

# A Comparative Overview of Prescription Omega-3 Fatty Acid Products

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## ABSTRACT

An estimated 25% of adults in the United States have elevated triglyceride (TG) levels. This is of particular concern given the evidence for a causal role of TG in the pathway of cardiovascular (CV) disease. Approved prescription omega-3 fatty acid products (RxOM3FAs) contain the long-chain fatty acids docosahexaenoic acid (DHA) and/or eicosapentaenoic acid (EPA) and are effective options for the treatment of high TG levels. RxOM3FAs that contain both EPA and DHA include omega-3-acid ethyl esters (ethyl esters of EPA and DHA; brand and generic products) and omega-3-carboxylic acids (free fatty acids primarily composed of EPA and DHA), while the RxOM3FA icosapent ethyl (the ethyl ester of EPA) contains EPA only. All RxOM3FA products produce substantial TG reduction and other beneficial effects on atherogenic lipid and inflammation-related parameters, blood pressure, and heart rate variability, but products that contain DHA may raise low-density lipoprotein-cholesterol (LDL-C). This commentary provides an overview of hypertriglyceridemia while summarizing the pharmacology, efficacy, and safety of prescription RxOM3FAs.

**Keywords:** eicosapentaenoic acid, docosahexaenoic acid, hypertriglyceridemia, omega-3 fatty acid, triglycerides

## INTRODUCTION

Prescription omega-3 fatty acid products (RxOM3FAs) are approved for use as an adjunct to diet to reduce triglyceride (TG) levels in adults with severe hypertriglyceridemia (TG levels of 500 mg/dL or more).<sup>1-4</sup> These products contain the long-chain omega-3 fatty acids (OM3FAs) docosahexaenoic acid (DHA) and/or eicosapentaenoic acid (EPA).<sup>5</sup> RxOM3FAs containing both DHA and EPA include Lovaza (omega-3-acid ethyl esters, GlaxoSmithKline) and generic versions of Lovaza (various manufacturers); Omtryg (omega-3-acid ethyl esters A, Trygg Pharma, Inc.), and Epanova (omega-3-carboxylic acids, AstraZeneca Pharmaceuticals LP). Vascepa (icosapent ethyl, Amarin Pharma Inc.) contains only the purified ethyl ester of EPA.

The efficacy of these RxOM3FAs in terms of lowering TG for patients with very high TG levels (500 mg/dL or more) as well as high TG levels (200–499 mg/dL) is well established; however, additional factors, such as differential effects on other atherogenic parameters, potential impact on cardiovascular (CV) outcomes, and cost-effectiveness, are relevant considerations in the managed care setting. This commentary will provide an overview of hypertriglyceridemia; briefly summarize the pharmacology, efficacy, and safety of RxOM3FAs; and discuss important issues in the treatment of hypertriglyceridemia levels with RxOM3FAs, including cost, effects on parameters beyond TGs, and the potential impact on CV outcomes.

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## OVERVIEW OF HYPERTRIGLYCERIDEMIA

### Prevalence of Elevated TG Levels and Association With CV Risk

Elevations in TG levels have long been associated with CV disease.<sup>6</sup> The overall prevalence of hypertriglyceridemia in U.S. adults was estimated to be 31% for TG levels of at least 150 mg/dL, 16.2% for TG levels of at least 200 mg/dL, and 1.1% for TG levels of at least 500 mg/dL in the period from 1999 to 2008.<sup>7</sup> More recent statistics report an estimated prevalence of 25.1% among adults for TG levels of at least 150 mg/dL in the period from 2009 to 2012.<sup>8</sup> Increased TG levels can be attributed to diet, a sedentary lifestyle, increased body weight, excessive alcohol intake, and cigarette smoking, as well as underlying medical conditions such as diabetes, which also contributes to CV risk.<sup>8-10</sup> Recent genetic evidence has underscored the role of TG levels in CV disease.<sup>11-13</sup> An analysis involving more than 75,000 individuals in two general-population studies (median follow-up, 34 years) demonstrated that loss-of-function mutations in the gene encoding apolipoprotein C3 (*APOC3*) were associated with low levels of nonfasting TGs and reduced ischemic CV disease risk.<sup>12</sup> In the general population, hazard ratios (HRs) for individuals with TG levels of less than 90 mg/dL compared with individuals with TG levels of at least 350 mg/dL were 0.43 (95% confidence interval [CI], 0.35–0.54) and 0.40 (95% CI, 0.31–0.52) for ischemic vascular disease and ischemic heart disease, respectively.<sup>12</sup> Findings from another recent analysis corroborate that loss of *APOC3* function, which is associated with low TG levels, may be cardioprotective.<sup>13</sup> Protein-coding regions in 3,734 persons were sequenced and four *APOC3* mutations were identified that were associated with a distinct atherogenic profile, including substantially lower TG levels and circulating *APOC3* levels. Patients with these *APOC3* mutations had a 40% lower risk of coronary heart disease (CHD) than those who did not carry these mutations. These studies suggest that TGs are in the causal pathway of atherosclerosis and, while they do not demonstrate that TG reduction via TG-lowering agents reduces CV events, they do suggest TGs as an appropriate potential therapeutic target. The effects of OM3FAs in interventional outcomes studies are discussed later.

### Economic Burden

In addition to the potential clinical burden, very high TG levels have been associated with increased health care costs. An observational study from a large health maintenance organization database (N = 108,324) showed that annual health care costs for patients with severe hypertriglyceridemia (TG levels of 500 mg/dL or more) were approximately 33% greater than costs for patients with lower TG levels.<sup>14</sup> Similarly, retrospective claims data (N = 26,896; TG levels of greater than 500 to less

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than 750 mg/dL, at least 750 to less than 1,500 mg/dL, and 1,500 mg/dL or more) showed that health care utilization and costs were higher among patients with higher TG levels and increased markedly over follow-up in all groups.<sup>15</sup>

The impact of lowering TG on health care costs is less clear. An observational study of patients with severe hypertriglyceridemia (N = 808) found no significant changes in all-cause mortality, hospitalizations, and cost with TG lowering of at least 60%.<sup>16</sup> In contrast, reports from retrospective database analyses of patients with severe hypertriglyceridemia (N = 41,210) have found that, with a mean follow-up of 825 days, TG levels of less than 500 mg/dL were associated with a significantly lower risk of adverse clinical events and lower cost than TG levels of at least 500 mg/dL, and TG levels of less than 200 mg/dL were associated with significantly lower rates of pancreatitis and CV events.<sup>17,18</sup>

### PHARMACOLOGY OF RxOM3FAs

#### OM3FA Content

Lovaza and Omtryg contain omega-3-acid ethyl esters (principally EPA and DHA: 0.465 g EPA and 0.375 g DHA in each 1-g capsule for Lovaza and 1.2-g capsule for Omtryg), whereas Epanova is a mixture of polyunsaturated free fatty acids, also referred to as carboxylic acids, the most abundant of which are EPA and DHA (0.550 g EPA and 0.200 g DHA in each 1-g capsule).<sup>1-3,19,20</sup> Vascepa is a high-purity formulation containing icosapent ethyl, the ethyl ester of EPA.<sup>4</sup> The chemical structure of the four products is shown in Figure 1. See Table 1 for the OM3FA content of the prescription products.

