 Omega-3 fatty acid concentrates in the treatment of moderate hypertriglyceridemia

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Background: Moderate hypertriglyceridemia is fairly common, and elevated triglycerides are a risk factor for coronary heart disease. The omega-3 fatty acids EPA and DHA have been shown to lower triglycerides in many clinical studies. Prescription omega-3 fatty acid concentrates (P-OM3) are indicated for use in people with very high triglycerides (> 500 mg/dl). Current guidelines recommend that triglycerides should be < 150 mg/dl. Objective: This review provides an overview of the use of omega-3 concentrates (both P-OM3 and over-the-counter fish oil) to lower triglycerides in people who have moderate hypertriglyceridemia (triglycerides in the range of 150 – 500 mg/dl). The objectives were to examine clinical evidence, describe the magnitude of effects and predict future clinical use of P-OM3.

Methods: Published, peer-reviewed studies of omega-3 concentrates were included if they were placebo-controlled, double-blind, of sufficient size to demonstrate triglyceride lowering, and studied a population described as having a mean baseline triglyceride value of 150 – 500 mg/dl. Studies using the 4-g dose of P-OM3 were used to develop a model of percent triglyceride lowering as a function of baseline levels. Results/conclusions: P-OM3 are effective in reducing triglycerides by ~30% in this population and are likely to be combined with other drugs (e.g., statins) to treat combined dyslipidemia.

Keywords: docosahexaenoic acid, dyslipidemia, eicosapentaenoic acid, ethyl ester, hypertriglyceridemia, omega-3, P-OM3, triglycerides


1. Overview of the market

Prevention of cardiovascular disease (CVD) has focused primarily on lowering of low-density lipoprotein cholesterol (LDL-C). However, there is greater appreciation in recent years for the role of triglycerides as a CVD risk factor. When triglycerides are specifically targeted in the case of severe elevations (> 500 mg/dl), it is primarily for preventing acute pancreatitis. Other reviews have examined effects of omega-3 fatty acid concentrates in that population [1,2]. This review addresses the treatment of moderate hypertriglyceridemia with omega-3 fatty acid concentrates.

1.1 Prevalence of moderate hypertriglyceridemia

Moderate hypertriglyceridemia is defined as triglycerides > 150 mg/dl and < 500 mg/dl (the cut-off for ‘very high’). At present, there are no prescription drugs indicated specifically for the treatment of moderately elevated triglycerides, although omega-3 fatty acids, fibrates, niacin and statins reduce triglycerides when prescribed for general atherogenic dyslipidemia.
Moderately elevated triglycerides are fairly common in the adult population and usually occur in conjunction with other risk factors for CVD (high LDL-C, low high-density lipoprotein cholesterol [HDL-C], obesity, hypertension, etc.). About 30% of the US population aged > 20 years have triglycerides > 150 mg/dl [3]. Isolated moderate hypertriglyceridemia is relatively uncommon, although some individuals have high triglycerides and low LDL-C, the result of a derangement in lipid metabolism.

Elevated triglycerides are more common in insulin resistance and metabolic syndrome and are characteristic of diabetic dyslipidemia (which also is characterized by small dense LDL-C and low HDL-C). Overweight/obesity, sedentary lifestyle, excessive alcohol consumption, a high glycemic index diet, and genetics are causes of elevated triglycerides.

1.2 Guidelines for triglyceride management

The National Cholesterol Education Program Adult Treatment Panel III (ATP III) [4] has defined an optimal triglyceride level as < 150 mg/dl. Triglyceride levels of 150 – 500 mg/dl are considered to be moderately elevated, and > 500 mg/dl is considered very high, and is usually associated with genetic factors or uncontrolled diabetes. Very high triglycerides may cause acute pancreatitis, which is the basis for prompt clinical intervention.

