CLINICAL REVIEW

Prescription omega-3 fatty acids for the treatment of hypertriglyceridemia

JAMES M. MCKENNEY AND DOMENIC SICA

Purpose. A review of the key properties and trial results associated with prescription omega-3 fatty acids (P-O3FA) and a description of its place in the treatment of hypertriglyceridemia and coronary heart disease (CHD) risk are presented.

Summary. P-O3FA is made from the fish oil extracted from the fish carcass, which is put through a purification process that refines, esterifies, purifies, and concentrates the ethyl esters of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Each 1-g capsule provides 840 mg of EPA and DHA; the remaining 160 mg contains other omega-3 and omega-6 fatty acids, saturated fatty acids, and monounsaturated acids. When used at a daily dose of 4 g in patients with very high triglycerides (≥500 mg/dL), P-O3FA reduces triglycerides by an average of 45% and very-low-density-lipoprotein cholesterol by more than 50%. Changes in high-density-lipoprotein (HDL) cholesterol and non-HDL cholesterol are usually modest. P-O3FA has been tested in the GISSI-Prevenzione trial—a large, multicenter, open-label, randomized, controlled trial conducted in 11,324 patients. The results of the trial demonstrated significant reductions in all endpoints with the use of P-O3FA.

Conclusion. P-O3FA has demonstrated an efficacy and safety in adult patients with high and very high triglycerides adjunct to diet, and the reduction in serum triglyceride levels was dependent on the baseline triglyceride levels. A large controlled clinical trial is necessary to determine if P-O3FA can be used to reduce CHD risk, either as combined with hydroxymethylglutaryl-coenzyme A reductase inhibitors or as monotherapy.

Index terms: Acids, fatty; Coronary disease; Fish oils; Hypertriglyceridemia; Toxicity

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In November 2004, the Food and Drug Administration (FDA) approved the labeling for a prescription form of omega-3 fatty acids (P-O3FA, Omacor capsules, Reliant Pharmaceuticals, Inc., Liberty Corner, NJ) for reducing very high triglycerides in adults (≥500 mg/dL [≥5.65 mmol/L]) as an adjunct to diet.[1] This product has been available for up to a decade in other countries for a similar indication and, in some countries, for preventing coronary heart disease (CHD) in patients who have experienced a myocardial infarction (MI).[1] P-O3FA represents the first prescription preparation of omega-3 fatty acid to become available for triglyceride management in the United States. This article provides a review of P-O3FA from preclinical pharmacology to clinical data supporting its use in the treatment of very high triglycerides and in the reduction of CHD risk. It will also summarize the National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III) recommendations for patients with high triglyceride levels and suggest where P-O3FA therapy may be used.

Chemistry

Each capsule of P-O3FA contains approximately 465 mg of eicosapentaenoic acid (EPA) ethyl ester and ap-

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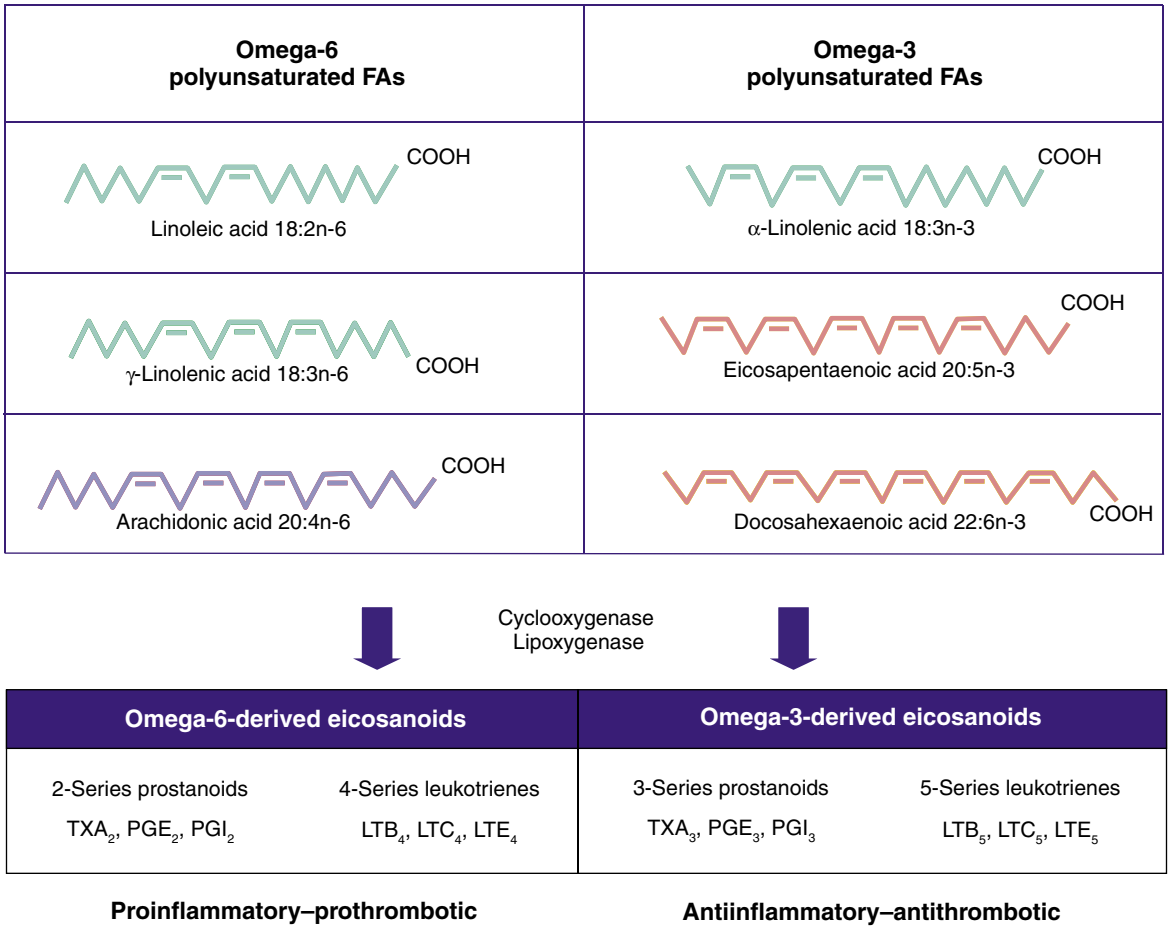
proximately 375 mg of docosahexaenoic acid (DHA) ethyl ester, the two active ingredients responsible for the pharmacologic and therapeutic effects of the product (Figure 1).[2,3] EPA is a 20-carbon-long molecule containing five double bonds beginning 3 carbons from the terminal end. DHA is a 22-carbon-long molecule with six double bonds beginning 3 carbons from the terminal end. The empirical formula for the ethyl ester of EPA is $C_{22}H_{34}O_2$ and of DHA is $C_{24}H_{36}O_2$.