#### Absorption and Plasma Levels

Following oral administration of Lovaza and Omtryg, there are significant dose-dependent increases in serum EPA, whereas increases in serum DHA are less marked and not dose dependent.<sup>1,2</sup> Head-to-head comparisons of OM3FA plasma concentrations have not included all approved RxOM3FA products.

In a 14-day, open-label, pharmacokinetic analysis of healthy subjects on a low-fat diet receiving either Lovaza 4 g per day or Epanova 4 g per day, substantially higher trough levels of unadjusted total EPA plus DHA and higher bioavailability were noted in the Epanova group.<sup>20</sup> Perhaps of greater clinical interest, plasma levels of EPA and DHA have also been reported in clinical studies of RxOM3FA products in diet-stable patients with dyslipidemia who were instructed to follow the National Cholesterol Education Program Therapeutic Lifestyle Changes diet (Table 1). The end-of-treatment plasma concentration of EPA reported with 4 g daily dosing in studies of Vascepa was comparable with the combined concentration of EPA plus DHA reported in studies of Epanova.<sup>19,21,22</sup> End-of-treatment plasma concentrations of EPA were reported to be higher in the Vascepa trials than in the Epanova trials, as expected for this EPA-only product.

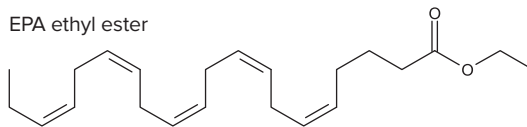
#### Drug Interactions

The following products have been investigated in clinical drug-drug interaction studies with the RxOM3FAs: warfarin (Vascepa, Epanova); omeprazole (Vascepa); rosiglitazone (Vascepa); atorvastatin (Lovaza, Vascepa, Omtryg); rosuvastatin

