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Editorial

Is the Effect of Omega-3 Polyunsaturated Fatty Acids Dependent on Life-Style, Severity of Disease, and Use of Concomitant Medications?

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An epidemiological study in the Danish Greenland Inuit suggested a key role of fish oil (omega-3 fatty acids) in the prevention of atherosclerotic diseases[1]. Following this landmark study, the health benefits of omega-3 fatty acids as part of a diet rich in fatty acids have been extensively researched, with large-scale epidemiological studies, clinical outcomes trials, and meta-analyses demonstrating statistically significant relative cardiovascular (CV) risk reductions with omega-3 fatty acids[2].

Hypertriglyceridemia is shown to be a major CV risk factor[3], and omega-3 fatty acids are reported to reduce serum triglyceride (TG) in patients with hypertriglyceridemia while at the same time increasing high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) levels, in addition to lowering small, dense LDL-C[2].

Although a highly purified eicosapentaenoic acid (EPA) preparation was developed and applied to humans in 1983 in Japan ahead of the rest of the world[4], omega-3 fatty acids have also been commercially available in many other parts of the world as Omacor/Lovaza (containing the same active ingredients as Lotriga®) (highly concentrated omega-3 fatty acid ethyl esters consisting of EPA ethyl ester (EPA-E) and docosahexaenoic acid ethyl ester (DHA-E) [EPA-E/DHA-E]). There were no direct comparisons between EPA-E alone versus EPA-E/DHA-E until a direct head-to-head comparison between EPA-E and EPA-E/DHA-E (Lotriga®) was made in a double blind (ORD) study of Japanese patients with hypertriglyceridemia for 12 weeks[5], in which the percent change in TG levels at the end of the study was −10.8 ± 22.6, −22.9 ± 23.1, and −11.2 ± 25.7 in the EPA-E/DHA-E 2 g/day, EPA-E/DHA-E 4 g/day, and EPA-E 1.8 g/day groups, respectively.

In this issue, Ta-Chen Su *et al.*, reported the efficacy and safety of Omacor®, a prescription ethyl-ester omega-3 fatty acid, in Taiwanese patients with hypertriglyceridemia for 8 weeks, in which the percent change in serum TG levels in both Omacor® 4 g/day (−32.1%) and 2 g/day (−29.7%) groups was larger than that in the placebo group (−5.4%) ($p<0.001$) without any drug-related serious adverse events[6]. Interestingly, the reduction rates of serum TG levels in Taiwanese patients were larger than those in Japanese patients, and the two doses of 4 g/day and 2 g/day achieved a very similar percentage of TG reduction, although it is widely accepted that the effect of this drug is dose-dependent[7]. The precise mechanism of these different results between the Japanese and Taiwanese patients is not known, but one possibility is the difference in lifestyle, especially food. Therefore, the clinical efficacy of omega-3 fatty acids might also be dependent on the life-style in each ethics, country, or area.

The effects of fish oil on CV diseases vary widely depending on the endpoints used and may be accounted for by the differences in the dosage of omega-3 fatty acids used, the duration of their use, and the patient background (particularly lifestyle, severity of disease, and use of concomitant medications) in the studies. Omacor® has been used for 20 years in Western countries with several large-scale studies conducted in the meantime (**Table 1**), and it has been shown to be effective in secondary prevention of myocardial infarction[8], as well as in reducing all-cause mortality in patients with CHF[9]. While Omacor® has not been shown to be efficacious in all these studies[10, 11], this may be due to the several major limitations, such as low dose of omega-3 fatty acids, insufficient statistical power, and patients populations whose baseline TG levels were normal or near normal[2].

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Table 1. Large-scale studies of Omacor® (Lotriga®) conducted to date

Study	GISSI-P[8]	GISSI-HF[9]	ORIGIN[11]	GISSI-R&P[10]
Subject background	Prior MI (within 3 mos)	CHF	IGT/IFG/DM	Multiple CV risks
Baseline TG (mg/dL)	162.1	NA	ω-3 group: 142 Control: 140	ω-3 group: 150 Control: 150
Dose (g/day)	1	1	1	1
No. of subjects	11,324	7,046	12,612	12,513
Follow-up (mos)	42	47	74.4	60
CV event reduction	Yes	Yes	No	No
Statin use	29%	23%	54%	62%
Use of ACE-I/ARB	41%	94%	71%	75%
Use of antiplatelets	88%	87%	79%	60%
Study period	1993-1995	2002-2005	2003-2005	2004-2007

From these viewpoints, two additional long-term CV interventional outcomes studies are ongoing using high-dose and prescription-strength omega-3 fatty acids. One is REDUCE-IT (NCT01492361) using Vascepa® containing high-purity icosapent ethyl, the ethyl ester of EPA, and the other is STRENGTH (NCT02104817) using Epanova®, which contains omega-3 fatty carboxylic acids, to evaluate the reduction of CV events in patients at a high risk for CV events and with persistently high TG levels while on statin therapy. The results are highly anticipated to help clarify the potential role of omega-3 fatty acids in reducing CV risk.

Disclosures

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