Triglycerides are important biomarkers of risk for heart disease and stroke, particularly when a patient has low high-density lipoprotein (HDL) cholesterol, elevated levels of low-density lipoprotein (LDL) cholesterol, or type 2 diabetes. Non-HDL cholesterol and apolipoprotein B are also predictors of coronary heart disease. Furthermore, triglyceride levels that exceed 1000 mg/dL are associated with acute pancreatitis, accounting for approximately 10% of all cases.

Triglycerides and Heart Disease

Over the past 3 decades, the mean triglyceride level of people in the United States has been on the rise, particularly given the increase in the prevalence of obesity, type 2 diabetes, and insulin resistance. An estimated 31% of the adult population in the United States has an elevated triglyceride level (≥150 mg/dL), which is also referred to as hypertriglyceridemia. Of US adults, 16.2% have high triglyceride levels, and approximately 1% have very high triglyceride levels (≥500 mg/dL). The current designations for hypertriglyceridemia are:

- Borderline high (150 mg/dL-199 mg/dL)
- High (200 mg/dL-499 mg/dL)
- Very high (≥500 mg/dL).

In a scientific statement, the American Heart Association (AHA) recommended that new triglyceride designations—an optimal fasting triglyceride level of <100 mg/dL, defined as a parameter of metabolic health, and nonfasting triglyceride levels to be used as a screening measure for individuals with high fasting triglyceride levels. A nonfasting level of <200 mg/dL is equivalent to a normal (<150 mg/dL) or to an optimal (<100 mg/dL) fasting triglyceride level, with no further testing required. To identify borderline high (150 mg/dL-199 mg/dL), high (200 mg/dL-499 mg/dL), and very high (≥500 mg/dL) triglyceride levels, fasting samples should be used.

The AHA statement includes several triglyceride-lowering strategies, including losing 5% to 10% of body weight, eating a Mediterranean-style diet versus a low-fat diet, adding a marine-derived polyunsaturated fatty acid (ie, eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]), reducing carbohydrate intake, eliminating trans fats, and implementing an exercise regimen. A 50% reduction in triglyceride levels can be attained when all of these strategies are combined. For patients with very high triglyceride levels or with a history of triglyceride-induced pancreatitis, the AHA statement recommends following the previously mentioned strategies, additional dietary changes (including abstinence from alcohol consumption), and the possible use of medium-chain triglycerides and pharmacologic therapies.

Pharmacologic therapies that are used to lower triglyceride levels include niacin, fibrates, statins, ezetimibe, and omega-3 fatty acid supplements, or appropriate combinations of these agents. Dietary sources of omega-3 fatty acids include alpha-linolenic acid, EPA, and DHA. Therapeutic doses of both EPA and DHA have been shown to reduce triglyceride levels in patients with varying baseline triglyceride levels. However, EPA and DHA differ in their effect on lipids. Unlike EPA, DHA has been shown to increase LDL cholesterol in patients with varying baseline triglyceride levels.

The continuation of a lipid-lowering diet and exercise regimen is important for patients treated for hypertriglyceridemia. The medical conditions associated with lipid abnormalities, including diabetes, metabolic syndrome, hypothyroidism, and renal disease, as well as alcohol intake, should be managed appropriately.

Despite clinical evidence demonstrating the important role of lipid-lowering therapy in cardiovascular health, medication adherence persists as a major challenge in the treatment of hyperlipidemia. A retrospective data analysis of 88,635 patients who received a new lipid-lowering therapy from 2007 to 2008 showed that 65% of patients were nonadherent to their prescribed medication (percentage of days covered, 0.33).

Hypertriglyceridemia-Related Costs

Hypertriglyceridemia is associated with substantial medical costs. An analysis of the medical records of 108,324 health plan members aged ≥18 years from 2008...
was conducted to assess the impact of hypertriglyceridemia on healthcare costs. Costs were adjusted for age, sex, blood pressure, body mass index, smoking history, LDL and HDL cholesterol levels, and conditions such as cardiovascular disease, diabetes, and kidney disease.