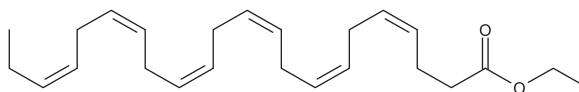
Figure 1 Chemical Structures

#### (a) Lovaza

EPA ethyl ester

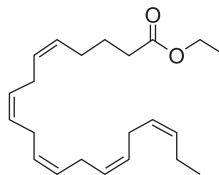


DHA ethyl ester



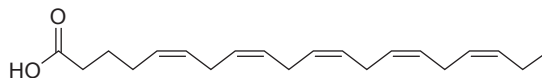
#### (b) Vascepa

Icosapent ethyl

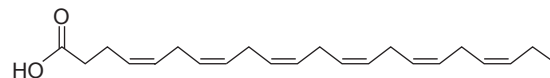


#### (c) Epanova

EPA free fatty acid

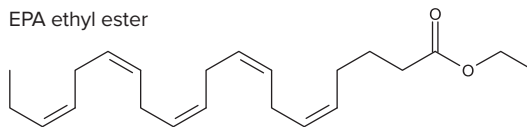


DHA free fatty acid

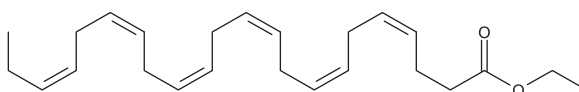


#### (d) Omtryg

EPA ethyl ester



DHA ethyl ester



DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid

## A Comparative Overview of Prescription Omega-3 Fatty Acid Products

**Table 1 Prescription Omega-3 Fatty Acid Product Information and Associated Trials**

Product	Lovaza <sup>a</sup> (Omega-3-Acid Ethyl Esters) <sup>1</sup>	Vascepa (Icosapent Ethyl) <sup>4</sup>	Epanova (Omega-3-Carboxylic Acids) <sup>3,19</sup>	Omtryg (Omega-3-Acid Ethyl Esters A) <sup>2</sup>
FDA approval	2004	2012	2014	2014
Indication	Indicated as an adjunct to diet to reduce TG levels in adult patients with severe hypertriglyceridemia (≥500 mg/dL)			
Description	<ul style="list-style-type: none"> <li>1-g transparent, soft-gelatin capsules filled with light-yellow oil</li> <li>Inactive ingredients include α-tocopherol, gelatin, glycerol, and purified water</li> </ul>	<ul style="list-style-type: none"> <li>1-g amber-colored, soft-gelatin capsules</li> <li>Inactive ingredients include tocopherol, gelatin, glycerin, maltitol, sorbitol, and purified water</li> </ul>	<ul style="list-style-type: none"> <li>1-g red/brown coated, soft-gelatin capsules</li> <li>Inactive ingredients include α-tocopherol, porcine Type A gelatin, glycerol, sorbitol, and purified water</li> </ul>	<ul style="list-style-type: none"> <li>1.2-g, transparent, soft-gelatin capsules filled with light yellow oil</li> <li>Inactive ingredients include α-tocopherol, gelatin, glycerol, and purified water</li> </ul>
Dosage	Total dose: 4 g/day, taken as: <ul style="list-style-type: none"> <li>Single 4-g dose (4 capsules)</li> <li>Two 2-g doses (2 capsules BID)</li> </ul>	Total dose: 4 g/day, taken as: <ul style="list-style-type: none"> <li>Two 2-g doses (2 capsules BID)</li> </ul>	Total dose: 2 g/day or 4 g/day, taken as: <ul style="list-style-type: none"> <li>Single 2-g dose (2 capsules)</li> <li>Single 4-g dose (4 capsules)</li> </ul>	Total dose: 4 g/day, taken as: <ul style="list-style-type: none"> <li>Single 4-g dose (4 capsules)</li> <li>Two 2-g doses (2 capsules BID)</li> </ul>
Omega-3 content	Contains at least 0.9 g of OM3FA ethyl esters from fish oils: <ul style="list-style-type: none"> <li>EPA ~0.465 g</li> <li>DHA ~0.375 g</li> </ul>	Contains 1 g of IPE: <ul style="list-style-type: none"> <li>EPA 1 g</li> </ul>	Contains 1 g of fish-oil-derived free FAs with at least 0.85 g of polyunsaturated FAs, including multiple OM3FAs from fish oils: <ul style="list-style-type: none"> <li>EPA 0.550 g</li> <li>DHA 0.2 g</li> </ul>	Contains at least 0.9 g of OM3FA ethyl esters from fish oils: <ul style="list-style-type: none"> <li>EPA ~0.465 g</li> <li>DHA ~0.375 g</li> </ul>
Trial(s) in patients with very high TG levels (≥500 mg/dL)	<p><i>Harris, et al.</i><sup>32</sup> Study design: 16-week, double-blind, randomized, placebo-controlled, multi-center study</p> <p>Inclusion criteria: patients 18–75 years of age, with TG levels ≥500 and &lt;2,000 mg/dL</p> <p>Study arms:</p> <ul style="list-style-type: none"> <li>OM3EE 4 g/day, n = 22</li> <li>Placebo, n = 20</li> </ul> <p>Baseline characteristics (OM3EE 4 g/day only):</p> <ul style="list-style-type: none"> <li>Age (mean), 46 years</li> <li>Gender, 77% male</li> <li>BMI (mean), 28 kg/m<sup>2</sup></li> </ul> <p><i>Pownall, et al.</i><sup>33</sup> Study design: 6-week, double-blind, randomized, placebo-controlled study</p> <p>Inclusion criteria: patients 18–70 years of age, with TG levels ≥500 and &lt;2,000 mg/dL</p> <p>Study arms:</p> <ul style="list-style-type: none"> <li>OM3EE 4 g/day, n = 20</li> <li>Placebo, n = 21</li> </ul> <p>Baseline characteristics (OM3EE 4 g/day only)</p> <ul style="list-style-type: none"> <li>Age (mean), 51 years</li> </ul>	<p><i>MARINE</i><sup>34</sup> Study design: 12-week, double-blind, randomized, placebo-controlled, multi-center study</p> <p>Inclusion criteria: patients &gt;18 years of age with TG levels ≥500 and ≤2,000 mg/dL and receiving either no lipid-altering therapy or a stable dose of statins (with or without ezetimibe)</p> <p>Study arms:</p> <ul style="list-style-type: none"> <li>IPE 4 g/day, n = 76</li> <li>IPE 2 g/day, n = 73</li> <li>Placebo, n = 75</li> </ul> <p>Baseline characteristics (IPE 4 g/day only):</p> <ul style="list-style-type: none"> <li>Age (mean), 52 years</li> <li>Gender, 77% male</li> <li>Race, 87% white</li> <li>BMI (mean), 30 kg/m<sup>2</sup></li> <li>Diabetes, 29%</li> </ul>	<p><i>EVOLVE</i><sup>19</sup> Study design: 12-week, double-blind, randomized, placebo-controlled study</p> <p>Inclusion criteria: patients ≥18 years of age with TG levels ≥500 and &lt;2,000 mg/dL and either untreated for dyslipidemia or receiving a stable dose of statin therapy</p> <p>Study arms:</p> <ul style="list-style-type: none"> <li>OM3FFA 4 g/day, n = 99</li> <li>OM3FFA 3 g/day, n = 97</li> <li>OM3FFA 2 g/day, n = 99</li> <li>Placebo, n = 98</li> </ul> <p>Baseline characteristics (OM3FFA 4 g/day only):</p> <ul style="list-style-type: none"> <li>Age (mean), 53 years</li> <li>Gender, 72% male</li> <li>Race, 89% white</li> <li>BMI (mean), 31 kg/m<sup>2</sup></li> <li>Diabetes, 36%</li> </ul>	<p><i>NCT01229566</i><sup>1</sup> Study design: 12-week, double-blind, randomized, placebo-controlled study</p> <p>Inclusion criteria: patients 18–79 years of age with TG levels ≥500 and ≤1,500 mg/dL</p> <p>Study arms:</p> <ul style="list-style-type: none"> <li>OM3EE (Omtryg), n = 104</li> <li>OM3EE (Lovaza), n = 103</li> <li>Placebo, n = 43</li> </ul> <p>Baseline characteristics:</p> <ul style="list-style-type: none"> <li>Age (mean), 51 years</li> <li>Gender, 72% male</li> <li>Race, 92% white</li> <li>BMI (mean), 33 kg/m<sup>2</sup></li> </ul>

## A Comparative Overview of Prescription Omega-3 Fatty Acid Products

**Table 1 Prescription Omega-3 Fatty Acid Product Information and Associated Trials (continued)**

Product	Lovaza <sup>a</sup> (Omega-3-Acid Ethyl Esters) <sup>1</sup>	Vascepa (Icosapent Ethyl) <sup>4</sup>	Epanova (Omega-3-Carboxylic Acids) <sup>3,19</sup>	Omtryg (Omega-3-Acid Ethyl Esters A) <sup>2</sup>
Trial(s) in patients with high TG levels (200 to <500 mg/dL)	<p><i>COMBOS</i><sup>35</sup> Study design: 8-week, double-blind, randomized, placebo-controlled, multi-center study</p> <p>Inclusion criteria: patients 18–79 years of age with TG levels ≥200 and &lt;500 mg/dL and receiving stable dose of statins</p> <p>Study arms:</p> <ul style="list-style-type: none"> <li>• OM3EE 4 g/day + statin, n = 122</li> <li>• Placebo + statin, n = 132</li> </ul> <p>Baseline characteristics (OM3EE 4 g/day only):</p> <ul style="list-style-type: none"> <li>• Age (mean), 60 years</li> <li>• Gender, 54% male</li> <li>• Race, 95% white</li> <li>• BMI (mean), 31 kg/m<sup>2</sup></li> </ul>	<p><i>ANCHOR</i><sup>36</sup> Study design: 12-week, double-blind, randomized, placebo-controlled, multi-center study</p> <p>Inclusion criteria: patients &gt;18 years of age with high risk of CVD, TG levels ≥200 and &lt;500 mg/dL,<sup>b</sup> and receiving stable dose of statins (with or without ezetimibe)</p> <p>Study arms:</p> <ul style="list-style-type: none"> <li>• IPE 4 g/day + statin, n = 226</li> <li>• IPE 2 g/day + statin, n = 234</li> <li>• Placebo + statin, n = 227</li> </ul> <p>Baseline characteristics (IPE 4 g/day only):</p> <ul style="list-style-type: none"> <li>• Age (mean), 61 years</li> <li>• Gender, 61% male</li> <li>• Race, 97% white</li> <li>• BMI (mean), 33 kg/m<sup>2</sup></li> <li>• Diabetes, 73%</li> </ul>	<p><i>ESPRIT</i><sup>22</sup> Study design: 6-week, double-blind, randomized, placebo-controlled, multi-center study</p> <p>Inclusion criteria: patients ≥18 years of age with high risk of CVD, TG levels ≥200 and &lt;500 mg/dL, and either at/near NCEP goal for LDL-C or on a maximally tolerated stable statin dose</p> <p>Study arms:</p> <ul style="list-style-type: none"> <li>• OM3FFA 4 g/day + statin, n = 207</li> <li>• OM3FFA 2 g/day + statin, n = 209</li> <li>• Placebo + statin, n = 211</li> </ul> <p>Baseline characteristics (OM3FFA 4 g/day only):</p> <ul style="list-style-type: none"> <li>• Age (mean), 60 years</li> <li>• Gender, 63% male</li> <li>• Race, 94% white</li> <li>• BMI (mean), 33 kg/m<sup>2</sup></li> <li>• Diabetes, 69%</li> </ul>	None reported
EPA and DHA levels with 4 g/day dosing in clinical studies of patients with very high TG levels <sup>c</sup>	NR	<p><i>MARINE</i><sup>21</sup> Baseline EPA: 61.2 ± 67.4 mcg/mL Follow-up EPA: 326.7 ± 205.7 mcg/mL</p>	<p><i>EVOLVE</i><sup>19</sup> Baseline EPA: 25.7 ± NR mcg/mL Baseline DHA: 91.8 ± NR mcg/mL Follow-up EPA: 170 ± NR mcg/mL Follow-up DHA: 169 ± NR mcg/mL</p>	NR
EPA and DHA levels with 4 g/day dosing in clinical studies of patients with high TG levels <sup>c</sup>	NR	<p><i>ANCHOR</i><sup>21</sup> Baseline EPA: 28.1 ± 18.8 mcg/mL Follow-up EPA: 182.6 ± 71.7 mcg/mL</p>	<p><i>ESPRIT</i><sup>22</sup> Baseline EPA: 24.3 ± 23.9 mcg/mL Baseline DHA: 61.7 ± 33.9 mcg/mL Follow-up EPA: 105.2 ± 51.5 mcg/mL Follow-up DHA: 99.5 ± 27.7 mcg/mL</p>	NR