P-O3FA is made from the fish oil extracted from the fish carcass, which is put through a patented purification process that refines, esterifies, purifies, and concentrates the ethyl esters of EPA and DHA.[3] Unlike dietary supplements of omega-3 fatty acids, P-O3FA is required to comply with FDA good manufacturing practices and to undertake quality assurance procedures to ensure batch-to-batch consistency and purity. Each 1-g capsule contains approximately 840 mg (84%) of EPA and DHA, approximately 60 mg (6%) of other omega-3-acid ethyl esters, and 100 mg (10%) of a combination of omega-6-acid ethyl esters, monounsaturated fatty acids, saturated fatty acids, and cholesterol. P-O3FA undergoes monitoring to ensure that FDA quality standards are met, including the presence of the trans fatty acids of EPA and DHA (each <0.05%), heavy metals including methylmercury (undetectable levels) and environmental toxins including dioxins and polychlorinated biphenyls (below FDA-specified limits).[3]

Pharmacology

There are two classes of essential fatty acids, the omega-6 (linoleic acid, γ-linolenic acid, and arachidonic acid) and the omega-3 (α-linolenic acid, EPA, and DHA) fatty acids, collectively referred to as polyunsaturated fatty acids (Figure 1).[4-7] Whereas the nonessential fatty acids can be synthesized by mammalian cells de novo, essential fatty acids cannot because the enzymes required for adding double bonds

Figure 1. Essential fatty acids (FA). TXA_2 = thromboxane, PGE_2 = prostaglandin E2, PGI_2 = prostacyclin I2, LTB_4 = leukotriene B4, LTC_4 = leukotriene C4, LTE_4 = leukotriene E4, TXA_3 = thromboxane A3, PGE_3 = prostaglandin E3, PGI_3 = prostacyclin I3, LTB_5 = leukotriene B5, LTC_5 = leukotriene C5, LTE_5 = leukotriene E5.



onto these molecules are not present in mammalian cells.[6,7] Although α-linolenic acid, which is derived from plants (the main sources are canola and soybean oils, flaxseed, and walnuts), can undergo conversion to EPA in vivo, this conversion is quite modest (<1%), and further transformation to DHA is very low.[8-10] Thus, for the most part, EPA and DHA must be obtained through dietary sources or dietary supplementation. Omega-6 fatty acids are converted into 2-series prostanoids and 4-series leukotrienes that are associated with proinflammatory and prothrombotic activity, while omega-3 fatty acids are converted into 3-series prostanoids and 5-series leukotrienes that are associated with antiinflammatory and antithrombotic properties.

The beneficial effects of omega-3 fatty acids on cardiovascular health have long been recognized, beginning with the observation that indigenous populations that consumed large amounts of foods such as seal, whale, and fatty fish, which contain high concentrations of omega-3 fatty acids, have low rates of CHD, despite the high-fat content of their diets.[4,11-13] Fatty fish and marine mammals are rich in EPA and DHA, and a wide body of research has established these fatty acids as the active agents in fish oil.[14] Among the many effects of omega-3 fatty acids that are believed to contribute to their cardiovascular benefits are (1) small reductions in blood pressure, (2) decreases in platelet aggregation, (3) modest increases in bleeding time, (4) reductions in heart rate, and (5) potential antiarrhythmic effects.[9,12,15-17] The growing database on the benefits of omega-3 fatty acids has even led to a proposal that blood levels of EPA and DHA should be evaluated as a new, modifiable, and clinically relevant risk factor for CHD mortality.[18]

The triglyceride-reducing effects of EPA and DHA have been detailed in numerous studies among a wide range of patient types.[8,14] A dose–response relationship between EPA or DHA and triglyceride lowering has been demonstrated, with doses between 2 and 4 g/day lowering serum triglycerides by approximately 20–50%.[4,9,11] As with fibric acid derivatives (fibrates) and nicotinic acid (niacin), reductions in triglycerides and very-low-density-lipoprotein (VLDL) cholesterol are generally greater in patients with higher baseline triglyceride levels.[8,19] An increase in low-density-lipoprotein (LDL) and high-density-lipoprotein (HDL) cholesterol can accompany a reduction in triglycerides; the higher the baseline triglyceride level, the greater these lipids may be increased. In most cases, the rise in LDL cholesterol is less than the reduction in VLDL cholesterol, resulting in a net decrease in non-HDL cholesterol (VLDL cholesterol plus LDL cholesterol). In addition, the LDL cholesterol in patients with very high triglycerides is usually very low; so if LDL cholesterol is increased with omega-3 fatty acid therapy, it is still in a relatively low range.