The role of triglycerides as an independent CVD risk factor has been historically debated. Current treatment guidelines focus on reducing LDL-C levels [5] and do not specifically address moderately elevated triglycerides. It has been suggested that triglyceride levels are not an independent predictor for heart disease because they are confounded by insulin/glucose, central adiposity and low HDL-C, and it is true that risk resulting from elevated triglycerides is reduced when models are adjusted for these factors. However, many recent studies, editorials, reviews and scientific statements agree that moderately elevated triglycerides are linked to increased cardiovascular risk [4,6-9]. The Copenhagen Male Study found that men in the highest tertile of fasting triglycerides (> 142 mg/dl, average 218 mg/dl) experienced more than twice the risk for ischemic heart disease vs those in the lowest tertile (< 97 mg/dl, average 78 mg/dl) [7]. Even after adjustment for HDL-C concentrations, each 89 mg/dl increase in triglycerides increases the risk of CVD 37% in women and 14% in men [10]. Two large, long-term prospective cohort studies have shown that non-fasting triglycerides may be a more potent predictor of cardiovascular risk than fasting triglyceride levels [11-13]. Non-fasting triglycerides may be a better indicator of atherogenic remnant lipoprotein concentrations. Most clinicians order a fasting lipid panel, and there are no guidelines as yet for non-fasting triglyceride levels. It seems clear that elevated triglycerides signal cardiovascular risk, but research continues to define optimal measuring and interpretation of triglyceride levels.

Despite this evidence that triglyceride lowering may be important in managing CVD risk, LDL-C remains the focus of lipid treatment guidelines, and patients with moderately elevated triglycerides may not be identified as candidates for lipid-lowering therapy. After LDL-C goals are met, lipid treatment targets non-HDL-C levels (the total of very low density lipoprotein cholesterol [VLDL-C], intermediate density lipoprotein cholesterol and LDL-C) [4].

The American Heart Association recommends that 2 – 4 g of eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) can be used under a physician’s care to lower elevated triglycerides [14]. Some physicians believe that the higher dose in this range is indicated because of greater efficacy [15]. In comparison with 2 g, 4 g appears to be much more effective in reducing elevated triglycerides, although, this should be considered a pharmacological intake, whereas 2 g/day could be achieved by very high intake of oily fish.

The gold standard for treating isolated moderately elevated triglycerides remains to be weight loss, exercise, reduced intake of refined carbohydrate and treatment of untreated hypothyroidism or alcohol cessation, where relevant. Use of oral estrogen therapy, β-blockers or thiazide diuretics may also cause elevated triglyceride levels, so in these cases, changes in drug therapy may be the most effective treatment.

1.3 Pharmaceutical treatment options

Many prescription drugs used to treat general dyslipidemia, specifically elevated LDL-C or low HDL-C, also reduce triglycerides. Statins, fibrates, thiazolidinediones, and nicotinic acid reduce triglyceride levels. However, there are side effects for some of these drugs. For example, niacin is associated with intense flushing and can increase glucose levels in some individuals. Fibrates are probably the most commonly used drug class to improve low HDL-C and high triglycerides, although the combination of fibrate and statin may be more likely to produce myopathy than statin alone.

2. Introduction to compound

EPA and DHA are long chain polyunsaturated omega-3 fatty acids found predominantly in oily fish. Processed algae oil also is a source of supplemental DHA. EPA and DHA can be obtained over the counter as 'fish oil’ and ‘omega-3 concentrate’ supplements containing varying amounts of EPA and DHA. Dietary and supplemental EPA and DHA are provided as triglycerides. Prescription omega-3 ethyl ester concentrates (P-OM3) are also available under the trade name Lovaza™. (Lovaza was initially introduced in the American market under the trade name Omacor®, but was renamed in 2007 due to confusion with the drug Amicar® [used for acute bleeding syndromes]. P-OM3 have a longer history of being available in Europe under the trade name Omacor.) Alpha linolenic acid from various sources including flaxseed oil, canola oil, and walnuts is not bioequivalent to EPA and DHA, and very little is converted to EPA in vivo [16-19].

P-OM3 is more highly concentrated than most over-the-counter fish oil supplements; ~ 85% of its content
is ethyl esters of EPA and DHA. Therefore, four daily capsules are needed to provide 3.4 g EPA plus DHA (versus ~11 capsules for standard fish oil containing 18% EPA and 12% DHA). The FDA has advised that the unsupervised dietary intake of EPA plus DHA should not be > 3 g/day, and that no more than 2 g/day should be provided as supplements [20].

3. Chemistry

EPA is a 20-carbon fatty acid containing five cis double bonds that are methylene interrupted starting from the third carbon from the methyl (omega) end. DHA is 22 carbons long and has six double bonds and, like EPA, has methylene interrupted cis double bonds from the third carbon from the omega end.