<sup>a</sup> Also approved as generic.

<sup>b</sup> Entry criteria were expanded so the mean of the 2 TG-qualifying values was ≥185 mg/dL with ≥1 of the 2 values ≥200 mg/dL.

<sup>c</sup> All studies were in diet-stable patients who were instructed to follow the NCEP Therapeutic Lifestyle Changes diet; values are mean ± standard deviation; follow-up values represent end-of-treatment values in the respective studies.

BID = twice daily; BMI = body mass index; COMBOS = Combination of Prescription Omega-3 With Simvastatin trial; CVD = cardiovascular disease; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; ESPRIT = Epanova Combined With a Statin in Patients With Hypertriglyceridemia to Reduce Non-HDL Cholesterol study; EVOLVE = The Epanova for Lowering Very High Triglycerides trial; FA = fatty acid; FDA = Food and Drug Administration; IPE = icosapent ethyl; LDL-C = low-density lipoprotein-cholesterol; MARINE = Multi-Center, Placebo-Controlled, Randomized, Double-Blind, 12-Week Study With an Open-Label Extension; NCEP = National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III); NR = not reported; OM3EE = omega-3-acid ethyl ester; OM3FA = omega-3 fatty acid; OM3FFA = omega-3 free fatty acid; TG = triglyceride.

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tatin (Lovaza, Omtryg); and simvastatin (Lovaza, Omtryg, Epanova).<sup>1-4,23-28</sup> No drug–drug interactions were observed. The package inserts for all RxOM3FAs note that patients who are receiving drugs that affect coagulation should be monitored periodically because prolongation of bleeding time has been noted in some published studies of OM3FAs.<sup>1-4</sup> However, the package inserts note that the prolongation of bleeding time in those studies did not exceed normal limits and did not produce clinically significant bleeding episodes. Furthermore, evidence-based reviews have concluded that OM3FAs do not increase the risk of clinically significant bleeding, including in patients receiving medications that affect coagulation.<sup>29-31</sup>

### CLINICAL EFFICACY OF RxOM3FAs Patients With Very High TG Levels

An overview of pivotal clinical trials for each RxOM3FA in patients with very high TG levels (at least 500 mg/dL) is provided in Table 1.<sup>2,19,32-34</sup> Although there are no head-to-head clinical trials comparing all of the approved RxOM3FAs, it is informative to compare the results of these pivotal studies. At the end of treatment, statistically significant median TG reductions of approximately 12% to 52% compared with placebo were reported across these studies of RxOM3FAs (Figure 2).<sup>1-3,34</sup> The observed range of TG lowering is likely due to substantial differences in baseline TG levels between studies (discussed below).

While all RxOM3FAs markedly reduced TG levels, effects on levels of low-density lipoprotein-cholesterol (LDL-C) differed among products: DHA-containing RxOM3FAs significantly increased median LDL-C (up to approximately 49%) compared with placebo, whereas no significant change was observed with Vascepa.<sup>1-3,34</sup> Increases in median high-density lipoprotein-cholesterol (HDL-C) of less than 10% were reported with the DHA-containing products, while no significant change was observed with Vascepa compared with placebo.<sup>1-3,34</sup>

All the RxOM3FAs reduced levels of non-HDL-C, total cholesterol (TC), and very-low-density lipoprotein-cholesterol (VLDL-C) compared with placebo.<sup>1-3,34</sup> Changes in atherogenic parameters compared with placebo for RxOM3FAs in studies of patients with very high TG levels are summarized in Figure 2.<sup>1-3,19,32-34</sup> Vascepa significantly reduced apolipoprotein B (ApoB) by 9% compared with placebo, but no significant change was observed in ApoB levels with Epanova compared with placebo.<sup>2,3,34</sup>

**Figure 2 Median Percent Changes From Baseline to Study End in Lipid Parameters Compared With Placebo in Studies of Patients With Very High Triglyceride Levels Receiving Prescription Omega-3 Fatty Acid Products**