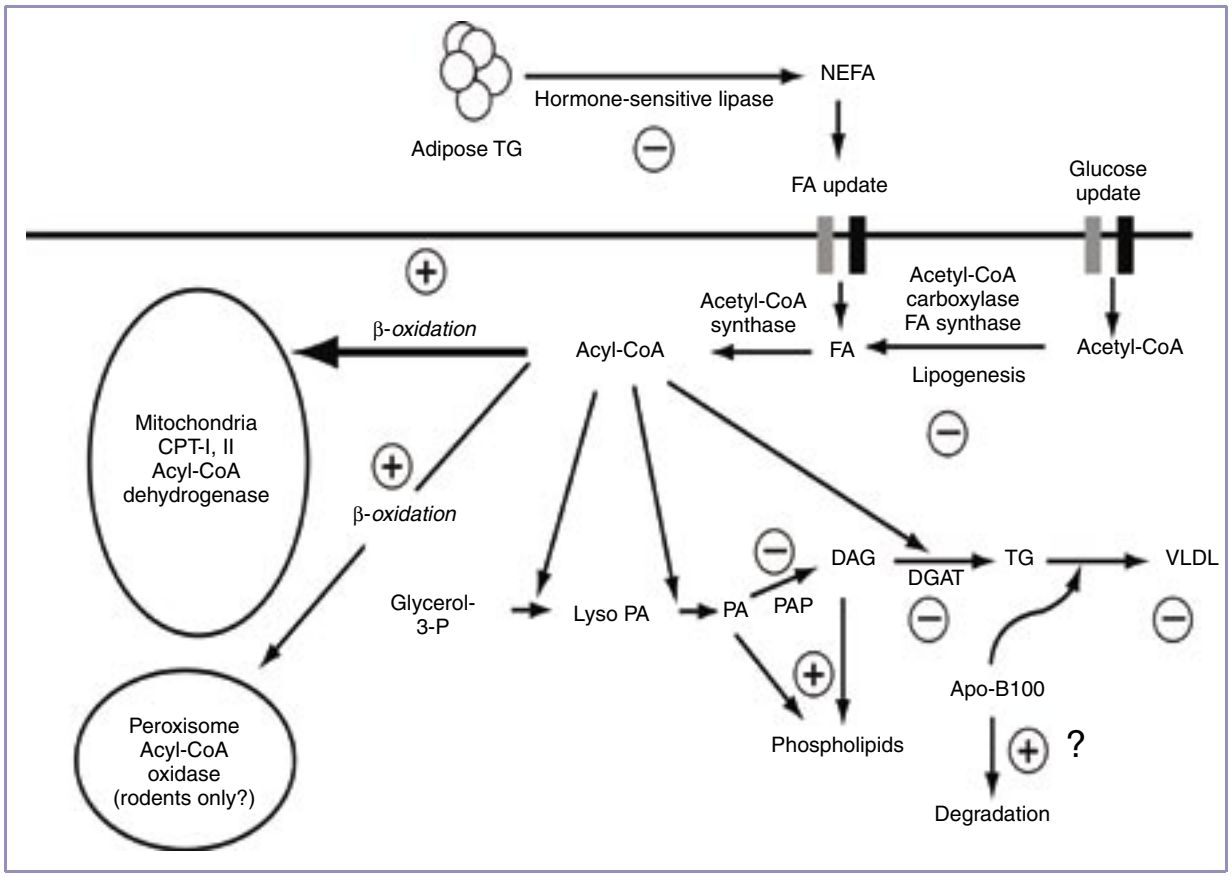
Although the mechanism of action of omega-3 fatty acids is not completely understood, two main actions are believed to cause the reduction of serum triglycerides (Figure 2).[20] First, triglyceride synthesis in the liver may be reduced by omega-3 fatty acids due to the inhibition of acyl coenzyme A (CoA): 1,2-diacylglycerol-*O*-acyltransferase.[21] Because omega-3 fatty acids such as EPA and DHA have substantial affinity to, but are poor substrates for, the enzymes responsible for triglyceride synthesis, the esterification and release of other fatty acids are inhibited.[21,22] Second, omega-3 fatty acids appear to induce peroxisomal β-oxidation in the liver.[5] Hepatic nuclear receptors, such as peroxisome proliferator-activated receptors (PPARs), are thought to mediate the hypolipidemic effect of polyunsaturated fatty acids.[6] Because of a high affinity for PPAR-α and PPAR subclasses, omega-3 fatty acids may also upregulate the metabolism of fatty acids in the liver.[23]

Pharmacokinetics

After oral administration of P-O3FA, in both healthy volunteers and patients with hypertriglyceridemia, EPA and DHA are well absorbed.[2] P-O3FA induced significant, dose-dependent increases in serum phospholipid EPA content, although increases in DHA content were less marked and not dose dependent when administered as ethyl esters. The uptake of EPA and DHA into serum phospholipids in participants treated with P-O3FA was independent of age (i.e., similar concentrations were achieved in patients <49 years versus ≥49 years). Female participants tended to have more uptake of EPA into serum phospholipids compared with male participants. Pharmacokinetic data on P-O3FA in children are not available.

Another way to appreciate the activity of P-O3FA is to study the pharmacokinetics of lipoproteins. In one such study of 24 viscerally obese men who had mean baseline triglycerides of 178 mg/dL, administration of P-O3FA 4 g/day for six weeks resulted in a 20% reduction in the VLDL apolipoprotein B level but without any significant change in the level of LDL apolipoprotein B.[24] The rate of production of VLDL apolipoprotein B particles decreased by 32% while that for LDL apolipoprotein B increased by 25%. Importantly, the conversion of VLDL to LDL particles increased 93% under the influence of P-O3FA. These results illustrate that the enhanced catabolism of triglycerides produced by P-O3FA results in less secretion and more rapid removal of VLDL particles. The results also show that VLDL particles are rapidly converted to LDL particles, thus explaining why LDL cholesterol levels may rise in patients with very high triglycerides when given P-O3FA therapy.