The process used to concentrate fish oil to the potency of P-OM3 requires that the triglyceride fatty acids be converted to ethyl esters. Therefore, P-OM3 contains EPA and DHA ethyl esters (Figure 1). Marine fatty acids provided as triglycerides and ethyl ester are believed to be equally bioavailable and efficacious in reducing triglycerides.

4. Pharmacodynamics

4.1 Mechanism of action

The triglyceride-lowering effect of omega-3 fatty acids is believed to be due to inhibition of the triglyceride synthetic enzyme acyl coenzyme A:1,2-diacylglycerol acyltransferase, decreased lipogenesis and increases in peroxisomal or mitochondrial β-oxidation [21]. It also has been shown that omega-3 fatty acid intake decreases apo C-III content in plasma lipoproteins and increases lipoprotein lipase gene expression in adipose tissue [22]. The mechanisms of triglyceride lowering by omega-3 fatty acids have been reviewed recently [23].

4.2 Safety

The safety profile of omega-3 concentrates is considered to be excellent. In clinical trials, the most often reported side effect is a 'fishy burp' that is reduced if the capsules are taken with food. Digestive side effects reported in the prescribing information for P-OM3 indicate that either dyspepsia or eructation occur in ~ 8% of people taking P-OM3 4 g (versus 4.8% of people taking placebo). Other side effects include taste perversion (2.7 versus 0% placebo), flu syndrome (3.5 versus 1.3%) and infection (4.4 versus 2.2%). It also has been observed that alanine transferase levels sometimes increase transiently to two times the upper normal of limit – without concomitant increases in aspartate transferase. The mechanism by which this occurs is not understood. It is generally recommended to periodically monitor liver enzymes in patients undergoing any lipid-lowering therapy.

Another consequence of omega-3 concentrates is that they increase LDL-C levels in proportion to triglyceride lowering. Thus, in patients with very high levels of triglycerides, the increase in LDL-C may be significant. When marked reduction of triglycerides occurs HDL-C often is likely to increase as well. For this reason, omega-3 concentrates should be combined with diet interventions and/or drug therapy for people with both high LDL-C and triglycerides. Patients should be educated per ATP III recommendations for LDL-C lowering and be advised to consume 10 – 25 g/day of soluble fiber and/or 2 g/day of plant sterols/stanols to prevent an increase in LDL-C following increased omega-3 fatty acid intake [4]. In addition, pharmacotherapy may be indicated for the management of elevated LDL-C in some patients.

There is no known drug interaction per se of omega-3 fatty acids. Some concern has been expressed about the antithrombotic effects of high-dose fish oil in conjunction with antiplatelet drugs. No clinical bleeding episodes

![Figure 1. Skeletal formula for EPA ethyl ester (top) and DHA ethyl ester (bottom).](image-url)
resulting from omega-3 concentrates have been reported to the authors' knowledge, and there is evolving consensus that
reducing coagulation is not an issue with omega-3 fatty acid
treatment, even at high doses [24]. Moreover, as elevations
in lipids are associated with increases in thrombogenesis,
an anti-thrombotic effect could be considered a positive side
effect of high omega-3 intake.

5. Pharmacokinetics

Like other dyslipidemia treatments, omega-3 concentrates are
effective in lowering triglycerides within 2 – 4 weeks. The effect on the lipid profile is equally rapid in ‘washing out’ after discontinuation of therapy. Omega-3 fatty acids are stored in tissues (such as red blood cell membranes and adipose) for a much longer period of time, so any benefits from tissue incorporation have a much longer pharmacokinetic profile [25,26]. Thus, triglyceride levels would return to baseline levels within 2 – 4 weeks after discontinuation, whereas erythrocyte levels might require up to 4 months in order to return to baseline levels.

6. Clinical efficacy

The efficacy of omega-3 fatty acids in lowering triglycerides was first established with studies of fish oil capsules and oily fish dietary intake as reviewed in the Evidence Report commissioned by the National Institutes of Health [27]. Briefly, most studies showed a decrease in triglycerides following high intakes of EPA plus DHA. Duration does not seem to be a contributing factor to the efficacy of triglyceride lowering so long as the treatment period is greater than 2 – 4 weeks. Generally, the percentage of triglyceride lowering depends on both dose and baseline triglyceride levels. As baseline values and dose increase, the magnitude of lowering increases.

