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Icosapent: New Panacea for Cardiovascular Risk Prevention?

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Abstract

Residual cardiovascular risk despite intensive statin therapy necessitates additional management in patients with dyslipidemia. Icosapent, an ethyl ester of eicosapentaenoic acid, is approved for hypertriglyceridemia. It improves atherogenic dyslipidemia characterized by reduction of triglycerides without an increase in low-density lipoprotein cholesterol. The REDUCE-IT study reported significantly reduced risk of ischemic events, including cardiovascular death, with icosapent therapy in patients with established cardiovascular disease or with diabetes and other risk factors who were receiving statin therapy. In this paper, we review the available clinical evidence for the effects of icosapent on athero-inflammatory-thrombotic processes and mechanisms for cardiovascular risk reduction.

Keywords: Icosapent; Cardiovascular; Atherosclerosis; Dyslipidemia; Mortality

Introduction

Atherosclerotic cardiovascular disease is an important cause of morbidity and mortality. In about 80% cases, a causal risk factor can be identified for atherosclerotic vascular disease [1]. Cardiovascular disease was the leading cause of death in the United States in 2016 [2].

Dyslipidemia is an established factor for atherosclerotic cardiovascular disease. Reduction of low-density lipoprotein cholesterol (LDL-C) with statin therapy significantly reduces the risk for cardiovascular disease (CTT 2015) [3]. Most guidelines recommend statins as first line therapy for lowering of LDL-C in patients with high cardiovascular risk due to dyslipidemia [4,5]. However, there remains a residual risk for cardiovascular disease despite lowering of LDL-C with statin therapy. This can possibly be explained by the inadequate reduction of LDL-C and aberrations in other dyslipidemic components, i.e., low high-density lipoprotein cholesterol (HDL-C) and/or high triglycerides (TGs) [6]. High levels of TGs have an important and recognized role in the pathophysiology of cardiovascular disease [7]. Besides LDL-C, high levels of non-HDL-C and apolipoprotein B (apoB) have been associated with the risks of cardiovascular events [8]. A second Phase III, double-blind, 12-week (ANCHOR) RCT study showed a reduction in median placebo-adjusted TG levels from baseline and lowered placebo-adjusted non-HDL-C, VLDL-C total cholesterol, and HDL-C. Regardless of, good LDL-C control at baseline, IPE 4 g/day lowered LDL-C levels by an additional 6.2% compared with placebo [4].

TGs are linked to cardiovascular disease (CVD). A small cross-sectional studyreported high level of TGs is more associated with CVD rather than hypercholesterolemia in men [9]. Published studies document that non-fasting triglycerides have been equally predictive of CVD risk as fasting hypertriglyceridemia and were associated with stroke risk [5,10]. A research study and meta-analysis showed that high levels of TGs are known risk factor for CVDs and associated with death, myocardial infarction, and cardiovascular events [11,12]. Icosapent is a high-purity ethyl ester of eicosapentaenoic acid (EPA), a long-chain omega-3 fatty acid. Following oral administration, it is de-esterified to the EHA. Icosapent is approved by the US FDA for lowering of TG levels in adult patients with severe (≥ 500 mg/dL [≥ 5.65 mmol/L]) hypertriglyceridemia [13,14]. We review the evidence for icosapent, which has an established role in TG reduction, in the prevention of cardiovascular risk along with the cellular and molecular mechanisms supporting the risk reduction.

Effect on TGs

High levels (150 mg/dL or 1.7 mmol/L) of TG are an established risk factor for cardiovascular events and associated high risk of death [11,12]. In a meta-analysis (35 observational studies), fasting hypertriglyceridemia was significantly associated with cardiovascular death (Odds ratio [OR]: 1.80; 95% Confidence Interval (CI): 1.31-2.49), cardiovascular events (OR: 1.37; 95% CI: 1.23-1.53), myocardial infarction (OR: 1.31; 95% CI: 1.15-1.49), and pancreatitis (One study; OR: 3.96; 95% CI: 1.27-12.34) [12]. Statins, that reduce TGs in a dose-dependent manner, are the preferred initial pharmacological treatment in patients with hypertriglyceridemia. However, high TGs may persist with optimized statin therapy suggesting a residual high clinical risk for cardiovascular events [15].

