Role of Prescription Omega-3 Fatty Acids in the Treatment of Hypertriglyceridemia

James M. McKenney, Pharm.D., and Domenic Sica, M.D.

A prescription form of omega-3 fatty acids has been approved by the United States Food and Drug Administration as an adjunct to diet for the treatment of very high triglyceride levels. The active ingredients of omega-3 fatty acids are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are responsible for the triglyceride lowering. The prescription product contains a total of 0.84 g of these two active ingredients in every 1-g capsule of omega-3 fatty acids. The total EPA and DHA dose recommended for triglyceride lowering is approximately 2–4 g/day. Fish oil products containing EPA and DHA are available without a prescription, but the American Heart Association advises that therapy with EPA and DHA to lower very high triglyceride levels should be used only under a physician’s care. In patients with triglyceride levels above 500 mg/dl, approximately 4 g/day of EPA and DHA reduces triglyceride levels 45% and very low-density lipoprotein cholesterol levels by more than 50%. Low-density lipoprotein cholesterol levels may increase depending on the baseline triglyceride level, but the net effect of EPA and DHA therapy is a reduction in non–high-density lipoprotein cholesterol level. Alternatively, patients may receive one of the fibrates (gemfibrozil or fenofibrate) or niacin for triglyceride lowering if their triglyceride levels are higher than 500 mg/dl. In controlled trials, prescription omega-3 fatty acids were well tolerated, with a low rate of both adverse events and treatment-associated discontinuations. The availability of prescription omega-3 fatty acids, which ensures consistent quality and purity, should prove to be valuable for the medical management of hypertriglyceridemia.

Key Words: hypertriglyceridemia, omega-3 fatty acids, eicosapentaenoic acid, EPA, docosahexaenoic acid, DHA, pancreatitis, coronary heart disease. (Pharmacotherapy 2007;27(5):715–728)
found to have triglyceride levels of 150 mg/dl or higher. Both lifestyle factors (e.g., obesity, physical inactivity) and genetics play important roles in determining triglyceride levels. The higher the triglyceride level, the more likely genetics play a role. For example, triglyceride levels above 500 mg/dl are often seen in patients with familial hypertriglyceridemia and are due to an overproduction of triglyceride-rich very low-density lipoprotein (VLDL) particles, whereas levels above 1000 mg/dl are most often seen in patients with an increased concentration of VLDL and chylomicron particles and are due to impaired catabolism linked to a genetic defect in lipoprotein lipase or apolipoprotein C-II.

Pancreatitis has long been recognized as an acute and potentially life-threatening complication of very high triglyceride levels (> 1000 mg/dl; Table 1). Acute pancreatitis typically occurs in patients with preexisting lipid disorders in which the presence of one or more secondary factors (e.g., poorly controlled diabetes mellitus, excessive alcohol use, or use of certain drugs) contribute to a marked additional elevation in triglyceride levels. In patients with a triglyceride level exceeding 1000 mg/dl, an aggressive reduction in serum triglyceride levels is warranted to reduce the risk of pancreatitis.

At the other end of the triglyceride continuum, levels of 200–499 mg/dl are associated with increased risk of coronary heart disease (CHD; Table 1). The CHD risk associated with elevated triglyceride levels has been intensely debated, and our understanding of the relationship between triglyceride levels and CHD continues to evolve. Elevated triglyceride levels are often closely associated with other CHD risk factors, such as diabetes (a CHD risk equivalent) and the metabolic syndrome, as well as low high-density lipoprotein cholesterol (HDL) levels. Although univariate analyses of high-risk populations have shown a consistent positive relationship between triglyceride levels and the risk of CHD, when multivariate analyses were performed—in which adjustments were made for the presence of other major CHD risk factors—triglyceride level typically was eliminated as a significant predictor of CHD events.

More recent findings suggested that high triglyceride levels are an independent risk factor for CHD. A sophisticated meta-analysis of 17 large, population-based studies (> 56,000 patients) showed, after correcting for HDL levels, that for every 88-mg/dl (1-mmol/L) increase in triglyceride level, the risk of CHD is increased by 14% in men and 37% in women. These findings are supported by data from the Copenhagen Male Study, which showed that the rate of ischemic heart disease in middle-aged men without overt CHD at baseline rose with increasing baseline triglyceride levels within each tertile of HDL level, and by data from families with familial hypertriglyceridemia and patients with premature familial coronary artery disease.

The conclusion that can be drawn from these and other studies is that, although high triglyceride levels do demonstrate an independent influence on CHD risk, the influence appears to be modest compared with that of low-density lipoprotein cholesterol (LDL) and HDL levels. However, the CHD risk of high triglyceride levels likely is mediated through other lipid and nonlipid risk factors, and the risk signal imparted by a high triglyceride level is really rather profound and, in fact, exceeds the risk of these other lipid risk factors. The key to understanding this enhanced risk is an understanding of the mechanisms underlying atherogenic dyslipidemia.

### Atherogenic Dyslipidemia

Three metabolic processes can elevate triglyceride levels: hepatic overproduction of triglyceride-rich VLDL particles, reduced lipolysis of VLDL triglycerides through lipoprotein lipase, and/or delayed removal of small (i.e., remnant) VLDL particles. Both environmental factors (e.g., obesity and physical inactivity) and

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Table 1. Triglyceride Continuum: Risks Factors Associated with Triglyceride Levels of 200 mg/dl or Higher

<table>
<thead>
<tr>
<th>Triglyceride Level</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>200–499 mg/dl</td>
<td>CHD: familial combined hyperlipidemia, metabolic syndrome, diabetes mellitus, atherogenic dyslipidemia (remnant cholesterol; small, dense LDL particles; low HDL level; increased particle number)</td>
</tr>
<tr>
<td>&gt; 1000 mg/dl</td>
<td>Pancreatitis: familial hypertriglyceridemia, familial dysbetalipoproteinemia (type III), diabetes mellitus, hyperchylomicronemia, metabolic syndrome</td>
</tr>
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</table>

CHD = coronary heart disease; LDL = low-density lipoprotein cholesterol; HDL = high-density lipoprotein cholesterol.