Many published, placebo-controlled studies have reported the efficacy of omega-3 fatty acid concentrates (either triglycerides or ethyl esters) on triglyceride lowering in people with moderately elevated triglycerides (Table 1). In many of these studies, triglyceride lowering was not a primary end point. Population characteristics were highly variable across this group of randomized clinical trials. Studies of patients with coronary artery disease typically include patients with diabetes and a variety of concurrent drug therapies. These studies administered doses in the range of 0.85 – 5.1 g EPA + DHA.

For subjects at the higher end of moderate hypertriglyceridemia (mean > 250 mg/dl), the average triglyceride lowering with P-OM3 4 g was ~ 30% for most studies [28-35]. In a study of subjects with lower triglyceride concentrations at baseline, the reduction was 21% [36]. A similar level of reduction is observed when P-OM3 3 g is given to subjects with higher baseline triglycerides [37]. Likewise, P-OM3 6 g decreased triglycerides by ~ 30% in subjects with lower baseline levels [38]. Thus, pretreatment triglyceride status and dose of P-OM3 have independent and additive effects on triglyceride response. When EPA plus DHA < 1 g is used, effects on triglycerides are minimal [39].

Effects on cholesterol concentration are of interest in treating patients with combined dyslipidemia. Most studies reported an increase in HDL-C in subjects characterized by moderately elevated triglycerides [29,31-34,36-38,40]. Many studies reported increases in LDL-C [30,31,34,35,40-44], which is probably due to increased particle size rather than particle number. One study reported that the LDL-C increase was due to the particles becoming more buoyant [30].

As with studies of fish oil capsules and dietary fish intake, studies of P-OM3 also indicate that the percent triglyceride lowering achieved is dependent on the dose administered and baseline triglyceride values in the subject population. Figure 2 presents the percent triglyceride lowering achieved as function of mean triglyceride values for the seven studies in Table 1 that administered P-OM3 4 g (the most often studied dose and indicated prescription dose) [28-32,34,36]. Thus, on average, patients with lower baseline triglyceride levels will be expected to experience a smaller percent reduction than people with higher triglycerides when P-OM3 4 g is administered.

Some of the most high impact recent studies of omega-3 fatty acid concentrates for treatment of moderate hypertriglyceridemia are studies that have combined P-OM3 with statin therapy [45]. One study evaluated the effects of adding P-OM3 4 g to a stable dose of simvastatin (10 – 40 mg/day) in 59 subjects with coronary heart disease and moderate hypertriglyceridemia [28]. After 24 weeks of being randomized to P-OM3 versus placebo treatment, 46 subjects elected to continue in a 24-week, open-label treatment with P-OM3. There was a sustained decrease in triglycerides of 20 – 30% (p < 0.005) at 3, 6 and 12 months in subjects receiving active treatment. No adverse effects of any kind were reported, and the authors specifically addressed glycemic control in diabetic subjects, LDL-C levels and hematological tests.

More recently, in the COMBOS (Combination of Prescription Omega-3 Plus Simvastatin) study [29] P-OM3 4 g (3.4 g EPA + DHA) was added to stable therapy with simvastatin (40 mg/day). At baseline, participants (n = 254) had triglyceride levels of 200 – 500 mg/dl and had met their National Cholesterol Education Program ATP III goal for LDL-C levels by taking simvastatin alone. In patients randomized to treatment with P-OM3, triglycerides decreased by 29.5% (versus 6.3% with placebo). HDL-C increased by 3.4% (versus -1.2% in the statin plus placebo group). The 340 ratio of total cholesterol:HDLC decreased by 9.6 versus 0.7% in the placebo group (p < 0.001). The mean percent changes in lipid levels are presented in Figure 3. Moreover, there was no significant difference in the frequency of adverse events between the groups. Dyspepsia and diarrhea were reported in 2.5% of the population receiving P-OM3 (three subjects), which is often the biggest concern for

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Table 1. Randomized controlled trials reporting efficacy of triglyceride-lowering by omega-3 concentrates in subjects with moderate elevations prior to treatment (150 – 500 mg/dl).

