Addressing cardiovascular risk: Anti-inflammatory properties and pleiotropic effects of eicosapentaenoic acid

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SUMMARY: Cardiovascular disease continues to be a major threat to women. Inflammation and undertreatment of dyslipidemia are key contributing factors. A proactive approach is required to help mitigate cardiovascular risk in women. The Ω3 fatty acid eicosapentaenoic acid has anti-inflammatory properties, reduces atherogenic lipids, and has pleiotropic effects on multiple cellular and molecular mechanisms of atherosclerosis.

Cardiovascular risk in women
Despite public health awareness efforts, cardiovascular disease (CVD) remains the leading cause of mortality among women, a fact that is often overlooked by women and their healthcare providers. Especially concerning is that, although coronary heart disease death rates have been declining in the overall population in the past several decades, rates in women aged 35 to 54 years have actually increased. Undertreatment of dyslipidemia may be a major contributor to this gender disparity. Furthermore, women report barriers to taking preventive action to reduce CVD risk such as caregiving and family responsibilities, lack of self or healthcare provider recognition that preventive action is needed, and lack of clear direction as to what is needed. Thus, to reduce CVD risk, there should be a high priority in women’s health clinical practice settings to proactively identify women with elevated CVD risk and to implement measures that address multiple facets of dyslipidemia and atherosclerosis.

Inflammation in atherosclerosis
Atherosclerosis is a process of chronic inflammation in the arterial wall that arises from pathologic interactions between atherogenic lipoproteins, immune cells (ie, monocyte-derived macrophages, T cells), and other local cellular elements, ultimately leading to plaque development (Figure 1). In addition, factors such as oxidative stress contribute to endothelial dysfunction, an early manifestation of atherogenesis that underlies multiple cardiovascular risk factors and diseases. Although the pathogenic role of low-density lipoprotein cholesterol (LDL-C) is well established, there is increasing recognition of the contribution of other lipid parameters that are strong predictors of atherogenicity, such as triglycerides and triglyceride-rich lipoproteins, which produce remnant-like lipoproteins (eg, chylomicrons, very-low-density lipoproteins, and intermediate-density lipoproteins). Ideally, treatment strategies that mitigate atherothrombotic inflammation and help slow progression of atherosclerosis would prevent plaque rupture and associated adverse cardiovascular events.

Potential beneficial effects of EPA
Long-chain omega-3 fatty acids (Ω3s) such as eicosapentaenoic acid (EPA) are reported to be associated with beneficial effects in multiple areas of health including inflammation, insulin resistance, arthritis, heart failure, depression, cancer, aging, hypertension, obesity, brain development, and eye health. It is important to note, however, that there are no FDA-approved indications to treat any disease/condition related to these areas with an Ω3 product. Nonetheless, there is mounting evidence for the beneficial effects of EPA on atherogenic lipids/lipoproteins, inflammation, and multiple atherosclerotic processes. Several prescription Ω3 drug products are FDA approved and indicated for use as an adjunct to diet to reduce triglyceride levels in adult patients with severe (>500 mg/dL) hypertriglyceridemia.

Pleiotropic effects of EPA in atherosclerosis
The potential beneficial effects of EPA on multiple factors that contribute to atherosclerosis, including endothelial function/dysfunction, monocytes, macrophages, foam cells, inflammation, cytokines, atherosclerotic plaque (progression, formation, vulnerability), and thrombus formation have been reviewed extensively and are summarized in Figure 1. Notably, the lipophilic nature of EPA allows for its direct incorporation into the atherosclerotic plaque, even in advanced atherosclerosis, where the EPA molecule can exert localized effects to reduce inflammation and increase plaque stability. EPA also inhibits glucose-induced lipid peroxidation and exerts antioxidant effects, which improve the balance between nitric oxide and reactive oxygen species and may lead to improved endothelial function. Finally, imaging studies have shown that EPA exhibits inhibitory effects on plaque formation and progression and leads to plaque regression. Based on the collective data, it is evident...
that EPA has the potential for beneficial effects at multiple steps throughout the atherosclerotic process, including many that are directly related to inflammation.