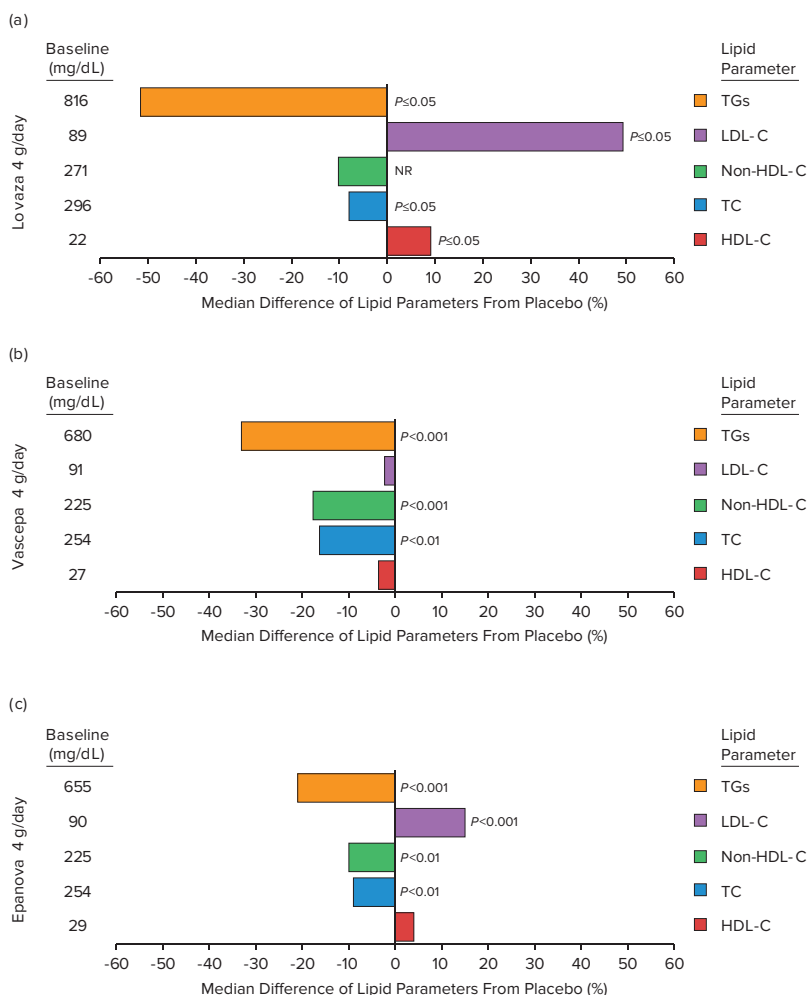
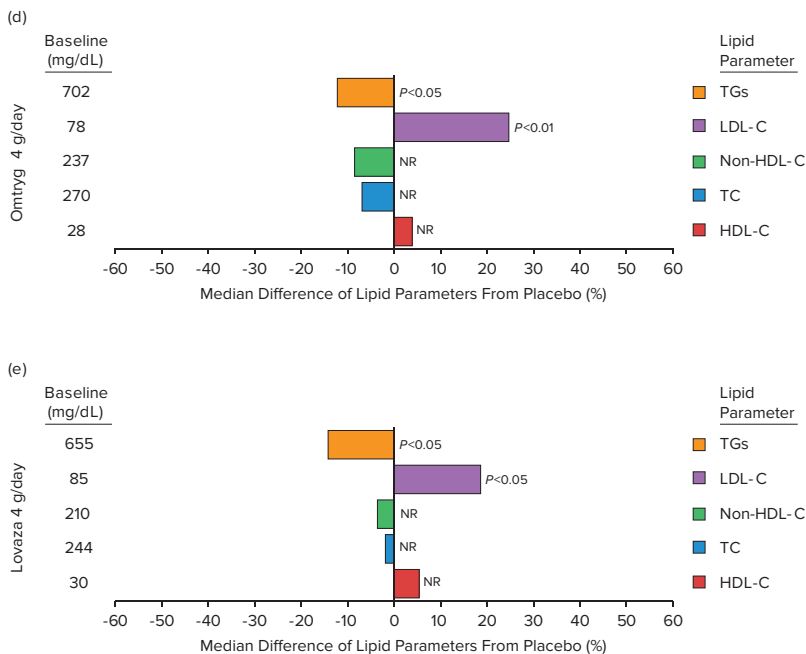


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### Patients With High TG Levels

Clinical studies in patients with high TG levels (200 to less than 500 mg/dL) have been conducted with three of the RxOM3FAs (Lovaza, Vascepa, and Epanova) with concomitant statin therapy (Table 1).<sup>22,35,36</sup> Median changes in atherogenic parameters compared with placebo for Lovaza and Vascepa in studies of patients with high TG levels are summarized in Figure 3.<sup>35-37</sup> Substantial and comparable reductions in median TG levels compared with placebo of approximately 22% to 23% were reported for Lovaza and Vascepa (Figure 3).<sup>35,36</sup> Similar to the findings in patients with very high TG levels, differential effects on LDL-C were observed. No significant increase in median LDL-C compared with placebo was reported with Lovaza, whereas Vascepa demonstrated a small but significant reduction in LDL-C compared with placebo.<sup>22,35,36</sup> For HDL-C, Lovaza slightly increased median levels, while Vascepa resulted in a small but significant reduction.<sup>22,35,36</sup> In the Epanova study,

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(a) Lovaza 4 g/day: values represent [Lovaza median % change minus placebo median % change]. Statistical significance was not reported in pooled analysis in prescribing information but was reported in corresponding study publications.<sup>1,19,32,33</sup> (b) Vascepa 4 g/day: values represent the median of [Vascepa % change minus placebo % change] (Hodges-Lehmann estimate).<sup>34</sup> (c) Epanova 4 g/day treatment group: values represent the median of [Epanova % change minus placebo % change] (Hodges-Lehmann estimate). *P* values were not reported in prescribing information but were reported in corresponding study publication.<sup>3,19</sup> (d) Omtryg 4 g/day: values represent the Hodges-Lehmann median of all pairwise differences from placebo.<sup>2</sup> (e) Lovaza 4 g/day (data versus placebo from the head-to-head study with Omtryg; data for Omtryg versus placebo in this study are shown in panel d); values represent the Hodges-Lehmann median of all pairwise differences from placebo.<sup>2</sup>

HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; NR = *P* value/statistical significance not reported; TC = total cholesterol; TG = triglyceride.

AE for the EPA-only product Vascepa was arthralgia; there was no noted increase in the incidence of GI AEs compared with placebo (Table 2).<sup>4</sup> When considering AE data across RxOM3FA studies, it should be noted that different placebos were used: corn oil was used in the Lovaza studies, olive oil was used in the Epanova studies, and light liquid paraffin was used in the Vascepa studies.

### Contraindications, Warnings, Precautions, and Monitoring

The product labels for the DHA-containing RxOM3FAs (Lovaza, Omtryg, and Epanova) state that LDL-C levels should be monitored periodically during therapy, as these products may increase LDL-C.<sup>1-3</sup> For all the RxOM3FAs, the labels specify that alanine aminotransferase and aspartate aminotransferase levels should be monitored in patients with hepatic impairment and that the products should be used with caution in patients with known hypersensitivity to fish and/or shellfish.<sup>1-4</sup> For Lovaza and Omtryg, the labels note a possible association with more frequent recurrences of symptomatic atrial fibrillation or flutter in patients with paroxysmal or persistent atrial fibrillation, particularly within the first months of initiating therapy.<sup>1,2</sup>

### ADDITIONAL CONSIDERATIONS

#### Cost-Effectiveness

Data on the cost-effectiveness of RxOM3FAs for TG lowering are limited, but it has been estimated that the monthly cost of RxOM3FAs is \$221 to \$236 (average wholesale price [AWP]).<sup>39</sup> Generic fibrates and niacin offer lower-cost options for lowering TG levels (AWP less than \$60).<sup>39</sup>

absolute least-squares geometric mean (LSGM) changes in lipid parameters were reported rather than median changes compared with placebo: the 4-g dose reduced LSGM TG levels by 21% (statistically significant compared with placebo) and no significant change was observed in LSGM LDL-C and HDL-C levels.<sup>22</sup> Lovaza, Vascepa, and Epanova all produced significant reductions in non-HDL-C, ApoB, TC, and VLDL-C compared with placebo.<sup>22,35,36</sup>