Figure 2. The mechanism of action of omega-3 fatty acids. Omega-3 fatty acids have been reported to inhibit (–) lipogenesis and the activities of diacylglycerol acyltransferase (DGAT), phosphatidic acid (PA), and hormone-sensitive lipase, and to stimulate (+) β-oxidation, phospholipid synthesis, and apo-B degradation. The end result is a reduced rate of secretion of very-low-density-lipoprotein (VLDL) triglyceride.[20] DAG = diacylglycerol, TG = triglyceride, PAP = phosphohydrolase, FA = fatty acids, NEFA = nonesterified fatty acids. Reproduced, with permission, from reference 20.



Clinical efficacy

Two randomized, double-blind, placebo-controlled clinical trials formed the basis for the approval of P-O3FA monotherapy in conjunction with diet for the treatment of patients with severe hypertriglyceridemia (i.e., ≥500 mg/dL [≥5.65 mmol/L]) (Table 1).[25,26] In one trial, P-O3FA 4 g/day was compared with placebo (corn oil) in 42 patients who had triglycerides of ≥500 mg/dL (≥5.65 mmol/L) and <2000 mg/dL (<22.60 mmol/L) for 16 weeks.[25] In 16 weeks, P-O3FA increased the serum concentration of phospholipid-bound EPA and DHA by twofold to threefold, from 1.4% at baseline to 4.1% for EPA and from 2.5% at baseline to 5.9% for DHA. Triglycerides were reduced a mean of 45% with P-O3FA while they rose 16% with placebo ($p < 0.0001$). P-O3FA was also associated with a 32% reduction in VLDL cholesterol ($p = 0.001$), a 20% reduction in the total cholesterol:HDL cholesterol ratio ($p = 0.0013$), and a 13% increase in HDL cholesterol ($p = 0.004$). LDL cholesterol increased 32% (from 79 mg/dL [2.04 mmol/L] at baseline to 104 mg/dL [2.69 mmol/L] at 16 weeks [$p = 0.0014$]).

The second pivotal study compared P-O3FA 4 g/day with placebo (corn oil) in 40 patients with fasting serum triglycerides of ≥500 mg/dL (≥5.65 mmol/L) and <2000 mg/dL (<22.60 mmol/L) (Table 1).[26] P-O3FA reduced triglycerides by 40% from a baseline of 801 mg/dL (9.0 mmol/L), while triglycerides increased 8% in the placebo group ($p = 0.001$). In addition, P-O3FA treatment was associated with a 29% reduction in median VLDL cholesterol, a 17% increase in median LDL cholesterol, and a 6% increase in median HDL cholesterol ($p = 0.057$).

Perhaps a more important issue, especially with regard to the size of the affected population, is the efficacy of P-O3FA in reducing non-HDL cholesterol (and presum-

Table 1.
Changes in Lipid Parameters with P-O3FA (4 g/day)[a]

Ref.	No. Patients	Inclusion Criteria (mg/dL)	% TG Reduction (range, mg/dL)	% LDL-C Change (range, mg/dL)	% HDL-C Change (range, mg/dL)
24	42	TG 500–2000	45 (919–505)	+32 (79–104)	+13 (30–34)
25	41	TG 500–2000	39 (801–512)	+17 (43–53)	+6 (17–18)
27	95	TG 175–885 + T.Chol >200	28 (353–254)	NR	NR
28	14	Familial combined HPL	27 (251–184)	+22 (167–203)	+2 (41.5–42.5)
29	NR	TG >175, T.Chol >230	28	. . .	. . .
30[b]	43	TG >106, T.Chol >202	Atorvastatin: 26 Index: 25 Combo: 40	Atorvastatin: –52 Index: –6 Combo: –47	Atorvastatin: +4 Index: +1 Combo: +14
31[c]	59	TG > 204	24	–6	–9

[a]Combo = combination, HDL-C = high-density lipoprotein cholesterol, HPL = hyperlipidemia, LDL-C = low-density lipoprotein cholesterol, P-O3FA = prescription omega-3 fatty acids, T.Chol = total cholesterol, NR = not reported, TG = triglycerides.
[b]Atorvastatin 40 mg/day, index: P-O3FA, combination: atorvastatin 40 mg/day + P-O3FA 4 g/day.
[c]Background simvastatin at an average of 33 mg/day

ably CHD risk) in patients with triglyceride concentrations between 200 and 500 mg/dL. According to the NCEP ATP III, triglyceride levels in this range signal the presence of an atherogenic dyslipidemia, which adds significantly to CHD risk even if LDL cholesterol levels are below the recommended goals.[19] The manufacturer of P-O3FA has received an approvable letter for this indication from FDA and is currently conducting studies to document this effect. The following is a summary of the published studies with P-O3FA in this population.

The first study was a 12-week randomized, placebo-controlled trial in which patients with mean fasting triglycerides of ≥175 mg/dL (≥1.97 mmol/L) and ≤885 mg/dL (≤9.99 mmol/L) and a mean fasting total cholesterol of ≥200 mg/dL (≥5.17 mmol/L) were randomized to P-O3FA 4 g/day (n = 29) or matching placebo (corn oil) (n = 26) for a 12-week evaluation (Table 1).[27] There was a significant increase in the EPA and DHA content of serum phospholipids after treatment with P-O3FA (p < 0.0001) and no change with placebo. Mean serum triglycerides decreased by 28% in the P-O3FA group and increased by 9% in the placebo group (p < 0.0001). There were no significant changes in total cholesterol or HDL cholesterol in either group. The non-HDL cholesterol decreased by an estimated (not reported in the study) 0.5% with P-O3FA.