**Potential benefits of EPA on inflammation**

One mechanism by which EPA may reduce inflammation is by displacing arachidonic acid (AA) and thereby reducing proinflammatory AA-derived eicosanoids.14-15 EPA has also been associated with increased production of anti-inflammatory resolvins and protectins (both of which reduce neutrophil recruitment).6,28,30

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The anti-inflammatory properties of EPA are further supported by analyses of circulating markers of inflammation in clinical studies of icosapent ethyl (the ethyl ester of EPA) in patients with high or very high triglyceride levels.14-15 In addition to favorable effects on lipid panel parameters, treatment with icosapent ethyl 4 g/day (alone or in combination with statins) over 12 weeks reduced high-sensitivity C-reactive protein (hsCRP), lipoprotein-associated phospholipase A2 (Lp-PLA2), and oxidized LDL (ox-LDL) compared with placebo (Figure 2).12-14 Similar effects were found in the subgroup of patients with high triglyceride levels and diabetes.34

The impact of icosapent ethyl on hsCRP was assessed by statin use in patients with very high triglyceride levels, and, while icosapent ethyl 4 g/day significantly reduced hsCRP regardless of whether patients were receiving statin therapy, the effect appeared even more pronounced in statin-treated patients (27.4% reduction without statins and 67.9% reduction with statins vs placebo).14 Another subanalysis of these clinical studies focused on the impact of icosapent ethyl on hsCRP in patients with metabolic syndrome and reported similar findings to those in the overall study populations.35

**Implications of EPA anti-inflammatory effects for CVD risk**

As already noted, the anti-inflammatory properties of EPA may be related to its antagonism of AA. Of interest is a subgroup analysis of the Japan EPA Lipid Intervention Study (JELIS) that showed higher EPA/AA ratios were associated with a significantly lower risk of major coronary events (MCE) (eg, hazard ratio, 0.83 [P=0.031] for EPA/AA ≥0.75 vs <0.75).29 In JELIS, approximately two-thirds of the study population were postmenopausal women, and the study found that treatment with EPA plus a statin was associated with a 19% relative reduction in coronary artery disease risk compared with treatment with a statin alone.35 It is important to note that patients in JELIS did not have particularly elevated triglyceride levels (mean triglyceride level, 153 mg/dL); therefore, the benefits of EPA may have extended beyond triglyceride-lowering effects.35 In JELIS patients treated with EPA, a clear association between high EPA levels and significantly lower MCE risk was observed.29 An additional Japanese study in a secondary prevention population utilizing EPA plus statin versus statin monotherapy on MCE is ongoing.36 These clinical observations support imaging data noted earlier suggesting that EPA may be particularly suited for improving stabilization and adherence of soft plaque.25 Clinical and preclinical...
Distinctions between Ω3 products

Ω3 prescription products

FDA-approved prescription Ω3 products share a common indication for use as an adjunct to diet to reduce triglyceride levels in adults with severe (≥500 mg/dL) hypertriglyceridemia. All but one of these products contain both EPA and docosahexaenoic acid (DHA). The EPA-only product is icosapent ethyl, the ethyl ester of EPA, available as a highly purified prescription product. Substantial triglyceride reduction has been demonstrated in each of the prescription Ω3 products, whether used alone or in combination with statins, in their respective randomized, placebo-controlled clinical studies. A major difference between these products is that the DHA-containing products can raise LDL-C levels while EPA does not. These differential LDL-C effects are reflected in the prescribing information for DHA-containing products, which include warnings that LDL-C levels may rise during treatment and should be monitored. The labeling for icosapent ethyl does not include this warning. The potential for DHA-containing products to increase LDL-C levels is an important clinical consideration when selecting Ω3 treatment, as such unwanted changes would complicate management of patients with dyslipidemia. A potential mechanism by which DHA may increase LDL-C is downregulation of hepatic LDL receptors. Moreover, EPA plus DHA combination products should not be substituted for or be considered interchangeable with the EPA-only product, as these products are not therapeutically equivalent based on FDA definitions/codes.