*Risk of CHD extends into the 500–1000-mg/dl range, where there is also an increased risk of pancreatitis.
nonenvironmental factors (i.e., genetics) contribute to these actions. For example, patients with obesity, diabetes, or the metabolic syndrome have an increased mobilization of fatty acids in the liver, leading to overproduction of triglyceride-enriched VLDL particles. The secreted VLDL particles are also likely to contain more apolipoprotein C-III, which causes a reduction in the activity of lipoprotein lipase, which then impedes the removal of triglycerides from VLDL particles. The triglyceride content of these particles may be exchanged with cholesteryl esters from HDL through the action of cholesterol ester transfer protein. The result is an increase in the concentration of highly atherogenic cholesterol-enriched VLDL remnant particles (also called β-VLDL) and a decrease in the concentration of HDL. As some of the triglyceride-enriched VLDL particles are catabolized to smaller triglyceride-enriched LDL particles, hepatic lipase acts to remove the triglycerides, thus forming cholesterol deficient, but highly atherogenic, small LDL particles.

Of importance, through the enhanced secretion of VLDL particles and altered catabolism of VLDL and LDL particles, the number (concentration) of atherogenic particles increases substantially, as reflected by an increase in apolipoprotein B; this arguably represents the most significant factor that increases CHD risk in patients with high triglyceride levels.

The result of these complex processes is a lipid profile characterized by cholesterol-enriched remnant VLDL; small, dense LDL; low HDL levels; and increased particle number, which has been termed “atherogenic dyslipidemia.” The presence of atherogenic dyslipidemia should be strongly suspected in patients who have triglyceride levels of 200–499 mg/dl. Some clinicians recommend a complex and costly subtraction analysis of the major lipid particles to better define this lipid disorder.

The National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III has offered a far easier and arguably more evidence-based alternative, the computation of non-HDL levels. Non-HDL level is the sum of VLDL and LDL levels, calculated by subtracting HDL level from total cholesterol level. An elevated non-HDL level reflects an increased remnant VLDL concentration, an increase in small dense LDL particles, a decrease in HDL level, and an increase in total atherogenic particle number. Non-HDL is also highly correlated with apolipoprotein B, a marker of particle number.

Non-HDL is a secondary treatment target in patients who have triglyceride levels of 200–499 mg/dl after the LDL treatment target has been achieved. When triglyceride levels are 500 mg/dl or higher, triglyceride lowering becomes first priority, but when triglyceride levels are below 500 mg/dl, LDL lowering is the priority. In the former patient population, when levels are brought below 500 mg/dl, attention should be refocused on LDL lowering to reduce risk for CHD. Whenever the LDL-lowering treatment goal is reached and triglyceride levels remain in the 200–500-mg/dl range, a non-HDL goal set 30 mg/dl above the LDL goal should be pursued. In this case, a statin should be prescribed (to lower LDL levels) in combination with a fibrate, niacin, or omega-3 fatty acid product (to lower triglyceride levels).

**Fibrates and Niacin for Treatment for Hypertriglyceridemia**

**Clinical Trials**

A number of randomized, placebo-controlled clinical trials have been conducted in patients with high triglyceride levels to evaluate the benefits of fibrates and niacin in reducing CHD risk. Determining the distinct benefit of lowering triglyceride levels with these agents has proved difficult, however, because these drugs also lower LDL levels and raise HDL levels, and, as previously indicated, patients with high triglyceride levels often have multiple lipid abnormalities. Of interest, post hoc analyses of several of these trials showed significant reductions in CHD risk in the subgroup of patients with lipid profiles characterized by elevated triglyceride levels and low HDL levels (i.e., atherogenic dyslipidemia).

In the Helsinki Heart Study, treatment of 4081 asymptomatic men with gemfibrozil 1200 mg/day or placebo resulted in a 34% reduction in CHD events after 5 years in the gemfibrozil group (p<0.02). Post hoc analysis showed that the greatest benefit from gemfibrozil treatment was realized by patients with baseline triglyceride levels above 200 mg/dl and HDL levels below 40 mg/dl.

In the Bezafibrate Infarction Prevention (BIP) trial, bezafibrate therapy (not available in the United States) was associated with a nonsignificant 9% decrease in the rate of nonfatal myocardial infarction or CHD-related death in 3090 patients who had histories of myocardial infarction or stable angina, but a highly significant 42% reduction in the same end
point in the subpopulation with HDL levels below 35 mg/dl and triglyceride levels of 200 mg/dl or higher. In the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT), 2531 men with CHD were treated with gemfibrozil 1200 mg/day or placebo for 5.1 years. After 1 year, gemfibrozil lowered triglyceride levels by 31% and increased HDL levels by 6%, with no change in LDL levels. This was associated with a highly significant (p<0.001) 24% reduction in the combined outcome of death from CHD, nonfatal myocardial infarction, and stroke.

More recently, in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, fenofibrate or placebo was administered to 9795 patients with diabetes mellitus, some of whom presumably had atherogenic dyslipidemia. Results showed a nonsignificant 11% reduction in the primary end point (i.e., the composite of CHD-related death or nonfatal myocardial infarction) and a nonsignificant increase in total, cardiovascular, and CHD mortality, but a significant reduction in nonfatal myocardial infarction, total cardiovascular events, and coronary revascularizations. The investigators attributed these unexpected results to a high dropout rate of actively treated patients and, even more, to a large and imbalanced rate of patients starting statin therapy. In the Coronary Drug Project, the only placebo-controlled end-point study to have evaluated nicotinic acid (niacin), treatment of 3908 men with CHD with immediate-release niacin 3 g/day or placebo for 5 years lowered total cholesterol levels by 10% and triglyceride levels by 26% in the niacin group. Major cardiovascular events were also reduced with niacin: CHD events by 13%, nonfatal myocardial infarction by 27%, and cerebrovascular events by 21%. A post hoc analysis found that the reduction in nonfatal myocardial infarction in patients with diabetes (and presumably high triglyceride levels) was similar to that in nondiabetic patients. In a 10-year follow-up after the conclusion of this study, patients receiving niacin during the study were found to have a statistically significant reduction in total mortality.

