



# Effects of Icosapent Ethyl (Eicosapentaenoic Acid Ethyl Ester) on Atherogenic Lipid/Lipoprotein, Apolipoprotein, and Inflammatory Parameters in Patients With Elevated High-Sensitivity C-Reactive Protein (from the ANCHOR Study)

Michael Miller, MD<sup>a,\*</sup>, Christie M. Ballantyne, MD<sup>b</sup>, Harold E. Bays, MD<sup>c</sup>,  
Craig Granowitz, MD, PhD<sup>d</sup>, Ralph T. Doyle, Jr., BA<sup>d</sup>, Rebecca A. Juliano, PhD<sup>d</sup>, and  
Sephyl Philip, RPh, PharmD<sup>d</sup>

**Icosapent ethyl is pure prescription eicosapentaenoic acid approved at 4 g/day as an adjunct to diet to reduce triglycerides (TG) in adults with TG  $\geq$ 500 mg/dl. Elevated high-sensitivity C-reactive protein (hsCRP) is associated with increased cardiovascular risk. The 12-week ANCHOR study randomized 702 statin-treated patients at increased cardiovascular risk with TG 200 to 499 mg/dl despite low-density lipoprotein cholesterol (LDL-C) control (40 to 99 mg/dl). This post hoc analysis assessed 246 ANCHOR patients with baseline hsCRP  $\geq$  2.0 mg/L randomized to icosapent ethyl 4 g/day (n=126; approved dose) or placebo (n=120). Without increasing LDL-C, icosapent ethyl significantly reduced median TG (–20%; p < 0.0001), non-high-density lipoprotein cholesterol (–12.3%; p < 0.0001), total cholesterol (–11.1%; p < 0.0001), high-density lipoprotein cholesterol (–5.2%; p = 0.0042), very LDL-C (–21.0%; p < 0.0001), very low-density lipoprotein TG (–22.9%; p < 0.0001), remnant lipoprotein cholesterol (–23.0%; p = 0.0125), apolipoprotein B (–7.4%; p = 0.0021), apolipoprotein C-III (–16%; p < 0.0001), oxidized LDL (–13.7%; p = 0.0020), lipoprotein-associated phospholipase A<sub>2</sub> (–19.6%; p < 0.0001), and hsCRP (–17.9%; p = 0.0213) versus placebo, while interleukin-6 and intercellular adhesion molecule-1 were not significantly changed. Eicosapentaenoic acid increased with icosapent ethyl 4 g/day +637% in plasma and +632% in red blood cells versus placebo (both p < 0.0001). Icosapent ethyl exhibited a safety profile similar to placebo. In conclusion, in statin-treated patients with hsCRP  $\geq$  2.0 mg/L and TG 200 to 499 mg/dl at baseline, icosapent ethyl 4 g/day significantly and safely reduced TG and other atherogenic and inflammatory parameters without increasing LDL-C versus placebo. © 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license. (<http://creativecommons.org/licenses/by-nc-nd/4.0/>) (Am J Cardiol 2019;124:696–701)**

Elevated high-sensitivity C-reactive protein (hsCRP), a known biomarker of systemic inflammation, is associated with increased cardiovascular (CV) risk.<sup>1</sup> Major associations have supported inclusion of hsCRP  $\geq$  2.0 mg/L in CV risk assessment.<sup>2,3</sup> Clinical studies suggest that reduction in CVD risk factors, including hsCRP, is associated with decreased risk of recurrent CV events.<sup>4–7</sup> Eicosapentaenoic acid (EPA) is an omega-3 fatty acid that lowers triglycerides (TG) and TG-rich lipoproteins with or without statin therapy.<sup>8</sup> In the ANCHOR study of adults with residually high TG (200 to 499 mg/dl) despite stable statin therapy, icosapent ethyl

(pure ethyl ester of EPA; Vascepa, Amarin Pharma Inc, Bedminster, NJ) significantly reduced TG, demonstrated a safety profile similar to placebo, and significantly improved lipid, lipoprotein, and oxidative and inflammatory parameters.<sup>9–13</sup> The purpose of this post hoc analysis was to examine the effects of icosapent ethyl 4 g/day (approved dose) compared with placebo on TG, hsCRP, and other atherogenic parameters in the subgroup of patients from ANCHOR with baseline hsCRP  $\geq$  2.0 mg/L.