### SAFETY AND TOLERABILITY OF RxOM3FAs

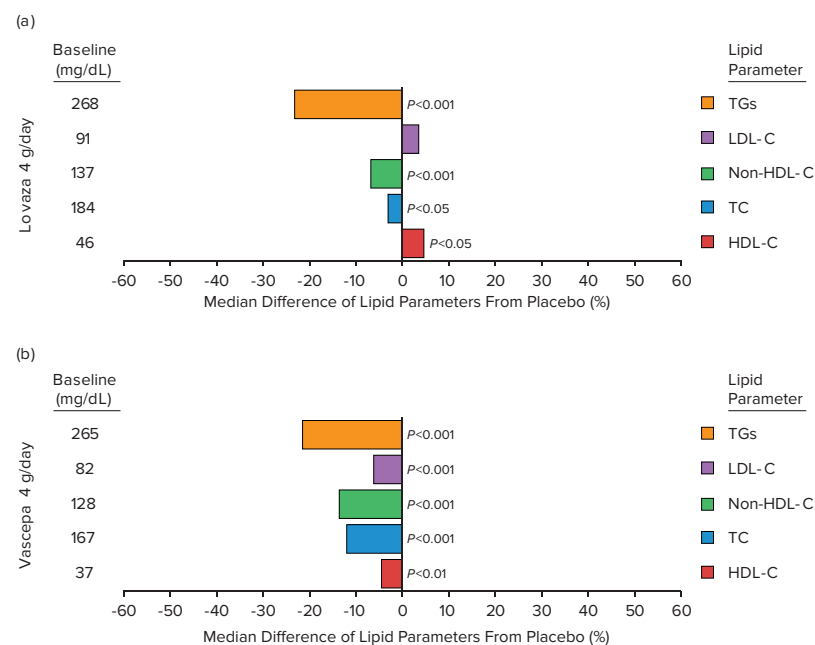
As a class, RxOM3FAs have a well-established safety profile.<sup>1-4</sup> Although RxOM3FAs containing a combination of DHA and EPA are generally well tolerated, gastrointestinal (GI) symptoms may have implications for patient adherence (Table 2).<sup>1,2</sup> Epanova was associated with GI adverse events (AEs)<sup>3</sup> despite the polyacrylate coating used to delay release in the gut and mitigate such side effects (Table 2).<sup>38</sup> The most commonly reported

However, concerns with niacins (flushing, hepatotoxicity, increased glucose levels, myopathy) and fibrates (increased LDL-C levels and myopathy) have limited their use; notably, in a recent label update, use of niacins or fibrates in combination with statin therapy in patients with mixed dyslipidemia has been removed from product prescribing information.<sup>40,41</sup>

The cost of OM3FA therapy may be offset by the potential benefits in terms of reduced CV morbidity and mortality.<sup>42-44</sup> For example, an analysis based on outcomes data for OM3FAs (from Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico [GISSI]-Prevenzione), which investigated omega-3-acid ethyl esters at a dose of approximately 0.9 g per day, found that cost-effectiveness (direct costs) of long-term OM3FA treatment was comparable to that of statins (i.e., annual costs to save one patient were comparable between OM3FAs and simvastatin).<sup>45</sup> Similarly, at least two additional economic modeling studies based on GISSI-Prevenzione have concluded

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**Figure 3 Median Percent Changes From Baseline to Study End in Lipid Parameters Compared With Placebo in Studies of Patients With High Triglyceride Levels Receiving Prescription Omega-3 Fatty Acid Products**



(a) Lovaza 4 g/day: values represent [Lovaza median % change minus placebo median % change].<sup>35,37</sup> (b) Vascepa 4 g/day: values represent the median of [Vascepa % change minus placebo % change] (Hodges-Lehmann estimate).<sup>36</sup> Median changes from baseline to study end compared with placebo have not been reported for Epanova. Clinical study results have not been reported for Omtryg in patients with high TGs.

HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; TC = total cholesterol; TG = triglyceride.

sion.<sup>50</sup> Emerging data suggest that DHA down-regulates the LDL-receptor gene in humans.<sup>51</sup> Other potential mechanisms may include increased conversion of VLDL to LDL and increased LDL particle size observed with DHA.<sup>49</sup>

### Current LDL-C Considerations

In 2014, the American College of Cardiology (ACC) and American Heart Association (AHA) issued joint updated guidelines that removed LDL-C targets in primary and secondary prevention of atherosclerotic CV disease, and the National Committee for Quality Assurance (NCQA) eliminated cholesterol screening and LDL-C targets as a measure for the 2015 Healthcare Effectiveness Data and Information Set (HEDIS) and the Centers for Medicare and Medicaid Services Five-Star Quality Rating System.<sup>52,53</sup> While the new ACC/AHA guidelines have caused considerable controversy, the National Lipid Association (NLA) retained a target LDL-C level of less than 100 mg/dL in its 2014 dyslipidemia recommendations and has argued that important data supporting the relationship between LDL-C and CV risk were not considered by the ACC/AHA task force.<sup>52-55</sup> Additional organizations have recently advocated having an LDL-C target of less than 100 mg/dL in lipid management.<sup>56,57</sup>

In light of recently reported data from the Improved Reduction of Outcomes:

Vytorin Efficacy International Trial (IMPROVE-IT), which demonstrated the impact of incremental LDL-C changes on coronary artery disease events,<sup>58</sup> the importance of LDL-C in lipid management in high-risk patients has been underscored. This highlights the consideration that the potential LDL-C increases associated with DHA-containing products may complicate optimal management.

### Parameters Beyond LDL-C

While LDL-C has long been a focus of CV risk assessment, several additional atherogenic parameters may help inform the assessments of CV risk and treatment efficacy, including ApoB, non-HDL-C, and LDL particle (LDL-P) levels.<sup>59-62</sup> In a pooled analysis of two statin clinical trials (N = 18,018), it was observed that even patients who achieved LDL-C levels of 100 mg/dL or less had a residual risk of major CV events, and that this risk could be discerned through assessment of non-HDL-C or ApoB levels.<sup>61</sup> Thus, both of these parameters were more closely associated with CV outcomes than LDL-C. A meta-analysis of eight statin studies (N = 62,154) found that, compared with LDL-C and ApoB, non-HDL-C had a stronger association with the risk of major CV events.<sup>60</sup> The 2014 NLA recommendations recognize that both non-HDL-C and ApoB are better predictors of CV event risk compared with LDL-C.<sup>55</sup>

that treatment with OM3FAs for secondary prevention of myocardial infarction (MI) is cost-effective.<sup>46,47</sup>