Recommendations Based on Clinical Trial Results

Consideration of these findings led the NCEP ATP III to revise the definitions for triglyceride abnormalities (Table 2). It was recommended that patients with borderline and high triglyceride levels be treated with lifestyle modifications, including increased physical activity, loss of weight, and a low-fat, low-carbohydrate diet. In addition, for patients with high triglyceride levels (200–499 mg/dl) after the LDL goal has been achieved, therapy with drugs that target non-HDL (statins, fibrates, and niacin) may be added. Patients with serum triglyceride levels of 500 mg/dl or higher also are candidates for diet, weight reduction, and increased physical activity, but most will require pharmacologic therapy as well. When the NCEP ATP III guidelines were updated in 2002, two prescription options were available for treating very high triglyceride levels: fibric acid derivatives and niacin. Both of these agents are effective in dose-dependent lowering of triglyceride levels, on average by 30–60%, and increasing HDL levels by approximately 10–35%. When these drug classes are combined, triglyceride reductions of 50–70% may be achieved. This is substantially better than the triglyceride lowering associated with statin therapy.

Adverse Effects

Adverse effects associated with niacin and/or fibrates can limit their use. Crystalline niacin is associated with vasodilator-related adverse events (flushing, itching, and headache). Sustained-release formulations of niacin are available without a prescription as a dietary supplement ostensibly for the treatment of niacin deficiency. The sustained-release formulations, although associated with a lower frequency of vasodilator-related adverse events than the crystalline preparation, can cause serious dose-related liver toxicity and are not recommended for the management of lipid disorders. In one study, therapy was discontinued in approximately 75% of the patients receiving a sustained-release formulation, mostly because of hepatic transaminase level elevations greater than 3 times the upper limit of normal, but also because of symptoms of hepatic dysfunction. None of the

<table>
<thead>
<tr>
<th>Category</th>
<th>Triglyceride Level (mg/dl)</th>
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<tbody>
<tr>
<td>Normal</td>
<td>&lt; 150</td>
</tr>
<tr>
<td>Borderline high</td>
<td>150–199</td>
</tr>
<tr>
<td>High</td>
<td>200–499</td>
</tr>
<tr>
<td>Very high</td>
<td>≥ 500</td>
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patients receiving crystalline niacin experienced these problems. Vasodilator-related adverse events also occur in patients receiving prescription extended-release niacin, but the frequency and severity of events (30–70%) is much reduced.\(^4\) Niacin may increase serum glucose levels modestly in patients with diabetes, requiring a change in the dosage of the hypoglycemic therapy in 10–35% of patients.\(^22\)

Fibrates are also associated with treatment-limiting adverse events.\(^23, 24\) For example, fibrates may cause rhabdomyolysis, especially when combined with statins, and particularly if the fibrate being given is gemfibrozil.\(^23–25\) A particularly concerning finding in the FIELD trial\(^19\) was the lack of a reduction in overall mortality rates with fenofibrate therapy. A recent meta-analysis of 97 randomized controlled trials comparing lipid-lowering agents or dietary intervention with placebo or usual care also showed that fibrate treatment was associated with an increased risk of death from noncardiovascular causes (relative risk 1.13, 95% confidence interval [CI] 1.01–1.27),\(^28\) further raising concerns with this class of agents.

**Dietary and Supplemental Omega-3 Fatty Acids**

The NCEP ATP III guidelines also recommend omega-3 fatty acids, as adjunctive therapy or as an alternative to fibrates and nicotinic acid (niacin), to lower triglyceride levels in order to prevent pancreatitis in patients with very high triglyceride levels.\(^2\) Omega-3 fatty acids (i.e., \(\alpha\)-linolenic acid, eicosapentaenoic acid [EPA], and docosahexaenoic acid [DHA]) are one of two classes of essential fatty acids (the other being the omega-6 fatty acids—linolenic acid, \(\gamma\)-linolenic acid, and arachidonic acid).\(^26–30\) Unlike nonessential fatty acids, essential fatty acids cannot be manufactured by mammalian cells because certain obligatory enzymes are absent.\(^28–30\) Furthermore, only small amounts of the plant-derived omega-3 fatty acid \(\alpha\)-linolenic acid (from canola and soybean oil, flaxseed, and walnuts) are converted to EPA in vivo, and further transformation to DHA is very low.\(^31–33\) Thus, preformed EPA and DHA must be obtained directly through dietary sources (e.g., fatty fish) or by supplementation (e.g., fish oil). A wide range of research has shown that the active agents in fish oil are, in fact, the omega-3 fatty acids EPA and DHA.\(^34\)

Our understanding of the benefits of omega-3 fatty acids on cardiovascular health has been evolving over several decades. Populations that routinely consume fish, especially cold-water fatty fish, have lower CHD events and strokes. For example, one meta-analysis of 13 population cohorts involving 222,000 individuals followed for a mean of 11.8 years found that increasing fish consumption had a direct, dose-dependent association with reduced CHD-related mortality.\(^35\) These investigators reported that every 20-g increase in fish intake was associated with a 7% reduction in risk. Randomized clinical trials testing both fish diets and omega-3 fatty acid supplements have also been conducted.\(^36\) Only two fish diet trials had a randomized controlled design with predefined measures of cardiovascular disease end points and at least 1 year of follow-up; one of these was limited from a methodologic standpoint. The best study in this category, the Diet and Reinfection Trial (DART), randomly assigned 2033 men 4–6 weeks after a myocardial infarction to receive advice on either reduced fat intake, increased fiber intake, or increased fatty-fish intake.\(^37\) Advice concerning fish intake was associated with a 29% reduction in total mortality, 33% reduction in cardiac death, and no change in nonfatal myocardial infarction.