The TG lowering action of icosapent can potentially be explained by reduction in hepatic synthesis of VLDL-TG synthesis, and the secretion and enhanced clearance of TGs from circulating VLDL particles, decreased hepatic lipogenesis, increased β-oxidation and plasma lipoprotein lipase activity, and inhibition of acyl-CoA:1,2-diacylglycerol acyltransferase [8,15].

In the phase III, randomized, double-blind, 12-week, placebo-controlled, MARINE study, oral icosapent ethyl 4 g/day significantly reduced the placebo-corrected median TG level by 33.1% from baseline in adults with very high (≥ 500 and ≤ 2,000 mg/dL) fasting hypertriglyceridemia. When compared to placebo, it also significantlyreduced non-high-density lipoprotein cholesterol, apolipoprotein B, lipoprotein-associated phospholipase A(2), very low-density lipoprotein cholesterol, and total cholesterol without any significant increase in the low-density lipoprotein levels [16]. Similar results were reported in the randomized, double-blind, placebo-controlled ANCHOR study in patients with high cardiovascular disease risk and adequate LDL-C control (≥ 40 and <115 mg/dL) with

statins ± ezetimibe but with high TG levels (≥ 200 and <500 mg/dL) (Table 1) [4].

The reduction in cardiovascular risk with icosapent can be explained by reduction of atherogenic dyslipidemia [17]. Atherogenic dyslipidemia is associated with a significant residual cardiovascular risk in addition to that conferred by LDL-C and that continue to persist with optimal LDL-C control [18]. The beneficial effects of icosapent in atherogenic dyslipidemia have been established in the MARINE and ANCHOR studies (Table 1) [8]. In MARINE study, statin-treated patients with a baseline TG level >750 mg/dl, EPA 4 g/day reduced the placebo-corrected median TG levels by 45.4%. In the subgroup treated with statins with a baseline TG level >500 mg/dl, EPA 4 g/day significantly reduced placebo-corrected median TG levels by 65% [16]. Station-treated patients with persistently high TG will need add-on therapy to correct dyslipidemia [6]. Icosapent has been used in both statin-naïve and statin-treated patients for the correction of dyslipidemia.

	Marine (n=229) [7]	**Anchor (n=702) [4]**
TG	-33.1 (p<0.0001)	-21.5 (p<0.0001)
LDL-C	-2.3 (NS)	-6.2 (p=0.0067)
HDL-C	-3.6 (NS)	-4.5 (p=0.0013)
Non-HDL-C	-17.7 (p<0.0001)	-13.6 (p<0.0001)
Apo B	-8.5 (p=0.0019)	-9.3 (p<0.0001)
TC	-16.3 (p<0.0001)	-12.0 (p<0.0001)

Abbreviations: Apo B: Apolipoprotein B; HDL-C: High-Density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; MARINE: Multi-Center, Placebo-Controlled, Randomized, Double-Blind, 12-Week Study with an Open-Label Extension; non-HDL-C: Non-High-Density Lipoprotein Cholesterol; NS: Not Statistically Significant; TC: Total Cholesterol; TG: Triglycerides.

Note: Values indicate median placebo-adjusted percentage change from baseline. The MARINE study enrolled patients with TG ≥ 500 and ≤ 2000 mg/dL with or without background statin therapy and the ANCHOR study enrolled patients with TG ≥ 200 and <500 mg/dL; LDL-C ≥ 40 and <115 mg/dL on optimized statin therapy.

Table 1: Efficacy of icosapent (4 g/day) for dyslipidemia.

Effects on Atherosclerosis

As a class, omega-3 fatty acids have cardiovascular benefits. These benefits can be explained by the antiatherogenic, antithrombotic, anti-inflammatory, antidysrhythmic, antihypertensive, and endothelial protective effects [8]. Omega-3 fatty acids, including EPA, have beneficial effects on dyslipidemia and can stabilize atherogenic plaques. In addition, the rheologic benefits and reduced platelet aggregation along with vasodilation and reduced systolic and diastolic blood pressure can help to improve blood flow. Omega-3 fatty acids also reduce proinflammatory eicosanoids and leukotrienes [7].

EPA, with beneficial effects on lipids, lipoproteins, phospholipid membranes, and the atherosclerotic plaque itself, has been shown to reduce atherosclerotic inflammation [19]. In membrane models mimicking atherosclerosis, EPA reduces membrane fluidity, inhibits cholesterol domain formation, and normalizes bilayer width [20].