<table>
<thead>
<tr>
<th>Study/year</th>
<th>Design</th>
<th>Subject characteristics</th>
<th>Mean baseline triglycerides</th>
<th>N (total)</th>
<th>Fatty acid preparation</th>
<th>EPA + DHA daily dose</th>
<th>Treatment period duration</th>
<th>Effect on triglycerides</th>
<th>Effect on cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bairati et al. 1992</td>
<td>Parallel</td>
<td>Coronary artery disease</td>
<td>204 mg/dl</td>
<td>125</td>
<td>15 g MaxEPA</td>
<td>4.5 g</td>
<td>6 months</td>
<td>↓ trigs 39%</td>
<td>↑ HDL-C, LDL-C</td>
</tr>
<tr>
<td>Calabresi et al. 2004</td>
<td>Crossover</td>
<td>Familial combined hyperlipidemia</td>
<td>378 mg/dl</td>
<td>14</td>
<td>4 g ethyl esters</td>
<td>3.4 g</td>
<td>8 weeks</td>
<td>↓ trigs 44%</td>
<td>↑ HDL-C, LDL-C</td>
</tr>
<tr>
<td>Calabresi et al. 2000</td>
<td>Crossover</td>
<td>Familial combined hyperlipidemia</td>
<td>251 mg/dl</td>
<td>14</td>
<td>4 g ethyl esters</td>
<td>3.4 g</td>
<td>8 weeks</td>
<td>↓ trigs 27%</td>
<td>↑ LDL-C (more bouyant)</td>
</tr>
<tr>
<td>Davidson et al. 2007</td>
<td>Parallel</td>
<td>Moderately elevated triglycerides while taking 40 mg simvastatin</td>
<td>282 mg/dl</td>
<td>254</td>
<td>4 g ethyl esters</td>
<td>3.4 g</td>
<td>8 weeks</td>
<td>↓ trigs 29.5 (versus 6.3% on placebo)</td>
<td>↑ HDL-C</td>
</tr>
<tr>
<td>Durrington et al. 2001</td>
<td>Parallel</td>
<td>CHD taking 10 – 40 mg simvastatin</td>
<td>409 mg/dl</td>
<td>59</td>
<td>4 g ethyl esters</td>
<td>3.4 g</td>
<td>24 weeks</td>
<td>↓ trigs 20 – 30%</td>
<td>↔ LDL-C, HDL-C</td>
</tr>
<tr>
<td>Ericksen et al. 1996</td>
<td>Parallel</td>
<td>Patients undergoing coronary artery bypass grafting</td>
<td>175 mg/dl</td>
<td>610</td>
<td>4 g ethyl esters</td>
<td>3.4 g</td>
<td>9 months</td>
<td>↓ trigs 19%</td>
<td>↑ HDL-C, LDL-C</td>
</tr>
<tr>
<td>GISSI-P Investigators 1999</td>
<td>Parallel</td>
<td>Recent myocardial infarction</td>
<td>– 162 mg/dl</td>
<td>11324</td>
<td>1 g ethyl esters</td>
<td>0.85 g</td>
<td>6 months</td>
<td>↓ trigs slightly (~ 1 – 6%)</td>
<td>↔ LDL-C, HDL-C</td>
</tr>
<tr>
<td>Johansen et al. 1999</td>
<td>Parallel</td>
<td>Trigs &gt; 178 mg/dl</td>
<td>not available</td>
<td>57</td>
<td>4 g ethyl esters</td>
<td>3.4 g</td>
<td>12 weeks</td>
<td>↓ trigs 28%</td>
<td>↑ HDL-C</td>
</tr>
<tr>
<td>Howe et al. 1999</td>
<td>Parallel</td>
<td>Middle-aged men</td>
<td>174 mg/dl</td>
<td>32</td>
<td>8 g tuna oil or 8 g MaxEPA</td>
<td>~ 2.5 g</td>
<td>16 weeks</td>
<td>↓ trigs 26%</td>
<td>↑ LDL-C</td>
</tr>
<tr>
<td>Kelley et al. 2007</td>
<td>Parallel</td>
<td>Coronary artery disease</td>
<td>150 mg/dl</td>
<td>31</td>
<td>6 g ethyl esters</td>
<td>5.1 g</td>
<td>4 weeks</td>
<td>↓ trigs 30%</td>
<td>↑ HDL-C</td>
</tr>
<tr>
<td>Leigh-Firbank et al. 2002</td>
<td>Parallel</td>
<td>Healthy middle aged men, trigs 150 – 400 mg/dl</td>
<td>227 mg/dl</td>
<td>34</td>
<td>7.5 g algae oil</td>
<td>~ 3 g (DHA only)</td>
<td>45 days</td>
<td>↓ trigs 24 – 25%</td>
<td>↑ LDL-C</td>
</tr>
<tr>
<td>Lungenshausen et al. 1994</td>
<td>Parallel</td>
<td>Hypertension treated with diuretics and/or β-blockers</td>
<td>150 mg/dl</td>
<td>43</td>
<td>4 g ethyl esters</td>
<td>3.4 g</td>
<td>6 weeks</td>
<td>↓ trigs 21%</td>
<td>↑ HDL-C</td>
</tr>
</tbody>
</table>