Six randomized trials have been conducted to test the benefit of omega-3 fatty acid supplements.\(^36\) The largest of these, the Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico (GISSI)-Prevenzione trial, used prescription omega-3 fatty acid (discussed later in this article).\(^38\) In this study, 11,323 patients who had experienced a myocardial infarction within 3 months of study entry were randomly assigned to receive an open-label, pharmaceutical-grade, concentrated fish oil supplement containing 850 mg of EPA plus DHA or to be part of a control group (that did not take a supplement). Both groups were followed for 3.5 years. All patients were encouraged to follow a healthy Mediterranean diet and received standard pharmacologic therapy for secondary CHD prevention. Fish oil supplementation was associated with a 20% reduction in the primary end point of the combination of death, nonfatal myocardial infarction, and stroke. There was a 20% reduction in total mortality, which was driven by a 45% reduction in sudden death, suggesting an antiarrhythmic effect; there was no change in nonfatal myocardial infarction. Significant reductions in total, cardiovascular, and coronary death rates were observed within months of starting omega-3 fatty acid supplementation.
In a meta-analysis of 11 trials involving 7951 subjects in the intervention groups and 7855 in the control groups followed for more than 1 year, those who received a diet enhanced with omega-3 fatty acids had hazard ratios for nonfatal myocardial infarction of 0.8 (95% CI 0.5–1.2, p=0.16), for fatal myocardial infarction of 0.7 (95% CI 0.6–0.8, p<0.001), for sudden death of 0.7 (95% CI 0.6–0.9, p<0.01), and for total mortality of 0.8 (95% CI 0.7–0.9, p<0.001). These data suggest a CHD risk reduction that may operate through an antiarrhythmic effect, an effect that may be additive to the antiatherosclerotic effect of standard lipid-modifying therapy. Other large clinical trials are under way with omega-3 fatty acid supplementation, the results of which may support a CHD risk reduction indication.

Prescription Omega-3 Fatty Acids

In late 2004, the United States Food and Drug Administration (FDA) approved prescription omega-3 fatty acid capsules (Omacor; Reliant Pharmaceuticals, Inc., Liberty Corner, NJ) as an adjunct to diet to reduce very high (≥500 mg/dl) triglyceride levels in adults. This product is manufactured as the ethyl esters of omega-3 fatty acids, which allows a greater concentration of EPA and DHA to be obtained during the manufacturing process. Each 1-g capsule of prescription omega-3 fatty acids contains 90% omega-3 acid ethyl esters, consisting of 465 mg (46%) EPA ethyl ester, 375 mg (38%) DHA ethyl ester, and approximately 60 mg (6%) of other omega-3 acid ethyl esters. The remaining 10% of the prescription product is mostly omega-6 fatty acids. The omega-3 fatty acids in this formulation come entirely from a natural marine origin (including mackerel, pompano, herring, smelts, and salmon fish). An FDA-monitored, multistep, patented purification process is applied to refine and purify the oil expressed from the fish carcas to a highly concentrated EPA and DHA product.

Although reductions in serum triglyceride levels after ingestion of omega-3 fatty acids (including the prescription product) are well documented, the exact mechanism underlying this effect is not completely understood. Both animal and human studies have suggested a number of important effects of EPA and DHA. First, secretion of triglyceride-rich lipoproteins is dependent on hepatic triglyceride biosynthesis. In whole-animal rodent studies or with cultures of rat hepatocytes, EPA and fish oil have been shown to inhibit two key enzymatic activities involved in triglyceride biosynthesis, acyl-coenzyme A:1,2-diacylglycerol acyltransferase and phosphatidate hydrolysis. Second, the processes of in vivo fatty acid oxidation and triglyceride biosynthesis compete with each other for the use of fatty acids as substrates. Thus, slower formation of triglyceride-rich VLDL in rodents, who were fed fish oil or EPA, has been linked to a faster rate of hepatic fatty acid oxidation, primarily within mitochondria. Evidence for this effect has also been seen in healthy human subjects receiving dietary supplementation with fish oil 30 g/day, containing 8 g/day of EPA and DHA (at least 3 times the dose of EPA and DHA contained in 4 g/day of prescription omega-3 fatty acids). Finally, triglyceride clearance may be enhanced by omega-3 fatty acids through increases in endogenous lipoprotein lipase activity.

The effect of prescription omega-3 fatty acids on lipoprotein pharmacodynamics also sheds light on the mechanism underlying its triglyceride-lowering effects. In a study in 24 viscerally obese men with mean baseline triglyceride levels above 178 mg/dl and total cholesterol levels above 230 mg/dl, 6 weeks of treatment with prescription omega-3 fatty acids 4 g/day reduced triglyceride levels by 25% and VLDL triglyceride levels by 40%. Compared with the placebo group, subjects receiving prescription omega-3 had a 20% reduction in the VLDL apolipoprotein B pool size but without any significant change in the pool size of LDL apolipoprotein B. The rate of production of VLDL apolipoprotein B particles decreased by 32% with prescription omega-3, whereas it increased by 25% for LDL apolipoprotein B. Of importance, the conversion of VLDL to LDL particles was found to be increased by 93% under the influence of prescription omega-3. These results illustrate that with prescription omega-3, fewer VLDL particles are secreted into the systemic circulation, and secreted VLDL particles are rapidly converted to LDL particles, thus explaining why LDL levels may increase in patients with very high triglyceride levels when given prescription omega-3 therapy. Data in this study did not demonstrate a change in the fractional catabolic rate of either apolipoprotein B particles or chylomicron remnants.