Concerns with Ω3 dietary supplements

Dietary supplements containing Ω3 fatty acids are derived from a range of sources including fish oil, krill oil, algae oil, and various plant oils. These products are especially popular among women. They may be used for general promotion of health, but they are not approved for the treatment of any disease. A common misconception among patients, pharmacists, and prescribing physicians is that Ω3 dietary supplements are over-the-counter (OTC) versions of prescription Ω3 products when, in fact, dietary supplements are not approved OTC Ω3 products, prescribing physicians should be aware and advise their patients that Ω3 dietary supplements are not appropriate substitutes for prescription Ω3 products, not only because supplements are not approved for the treatment of hypertriglyceridemia or any other condition but also due to potential efficacy, quality, and safety considerations.

Clinical perspectives

Proactive measures can help address the undertreatment of women who have CVD or are at risk for CVD. Ideally, the focus in women’s cardiovascular healthcare should shift to prevention of primary events rather than post-event management. For women with hypertriglyceridemia, prescription Ω3 fatty acids offer a clearly effective treatment option, with or without statins. The prescription EPA-only product icosapent ethyl may be preferable in patients with dyslipidemia because the EPA plus DHA combination products may increase LDL-C.

Icosapent ethyl is safe and well tolerated, and given the anti-inflammatory and multiple antiatherosclerotic effects of EPA, it may emerge as a preventive strategy for women at risk for atherosclerosis and CVD. The results of the ongoing REDUCE-IT study will be an important addition to the clinical data on icosapent ethyl in patients at risk for CVD. In terms of future research, the anti-inflammatory benefits of EPA may extend beyond atherosclerosis to other chronic inflammatory processes/diseases. For example, in my clinical practice, patients prescribed icosapent ethyl have reported improvement in comorbid conditions including rheumatoid and psoriatic arthritis as well as colitis and Crohn’s disease. There may also be a beneficial effect in degenerative neurologic processes.

Conclusion

Cardiovascular risk continues to be a major health concern for women. Ongoing discussions between women and their healthcare practitioners regarding reduction of cardiovascular risk are therefore warranted. Women at risk for CVD may benefit from use of prescription Ω3 products. Although Ω3 dietary supplements are widely available, these products should not be substituted for prescription products due to potential efficacy, safety, and quality issues. EPA plus DHA combination products (prescription and dietary supplements) have been associated with unwanted increases in LDL-C, which can complicate management of dyslipidemia. Therefore, the prescription EPA-only product icosapent ethyl may be preferred. In clinical trials, icosapent ethyl demonstrated significant reductions in triglyceride levels and other atherogenic lipoproteins and markers of inflammation, adding to the body of literature supporting the potential beneficial effects of EPA in the atherosclerotic pathway. Outcomes data from the ongoing REDUCE-IT trial of the high-dose prescription EPA-only product, icosapent ethyl, will help establish whether these promising findings translate to reduced CVD events in statin-treated patients.

Acknowledgments

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REFERENCES


VASCEPA® (icosapent ethyl) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adults with persistent elevated TG levels (≥500 mg/dL) hypertriglyceridemia.

1 INDICATIONS AND USAGE

VASCEPA® (icosapent ethyl) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adults with persistent elevated TG levels (≥500 mg/dL) hypertriglyceridemia.

2 DOSAGE AND ADMINISTRATION

The daily dose of VASCEPA is 4 grams per day taken as 2 capsules twice daily with food.

4 CONTRAINDICATIONS

VASCEPA is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to VASCEPA or any of its components. Patients should be advised to swallow VASCEPA capsules whole. Do not break open, crush, dissolve, or chew VASCEPA.