## Methods

ANCHOR (NCT01047501) was a phase 3, multicenter, placebo-controlled, randomized, double-blind, 12-week clinical study conducted at 97 sites in the United States from December 2009 to February 2011.<sup>9</sup> Study design and participant eligibility criteria were previously reported.<sup>9</sup> Briefly, eligible adults had high CV risk and residually high TG (200 to 499 mg/dl) despite controlled low-density lipoprotein cholesterol (LDL-C; 40–99 mg/dl) on stable statin therapy (atorvastatin, rosuvastatin, or simvastatin; with or

<sup>a</sup>Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland; <sup>b</sup>Department of Medicine, Baylor College of Medicine and the Houston Methodist DeBakey Heart and Vascular Center, Houston, Texas; <sup>c</sup>Louisville Metabolic and Atherosclerosis Research Center, Louisville, Kentucky; and <sup>d</sup>Amarin Pharma Inc, Bedminster, New Jersey. Manuscript received February 20, 2019; revised manuscript received May 21, 2019; revised manuscript received and accepted May 21, 2019.

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\*Corresponding author: Tel: 410-328-6299; fax: 410-328-3530.

E-mail address: [mmiller@som.umaryland.edu](mailto:mmiller@som.umaryland.edu) (M. Miller).

without ezetimibe).<sup>9</sup> High CVD risk was defined as a history of coronary artery disease (i.e., history of myocardial infarction, unstable or stable angina, coronary artery interventions, or clinically significant myocardial ischemia), noncoronary forms of clinical atherosclerosis (i.e., peripheral arterial disease, abdominal aortic aneurysm, or carotid artery disease), or type 1 or 2 diabetes mellitus.

The design included a 4- to 6-week diet and lifestyle-stabilization lead-in period during which other TG-lowering medications were washed out and statin therapy was stabilized for baseline measurement determination.<sup>9</sup> Patients were randomized to icosapent ethyl 4 g/day, icosapent ethyl 2 g/day, or matched placebo. This post hoc analysis evaluated the subgroup of 246 patients from the ANCHOR intent-to-treat (ITT) population with baseline hsCRP  $\geq$  2.0 mg/L who were randomized to icosapent ethyl 4 g/day (the US Food and Drug Administration–approved dose) or placebo.

The ITT population was defined as all randomized patients who had a baseline TG measurement, received  $\geq$  1 dose of study drug, and had  $\geq$  1 postrandomization efficacy measurement. ANCHOR was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The appropriate institutional review boards approved the protocol, and all patients provided written informed consent.<sup>9</sup>

Efficacy variables included the median difference in percent change from baseline to week 12 between the icosapent ethyl 4 g/day and placebo groups for fasting plasma TG (primary variable), total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), very low-density lipoprotein cholesterol, very low-density triglycerides, remnant lipoprotein cholesterol (RLP-C), non-HDL-C, apolipoprotein B, apolipoprotein C-III (Apo C-III), lipoprotein-associated phospholipase A<sub>2</sub> (Lp-PLA<sub>2</sub>), hsCRP, oxidized low-density lipoprotein (ox-LDL), interleukin-6 (IL-6), intercellular adhesion molecule-1, and plasma and red blood cell concentrations of EPA. These parameters were measured as previously described (LDL-C and RLP-C were not calculated but were measured by beta-quantification and immunoseparation assays, respectively).<sup>10,13–17</sup> The protocol prespecified that EPA levels were to be measured with liquid chromatography using tandem mass spectroscopy methodology in approximately the first 216 patients in ANCHOR with complete sample datasets.