### LDL-C and Other Atherogenic Parameters

#### Differential Effects on LDL-C

EPA alone appears to minimally decrease or have a neutral effect on LDL-C, while DHA/EPA combination products have been shown to increase LDL-C, which may be an important consideration for patients with atherosclerotic disease and/or risk factors for CV disease. In addition to the clinical trial data described earlier, a pooled analysis of 16 DHA studies showed a significant estimated increase in LDL-C of 7.23 mg/dL (95% CI, 3.98-10.5) compared with placebo, whereas pooled data from nine EPA studies did not show a significant change in LDL-C compared with placebo.<sup>48</sup> In a systematic review of EPA and DHA, analysis of six studies that directly compared DHA with EPA showed that DHA increased LDL-C by 2.6% on average, while EPA minimally affected LDL-C (a 0.7% decrease).<sup>49</sup>

Differences in how DHA and EPA affect the clearance of LDL-C may, in part, contribute to their varying impact on LDL-C levels: a preclinical animal study designed to explore potential underlying mechanisms found that DHA, but not EPA, increased plasma cholesteryl ester transfer protein activity and significantly decreased hepatic LDL receptor expres-

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**Table 2 Adverse Events With Prescription Omega-3 Fatty Acid Products<sup>1-4</sup>**

	4 g/day	Placebo	Additional AEs From Clinical Studies
Lovaza <sup>a</sup> /Omtryg <sup>a,b</sup>	n = 655	n = 370	Constipation, gastrointestinal disorder, vomiting, increased alanine aminotransferase, increased aspartate aminotransferase, pruritus, and rash
• Eructation	4%	1%	
• Dyspepsia	3%	2%	
• Taste perversion	4%	<1%	
Vascepa <sup>c</sup>	n = 622	n = 309	Oropharyngeal pain
• Arthralgia	2%	1%	
Epanova <sup>d</sup>	n = 315	n = 314	Abdominal distension, constipation, vomiting, fatigue, nasopharyngitis, arthralgia, and dysgeusia
• Diarrhea	15%	2%	
• Nausea	6%	1%	
• Abdominal pain or discomfort	5%	2%	
• Eructation	3%	<1%	

<sup>a</sup> Pooled safety data across 23 clinical studies involving 1,025 patients. Reported adverse reactions in patients receiving Lovaza/Omtryg occurring at an incidence  $\geq 3\%$  and greater than placebo are listed per package inserts.

<sup>b</sup> Safety data identical to Lovaza.

<sup>c</sup> Pooled safety data across 2 clinical studies involving 931 patients. Reported adverse reactions in patients receiving Vascepa occurring at an incidence  $>2\%$  and greater than placebo are listed per the package insert.

<sup>d</sup> Pooled safety data across 2 clinical studies involving 944 patients. Reported adverse reactions in patients receiving Epanova 4 g and at an incidence  $\geq 3\%$  and greater than placebo are listed per the package insert. Additional reactions occurred more often in Epanova-treated patients from a pool of two longer-term, 52-week studies involving 748 patients with chronic gastrointestinal disease.

AEs = adverse events.

be considered clinically important, and recent studies suggest that HDL-C changes may not be as important as previously thought.<sup>66-69</sup>

### Influence of Baseline TG Levels on TG Lowering

Baseline TG levels have been shown to affect the degree of TG reduction achieved by RxOM3FAs. A pooled analysis of clinical studies of Lovaza showed greater TG reductions in the population of patients with baseline TG levels of 500–2,000 mg/dL compared with patients with baseline TG levels of 177–885 mg/dL.<sup>49</sup> Similarly, an analysis by baseline TG level in the MARINE study demonstrated that baseline TG levels of more than 750 mg/dL and 750 mg/dL or less were associated with reductions in TG levels of approximately 45% and 25%, respectively.<sup>34</sup> The influence of baseline TG levels helps explain the greater TG lowering observed in the pivotal trials of Lovaza compared with the TG lowering in trials of other RxOM3FAs in patients with very high TG levels: Patients treated with Lovaza had a median baseline TG level of 816 mg/dL, whereas patients treated with Omtryg, Vascepa, and Epanova in comparable studies had lower median baseline TG levels, ranging from 655 to 702 mg/dL.<sup>1-3,32-34</sup>

However, the recommendations also note that since discordance in lipid parameters may occur, effective patient management should achieve goals for both LDL-C and non-HDL-C.<sup>55</sup> All RxOM3FAs have been shown to reduce non-HDL-C levels in clinical studies of patients with elevated TG levels, whereas, as noted previously, effects on ApoB are less consistent.<sup>1-4,22,35,36</sup> While the clinical importance of these parameters is clear, the cost-effectiveness of treating to a non-HDL-C or ApoB target has not been firmly established. Non-HDL-C is a readily available laboratory measurement and thus is considered to be cost-effective in terms of risk/treatment monitoring; however, there are no direct cost-effectiveness data/models for treating to a specific goal.

LDL-P level is another parameter that may be a better indicator of CV risk than LDL-C levels in certain patient populations. LDL-Ps of patients with hypertriglyceridemia are cholesterol-depleted, small in size, and large in number.<sup>62</sup> Recently, analysis of a large national sample of commercially insured high-risk patients found an association between LDL-P levels and CHD and stroke risk over three years of follow-up.<sup>62</sup> Increases in LDL-P levels were significantly associated with higher risk of CHD events (even after accounting for LDL-C levels). In exploratory analyses of the Multi-Center, Placebo-Controlled, Randomized, Double-Blind, 12-Week Study With an Open-Label Extension (MARINE) and ANCHOR studies, Vascepa 4 g per day significantly decreased total LDL-P levels.<sup>63,64</sup> A recently published cost-effectiveness analysis supports treating to LDL-P goal.<sup>65</sup>

With regard to HDL-C, the increase with Lovaza and the lack of significant changes noted earlier with Vascepa may not

### Concerns With Dietary Supplements

In addition to the RxOM3FAs described here, there are more than 100 dietary fish-oil and/or OM3FA supplements containing both DHA and EPA; however, there are important distinctions between the prescription treatments and dietary supplements.<sup>70</sup> When dosing with dietary fish-oil supplements, a high number of pills/servings may be required to achieve clinically appropriate doses in certain patients. For example, for patients with hypertriglyceridemia, the AHA suggests a prescription-strength OM3FA dose of 2 g to 4 g per day; it has been estimated that the median number of daily servings of fish-oil supplements needed to achieve an OM3FA dose of 3.36 g per day is 11.2.<sup>70,71</sup> Such a high pill burden could have a negative impact on patient adherence.<sup>72</sup> The AHA also recommends that patients taking more than 3 g per day of OM3FAs should be under a physician's care.