In a second trial, adult participants with fasting triglycerides of ≥175 mg/dL (≥1.97 mmol/L) and <885 mg/dL (<9.99 mmol/L) were randomized to P-O3FA 4 g/day (n = 47) or matching placebo (corn oil; n = 48) (Table 1). The median serum triglyceride level was significantly reduced by 28% with P-O3FA treatment at 14 weeks (p < 0.001 versus placebo). This was due largely to a decrease in VLDL cholesterol, which decreased by 25%, from a median of 57 mg/dL at baseline to 43 mg/dL at week 14 (p < 0.001 versus placebo). No significant changes were seen in total cholesterol, LDL cholesterol, or lipoprotein in the P-O3FA group.[28] There was a slight but nonsignificant rise in HDL cholesterol with P-O3FA. It is estimated (not reported in the study) that non-HDL cholesterol did not change in the patients with type IV hypertriglyceridemia who were randomized to P-O3FA but was reduced 6% in the patients with mixed hyperlipidemia who were randomized to P-O3FA therapy.

Two other studies in patients with combined hyperlipidemia are reported in Table 1 and confirm the efficacy of P-O3FA 4 g/day in reducing triglyceride levels, but neither study provides any estimate of a non-HDL-cholesterol-lowering efficacy.[29,30]

In most clinical situations, P-O3FA is most likely to be used as add-on therapy for non-HDL cholesterol lowering in patients who have achieved satisfactory LDL cholesterol lowering with a 3-hydroxy-3-methylglutaryl–CoA (HMG-CoA) reductase inhibitor or other agent. Two studies have been conducted that address this situation. In one, 48 obese men with plasma triglycerides >106 mg/dL (>1.19 mmol/L) and total cholesterol >200 mg/dL (>5.2 mmol/L) were randomized to atorvastatin 40 mg/day, P-O3FA 4 g/day, the combination, or placebo and followed for six weeks (Table 1).[31] Mean ± S.D. plasma EPA and DHA concentrations increased from 1.0% ± 0.4% to 3.5% ± 1.3% and from 1.6% ± 0.5% to 3.1% ± 0.8%, respectively (p < 0.01). Triglycerides were reduced from a baseline of 175 mg/dL by 26% with atorvastatin, 25% with P-O3FA, and 40% with the combination. Non-HDL cholesterol was reduced from a baseline of 190 mg/dL by 46% with atorvastatin, 10% with P-O3FA, and 47% with the combination. HDL cholesterol was

increased 14% with the combination, but no significant change was seen with either therapy alone.

A second study evaluated the efficacy of P-O3FA (2 g twice a day) when added to a stable regimen of simvastatin 10–40 mg/day in CHD patients who had triglycerides of >200 mg/dL (>2.26 mmol/L) (Table 1).[32] In patients receiving P-O3FA, the EPA concentrations rose by a mean of 260% (95% confidence interval [CI], 192–327%) at six months and the DHA concentrations by 54% (95% CI, 38–70%) at the same time points. P-O3FA treatment reduced serum triglycerides from a baseline of 407 mg/dL by 24% ($p < 0.0005$) and VLDL cholesterol from a baseline of 39 mg/dL by 40% ($p < 0.005$). These changes were not related to the dose of simvastatin.[31] LDL cholesterol was reduced about 6% with the addition of P-O3FA, and HDL cholesterol remained unchanged during P-O3FA treatment. Non-HDL cholesterol was reduced 13% from a baseline of 175 mg/dL with P-O3FA.

These studies provide evidence of the efficacy of P-O3FA in lowering triglyceride levels with a dose of 4 g/day. The magnitude of the reduction is highly dependent on the baseline triglyceride level as illustrated in Table 1. Mean triglyceride levels were reduced as little as 27% when baseline concentrations were about 250 mg/dL to as much as 45% when concentrations were about 900 mg/dL. The effect of P-O3FA on non-HDL cholesterol is not as clear. In general, reductions in this parameter were reported, but most were modest. Clearly, additional study in larger populations and with concurrent LDL cholesterol-lowering therapy is needed to establish the place of P-O3FA for this use.

The effect of P-O3FA on CHD events has been assessed in a large, multicenter, open-label, randomized, controlled trial, called the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione trial.[33] This trial randomized 11,324 patients who had experienced an MI within three months of study entry to P-O3FA 1 g/day alone (n = 2,836), vitamin E 300 mg/day alone (n = 2,830), both agents (n = 2,830), or nothing (n = 2,828) and followed these patients for three and a half years.[33] Patients were allowed to continue preventive therapies prescribed by their primary physicians (92% were receiving antiplatelet therapy, 47% were receiving angiotensin-converting enzyme inhibitor therapy, and 44% were receiving β-blocker therapy). At baseline, 4% of patients were receiving lipid therapy, but by the conclusion of the study 46% were. The primary efficacy measure was the combination of all-cause death, nonfatal MI, and nonfatal stroke. Treatment groups were well-balanced at baseline in terms of demographic and clinical characteristics. Mean lipid values at baseline were triglycerides 162 mg/dL, LDL cholesterol 137 mg/dL, and HDL cholesterol 42 mg/dL.