EPA has several beneficial effects in the pathophysiological cascade of atherosclerosis including oxidative stress, endothelial function, foam cell formation, immune-inflammatory mediators, platelet adherence and aggregation, thrombus formation, and plaque formation, progression, and rupture. The effects of EPA on athero-inflammatory-thrombotic processes are shown in Figure 1 [17].

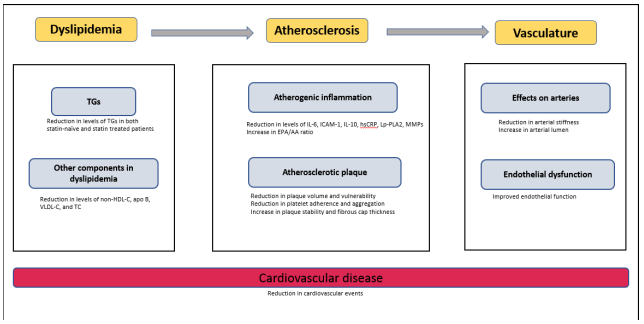

Figure 1: Mechanisms of cardiovascular risk reduction with eicosapentaenoic acid. Note: Apo B: Apolipoprotein B; EPA/AA: Eicosapentaenoic Acid/Arachidonic Acid Ratio; hsCRP: high-sensitivity C-Reactive Protein; non-HDL-C: non-High-Density Lipoprotein Cholesterol; ICAM: Intercellular Adhesion Molecule; IL: Interleukin; Lp-PLA2: lipoprotein-Associated Phospholipase A2; MMP: Matrix Metalloproteinases; TC: Total cholesterol; TG: Triglycerides; VLDL: Very Low-Density Lipoprotein Cholesterol.

Effects on Endothelium and Vasculature

EPA improves endothelial function by reducing the generation of reactive oxygen species and oxidative stress [21]. It also alters the expression of adhesion molecules and cytokines and inhibits membrane lipid peroxidation. EPA 4 g/day for 12 weeks reduced oxidized LDL when compared with placebo by 13.3% (p<0.0001) and 6.6% (p=0.055) in the ANCHOR and MARINE studies, respectively [8]. In a randomized study in patients with coronary artery disease on optimal statin therapy (n=80), addition of EPA (1.8 g/day for an average of 5 months) significantly improved flow-mediated dilation 2.6 ± 1.6% to 3.2 ± 1.6%, p=0.02) when compared to those who received only statins (2.7 ± 1.6% to 2.4 ± 1.7%, p=0.29) [22]. When added to optimal statintherapyin patients with type 2 diabetes and dyslipidemia (n=28), EPA (1.8 g/day for 6 months) significantly improved duration of reactive hyperemia indicating an improvement in vascular function [23]. EPA also causes vasodilation and reduces blood pressure [17]. EPA (1.8 g/day) for 3 months has been shown to reduce pulse wave velocity, an indicator of arterial stiffness, in obese adults with dyslipidemia [24].

Effects on Atherosclerotic Inflammation and Thrombosis

EPA has beneficial effects on vascular inflammation. This has been attributed to production of mediators such as resolvins and protectinswhich in turn reduce neutrophil recruitment and help in reduction of vascular inflammation [1,25]. EPA modulates the cellular response and levels of mediators and cytokines in inflammation. In obese adults with dyslipidemia, EPA (1.8 g/day) for 3 months significantly increased serum levels of the anti-inflmmatory cytokine IL-10, monocyte IL-10 expression, and EPA/arachidonic acid (AA) ratio [24].

Effects of EPA on markers of inflammation have been confirmed in clinical studies. In the MARINE and ANCHOR studies, icosapent 4 g/day significantly reduced plasma apolipoprotein C-III levels in patients with high TGs. When compared to placebo, icosapent 4 g/day significantly reduced oxidized LDL (13%, p<0.0001) in the ANCHOR study. In both the studies, icosapent also reduced lipoprotein-associated phospholipase A2 (14%, p<0.001, MARINE; 19%, p<0.0001, ANCHOR), and high-sensitivity C-reactive protein levels (36%, p<0.01, MARINE; 22%, p<0.001, ANCHOR). In RCT (ANCHOR STUDY) of statin-treated patients with optimized LDL cholesterol levels at baseline and residually elevated TG levels, EPA 4 and 2 g/day significantly reduced median placebo-adjusted TG levels from baseline by 21.5% and 10.1%, respectively. EPA 4 g/day decreasesLDL cholesterol levels by an additional 6.2% and additionally, reduced high-sensitivity C-reactive protein levels, non-HDL cholesterol, lipoprotein-associated phospholipase A2, and apolipoprotein B.