Studies in humans suggest that the reduction in triglyceride levels with dietary supplement fish oil or prescription omega-3 fatty acids is...
associated with increases in levels of EPA and DHA in multiple compartments including plasma, serum phospholipids, platelet phospholipids, and/or erythrocyte membranes. Treatment with prescription omega-3 fatty acids is reported to result in a phospholipid-bound EPA and DHA concentration of 6–8%, representing as much as a 2–3-fold increase from baseline. This increase is correlated with the level of triglyceride reduction. The uptake of EPA and DHA into serum phospholipids in subjects treated with prescription omega-3 appears to be independent of age (i.e., similar concentrations were achieved in patients < 49 yrs vs those ≥ 49 yrs); female subjects, however, tend to have greater uptake of EPA into serum phospholipids than do male subjects. Some authorities have suggested using the concentrations of phospholipid-bound EPA and DHA in defining the best possible dosage of prescription omega-3 fatty acids; although, more research is required to define this optimal concentration.

Clinical Efficacy

The triglyceride-reducing effects of prescription omega-3 fatty acids have been studied in 14 randomized clinical trials in a wide range of patient types, from cohorts with isolated high triglyceride levels (175–877 mg/dl) to very high (500–1999 mg/dl) triglyceride levels, to patients with other lipid abnormalities, such as combined hyperlipidemia and familial combined hyperlipidemia.

In six of the trials, triglyceride levels decreased by at least 35%, with most studies (13 of 14) reporting reductions of at least 25% (Table 3). Generally, prescription omega-3 reduces triglyceride levels to a greater extent in patients with higher baseline triglyceride levels (similar to other hypolipidemic agents). For example, in the two multicenter, double-blind, randomized, placebo-controlled studies that assessed the effect of prescription omega-3 4 g/day in patients with high or very high triglyceride levels (fasting triglyceride levels 175–877 mg/dl), serum triglyceride levels decreased by 28% in the prescription omega-3 groups after 12 or 14 weeks of treatment (p<0.001 vs placebo for both studies).

In contrast, in the two pivotal trials of prescription omega-3 monotherapy at doses of 4 g/day (both of which used prospective, randomized, double-blind, placebo-controlled study designs and evaluated a total of 82 patients with very high triglyceride levels [500–1999 mg/dl]), triglyceride levels decreased by 45% from a mean of 919 mg/dl at baseline (p<0.0001 vs placebo) and by 39% from a mean of 801 mg/dl at baseline (p=0.001 vs placebo).

In addition, these two trials showed that prescription omega-3 increased HDL levels from baseline by 13% (p=0.014) and 5.9% (p=0.057).

Prescription omega-3 fatty acids also have favorable effects on non-HDL levels. Corresponding to the reduction in triglyceride levels in patients treated with prescription omega-3 in the

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Baseline Triglyceride Level (mg/dl)</th>
<th>Omega-3 Fatty Acids Active Ingredients (%EPA/%DHA)</th>
<th>Triglyceride Level Reduction (%)</th>
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<tbody>
<tr>
<td>41</td>
<td>350</td>
<td>NR</td>
<td>28</td>
</tr>
<tr>
<td>57</td>
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<td>175</td>
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<td>378</td>
<td>47/37</td>
<td>44</td>
</tr>
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EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; NR = not reported.
two pivotal trials, VLDL levels decreased by 32% (p<0.0001) and 29% (p=0.001), and LDL levels increased by 32% (p=0.0014) and 17% (p=0.007). Overall, these changes are associated with a net decrease in non-HDL levels of 14% (p=0.0015) based on an analysis of pooled data from both trials (Figure 1).

Studies in patients with combined hyperlipidemia and familial combined hyperlipidemia have provided further evidence of the efficacy of prescription omega-3 fatty acids. In the first of these studies, 57 adult patients with triglyceride levels of 175–1325 mg/dl and total cholesterol levels of 230 mg/dl or higher after a 10-week dietary run-in period were randomized to receive prescription omega-3 4 g/day (28 patients) or placebo ([corn oil] 29 patients). Patients who had diabetes mellitus, previous myocardial infarction, or other serious diseases within 3 months before study entry were excluded. After 12 weeks of treatment, serum triglyceride levels decreased by 28% in the prescription omega-3 group (p<0.05). In both treatment groups, total serum cholesterol levels were reduced significantly (p<0.05). In patients receiving prescription omega-3, HDL levels were increased by 10% at weeks 4 and 8 (p<0.05), but this increase was less evident at week 12.

Prescription omega-3 may also alter lipoprotein particle size and composition in a favorable manner. In one study, prescription omega-3 4 g/day was compared with placebo (corn oil) in 14 patients with a stable diet and with familial combined hyperlipidemia. Patients received their treatment for 8 weeks followed by a crossover to the alternative treatment for an additional 8 weeks. Plasma triglyceride levels decreased by 27%, VLDL levels decreased by 18%, and LDL and apolipoprotein B levels increased by 21% and 6%, respectively (all statistically significant). As a consequence, the LDL:apolipoprotein B ratio increased after treatment with prescription omega-3 (from 1.27 ± 0.26 at baseline to 1.40 ± 0.17 at wk 8), suggesting that LDL particles become larger and more cholesterol enriched with prescription omega-3 treatment (i.e., there were fewer small, dense LDL particles), an observation confirmed by ultracentrifugation for particle size. A similar shift from small, dense LDL to larger LDL subfractions with prescription omega-3 therapy has been reported by other investigators.