Effects on LDL-C and HDL-C varied by study and were either neutral or increased.  
ATP: Adult Treatment Panel; CHD: Coronary heart disease; CVD: Cardiovascular disease; DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; P-OM3: Prescription omega-3 fatty acid concentrates; Trig: Triglyceride.
Table 1. Randomized controlled trials reporting efficacy of triglyceride-lowering by omega-3 concentrates in subjects with moderate elevations prior to treatment (150 – 500 mg/dl) (continued).

<table>
<thead>
<tr>
<th>Study/year</th>
<th>Design</th>
<th>Subject characteristics</th>
<th>Mean baseline triglycerides</th>
<th>N (total)</th>
<th>Fatty acid preparation</th>
<th>EPA + DHA daily dose</th>
<th>Treatment period duration</th>
<th>Effect on triglycerides</th>
<th>Effect on cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mackness et al. 1994 [32]</td>
<td>Parallel</td>
<td>Trigs &gt; 178 mg/dl</td>
<td>355 mg/dl</td>
<td>79</td>
<td>4 g ethyl esters</td>
<td>3.4 g</td>
<td>14 weeks</td>
<td>↓ trigs 28%</td>
<td>↑ HDL-C (subject with type IV only)</td>
</tr>
<tr>
<td>Maki et al. 2005 [42]</td>
<td>Parallel</td>
<td>HDL levels below sex-specific population median</td>
<td>179 mg/dl</td>
<td>57</td>
<td>4 g algae oil</td>
<td>1.5 g DHA only</td>
<td>6 weeks</td>
<td>↓ trigs 21%</td>
<td>↑ LDL-C</td>
</tr>
<tr>
<td>Meyer 2007 [46]</td>
<td>Parallel</td>
<td>Hyperlipidemic on stable statin therapy</td>
<td>196 mg/dl</td>
<td>40</td>
<td>8 g tuna oil</td>
<td>2.2 g</td>
<td>6 months</td>
<td>↓ trigs 27%</td>
<td>↔ LDL-C, HDL-C</td>
</tr>
<tr>
<td>Minihane et al. 2000 [43]</td>
<td>Crossover</td>
<td>Atherogenic lipoprotein phenotype</td>
<td>221 mg/dl</td>
<td>55</td>
<td>6 g fish oil concentrate</td>
<td>3.0 g</td>
<td>6 weeks</td>
<td>↓ trigs 35%</td>
<td>↑ LDL-C</td>
</tr>
<tr>
<td>Mori et al. 2000 [47]</td>
<td>Parallel</td>
<td>Overweight men</td>
<td>190 mg/dl</td>
<td>56</td>
<td>4 g ethyl esters of EPA OR DHA</td>
<td>3.8 g EPA or 3.6 g DHA</td>
<td>6 weeks</td>
<td>↓ trigs 20% (DHA) or 18% (EPA)</td>
<td>↔ LDL-C, HDL-C</td>
</tr>
<tr>
<td>Sirtori et al. 1998 [37]</td>
<td>Parallel</td>
<td>Trigs &gt; 200 mg/dl + cad risk factors (hypertension, diabetes)</td>
<td>– 300 mg/dl</td>
<td>935</td>
<td>3 g ethyl esters</td>
<td>1.7 g</td>
<td>6 months</td>
<td>↓ trigs 21.5%</td>
<td>↑ HDL-C</td>
</tr>
</tbody>
</table>

Effects on LDL-C and HDL-C varied by study and were either neutral or increased.

