent search indicates that the level of α-tocopherol is ≤ 4 mg per capsule in the approved prescription drugs to treat hypertriglyceridemia. At 4 soft gelatin capsules per day, this translates into a daily dose of 16 mg (or 35 IU). The RDA for α-tocopherol is 22.4 IU which implies that these hypertriglyceridemic drugs also supply an additional 156% of the RDA for Vitamin E, assuming an adequate dietary intake of Vitamin E. α-Tocopherol was not included in any of the placebos for any of these drugs and the FDA never questioned whether the antioxidant had an independent effect, if it acted synergistically with EPA; and if so, what was the magnitude of the contribution to the potential cardioprotective effect from the antioxidant component of the formulation. This is especially relevant because high dose or moderate supplementation with vitamin E; alone, or in combination with other antioxidants respectively; has been shown to protect LDL from lipid peroxidation, thus rendering it non-atherogenic. This mechanism plays directly into the formation of remnant-like particles as well as the particle size of LDL. Although none of the Vitamin E studies reached significance, that could – in part – have to do study design, as the success of REDUCE-IT demonstrates. REDUCE-IT may well become the progenitor for the axiom - there are no ineffective drugs, only poorly designed clinical studies – consequently, the effectiveness of moderately elevated α-tocopherol to reduce cardiovascular risk cannot yet be unequivocally ruled out.

The development of proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors has been another milestone in cardiology. These class of drugs act by increasing the uptake of LDL-C from the blood. The Medicines Company is conducting a phase III trial with its investigational small interfering ribonucleic acid (siRNA) oligonucleotide; Inclisiran; that inhibits the liver synthesis of PCSK9. Unlike other monoclonal antibodies (mABs) in the clinic that require monthly dosing, Inclisiran only requires SC dosing twice a year. Novartis recently bought the Medicines Company for $9.4 billion, illustrating the considerable clinical and economic potential of these new class of cholesterol reducers that are designed to be statin add-ons. Whether or not these combinations (if and when approved) better the clinical benefit of the EPA-statin combinations remains to be seen.

The fish oil, omega 3, EPA -purified ester progression, represents yet another page in the continuing saga of the elevation of foods, functional foods, nutraceuticals, supplements and/or excipients to FDA approved prescription medicines. The execution of a majority

of such events runs counter to Bayesian statistics, in that even though the light of new empirical evidence decreases the belief probability, the original instance of observation and inference derived from Kantian *a priori* constructivist intuitionism cannot be unequivocally disproved. This leads one to speculate whether Quercetin, a flavonoid antioxidant pigment that is available as a supplement and has been shown to reduce PCSK9 secretion and increase LDLR expression, could be the subject of a successful future statin-combination clinical study.