In most clinical settings, prescription omega-3 is likely to be used in combination with a statin. Recently, an open-label, randomized, two-way crossover study was undertaken to evaluate the pharmacokinetic interaction between prescription omega-3 fatty acids and simvastatin. Simvastatin 80 mg/day was administered with or without prescription omega-3 4 g/day to 24 healthy volunteers. After 14 consecutive days of dosing to achieve steady state, no significant differences were found in either the extent or rate of exposure (as defined by maximum concentrations) to simvastatin or its major β-hydroxymetabolite after coadministration of prescription omega-3 and simvastatin compared with administration of simvastatin alone. Thus, the coadministration of prescription omega-3 does not appear to affect the pharmacokinetics of simvastatin.

Two randomized, placebo-controlled studies have provided evidence that prescription omega-3 in combination with a statin is effective and safe. In the first study, 48 obese men (waist circumference > 100 cm, waist:hip ratio > 0.97, and body mass index > 29 kg/m²) with plasma triglyceride levels greater than 106 mg/dl and total cholesterol levels greater than 200 mg/dl were entered into a randomized, double-blind, placebo-controlled trial comparing atorvastatin 40 mg/day, prescription omega-3 fatty acids 4

![Figure 1. Effect of treatment with prescription omega-3 fatty acids 4 g/day on non–high-density lipoprotein cholesterol (i.e., very low-density lipoprotein cholesterol [VLDL] + low-density lipoprotein cholesterol [LDL] levels) in patients with very high triglyceride levels.](image-url)
g/day, the combination, or placebo and were followed for 6 weeks. Mean triglyceride levels were reduced from a baseline of 175 mg/dl by 26% with atorvastatin, 25% with prescription omega-3, and 40% with the combination. Mean non-HDL levels were reduced from a baseline of 190 mg/dl by 46% with atorvastatin, by 10% with prescription omega-3, and by 47% with the combination. The HDL level was increased by 14% with the combination, but only by 4% with atorvastatin and by 1% with prescription omega-3 alone.

In the second study, the authors evaluated the efficacy of prescription omega-3 when added to a stable regimen of simvastatin 10–40 mg/day in 59 patients with CHD who had triglyceride levels greater than 200 mg/dl. At 3, 6, and 12 months, prescription omega-3 treatment reduced mean serum triglyceride levels by 20–30% from a baseline of 408 mg/dl (p<0.0005) and VLDL levels by 30–40% from a baseline of 39 mg/dl (p<0.005). These changes were not related to the dose of simvastatin. Their LDL levels did not increase, nor did HDL levels decrease. Adverse events were reported by 22 patients in the prescription omega-3 group and by 17 in the placebo group. The events were generally mild and resulted in only one treatment discontinuation in the prescription omega-3 group.

An extensive body of data suggests that omega-3 fatty acids are cardioprotective, and in some European countries, regulatory authorities have approved prescription omega-3 fatty acids for use in patients with previous myocardial infarction to prevent CHD events. In the United States, the FDA has approved prescription omega-3 only for treatment of patients with triglyceride levels above 500 mg/dl as an adjunct to diet because it considers the data supporting CHD prevention to be incomplete. However, pharmacists may find that some physicians will prescribe omega-3 fatty acids 1 g/day in patients with previous myocardial infarction to reduce CHD risk based on published trials (e.g., GISSI-Prevenzione trial) and standard of care in other countries.

Safety

Pooled data from eight randomized, placebo-controlled, double-blind, parallel-group studies have shown that treatment with prescription omega-3 fatty acids is safe and well tolerated. The most common treatment-emergent adverse events (reported by at least 1% of patients treated with prescription omega-3 fatty acids) were eructation ([belching] 4.9%), infection (4.4%), flu-like syndrome (3.5%), and dyspepsia (3.1%; Table 4). The only adverse event occurring significantly more frequently with prescription omega-3 than with placebo was taste perversion (principally “fishy taste”) at a rate of 2.7% with prescription omega-3 vs 0% with placebo (p=0.0147). Adverse events led to treatment discontinuation in 3.5% of patients treated with prescription omega-3 compared with 2.6% of patients receiving placebo.

The antithrombotic potential of omega-3 fatty acids is well known. However, to our knowledge, no published studies have demonstrated significant changes in bleeding time or a propensity for bleeding among patients treated with FDA-approved doses of prescription omega-3. Omega-3 fatty acid therapy in patients receiving coumarin anticoagulants and aspirin and other older antiplatelet agents has not been associated with an increase in bleeding. We found no reports of experience with concurrent clopidogrel therapy. In a study of the interaction between fish oil and warfarin, no increases were noted in international normalized ratios, and no major bleeding episodes were seen, nor was a reduction in the dosage of warfarin necessary. As mandated by the FDA, patients taking large

<table>
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<tr>
<th>Table 4. Most Common Adverse Events Reported with Prescription Omega-3 Fatty Acids: Pooled Data from Eight Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Event</strong></td>
</tr>
<tr>
<td><strong>Group</strong></td>
</tr>
<tr>
<td>Body as a whole</td>
</tr>
<tr>
<td>Back pain</td>
</tr>
<tr>
<td>Flu-like syndrome</td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Pain</td>
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<tr>
<td>Cardiovascular</td>
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<tr>
<td>Angina pectoris</td>
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<tr>
<td>Digestive</td>
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<tr>
<td>Dyspepsia</td>
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<tr>
<td>Eruption</td>
</tr>
<tr>
<td>Skin</td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Taste perversion</td>
</tr>
</tbody>
</table>

Most common adverse events were those reported by ≥1% of patients treated with prescription omega-3 or placebo. Eighty (35.4%) and 63 (27.6%) patients reported one or more adverse event in the omega-3 fatty acids and placebo groups, respectively.
doses of omega-3 fatty acids should do so only with physician supervision. No additional blood testing beyond that associated with standard-of-care considerations is required during treatment with FDA-approved doses of prescription omega-3 fatty acids.