ATP: Adult Treatment Panel; CHD: Coronary heart disease; CVD: Cardiovascular disease; DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; P-OM3: Prescription omega-3 fatty acid concentrates; Trig: Triglyceride.
Figure 3. Lipid and lipoprotein results of the COMBOS (Combination of Prescription Omega-3 Plus Simvastatin) Trial. When P-OM3 4 g is provided to simvastatin-treated patients, triglycerides are decreased by ~30% without decreasing the LDL-C-lowering effectiveness of statin therapy. Bars represent mean changes and error bars denote standard error. Effects were significantly different between treatments for non-HDL-C, triglycerides, VLDL-C and HDL-C.

Adapted with permission from Davidson MH, Stein EA, Bays HE, et al. Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study. Clin Ther 2007; 29:1354-67 [29].

HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; VLDL-C: Very low density lipoprotein cholesterol.
people starting omega-3 therapy. In this study, the difference in LDL-C between the simvastatin plus placebo and simvastatin plus P-OM3 groups did not reach significance (−2.8 versus +0.7%, respectively, p = 0.052). This suggests that the LDL-C-raising potential of omega-3 concentrates is not a concern if LDL-C-lowering therapy is concurrently utilized. The results of this study are included in the recently revised prescription insert for P-OM3.

Similar results were observed when DHA was provided by an algae oil supplement [46]. In 45 patients with average triglyceride levels of 196 mg/dl despite stable statin therapy, plasma triglycerides were reduced by 27% by algae oil providing DHA 2.2 g/day [46]. Other studies have shown isolated EPA to have similar effectiveness to DHA [44,47]. Both EPA and DHA are effective in reducing moderately elevated triglycerides, even in addition to the benefits achieved by statin therapy.

Most importantly, supplemental intake of EPA and DHA is associated with reductions in cardiovascular events and mortality, as shown by two large interventional studies: the GISSI-P (GISSI-Prevenzione) Study and the JELIS (Japan EPA Lipid Intervention Study). GISSI-P studied 11,323 people who had survived a myocardial infarction (MI) and showed a significant 45% decrease in sudden death and 20% decrease in mortality only 4 months into the study [39]. Moreover, the recently published JELIS demonstrated that EPA ethyl ester 1.8 g in combination with statin therapy reduced major coronary events by 19% versus statin alone [48]. Treatment with omega-3 concentrates seems to be effective in reducing cardiovascular risk even when provided at doses below that which are indicated for lowering triglycerides. Research is ongoing to elucidate the mechanisms by which this is achieved.

7. Regulatory affairs

7.1 Current indications

Although it is clear that omega-3 fatty acid concentrates are effective in lowering triglycerides, even in individuals with only moderately elevated triglycerides (triglycerides > 150 mg/dl and < 500 mg/dl), P-OM3 is only FDA-approved for treating individuals with very high triglycerides (triglycerides > 500 mg/dl). It also is a pregnancy category C drug; there are no adequate and well-controlled studies in pregnant women. However, much research has investigated the potential benefits of omega-3 fatty acids in fetal and maternal nutrition [49].

P-OM3 is prescribed as a 4-g/day dose containing 3.4 g EPA + DHA (to be taken with meals). This is roughly seven times the current recommendation of the American Heart Association for primary prevention of coronary heart disease, which is 2 servings of oily fish per week (equivalent to about 500 mg EPA + DHA/day). Future research may show that some individuals will benefit from a lower dose, despite minimal effects on triglyceride levels. In Europe, it is common practice to prescribe a dose of P-OM3 1 g (850 mg/day was used in the GISSI-P study [39]) to patients who experience an MI.

7.2 Off-label and research use

In addition to low-dose use post-MI, omega-3 concentrates have been used in studies for a variety of inflammatory conditions including rheumatoid arthritis [50], inflammatory bowel disease [51,52], asthma [53] and depression [54]. Often, a triglyceride-lowering dose (3 – 4 g EPA + DHA) is used in studies of omega-3 fatty acids and various inflammatory diseases. For example, a very large clinical trial was conducted to test the effectiveness of a particular enteric-coated (stomach acid resistant) omega-3 concentrate (Epanova®, Tillotts Pharma Ag) on treating 762 patients with Crohn’s disease (a type of inflammatory bowel disease) following the promising results of the 1996 study performed by Belluzzi et al. [55]. The EPIC (Epanova in Crohn’s Disease) study was terminated early due to an unexpected high placebo response according to an online press release [56].