5 WARNINGS AND PRECAUTIONS

5.2 Fish Allergy

Patients receiving treatment with VASCEPA and other drugs affecting coagulation (e.g., anti-platelet agents) should be monitored periodically.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Several published studies with omega-3 fatty acids have demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in those studies has not exceeded normal limits and did not produce clinically significant bleeding episodes.

7 DRUG INTERACTIONS

7.1 Anticoagulants

In some published studies with omega-3 fatty acids, increased bleeding times have been observed. Patients receiving treatment with VASCEPA and other drugs affecting coagulation (e.g., anti-platelet agents) should be monitored periodically.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. It is unknown whether VASCEPA can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. VASCEPA should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus.

In a multi-regional developmental study in pregnant rats given oral gavage doses of 0.3, 1.3, 3 g/kg/day ethyl-EPA from gestation day 7-17, a significant increase in birth weights was observed with maternal body weight gain and body weight loss. VASCEPA did not have any known drug abuse or withdrawal effects.

11 NONCLINICAL TOXICOLOGY

11.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of tumor formation was observed in rats or mice following oral administration of ethyl-EPA. In a 6-month carcinogenicity study in Tg.rasH2 transgenic mice with oral gavage doses of 0.5, 1, 2, and 4.6 g/kg/day icosapent ethyl, drug-related incidences of benign squamous cell papilloma in the skin and subcutis of the tail was observed in high dose treated dams.

9 DRUG ABUSE AND DEPENDENCE

9.1 Information for Patients

See VASCEPA Full Package Insert for Patient Counseling Information.

Manufactured for: Amarin Pharma Inc., Bedminster, NJ, USA

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Addressing cardiovascular risk: Anti-inflammatory properties and pleiotropic effects of eicosapentaenoic acid

**VASCEPA® (icosapent ethyl):**

**Studied in statin-treated patients with triglyceride (TG) levels ≥200–499 mg/dL**

- Amarin may disclose truthful, non-leading information not included in the VASCEPA Prescribing Information to healthcare professionals
- Per Federal court order issued August 7, 2015, in Amarin et al. v. FDA et al. S.D.N.Y. (1:15-cv-03588-PAE)

**Indication and Limitations of Use**

VASCEPA® (icosapent ethyl) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia.

- The effect of VASCEPA on cardiovascular mortality and morbidity or on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined.

**Important Information About VASCEPA as Add-on to Statin Therapy in Patients with High (200–499 mg/dL) Triglycerides**

- Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease. VASCEPA should not be taken in place of a healthy diet and lifestyle or statin therapy.
- The ANCHOR trial demonstrates that VASCEPA lowers TG levels in patients with high (≥200 mg/dL and <500 mg/dL) TG levels not controlled by diet and statin therapy.
- In the ANCHOR trial, VASCEPA 4 g/day significantly reduced TG, non-HDL-C, Apo B, VLDL-C, TC, and HDL-C levels from baseline relative to placebo in patients with high (≥200 mg/dL and <500 mg/dL) TG levels not controlled by diet and statin therapy.
- The reduction in TG observed with VASCEPA in the ANCHOR trial was not associated with elevations in LDL-C relative to placebo.
- VASCEPA is not FDA-approved for the treatment of statin-treated patients with mixed dyslipidemia and high (≥200 mg/dL and <500 mg/dL) TG levels due to current uncertainty regarding the benefit, if any, of drug-induced changes in lipid/lipoprotein parameters beyond statin-lowered LDL-C on cardiovascular risk among statin-treated patients with residually high TG. No prospective study has been conducted to test and support what, if any, benefit exists.
- Recent cardiovascular outcomes trials (ACCORD Lipid, AIM-HIGH, and HPS2-THRIVE), while not designed to test the effect of lowering TG levels in patients with high TG levels after statin therapy, each failed to demonstrate incremental cardiovascular benefit of adding a second lipid-altering drug (fenofibrate or formulations of niacin), despite raising HDL-C and reducing TG levels, among statin-treated patients with well-controlled LDL-C.
- VASCEPA is not FDA-approved to reduce the risk of coronary heart disease.
- The effect of VASCEPA on the risk of cardiovascular mortality and morbidity has not been determined.
- A cardiovascular outcomes study of VASCEPA designed to evaluate the efficacy of VASCEPA in reducing cardiovascular mortality and morbidity in a high-risk patient population on statin therapy is currently underway (REDUCE-IT).
- VASCEPA may not be eligible for reimbursement under government healthcare programs (such as Medicare and Medicaid) to reduce the risk of coronary heart disease or for treatment of statin-treated patients with mixed dyslipidemia and high (≥200 mg/dL and <500 mg/dL) TG levels. We encourage you to check that for yourself.
- The ANCHOR trial was sponsored by Amarin Pharma, Inc. and its affiliates.