In studies involving human liver microsomes, a mixture of free fatty acids, EPA and DHA, and their albumin conjugate at a concentration of 23 µmol/L resulted in less than 20–32% inhibition of the enzymes involved in cytochrome P450 (CYP)–dependent metabolism, with the exception of CYP2E1 (68% inhibition). However, since free forms of EPA and DHA are not detected in the circulation (< 1 µmol/L), clinically significant drug-drug interactions due to the inhibition of this system are not expected.

In some patients taking prescription omega-3, increases in alanine aminotransferase (ALT) levels without a concurrent increase in aspartate aminotransferase levels were observed. Therefore, ALT levels should be monitored periodically. Because of the increase in LDL levels observed in some patients treated with prescription omega-3, LDL levels also should be periodically assessed during treatment.

**Indication, Dosage, and Administration**

The FDA-approved indication for prescription omega-3 fatty acids is as an adjunct to diet to reduce very high (≥ 500 mg/dl) triglyceride levels in adults. The approved daily dose of prescription omega-3 for triglyceride reduction is 4 g, taken either as a single dose (four 1-g capsules) or divided as two 2-g doses (two 1-g capsules twice/day). (Note that technically each 1-g capsule contains 840 mg of the active triglyceride-lowering ingredients EPA and DHA.)

If omega-3 is prescribed to prevent recurrent CHD in patients with previous myocardial infarction, the dosage recommended by the American Heart Association (AHA) is 1 g/day. Prescription omega-3 should be used with caution in patients with known sensitivity or allergy to fish. It is also contraindicated in patients who exhibit hypersensitivity to any component of the drug.

Reports have described some confusion between the drug names Omacor (omega-3-acid ethyl esters) and Amicar (aminocaproic acid; Xanodyne Pharmaceuticals, Inc., Newport, KY), which is used for enhancing hemostasis when fibrinolysis contributes to bleeding. Pharmacists should implement measures to ensure clarity of prescription orders to avoid inadvertently substituting these products. Verbal orders for the products should be spelled and the indication verified. The physical appearance of the products is distinctly different; one product is provided as capsules (Omacor), the other as tablets (Amicar). The dosage of Omacor is 1–4 g/day, whereas that for Amicar is highly variable but is usually 500–1000 mg (0.5–1 g) twice/day.

**Practical Considerations**

The treatment considerations recommended by the NCEP ATP III for patients with very high triglyceride levels (≥ 500 mg/dl) are shown in Table 5. Because excess body weight and/or alcohol intake are risk factors for the development of hypertriglyceridemia, every attempt should be made to control triglyceride levels through lifestyle changes, including control of body weight, restriction of alcohol use (if consumed in excess), stable glucose control in patients with diabetes, and regular physical activity. Moreover, emphasis should be placed on controlling medical conditions (e.g., diabetes and hypothyroidism) that may be contributing to the patient's triglyceride abnormalities, and on modifying drug regimens known to exacerbate hypertriglyceridemia (e.g., β-blockers, thiazide diuretics [although data are scant], and estrogens).

A number of national and international health authorities, including the NCEP ATP III and the AHA, have provided recommendations for the use of omega-3 fatty acids as it relates to their health benefits. For general health, the AHA recommends that people consume at least two servings of a variety of fish weekly to reduce CHD risk. For individuals with CHD, the organization recommends ingestion of EPA and DHA 1 g/day, preferably from the consumption of fatty fish or, alternatively, from an omega-3 fish oil product. The NCEP ATP III also recommends omega-3 fatty acids 1–2 g/day as a therapeutic option (after conventional approaches have been tried) in the secondary prevention of CHD. Treatment of hypertriglyceridemia, in particular very high triglyceride levels, to goal levels requires substantially larger doses of omega-3 fatty acids; the AHA recommends EPA and DHA 2–4 g/day for these patients (Table 6). It is important to note that the recommended dosages for these indications are defined as 840 mg (rounded to 1 g) of EPA and DHA and not
OMEGA-3 FATTY ACIDS AS TREATMENT FOR HYPERTRIGLYCERIDEMIA  McKenney and Sica  

31 Although the latter are often available commercially as 1000-mg and 1200-mg capsules, the actual EPA plus DHA content may only be 200–400 mg.

An important consideration in implementing these recommendations is determining when to use dietary supplements versus prescription omega-3 fatty acids. Dietary supplements of omega-3 fatty acids are ideal for use by individuals who wish to supplement their diets with these fatty acids because they do not like, do not have access to, or prefer not to eat adequate amounts of fish. However, use of these products as therapies for medical conditions may be impractical and even unwise, especially if the care takes place without the guidance of a trained health professional.

Most dietary supplement products available in the marketplace contain only modest amounts of the active ingredients, EPA and DHA fatty acids (generally 200–400 mg/1000–1200-mg fish oil capsule). This would require patients to administer 12–20 capsules/day to achieve a triglyceride-lowering dosage of 4 g/day of EPA and DHA.68 This number of capsules is likely to negatively influence compliance and persistence with therapy. In addition, if only 20–40% of the capsule is EPA and DHA, the remaining 60–80% may deliver excessive amounts of saturated fats, trans fats, and/or cholesterol. For example, these products often contain 4–8 mg of cholesterol/capsule. Thus, administration of 12–20 capsules/day to achieve a dose of 4 g of EPA and DHA would mean that patients would consume 48–160 mg/day of cholesterol from this source alone. This can be more than half the total daily intake advised by NCEP ATP III. Environmental toxins and other unknown ingredients may also be present in low amounts in each capsule, but when 12–20 capsules are administered, the patient’s exposure to these ingredients may be excessive.