A two-way intention-to-treat analysis showed that patients assigned to P-O3FA experienced a significant 10% reduction in the primary endpoint (95% CI, 0.82–0.99; $p = 0.048$).[33] A four-way analysis showed a 20% reduction in all-cause mortality ($p = 0.0064$), a 30% reduction in cardiovascular mortality ($p \leq 0.001$), a 35% reduction in coronary mortality ($p \leq 0.01$), and a 45% decrease in sudden death ($p = 0.0006$) associated with P-O3FA therapy. Nonfatal cardiovascular events (MIs and strokes) were not significantly reduced. No significant effect of vitamin E therapy was seen on primary or secondary endpoints. The reduction in total mortality with P-O3FA therapy was statistically significant after three months (relative risk [RR], 0.59; 95% CI, 0.36–0.97). The reduction in sudden death reached significance at four months (RR, 0.47; 95% CI, 0.219–0.995); reduced rates of cardiovascular, cardiac, and coronary death reached significance in subsequent months.[34] These data suggest that much of the benefit of P-O3FA in this study was due to a reduction in sudden cardiac death that was most likely to have resulted from an antiarrhythmic effect.

A subsequent meta-analysis of 11 randomized controlled outcome studies (2 of dietary intervention and 9 of omega-3 fatty acid supplementation, involving 15,806 patients including 11,324 from the GISSI-Prevenzione trial) compared omega-3 fatty acid therapy with controlled diets or placebo in patients with CHD.[17] The analysis reported a nonsignificant reduction in nonfatal MI (RR, 0.8; 95% CI, 0.5–1.2) and, in the 5 trials for which data were available to analyze, significant reductions in overall mortality (RR, 0.8; 95% CI, 0.7–0.9) and sudden death (RR, 0.7; 95% CI, 0.6–0.9). These data have caused some to recommend omega-3 fatty acid supplement therapy in patients who have experienced an MI. A broader discussion of this conclusion is provided below in the section, Role of P-O3FA.

Adverse effects

The most common treatment-emergent adverse events (reported by at least 1% of patients treated with P-O3FA or placebo) are shown in Table 2. These rates are based on pooled data from eight randomized, placebo-controlled, double-blind, parallel-group studies of P-O3FA at a dose of 4 g/day. The most common adverse events reported with P-O3FA were eructation (4.9%), infection (4.4%), flu-like syndrome (3.5%), and dyspepsia (3.1%), and these were not significantly different from placebo. The only adverse event occurring significantly more frequently with P-O3FA than with placebo was taste perversion (principally "fishy taste") at an incidence of 2.7% with P-O3FA versus 0% with placebo ($p = 0.0147$). Adverse events led to treatment

discontinuation in 3.5% of patients treated with P-O3FA and 2.6% of patients treated with placebo.[2]

The effect of a mixture of free fatty acids, EPA and DHA, and their free fatty acids albumin conjugate on cytochrome P-450 (CYP)-dependent monooxygenase activities was assessed in human liver microsomes.[2] At a concentration of 23 μM, free fatty acids resulted in <32% inhibition of CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A. At 23 μM, the conjugate of free fatty acids and albumin resulted in <20% inhibition of CYP2A6, 2C19, 2D6, and 3A and a 68% inhibition of CYP2E1. Since free forms of EPA and DHA are not detected in the circulation (<1 μM), clinically significant drug–drug interactions due to the inhibition of CYP-mediated metabolism are not expected in humans.[2]

An antithrombotic potential of omega-3 fatty acids was recognized more than 35 years ago.[35] More recently, omega-3 fatty acids were shown to reduce thrombin generation in a vitamin K-independent manner.[35] To date, no published studies have demonstrated significant changes in bleeding time or propensity for bleeding among patients treated with P-O3FA at dosage that are given in the FDA-approved labeling. Experience with the use of omega-3 fatty acid therapy in patients receiving warfarin, aspirin, and other older antiplatelet agents in clinical trials has not revealed increased bleeding; no experience with concurrent clopidogrel bisulfate therapy has been reported. A study of the interaction between fish oil (4 or 6 g/day) and warfarin did not show an increase in international normalized ratios or major bleeding episodes or the need to reduce the dosage of warfarin.[36] As a precaution, FDA advises that patients receiving treatment with both P-O3FA and anticoagulants be monitored periodically according to the standards of care for anticoagulant therapy and that patients should take large doses (interpreted to be >2 g/day) only under physician supervision.[37]

Table 2.
Most Common Adverse Events Reported with Prescription Omega-3 Fatty Acids (P-O3FA)[2,a]

Adverse Event	No. (%) Patients	
	P-O3FA (*n* = 226)	Placebo (*n* = 228)
Subjects with ≥1 adverse event	80 (35.4)	63 (27.6)
Body as a whole		
Back pain	5 (2.2)	3 (1.3)
Flu-like syndrome	8 (3.5)	3 (1.3)
Infection	10 (4.4)	5 (2.2)
Pain	4 (1.8)	3 (1.3)
Cardiovascular		
Angina pectoris	3 (1.3)	2 (0.9)
Digestive		
Dyspepsia	7 (3.1)	6 (2.6)
Eructation	11 (4.9)	5 (2.2)
Skin		
Rash	4 (1.8)	1 (0.4)
Special senses		
Taste perversion	6 (2.7)	0

[a]Reported by ≥1% of patients treated with P-O3FA or placebo. Pooled data from eight randomized, double-blind, placebo-controlled, parallel-group studies.

Dosage and administration

The recommended daily dose of P-O3FA for triglyceride reduction in adults is 4 g/day. The daily dose can be taken either as a single 4-g dose (four capsules) or as two 2-g doses (two capsules twice daily). Some cardiology and other lipid specialists may prescribe P-O3FA to reduce the risk of sudden death in post-MI patients at a dose of 1 g/day.[9]

P-O3FA is intended to be given as an adjunct to an effective therapeutic lifestyle program that includes control of body weight, restriction of alcohol use (if consumed in excess), good glucose control in patients with diabetes mellitus, and regular physical activity.[19] If P-O3FA treatment is initiated, patients should be counseled to continue to adhere to diet and other lifestyle modifications.