In a prospective randomized study in patients who underwent percutaneous coronary intervention after myocardial infarction, early treatment with EPA (1.8 g/day initiated within 24 hours and continued for 1 month) significantly reduced acute inflammatory response. Median (interquartile range) peak CRP levels were significantly lower in patients who received EPA (n=57) when compared to those who did not (n=58); 8.2 (5.6-10.2) mg/dl *vs.* 9.7 (7.6-13.9) mg/dl, p<0.01 [26].

EPA reduces platelet aggregation and checks the progression of thrombosis. The myriad of anti-thrombotic properties of EPA are dependent on adiponectin [27]. EPA may limit the size of an overlying thrombus in a ruptured atherosclerotic plaque by reducing platelet aggregation. This reduces ischemic risk to the viable myocardium.

Effects on Atherosclerotic Plaque

EPA has various beneficial effects in the atherosclerotic cascade including those on endothelial function, oxidative stress, inflammation, foam cell formation, plaque formation and progression, platelet adherence and aggregation, thrombus formation, and plaque rupture [17]. EPA helps to stabilize the atherosclerotic plaques and prevents plaque rupture. EPA has been shown to increase the thickness of fibrous caps in atherosclerotic plaques. Treatment with EPA (1.8 g/day) over 8 months significantly increased fibrous cap thickness on optical coherence tomography in patients with acute coronary syndrome without dyslipidemia [28]. Addition of EPA to statin therapy is reported to stabilize vulnerable plaques. In patients undergoing percutaneousintervention for acute coronary syndrome, addition of EPA (1.8 g/day) to rosuvastatin for 9 months produced a greater increase infibrous cap thickness (55 *vs.* 24 μm; p<0.0001) and greaterdecrease in plaque lipid arc (-34° *vs.* -13°; p=0.007) and lipid length (-2.8 *vs.* -1.2 mm; p=0.009) compared with rosuvastatin alone [29].

EPA has been shown to reduce plaque volume. In the prospective, parallel-group CHERRY (combination therapy of eicosapentaenoic acid and pitavastatin for coronary plaque regression evaluated by integrated backscatter intravascular ultrasonography) study, 193 patients who had undergone percutaneous coronary intervention were randomized to receive high-dose pitavastatin (PTV 4 mg/day) alone (n=96) or in combination with EPA acid (1800 mg/day; PTV/EPA, n=97). After 6-8 months of follow-up, the PTV/EPA group showed a superior plaque regression on intravascular ultrasound. There was a significant reduction from baseline in median plaque volume in the PTA/EPV group (-8.2 mm; p<0.001) when compared to the PTV group (-1.3 mm; p=0.086). Reductions in the median total atheroma volumes in the two groups were -9.3 (p<0.001) and -1.7 mm (p=0.024), respectively. This study reported a promising effect of additional EPA to reduce the residual risk of cardiovascular disease under intensive statin therapy [30].

The ongoing, randomized, doubleblind, placebocontrolled EVAPORATE study is evaluating the effects of icosapent 4g/d on atherosclerotic plaques in statintreated patients with coronary atherosclerosis and TG levels of 200 to 499mg/dL, and lowdensity lipoprotein cholesterol levels of 40 to 115mg/dL. This study is using Multidetector Computed Tomography Angiography (MDCTA) to detect changes in the lowattenuation plaque volume over 9 to 18 months. The results of this study, when available, will provide insights for the role of icosapent in the progression of atherosclerotic plaques (Budoff 2018).