**JELIS: Important Information for Healthcare Professionals Considering Co-administration Therapy with Statins for Additional Lipid Management in Mixed Dyslipidemia**

The publications, the study and sub-analyses, and the study sponsor

- Yokoyama et al. 2007: The primary publication presenting the results of a long-term cardiovascular outcomes study of a highly purified eicosapentaenoic acid (EPA) product coadministered with statin therapy in 18,645 Japanese patients, the Japan EPA Lipid Intervention Study (JELIS). JELIS was a Prospective, Randomized, Open-label trial with Blinded Endpoint evaluation (PROBE design)²
- Saito et al. 2008: A prespecified JELIS primary prevention sub-analysis that assessed, among other things, the differences in coronary artery disease (CAD) incidences in patients with high triglyceride (TG) and low high-density lipoprotein cholesterol (HDL-C) levels¹
- Matsuzaki et al. 2009: An additional JELIS sub-analysis that assessed the incidence of secondary major cardiovascular events in patients with established CAD³

JELIS was supported by grants from the manufacturer of the product, Mochida Pharmaceutical Co Ltd, Tokyo, Japan.

The product studied in JELIS and VASCEPA® (icosapent ethyl) capsules

The product studied in JELIS and VASCEPA are highly similar based on a US Food and Drug Administration (FDA) review of both a comprehensive analytical comparison and published reports on each product's content. Each product is highly purified EPA. The product studied in JELIS is not available in the United States.

The highly purified EPA studied in JELIS was administered at 1.8 grams/day (g/d). VASCEPA at 4 g/d is an FDA-approved product indicated for a different use than that investigated in JELIS (see VASCEPA (icosapent ethyl) Indication and Limitations of Use in left-hand column). The effect of VASCEPA on cardiovascular mortality and morbidity has not been determined. VASCEPA 4 g/d is under clinical investigation to evaluate its potential in reducing cardiovascular mortality and morbidity in a combined primary and secondary prevention (high-risk) patient population receiving statin therapy (see Ongoing Cardiovascular Outcomes Study of VASCEPA in Statin-treated Patients on page 8).

**Important information for healthcare professionals about JELIS**

- JELIS provides supportive but not conclusive data that EPA drug therapy may reduce major coronary events
  —JELIS reached its primary endpoint in the combined primary

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Full prescribing information for VASCEPA is available at www.vascepahcp.com.
and secondary prevention population showing a 19% relative risk reduction in major coronary events in statin-treated patients with hypercholesterolemia in Japan

- Major coronary events included sudden cardiac death, fatal and nonfatal myocardial infarction, and other nonfatal events, including unstable angina pectoris, angiplasty, stenting, or coronary artery bypass grafting
- The main component contributing to the primary endpoint results in JELIS summarized herein was unstable angina involving hospital treatment, which is a more subjective endpoint result than, for example, objective major adverse cardiovascular event endpoints (e.g., heart attack, stroke, or cardiovascular death)
- A subjective endpoint, such as unstable angina, may be particularly unreliable in an open-label trial, such as JELIS, where patients and healthcare professionals are making decisions regarding hospitalizations