It is thought that omega-3 fatty acids reduce inflammation by influencing eicosanoid production and affecting gene expression (e.g., PPAR-γ) [57]. With the discovery of novel pro-resolution mediators of inflammation derived from EPA and DHA called resolvins and protectins [58-60], future research may demonstrate that P-OM3 is a useful addition to the treatment regimens prescribed for a variety of clinical conditions. Resolvins and protectins are produced in greater quantities when low-dose aspirin is co-administered, which is often the case in people at risk of MI.

7.3 Adjunctive treatment

Although P-OM3 is not presently indicated for use as adjunctive therapy in people with elevated triglycerides who are on statin therapy, it is not unreasonable to speculate that it will receive regulatory approval in the future as an adjunctive therapy based on the results of the COMBOS study [29]. Like ezetimibe, it may become available as a combined therapy.

8. Expert opinion

8.1 Summary: omega-3 concentrates in treatment of moderate hypertriglyceridemia

Omega-3 fatty acid concentrates are effective in reducing moderately elevated triglycerides by ∼30% when provided at the dose indicated for very high triglycerides (P-OM3 4 g providing 3.4 g EPA + DHA). Because of the excellent 450 side-effect profile of omega-3 fatty acid concentrates, they likely will become an adjunctive therapy in combination with other established lipid-lowering therapies. Although omega-3 fatty acids may raise LDL-C in proportion to the amount of triglyceride lowering achieved, they often raise HDL-C as well. Because the majority of patients with moderately elevated triglycerides experience general...
dyslipidemia characterized by high LDL-C, high triglycerides and low HDL-C, omega-3 concentrates are likely to be combined with LDL-C-lowering therapies. As illustrated in Figure 4, there are many potential combinations that could be used to prevent any rise in LDL-C resulting from P-OM3 therapy. Combining omega-3 concentrates with a statin, ezetimibe, bile acid resins, niacin, plant sterols/stanol (≥ 2 g), and/or soluble fiber (10 – 25 g), would be expected to have beneficial effects on the lipid profile of individuals with moderately elevated triglycerides and concomitantly reduce both triglyceride and LDL-C levels. The choice of the combination used would be based on the patient’s characteristics, preferences and LDL-C treatment goals. It is also noted that P-OM3 could be combined with fibrate therapy for increased reduction of moderately elevated triglycerides. Because of the low side-effect profile of omega-3 concentrates, there is much potential for the use of P-OM3 in combination with other lipid-lowering therapies.

8.2 The future of omega-3 concentrates
There is growing public interest in complementary and alternative therapies, and fish oil has captured increasing attention. At present, low-dose omega-3 fatty acids (1 g/day) are recommended for patients with coronary disease in many countries, including the US. If regulatory authorities approve P-OM3 for a broader indication...
Omega-3 fatty acid

including moderately elevated triglycerides or in conjunction with statin therapy), there is the potential for wider acceptance of this approach for combined dyslipidemia. If ongoing and future research trials continue to demonstrate the benefits of omega-3 concentrates on CVD outcomes, they may compete with fibrates, which thus far have had mixed results. Already, over-the-counter fish oil products are very popular despite consumer fears of toxins or inferior quality in some non-regulated supplement products – and a greater number of capsules must be taken to achieve equivalent effects of P-OM3.

As research continues to elaborate on the mechanisms by which these compounds exert their beneficial effects, it will be better understood which populations benefit most and what dose is most effective. As discussed above, it also may be found that omega-3 concentrates are beneficial in treating some inflammatory conditions. In conclusion, omega-3 fatty acids are a safe and effective for the treatment of moderately elevated triglycerides, and will likely be used in conjunction with other lipid-lowering therapies. There is exciting potential for use of omega-3 concentrates beyond triglyceride-lowering purposes.

Declaration of interest

AC Skulas-Ray is co-investigator on a project supported in part by Reliant Pharmaceuticals and is supported by a grant from the National Fisheries Foundation. SG West and PM Kris-Etherton were both primary investigators on a project supported in part by Reliant Pharmaceuticals. MH Davidson has no stock ownership or options in Radiant Research, a division of Swiss Bioscience. MH Davidson has received grant/research support, honorarium, served as a consultant/speakers bureau for the following companies in the past 3 years, and has no stock ownership in any of the following companies: Abbott, Access health, AstraZeneca, Atherogenics, Daiichi-Sankyo, diaDexus, Merck, Merck/Schering-plough, Oscent, Pfizer, Reliant, Roche, sanofi-aventis, Takeda and Xinhria pharmaceuticals.

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