Cardiovascular Events

Reduction of TGs is associated with a reduced risk for major cardiovascular events [11]. In patients receiving statins and having well-controlled LDL-C, icosapent is an important therapeutic option beyond statin therapy alone. More recently, the effects of icosapent ethyl on total ischemic events in statin-treated patients were evaluated in the Reduction of Cardiovascular Events with EPA-Intervention Trial (REDUCE-IT). Patients (n=8179) with TG ≥ 135 and <500 mg/dL (median baseline of 216 mg/dL), LDL-cholesterol >40 and ≤ 100 mg/dL (median baseline of 75 mg/dL), and a history of atherosclerosis (71% patients) or diabetes (29% patients) were randomized to receive icosapent ethyl 4 g/day or placebo. The main outcomes were total (first and subsequent) primary composite endpoint events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina) and total key secondary composite endpoint events (cardiovascularH death, nonfatal myocardial infarction, or nonfatal stroke). In the two groups, a primary end-point and key secondary end-point occurred in 17.2% and 22.0% patients (hazard ratio [HR]: 0.75; 95% CI: 0.68 to 0.83; p<0.001)and 11.2% and 14.8% (HR: 0.74; 95% CI: 0.65 to 0.83; p<0.001). A further analysis showed that 1,606 (55.2%) first primary endpoint events and 1,303 (44.8%) subsequent primary endpoint events occurred (including 762 second events and 541 ≥ 3rd events). Overall, icosapent ethyl reduced total primary endpoint events (61 versus 89 per 1000 patient years; RR: 0.70, 95% CI: 0.62-0.78, p<0.0001) and total key secondary endpoint events (32 versus 44 per 1000 patient years; RR: 0.72, 95% CI: 0.63-0.82, p<0.0001) when compared to placebo. Icosapent can be a good substitute for statins in patients who cannot tolerate the latter and who do not attain desired TG reductions with dietary supplements containing fish oil [31-34].

The REDUCE-IT subanalysisstudy showed that Icosapent ethyl (Vascepa) reduces total cardiovascular events by 30% in a cohort of statin-treated patients with high TG levels and either established CVD or diabetes plus risk factors. Furthermore, first, second, third, and fourth or more events were also reduced substantially. Fatal or nonfatal MIs made up the largest proportion of first events (33%), while coronary revascularizations made up the majority of subsequent events (60%). Patients treated with icosapent ethyl had 25%fewer first events, 32% fewer second events, 31% fewer third events and 48% fewer fourth or more events. Icosapent ethyl was also associated with a reduction of total secondary endpoint events [35].

Based on the outcomes of the REDUCE-IT study, the American Diabetes Association (ADA) has recently issued an update for the Standards of Medical Care in Diabetes [2]. According to the ADA, icosapent should be considered to lower the cardiovascular risk in patients with diabetes and atherosclerotic cardiovascular disease or other cardiac risk factors and who have controlled LDL-C but high TG (135-499 mg/dL) on statin therapy.

In patients who underwent percutaneous coronary intervention after myocardial infarction, early treatment with EPA (1.8 g/day initiated within 24 hours and continued for 1 month) has also been shown to significantly reduced composite cardiac end points (cardiac death, stroke, re-infarction, ventricular arrhythmias, and paroxysmal atrial fibrillation; p=0.01), particularly the incidence of ventricular arrhythmias (p=0.03) when given to patients who underwent percutaneous coronary intervention after myocardial infarction [26].

In the JELIS study (ClinicalTrials.gov number NCT00231738), EPA (1.8 g/day) plus a statin significantly reduced risk of a major coronary event by 19% compared with statin monotherapy (HR: 0.81; 95% CI: 0.69-0.95; p=0.011) in 18,645 hypercholesterolemic Japanese patients who were followed up for a mean duration of 4.6 years. In this study, EPA showed significant reductions in major coronary events when used for secondary but not for primary prevention. In patients with a history of coronary artery disease, EPA reduced major coronary events by 19% (8.7% *vs.*10.7% in the EPA and control groups, respectively; p=0.048). In patients with no history of coronary artery disease, EPA reduced major coronary events by 18% (1.4% *vs.* 1.7% in the EPA and control groups, respectively; p=0.132) [36].

The RESPECT-EPA (Randomized Trial for Evaluation in Secondary Prevention Efficacy of Combination Therapy-Statin and Eicosapentaenoic Acid) is an ongoing open-label study in stain treated patients with stable coronary artery disease. This study is evaluating the effect of EPA (1.8 g/day) on a composite of coronary artery disease, including sudden cardiac death, myocardial infarction, revascularization, and hospitalization for unstable angina and a composite of cerebrovascular disorders including fatal and non-fatal stroke [37,38].