Furthermore, the efficacy and safety of prescription-candidate OM3FAs must be established prior to Food and Drug Administration (FDA) approval; these products are held to rigorous regulatory standards and manufacturing oversight.<sup>72,73</sup> In contrast to the stringent standards for prescription products, dietary supplements are subject only to the FDA's current good manufacturing practices for food products; the quality and quantity of the ingredients in supplements varies greatly despite what may be stated on their packaging.<sup>74</sup> Neither the safety nor the efficacy of dietary supplements is required to be demonstrated prior to marketing.



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## Cardiovascular Outcomes

### Overview of Published OM3FA CV Outcomes Data

OM3FAs not only lower TG levels, they also have potentially beneficial effects on other risk factors for CV outcomes, including lipoproteins, lipids, inflammation, thrombosis, endothelial function, blood pressure, and heart rate variability.<sup>5,71,75–79</sup> However, CV outcomes studies conducted thus far have yielded inconsistent results.<sup>80–89</sup> For example, in the GISSI-Prevenzione study of patients who had experienced a recent MI (N = 11,324), DHA+EPA treatment resulted in a significant reduction in the combined primary endpoint of death, nonfatal MI, and nonfatal stroke.<sup>80</sup> Such results have not been replicated in the era of statin therapy. However, in the Japan EPA Lipid Intervention Study (JELIS; N = 18,645 statin-treated patients), hypercholesterolemic patients receiving EPA had a relative risk reduction of 19% ( $P = 0.011$ ) for major coronary events (MCE), the primary composite endpoint, compared with patients on statins alone; reductions were also noted in unstable angina (24%;  $P = 0.014$ ) and nonfatal coronary events (19%;  $P = 0.015$ ).<sup>85</sup> An additional analysis of JELIS showed that among secondary prevention patients (n = 3,664), the five-year cumulative rate of total MCE was significantly lower in the EPA group compared with the control group (23% relative risk reduction; number needed to treat, 49;  $P = 0.017$ ).<sup>90</sup> In contrast to these studies, the Risk and Prevention Study of OM3FAs (1 g per day of DHA+EPA) in patients with multiple CV risk factors/atherosclerotic disease but no previous MI who were receiving the standard of care (N = 12,505) did not find evidence of any preventive effect on CV death or disease.<sup>89</sup> Similarly, OM3FA 1 g per day of DHA+EPA did not reduce death from CV causes over six years in patients with dysglycemia and additional CV risk factors in the Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial.<sup>83</sup>

Variable findings among the CV outcomes studies to date may, in part, be attributed to differences in baseline CV risk, OM3FA dose, type of OM3FA utilized (DHA+EPA combinations or EPA only), study duration, sample size, concomitant therapies, background dietary OM3FA intake, and baseline TG levels. For example, the dose of OM3FA and corresponding plasma levels may have an impact on the efficacy of these products, not only in TG lowering but also in CV outcomes. In an evidence-based review focused on OM3FA clinical trials reporting blood/plasma levels and relationship with CV risk, it was noted that beneficial effects on CV disease risk occurred mainly in subjects who achieved the highest levels of OM3FAs.<sup>91</sup> Data from the GISSI-Heart Failure study also support a relationship between OM3FA levels and CV risk, with low baseline plasma levels of EPA independently associated with CV mortality.<sup>92</sup>

The OM3FA levels achieved in outcomes studies demonstrating beneficial effects on CV outcomes may be of particular interest. In the JELIS trial, EPA 1.8 g per day significantly reduced the frequency of MCE over five years and was associated with a mean plasma EPA level of 169 mcg/mL.<sup>85,93</sup> A follow-up analysis of EPA levels in the JELIS trial found that patients with EPA levels of at least 150 mcg/mL were at a significantly lower risk of MCE.<sup>93</sup> In phase 3 clinical trials of Vascepa and Epanova, EPA plasma levels achieved at the end of the study with a 4-g per day dose were 327 mcg/mL and 170 mcg/mL in patients with very high TG levels and 183 mcg/mL and 100 mcg/mL in patients with high TG levels, respectively.<sup>19,21,22</sup>

Meta-analyses and systematic reviews of OM3FA outcomes studies have also been inconsistent.<sup>94–98</sup> For example, a meta-analysis including 20 randomized studies (N = 68,680) of primary or secondary CV prevention found no statistically significant association between OM3FA use and major CV outcomes.<sup>94</sup> These results would have achieved significance if a traditional alpha level of 0.05 rather than a threshold of 0.0063 had been used. Also, the mean and median OM3FA doses (DHA/EPA combined) in this analysis were low (1.5 g and 1 g per day, respectively). Additional analyses that focused on patients with a history of CV disease have produced contradictory findings: one analysis including 11 clinical trials (N = 15,348) in which the OM3FA dose was greater than 1 g per day found a statistically significant protective effect for cardiac death, sudden death, and MI,<sup>97</sup> whereas another analysis of 14 studies (N = 20,485; mean dose 1.7 g per day) concluded that the evidence of a secondary preventive effect of OM3FA was insufficient.<sup>96</sup>

### Ongoing High-Dose OM3FA CV Outcomes Trials

Two OM3FA randomized, double-blind, CV outcomes studies may address some limitations of previous outcomes studies and provide clarification regarding the potential CV benefit of RxOM3FA products. These studies are evaluating prescription-strength doses of OM3FAs in combination with statins in patients with hypertriglyceridemia at high risk for CV disease.<sup>99,100</sup> The Long-term Outcomes Study to Assess Statin Residual Risk Reduction with Epanova in High CV Risk Patients with Hypertriglyceridemia (STRENGTH, NCT02104817) will evaluate the impact of Epanova plus a statin on CV outcomes.<sup>99</sup> The Reduction of Cardiovascular Events with EPA—Intervention Trial (REDUCE-IT, NCT01492361) will evaluate the impact of Vascepa 4 g per day on CV outcomes in patients with persistent hypertriglyceridemia despite statin therapy.<sup>100</sup>

## CONCLUSION

Hypertriglyceridemia is a prevalent condition that has been linked with increased risk of adverse CV outcomes. RxOM3FAs are generally well tolerated and can produce substantial TG reductions in patients with high or very high TG levels. The magnitude of TG lowering is comparable between the prescription products but influenced by baseline TG levels. Based on available cost-effectiveness data, RxOM3FAs appear to be a cost-effective treatment option. While TG lowering is a consistent effect, RxOM3FAs differ in terms of effects on other atherogenic parameters. These differential effects may influence choice of therapy. In particular, products that contain DHA have been shown to increase LDL-C levels, which can complicate the management of patients who require LDL-C control. Vascepa, which contains EPA alone, does not raise LDL-C or ApoB; this may be one of many factors to consider. The impact of RxOM3FAs on other lipid and apolipoprotein parameters is an area of ongoing research and interest. Another key area of interest is whether OM3FAs can reduce the risk of adverse CV outcomes; however, studies to date have had variable findings. Two new CV outcomes studies target patients with a high risk of CV disease on background statin therapy and are expected to help determine the place in therapy of high-dose RxOM3FAs beyond TG lowering.

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