Laboratory monitoring of the patient's triglyceride levels with a consistent abnormality before initiating P-O3FA therapy and periodic measures during P-O3FA therapy are indicated.[2] Because of the increase in LDL cholesterol observed in some patients treated with P-O3FA, LDL cholesterol should also be monitored periodically during P-O3FA treatment. In some patients, increases in alanine aminotransferase levels without a concurrent increase in aspartate aminotransferase levels have been observed.[2] Therefore, alanine aminotransferase levels should be monitored periodically during P-O3FA therapy. No cases of jaundice or acute liver failure are known to have occurred as a result of P-O3FA therapy.[2]

Reports of confusion between the drug names Omacor (omega-3-acid ethyl esters) and Amicar (aminocaproic acid), which is used for enhancing hemostasis when fibrinolysis contributes to bleeding, have been described. Pharmacists should implement measures to assure clarity of prescription orders to avoid inadvertently substituting these drugs. Oral 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) and the other as tablets (Amicar [Wyeth-Ayerst, Collegeville, PA]). The dosage of Omacor is 1 to 4 g/day while the dosage for Amicar is highly variable but is usually 500 to 1000 mg (0.5 to 1 g) twice a day.

Role of P-O3FA

Very high triglycerides. While an increased risk of CHD may be present in patients with very high triglycerides (≥500 mg/dL [≥5.65 mmol/L]), the more urgent concern is the development of pancreatitis. The risk of pancreatitis increases with a rise in triglyceride levels and is especially concerning when concentrations exceed 1000 mg/dL. At these concentrations, chylomicrons and large VLDL particles are present. Triglyceride reduction is the treatment priority in these patients (appendix). Drugs that raise triglyceride levels should be identified and discontinued. Alcohol should be eliminated. A very-low-fat restricted diet (<15% of total calories), weight reduction, and increased physical activity are recommended. Because diet alone is unlikely to sufficiently reduce very high triglyceride levels to the degree required, the majority of these patients will require pharmacologic treatment. Options include fibrate, nicotinic acid, and omega-3 fatty acid therapy. Each of these options effectively lowers triglycerides by an average of 20–50%.[19] Comparative clinical trials of these drugs have not been conducted, so selection of the therapy is based on tolerability and risk of adverse events. The goal of therapy in these patients is to reduce triglyceride concentrations to <500 mg/dL. Thus, in patients with concentrations exceeding 1000 mg/dL, one triglyceride-lowering drug may be insufficient. Combination therapy with two or more triglyceride-lowering drugs may be required, and triglyceride reductions of 50% to 70% may be achieved.[11]

One of the fibrates, gemfibrozil or fenofibrate, has been the traditional choice for drug therapy to lower very high triglyceride levels owing to their greater tolerability compared with niacin. However, fibrates can cause myopathy and rhabdomyolysis and should be used with caution in individuals at a high risk of these problems.[11,38,39] In addition, fibrates should be used with caution in the elderly and patients with renal dysfunction since they are renally cleared and dosage adjustment may be necessary in some of these patients.[11] Niacin also effectively lowers triglycerides 25–50% with 2000 mg/day but is associated with flushing and related vasodilatory adverse effects in close to 90% of patients.[11] A prescriptive extended-release form of niacin does not cause serious hepatotoxicity and is better tolerated, but it still causes flushing in about 30% of patients.[40]

The NCEP ATP III guidelines recommended dietary supplement omega-3 fatty acids be used as adjunctive therapy or as an alternative to fibrates and nicotinic acid, particularly in patients with chylomicronemia.[19] With the availability of P-O3FA, it seems reasonable to consider P-O3FA as an alternative to, or a therapy to be combined with, a fibrate or niacin for management of very high triglyceride levels. The concentrated dose of EPA and DHA (the active ingredients for lowering triglycerides) and its tolerability make P-O3FA a good candidate for this clinical indication.

High triglycerides. On the basis of the association among elevated triglycerides, other lipid risk factors, and CHD risk in observational and clinical trials, NCEP ATP III has recognized that high triglyceride levels (i.e., 200 to 500 mg/dL) in patients whose LDL cholesterol is at goal is a signal of the presence of other atherogenic particles that accentuate CHD risk.[19] These abnormalities include increased cholesterol-enriched remnant VLDL; low HDL cholesterol; high levels of small, dense LDL; and an overall increase in the number of atherogenic, apolipoprotein B-containing particles. In these patients, NCEP ATP III recommends that a secondary goal, defined by non-HDL cholesterol, be established at 30 mg/dL above the patient's LDL cholesterol goal. As with the LDL cholesterol goal, treatment to reach the non-HDL cholesterol goal begins with therapeutic lifestyle changes with an emphasis on weight reduction and increased physical activity. Therapy with HMG-CoA reductase inhibitors should be maximized as these drugs effectively lower LDL cholesterol and non-HDL cholesterol. Second-line therapy for non-HDL cholesterol reduction includes fibrates and nicotinic acid, which may be added to therapy with an HMG-CoA reductase inhibitor as required to help achieve treatment goals. Based on the evidence available to date, the efficacy of non-HDL cholesterol lowering with P-O3FA is modest and not likely to improve treatment choices over those that are already available.[19]

CHD risk reduction. The results of the GISSI-Prevenzione trial provide compelling evidence that P-O3FA may assist in CHD risk reduction in post-MI patients by reducing sudden cardiac death. The fact that other, small studies and recent meta-analyses have demonstrated consistent findings has led many authorities to recommend omega-3 fatty acids for prophylatic therapy in post-MI patients. The NCEP ATP III and the American Heart Association (AHA) advocate omega-3 fatty acids as part of a lifestyle-modification approach, recommending a low-fat diet containing fresh vegetables and fruits, nuts, fish, and other sources of omega-3 fatty acids.[41] Both organizations also endorse the option of prescribing 1 g/day of omega-3 fatty acid therapy

as a preventive measure for patients who have experienced an MI. However, both emphasize that support for this recommendation is based on only moderately strong evidence that comes mostly from the one large clinical trial (GISSI-Prevenzione trial).[19,41] FDA has concluded that consumption of omega-3 fatty acids may reduce the risk of CHD but feels that the evidence is not conclusive and has not approved the labeling of P-O3FA for this indication. Other regulatory agencies in the world have approved P-O3FA for this indication.