- **JELIS results cannot be generalized to other populations**
  - Subjects in JELIS were limited to Japanese adults
  - The average dietary intake of fish in Japan is about 5 times higher than that in other countries
  - Baseline blood EPA levels in JELIS before pharmacotherapy with 1.8 g/d of EPA were higher than those recorded in the US population
  - Subjects in JELIS received a low dose of statin therapy based on then-current Japanese treatment guidelines that may be considered inadequate under current guidelines in the United States

- **FDA determined that JELIS results could not be used as support for or against the use of TG levels as a surrogate for cardiovascular risk reduction**
  - In the primary endpoint analysis, median baseline TG levels were not high (153 mg/dL [1.73 mmol/L])
  - Assessment of the TG-lowering benefits of EPA therapy in JELIS is complicated by the small number of subjects with high median TG levels (≥200 mg/dL) at baseline prior to statin treatment
  - A statin run-in or stabilization period prior to randomization to EPA would have likely further reduced the baseline median TG level

- **EPA + Statin Statin (Control) P value HR (95% CI)**

<table>
<thead>
<tr>
<th>Major Coronary Events</th>
<th>EPA + Statin</th>
<th>Statin (Control)</th>
<th>P value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yokoyama et al.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total population (n=18,645)</td>
<td>2.8%</td>
<td>3.5%</td>
<td>0.011</td>
<td>0.81 (0.69–0.95)</td>
</tr>
<tr>
<td>Primary prevention (n=14,981)</td>
<td>1.4%</td>
<td>1.7%</td>
<td>0.132</td>
<td>0.82 (0.63–1.06)</td>
</tr>
<tr>
<td>Secondary prevention (n=3,664)</td>
<td>8.7%</td>
<td>10.7%</td>
<td>0.048</td>
<td>0.81 (0.66–1.00)</td>
</tr>
<tr>
<td>Saito et al.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High TG (≥150 mg/dL)/low HDL-C (&lt;40 mg/dL) (n=957)*</td>
<td>3.3% for pooled treatment arms; event rates were not reported for each arm</td>
<td>0.043</td>
<td>0.47 (0.23–0.98)</td>
<td></td>
</tr>
<tr>
<td>Matsuzaki et al.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• CAD (n=3,664)*</td>
<td>8.7%</td>
<td>10.7%</td>
<td>0.017</td>
<td>0.77 (0.63–0.96)</td>
</tr>
</tbody>
</table>

CI, confidence interval; HR, hazard ratio.

* There was no suggestion of a difference in treatment effect between TG levels of ≥151 mg/dL (HR, 0.84; 95% CI, 0.68–1.04) and TG levels of <151 mg/dL (HR, 0.79; 95% CI, 0.61–1.02) when HDL-C is not considered (interaction P=0.75).

† When JELIS was conducted (over the period of 1996-2004), cholesterol management was not as aggressive as it is today for someone with established CAD. In addition, there was likely less use of antiplatelet/anticoagulant agents for someone with established CAD as there is in medical practice today.

### Major coronary events: JELIS and sub-analyses

Adapted from Yokoyama et al, Figure 3: Estimated hazard ratios of clinical endpoints stratified by prevention stratum; Saito et al, Figure 3: Effects of EPA on the incidence of MCE for the high TG/low HDL-C group; Matsuzaki et al, Figure 2a: Kaplan-Meier estimates of the incidence of the primary endpoint of coronary events occurring in the group of all patients.

- **Limitations of subpopulation analyses**
  - JELIS reached its primary endpoint in the combined primary and secondary prevention population
  - JELIS was not powered to evaluate primary and secondary prevention populations individually or those explored in the Saito and Matsuzaki publications
• Safety findings from JELIS
  —Gastrointestinal disturbances (3.8% on EPA + statin and 1.7% on statin alone; P<0.0001)
  o Skin abnormalities (1.7% on EPA + statin and 0.7% on statin alone; P<0.0001)
  • Hemorrhage (1.1% on EPA + statin and 0.6% on statin alone; P=0.006)
  —No between-group differences in stroke, including cerebral and/or subarachnoid hemorrhage
  • Abnormal laboratory data (slight excess of aspartate aminotransferase [AST] elevations, 0.6% on EPA + statin and 0.4% on statin alone; P=0.03)
  • The rate of discontinuation due to treatment-related adverse effects was 11.7% in the EPA group and 7.2% in the control group