After adjusting for these factors, mean total costs were significantly greater for patients with very high or severe hypertriglyceridemia ($8567; 99% confidence interval [CI], $7034-$10,100) compared with those with triglyceride levels of <150 mg/dL ($6186; 99% CI, $6058-$6314), those with borderline triglyceride levels of 150 mg/dL to 199 mg/dL ($6449; 99% CI, $6196-$6702), and those with high triglyceride levels of 200 mg/dL to 499 mg/dL ($6376; 99% CI, $6118-$6634).8

Overall, the costs associated with severe hypertriglyceridemia in this analysis were 33% to 38% higher annually, independent of diabetes, cardiovascular disease, heart failure, and hypertension. Outpatient and pharmaceutical costs accounted heavily for the differences in costs.8

### A New Treatment Option for Severe Hypertriglyceridemia

In July 2012, Vascepa (icosapent ethyl; Amarin Pharma), an ethyl ester of EPA, was approved by the US Food and Drug Administration (FDA) as an adjunct to diet to reduce triglyceride levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia.9 Icosapent ethyl is a pure omega-3 fatty acid and the first EPA-only omega-3 agent to be approved by the FDA for this indication.10

Patients should be placed on an appropriate lipid-lowering diet and exercise regimen before receiving icosapent ethyl and should continue the regimen while receiving icosapent ethyl. Attempts should be made to control any medical problems, such as diabetes mellitus and hypothyroidism, and to limit alcohol consumption, which may contribute to lipid abnormalities. Lipid levels should be consistently abnormal before initiating icosapent ethyl. Medications known to exacerbate hypertriglyceridemia (ie, beta-blockers, thiazides, and estrogens) should be discontinued or changed, if possible, before the consideration of triglyceride-lowering drug therapy.4

The effect of icosapent ethyl on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined. In addition, the effect of icosapent ethyl on cardiovascular morbidity and mortality in patients with severe hypertriglyceridemia has not been determined.4

### Dosing

Icosapent ethyl is available as a 1-g soft-gelatin capsule for oral use. The daily dose of icosapent ethyl is 4 g taken as 2 capsules twice daily with food. Icosapent capsules should be swallowed whole and should not be broken open, crushed, dissolved, or chewed.

The patient’s lipid levels should be assessed before initiating therapy, and other causes of high triglyceride levels should be identified and managed as appropriate. Patients should engage in appropriate nutritional intake and physical activity before receiving icosapent ethyl, which should continue during treatment with icosapent.4

### Clinical Pharmacology

Evidence suggests that EPA reduces hepatic very-low-density lipoprotein (VLDL) triglycerides synthesis and/or secretion and enhances triglyceride clearance from circulating VLDL particles. Potential mechanisms of action include increased beta oxidation; inhibition of acyl-coenzyme A 1,2-diacylglycerol acyltransferase; decreased lipogenesis in the liver; and increased plasma lipoprotein lipase activity.4

Peak plasma concentrations of EPA were reached approximately 5 hours after oral administration of icosapent ethyl. EPA is mainly metabolized by the liver via beta-oxidation similar to dietary fatty acids. The total plasma clearance of EPA at steady state is 684 mL per hour. The plasma elimination half-life of EPA is approximately 89

### Table 1 Characteristics of Patients in the MARINE Study

<table>
<thead>
<tr>
<th>Category</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline triglyceride levels, range</td>
<td>500-2000 mg/dL</td>
</tr>
<tr>
<td>Median baseline triglyceride level</td>
<td>684 mg/dL</td>
</tr>
<tr>
<td>Median baseline LDL cholesterol levels</td>
<td>86 mg/dL</td>
</tr>
<tr>
<td>Median baseline HDL cholesterol levels</td>
<td>27 mg/dL</td>
</tr>
<tr>
<td>Patients with triglyceride levels of &gt;750 mg/dL</td>
<td>39%</td>
</tr>
</tbody>
</table>

**Randomized population**

<table>
<thead>
<tr>
<th>Race</th>
<th>White, 88%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male, 76%</td>
</tr>
<tr>
<td>Mean age</td>
<td>53 yrs</td>
</tr>
<tr>
<td>Mean body mass index</td>
<td>31 kg/m²</td>
</tr>
<tr>
<td>Patients receiving concomitant statin therapy</td>
<td>25%</td>
</tr>
<tr>
<td>Patients with diabetes</td>
<td>28%</td>
</tr>
</tbody>
</table>

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; MARINE, Multicenter, Placebo-Controlled, Randomized, Double-Blind, 12-Week Study with an Open-Label Extension.

Icosapent ethyl does not undergo renal excretion. In clinical trials, plasma total EPA concentrations did not differ significantly between men and women. Based on studies of a 4-g daily dose of icosapent ethyl, no drug–drug interactions were observed in patients taking medications that are typical substrates of cytochrome P450 enzymes, including omeprazole, rosiglitazone, warfarin, and atorvastatin.