The manufacturer of prescription omega-3 fatty acids, as with any prescription product, had to present efficacy and safety information for FDA review before receiving approval to market the product, must maintain a surveillance system to monitor the product’s safety,2 must follow Good Manufacturing Practices, must implement systems to ensure product quality, and must submit to periodic regulatory inspections and reviews.69 With nonprescription supplements, however, other than granting “generally recognized as safe” status to these products, the FDA does not examine the efficacy and safety of the products, monitor any ongoing surveillance

<table>
<thead>
<tr>
<th>Goals of Triglyceride-Lowering Therapy</th>
<th>Treatment Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>First priority: prevent acute pancreatitis</td>
<td>Very low-fat diet (&lt; 15% of total calories as fat) when triglyceride level &gt; 1000 mg/dl</td>
</tr>
<tr>
<td>Second priority: prevent coronary heart disease</td>
<td>Efficacy of drug therapy to prevent coronary heart disease in patients with very high triglyceride levels not demonstrated in clinical trials</td>
</tr>
</tbody>
</table>

### Table 5. National Cholesterol Education Program Special Treatment Considerations for Patients with Very High Triglyceride Levels

<table>
<thead>
<tr>
<th>Goals of Triglyceride-Lowering Therapy</th>
<th>Treatment Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>First priority: Very low-fat diet (&lt; 15% of total calories as fat) when triglyceride level &gt; 1000 mg/dl</td>
<td>Medium-chain triglycerides when triglyceride level &gt; 1000 mg/dl (can replace long-chain triglycerides in diet)</td>
</tr>
<tr>
<td>First priority: Very low-fat diet (&lt; 15% of total calories as fat) when triglyceride level &gt; 1000 mg/dl</td>
<td>Weight reduction and physical activity</td>
</tr>
<tr>
<td>First priority: Very low-fat diet (&lt; 15% of total calories as fat) when triglyceride level &gt; 1000 mg/dl</td>
<td>Fish oils (replace some long-chain triglycerides in diet)</td>
</tr>
<tr>
<td>First priority: Very low-fat diet (&lt; 15% of total calories as fat) when triglyceride level &gt; 1000 mg/dl</td>
<td>Triglyceride-lowering drugs (fibates and nicotinic acid [niacin]) are most effective</td>
</tr>
<tr>
<td>First priority: Very low-fat diet (&lt; 15% of total calories as fat) when triglyceride level &gt; 1000 mg/dl</td>
<td>Statins not first-line agents for patients with very high triglyceride levels (statins do not lower triglyceride levels to a significant extent)</td>
</tr>
<tr>
<td>Second priority: Efficacy of drug therapy to prevent coronary heart disease in patients with very high triglyceride levels not demonstrated in clinical trials</td>
<td></td>
</tr>
</tbody>
</table>

### Table 6. Summary of American Heart Association Recommendations for Omega-3 Fatty Acids

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Recommendations</th>
</tr>
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<tbody>
<tr>
<td>No CHD</td>
<td>Eat a variety of fatty fish ≥ twice/wk include oils and other foods rich in α-linolenic acid (flaxseed, canola, and soybean oils; flaxseed and walnuts)</td>
</tr>
<tr>
<td>CHD present</td>
<td>1 g/day of EPA + DHA, preferably from fatty fish; use supplements after consulting a physician</td>
</tr>
<tr>
<td>High triglyceride levels</td>
<td>2–4 g/day of EPA + DHA, under a physician’s care</td>
</tr>
</tbody>
</table>

CHD = coronary heart disease; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid.
systems, or inspect or regulate manufacturing standards. Moreover, the FDA has indicated that it does not consider dietary supplements to be therapeutic options for disease treatment, nor do they permit, by statute, manufacturers of these products to claim that they “treat, cure, or prevent any disease” (only drugs approved by the FDA can legally make such claims). In addition, the FDA has recommended that the dosage of EPA and DHA as a dietary supplement not exceed 2 g/day. The reason for this is partly to discourage self-treatment of potentially serious medical conditions.

Pharmacists play an important role in counseling patients who are prescribed omega-3 fatty acids or who are using omega-3 fatty acid dietary supplements for hypertriglyceridemia or other medical indication. The following are guidelines for pharmacists to help counsel these patients:

- Help the patient understand the reason for omega-3 fatty acid therapy.
- If omega-3 fatty acid therapy is being given to prevent pancreatitis, emphasize the critical importance of compliance with lifestyle modification and prescribed therapy in conjunction with physician instruction.
- If the patient is taking aspirin, clopidogrel, and/or warfarin, advise the patient to report bruising or other signs of bleeding.
- Advise the patient that gastrointestinal adverse effects may be reduced by taking the product with food.

Clearly, patients need to understand their medical conditions and the rationale for omega-3 fatty acid therapy. Patients should be encouraged to be under the care of health professionals when omega-3 fatty acids are being used for therapeutic (not supplement) purposes. The critical importance of adherence to omega-3 fatty acid therapy and other lifestyle (dietary) restrictions is especially important for pharmacists to emphasize to patients taking these products to reduce very high triglyceride levels. Although bleeding complications in patients taking these products have been rarely observed, ongoing surveillance of patients taking concurrent antiplatelet and anticoagulant therapies appears warranted.

Conclusion

High doses of omega-3 fatty acids (2–4 g/day) are useful adjuncts to diet for the reduction of very high triglyceride levels in order to prevent pancreatitis. At these doses, the AHA recommends that treatment with omega-3 fatty acids be undertaken only under the supervision of a qualified health professional. In patients with very high triglyceride levels, prescription omega-3 fatty acids 4 g/day can substantially reduce triglyceride and VLDL levels and may increase LDL levels, but the net effect is a reduction in non-HDL levels. Modest increases in HDL level are also common in patients treated with prescription omega-3 fatty acids. Results from randomized controlled trials confirm the utility of this agent as a triglyceride-lowering therapy. The availability of prescription omega-3 fatty acid (ethyl esters) ensures consistent quality and purity, and should prove to be useful in the medical management of hypertriglyceridemia.

References


54. Pownall H, Brauchi D, Kilinc C, et al. Correlation of serum triglyceride and its reduction by w-3 fatty acids with lipid