Other cardiovascular outcomes trials in the omega-3 class have reported negligible impact on cardiovascular events
JELIS is the only cardiovascular outcomes trial that has examined the effects of EPA (1.8 g/d) plus statin vs statin alone. The 12-week end-of-treatment blood levels after 4 g/d of EPA in an American population achieved approximately the same end-of-treatment blood levels of EPA observed in the Japanese population studied in JELIS. 7 The clinical relevance of EPA blood levels on cardiovascular outcomes has not been determined.

Following JELIS and GISSI-P (Gruppo Italiano per lo Studio della Sopravvivenza nell’infarto miocardico-Prevenzione), 8 randomized placebo-controlled trials have failed to confirm definite cardiovascular benefit with similarly low (<2 g/d) doses of omega-3 fatty acid mixtures. GISSI-P is an open-label outcomes trial (1 g omega-3 fatty acid mixture), conducted in Italy, that supported the hypothesis that omega-3 fatty acids likely exert their cardioprotective effects through nonlipid-mediated mechanisms. But, in GISSI-P, only ~5% of patients were receiving statins at baseline compared with >40%-50% in more recent, similarly low-dose omega-3 trials that failed to confirm benefit. GISSI-P did not suggest an effect on the incidence of nonfatal cardiovascular events and the effects of omega-3 fatty acids on lipids, including serum TGs, were negligible.

The omega-3 fatty acid mixtures studied in such other outcomes trials were primarily comprised of EPA and docosahexaenoic acid (DHA) (typically, approximately 900 mg total per 1 gram capsule) and also typically included a number of other omega-3 and omega-6 acids, as well as other constituents. No head-to-head cardiovascular outcomes study of EPA vs a mixture of omega-3 acids has been conducted. No cardiovascular outcomes trial has been completed with sufficient power to prospectively evaluate the effect of EPA or omega-3 fatty acid mixtures in statin-treated patients, either with high TG levels (~200 mg/dL) or with both high TG and low HDL-C levels.

Ongoing Cardiovascular Outcomes Study of VASCEPA® in Statin-treated Patients
The encouraging results of JELIS contributed to the justification to investigate the potential of VASCEPA to reduce cardiovascular risk. A cardiovascular outcomes study of VASCEPA designed to evaluate the efficacy of 4 g/d of VASCEPA in reducing cardiovascular mortality and morbidity in a high-risk patient population on statin therapy is currently underway (REDUCE-IT). The sponsor of REDUCE-IT, Amarin Pharma Inc., and the FDA are strongly aligned in recognizing the importance of continuing to collaborate to complete REDUCE-IT so that a definitive answer may be provided to answer the question of whether VASCEPA, in combination with a statin, results in reduction of cardiovascular risk over a statin alone.

Participants in the clinical investigation of VASCEPA currently underway (REDUCE-IT) should not be advised to use VASCEPA in place of participation in that study. VASCEPA should not be taken in place of a healthy diet and lifestyle or statin therapy.

Important Safety Information for VASCEPA® (icosapent ethyl)
• VASCEPA is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to VASCEPA or any of its components.
• Use with caution in patients with known hypersensitivity to fish and/or shellfish.
• The most common reported adverse reaction (incidence >2% and greater than placebo) was arthralgia (2.3% VASCEPA, 1.0% placebo).
• Patients receiving treatment with VASCEPA and other drugs affecting coagulation (e.g., anti-platelet agents) should be monitored periodically.
• In patients with hepatic impairment, monitor ALT and AST levels periodically during therapy. Patients should be advised to swallow VASCEPA capsules whole; not to break open, crush, dissolve, or chew VASCEPA.
• Adverse events may be reported by calling 1-855-VASCEPA or the FDA at 1-800-FDA-1088.

References