Cardiologists and other health professionals who study the breadth of evidence from observational, dietary, and clinical trials may conclude that P-O3FA therapy may offer value to their patients. Most interesting is the fact that P-O3FA appears to offer a CHD risk-reducing mechanism that is unique, namely, reduction in sudden CHD death, apparently through an antiarrhythmic effect. If this effect is confirmed through subsequent testing, P-O3FA may well complement the risk reduction achieved by altering blood lipids and modifying atherosclerosis and endothelial function. Obviously, there is a need for a large clinical trial in which P-O3FA and placebo are randomized as add-on therapy to a background treatment with an HMG-CoA reductase inhibitor in a high CHD risk population. Until this is done, there will continue to be lack of clarity regarding the use of P-O3FA for CHD risk reduction.

P-O3FA versus dietary-supplement omega-3 fatty acid therapy. Dozens of dietary-supplement omega-3 fatty acid preparations are currently available on the market. None have presented clinical trial evidence of efficacy or received FDA-approved labeling for triglyceride lowering or CHD risk reduction. Very few have concentrated the active ingredients, EPA and DHA, to the extent of P-O3FA. In each 1-g capsule, most dietary supplements contain about 200 to 500 mg of EPA and DHA.[41] None undergo periodic FDA inspection to ensure compliance to good manufacturing practices and few provide reports from independent laboratories on the presence of environmental contaminants (e.g., heavy metals, pesticides).

Dietary-supplement omega-3 fatty acids are best used for people who do not like fish or wish to supplement or replace their diet with these supplements. When omega-3 fatty acids are used for medicinal purposes, such use should be done under the supervision of a health professional who understands the patient's condition and can provide informed advice. Given the quality assurance health professionals have come to expect from prescription-grade medications, P-O3FA may be preferred when lowering triglycerides or providing prophylaxis for CHD risk. If a health professional chooses to use a dietary supplement for therapeutic purposes, he or she should be assured of the batch-to-batch consistency and purity of the product.

Instructions to the patient

Patients receiving P-O3FA, especially those being treated for very high triglycerides, need to be reminded of the critical importance of an effective therapeutic lifestyle program, including rigorous compliance to a low-fat diet, weight loss, and physical exercise. Abstinence from alcohol is highly recommended. Patients should be counseled to discuss their current drug therapies with providers to avoid receiving drugs that may exacerbate their triglyceride problem. Patients receiving P-O3FA for triglyceride management should be given their treatment target, helped in obtaining triglyceride level results, guided in monitoring their progress, and given an explanation of their test results. Those patients who are allergic to fish should be cautioned that they may experience a similar reaction to P-O3FA. If they are receiving oral anticoagulant and possibly other antithrombotic agents, patients should be encouraged to return to their primary health providers for periodic laboratory tests. Patients should be advised not to substitute their P-O3FA for a dietary supplement without the advice and guidance of an informed health professional. Also, patients should be helped to understand that the dose for triglyceride lowering is 4 g/day and that a reduction in this dose will lead to a proportionate reduction in efficacy. As no adequate and well-controlled studies have been conducted in pregnant women, women of child-bearing potential, women who are or are trying to become pregnant, or those who are breast feeding should consult with their health professionals before taking P-O3FA. Finally, patients should be warned of the more common adverse effects they may encounter, including belching, upset stomach, and change in the sense of taste. These symptoms may be reduced by dividing doses and administering doses with food.

Formulary recommendations

P-O3FA should be made available for the treatment of very high triglycerides as an adjunct to diet alone or together with a fibrate or niacin and for the optional use in reducing CHD risk in post-MI patients.

Conclusion

P-O3FA has demonstrated an efficacy and safety in adult patients with high and very high triglycerides adjunct to diet, and the reduction in serum triglyceride levels was dependent on the baseline triglyceride levels. A large controlled clinical trial is necessary to determine if P-O3FA can be used to reduce CHD risk, either as combined with HMG-CoA reductase inhibitors or as monotherapy.

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Appendix—National Cholesterol Education Program's special treatment considerations for very high triglycerides[19]

Goals of therapy

- Triglyceride lowering to prevent acute pancreatitis (first priority)
- Prevention of coronary heart disease (CHD) (second priority)

Triglyceride lowering to prevent pancreatitis

- Initiate a very-low-fat diet when triglycerides >1000 mg/dL (>11.29 mmol/L) (<15% of total calories as fat)
- Discontinue drugs that raise triglycerides. Eliminate alcohol
- Manage hyperglycemia, if present
- Initiate weight reduction and increased physical activity
- Initiate triglyceride-lowering drugs (fibrate or nicotinic acid)
- Omega-3 fatty acids may be used as adjunctive therapy to lower triglycerides
- Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors are not first-line agent for very high triglycerides
- Bile-acid sequestrants are contraindicated as they tend to raise triglycerides

Triglyceride lowering to prevent CHD

- Efficacy of drug therapy to prevent CHD in persons with very high triglycerides has not been demonstrated by clinical trials