**Clinical Trials**

The FDA approval of icosapent ethyl was based on the Multicenter, Placebo-Controlled, Randomized, Double-Blind, 12-Week Study with an Open-Label Extension (MARINE)—a randomized, placebo-controlled, double-blind, phase 3 study of adult patients (N = 151) with severe hypertriglyceridemia (≥500 mg/dL). The primary end point of the 12-week MARINE study was the percentage change in triglycerides from baseline to week 12. The baseline characteristics of patients in this study are outlined in Table 1. In this study, icosapent ethyl 4 g daily also demonstrated significant placebo-adjusted median reductions from baseline in non-HDL cholesterol (18%) and in total cholesterol (16%; P <.001 for both).

In a follow-up exploratory analysis of the MARINE trial, icosapent ethyl 4 g daily demonstrated a significant reduction in particle concentrations of large VLDL, total LDL, small LDL, and total HDL, and a significant reduction in VLDL particle size in patients with triglycerides ≥500 mg/dL.

**Safety Profile**

In clinical studies, icosapent ethyl was generally well tolerated, with a safety profile similar to that of placebo. The most common adverse reaction (incidence, >2%, and greater than placebo) was arthralgia (2.3% for icosapent vs 1.0% for placebo).

Omega-3 acids may prolong bleeding time. Patients receiving treatment with icosapent ethyl and other drugs that affect coagulation (eg, antiplatelet agents) should be monitored periodically.

In patients with hepatic impairment, alanine amino-

---

**Table 2: Icosapent Ethyl versus Placebo: Percent Change from Baseline in Lipid Parameters in Patients with Severe Hypertriglyceridemia (≥500 mg/dL)**

<table>
<thead>
<tr>
<th>Lipid parameters</th>
<th>Icosapent ethyl 4 g daily (N = 76)</th>
<th>Placebo (N = 75)</th>
<th>Differencea (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>680 −27 mg/dL</td>
<td>703 +10 mg/dL</td>
<td>−33b (−45 to −22)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>91 −5 %</td>
<td>86 −3 %</td>
<td>−2 (−13 to +8)</td>
</tr>
<tr>
<td>Non-HDL cholesterol</td>
<td>225 −8 %</td>
<td>229 +8 %</td>
<td>−18 (−25 to −11)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>254 −7 %</td>
<td>256 +8 %</td>
<td>−16 (−22 to −11)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>27 −4 %</td>
<td>27 0 %</td>
<td>−4 (−9 to +2)</td>
</tr>
<tr>
<td>VLDL cholesterol</td>
<td>123 −20 %</td>
<td>124 +14 %</td>
<td>−29c (−43 to −14)</td>
</tr>
<tr>
<td>Apo B</td>
<td>121 −4 %</td>
<td>118 +4 %</td>
<td>−9c (−14 to −3)</td>
</tr>
</tbody>
</table>

a The difference is the median of the icosapent ethyl percent change less the placebo percent change (Hodges-Lehmann estimate).
b P <.001.
c P <.05 (key secondary efficacy end points determined to be significant according to the prespecified multiple comparison procedure).

P values are from the Wilcoxon Rank-Sum Test.

Apo B indicates apolipoprotein B; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

transferase and aspartate aminotransferase levels should be monitored periodically during therapy.\textsuperscript{4}

Icosapent ethyl contains ethyl esters of the omega-3 fatty acid EPA, which are obtained from the oil of fish. Because it is not known whether patients with allergies to fish and/or shellfish are at an increased risk of an allergic reaction, icosapent ethyl should be used with caution in patients who have a known hypersensitivity to fish and/or shellfish.\textsuperscript{4}

**Conclusion**

With the FDA approval of icosapent ethyl in 2012, a new treatment option became available for patients with severe hypertriglyceridemia, a condition that is associated with an increased risk of cardiovascular disease, particularly in the presence of low HDL cholesterol levels and/or elevated LDL cholesterol levels. Icosapent ethyl is the first EPA-only omega-3 agent indicated to reduce triglyceride levels in adults with elevated levels to be used as an adjunct to a lipid-lowering diet and exercise regimen.

In patients with severe hypertriglyceridemia, the daily use of icosapent ethyl for 12 weeks demonstrated a significant reduction in triglycerides, without an increase in LDL cholesterol levels. Moreover, this new medication has shown significant reductions from baseline in non-HDL cholesterol, total cholesterol, VLDL cholesterol, and apolipoprotein B levels. Icosapent ethyl has been shown to be generally well tolerated for severe hypertriglyceridemia, offering patients a safe and effective treatment option, with a new mechanism of action that may be particularly helpful in some patients.\textsuperscript{4}

**References**