Reduction of cardiovascular events has been evaluated for another class of pharmacotherapies in dyslipidemia. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, fenofibrate when added to simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke, as compared with simvastatin alone in patients with type 2 diabetes mellitus who were at high risk for cardiovascular disease [39]. Similarly, in the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) study, there was no incremental clinical benefit for risk of cardiovascular events with the addition of niacin to statin therapy in patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of <70 mg/dl (1.81 mmol/L) who received simvastatin and ezetimibe [40]. In the Heart Protection Study 2, Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) study, the combination of extended release niacin and laropiprant, when added to an effective statin-based treatment, did not produce clinically meaningful reductions in the rate of major vascular events. Additionally, the combination demonstrated a significant increase in non-fatal serious adverse events including bleeding, infections, myopathy, and type 2 diabetes [41].

Combinations of different omega-3 fatty acids have also failed to demonstrate any beneficial reduction of cardiovascular events. In the Outcome Reduction with Initial Glargine Intervention (ORIGIN) study, daily supplementation with n-3 fatty acids (EPA and docosahexaenoic acid [DHA]) did not reduce the rate of cardiovascular events in high-risk patients [42]. In a double-blind, placebo-controlled trial (n=4837), low-dose supplementation with EPA-DHA or alpha-linolenic acid did not significantly reduce the rate of major cardiovascular events among patients who had experienced a myocardial infarction and who were receiving antihypertensive, antithrombotic, and lipid-modifying therapy [43]. In the randomized, placebo-controlled, double-blind OMEGA study (n=3851), omega-3 fatty acids (EPA+DHA, 1 g/day for 1 year) did not significantly lower the rate of sudden cardiac death (1.5% *vs.* 1.5%; p=0.84) when added to guideline-adjusted treatment in patients with acute myocardial infarction. There were no reductions in total mortality (4.6% *vs.* 3.7%; p=0.18), major adverse cerebrovascular and cardiovascular events (10.4% *vs.* 8.8%; p=0.1), and revascularization in survivors (27.6% *vs.* 29.1%; p=0.34) [44-50].

Safety of Icosapent

Icosapent is well tolerated. In the MARINE and ANCHOR studies, most adverse events with icosapent therapy were mild, unrelated to treatment, and not significantly different from those reported in the placebo groups [4,16]. In these studies, icosapent did not impact blood glucose levels, HbA1c, and hepatic or renal functions. Patients showed high compliance with >90% rates of study completion. In the ANCHOR study, EPA was found to be safe and well-tolerated at the 2 g/day and 4 g/day doses. Most of the treatment-emergent adverse events (TEAEs) were mild or moderate in severity. TEAEs such as diarrhea, nausea, nasopharyngitis, and arthralgia occurred in 3% ofpatients. Arthralgia was reported to occur in a larger percentageof patients treated with EPA versus placebo [4]. In the REDUCE-IT study, serious bleeding events were reported in 2.7% and 2.1% of the patients in the icosapentand placebo groups, respectively (p=0.06) [51-54]. However, more patients receiving icosapent than placebo were hospitalized for atrial fibrillation or flutter (3.1% vs. 2.1%, p=0.004) and developed peripheral edema (6.5 vs. 5.0, p=0.002) or constipation (5.4% vs. 3.6%, p<0.001) [31].

Conclusion

There is a clear causal role of high TGs for vascular risk. The reduction of cardiovascular events in the REDUCE-IT study may be attributed to reduction in TGs as well as the pleiotropic effects of icosapent in atherosclerotic cardiovascular disease. Icosapent improves atherogenic dyslipidemia characterized by reduction of TGs without raising LDL-C. EPA has a broader role in the pathophysiology of atherosclerosis. EPA is incorporated into membrane phospholipids and atherosclerotic plaques and exerts beneficial effects on the pathophysiologic cascade of atherogenic inflammation. EPA also causes vasodilation, reduces arterial stiffness, and improves endothelial dysfunction. The effects of EPA on dyslipidemia, atherosclerosis, and vasculature together may explain the reduction of cardiovascular events with EPA. Icosapent is well tolerated. Significant reductions in fatal and nonfatal stroke (28%), cardiac arrest (48%), sudden death (31%), and cardiovascular death (20%) are reported with icosapent therapy in patients with high cardiovascular risk. Though there were reported risks of serious bleeding and hospitalization for atrial fibrillation or flutter in the REDUCE-IT study, the aversion of large

numbers of ischemic events with icosapent make it a recommended therapy for patients with high cardiovascular risk.

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All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, take responsibility for the integrity of the work and have given final approval of the version to be published.

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