The evaluation of safety included monitoring of treatment-emergent adverse events (TEAEs), defined as any AEs that began after the first dose of study medication or that worsened in severity during the double-blind treatment period. TEAEs reported herein included total TEAEs and those occurring in  $\geq$  3% of patients in any treatment group of the overall ANCHOR study population (i.e., nausea, diarrhea, nasopharyngitis, and arthralgia).<sup>9</sup>

The present subgroup analysis of patients with baseline hsCRP  $\geq$  2.0 mg/L was not prespecified in the ANCHOR study protocol. Similar to the analyses conducted in the full study population, these post hoc analyses were primarily performed as in the ITT population. Median differences in percent change from baseline between the icosapent ethyl 4 g/day and placebo groups for the primary efficacy variable and additional assessments were estimated with the

Hodges-Lehmann method (p values from the Wilcoxon rank sum test for treatment comparisons), where departures from normality were observed; for normally distributed parameters, an analysis of covariance model was used with least squares means and standard errors. Missing values were imputed using the last-observation-carried-forward method. For all post hoc analyses, the alpha level for statistical significance was 0.05. Safety analyses were based on the safety population (all randomized patients who received  $\geq$  1 dose of the study drug). These analyses were conducted with SAS/STAT 9.22 software (SAS Institute Inc, Cary, NC).

## Results

ANCHOR randomized 702 statin-treated patients to icosapent ethyl 4 g/day, icosapent ethyl 2 g/day, or placebo.<sup>9</sup> Median baseline hsCRP for the icosapent ethyl 4 g/day, 2 g/day, and placebo arms of the full ANCHOR cohort were 2.2, 2.0, and 1.8 mg/L, respectively. The present post hoc subgroup analysis included 246 patients from the ANCHOR ITT group with baseline hsCRP  $\geq$  2.0 mg/L randomized to receive icosapent ethyl 4 g/day (n = 126) or placebo (n = 120). Four patients in the icosapent ethyl 4 g/day group and 6 patients in the placebo group discontinued study medication. Baseline characteristics were similar in the icosapent ethyl 4 g/day and placebo groups (Table 1). Median (interquartile range) hsCRP at baseline was 3.9 (3.2) mg/L in the icosapent ethyl 4 g/day group and 4.6 (4.4) mg/L in the placebo group.

Table 1  
Baseline characteristics of patients from ANCHOR ITT population with baseline hsCRP  $\geq$  2.0 mg/L\*

Variable	Icosapent Ethyl 4 g/day (n = 126)	Placebo (n = 120)
Age, mean (SD) (years)	60.2 (9.7)	61.0 (9.9)
Male	72 (57.1%)	64 (53.3%)
Female	54 (42.9%)	56 (46.7%)
White	124 (98.4%)	116 (96.7%)
Body mass index, mean (SD) (kg/m <sup>2</sup> )	33.7 (5.1)	34.0 (5.2)
Diabetes mellitus	93 (73.8%)	92 (76.7%)
Atorvastatin use	24 (19.1%)	20 (16.7%)
Rosuvastatin use	30 (23.8%)	31 (25.8%)
Simvastatin use	72 (57.1%)	69 (57.1%)
Low statin intensity <sup>†</sup>	9 (7.1%)	8 (6.7%)
Medium statin intensity <sup>†</sup>	80 (63.5%)	74 (61.7%)
High statin intensity <sup>†</sup>	37 (29.4%)	38 (31.7%)
hsCRP, median (IQR) (mg/L) <sup>‡</sup>	3.9 (3.2)	4.6 (4.4)

hsCRP = high-sensitivity C-reactive protein; ITT = intent-to-treat; IQR = interquartile range; SD = standard deviation.

\* There were no significant differences in baseline characteristics among treatment groups in the total randomized ANCHOR population (hsCRP was an exploratory endpoint and was not tested).

<sup>†</sup> Lower-intensity statin regimens, simvastatin 5 to 10 mg; medium-intensity statin regimens, rosuvastatin 5 to 10 mg, atorvastatin 10 to 20 mg, simvastatin 20 to 40 mg, simvastatin 10 to 20 mg plus ezetimibe 5 to 10 mg; higher-intensity statin regimens, rosuvastatin 20 to 40 mg, atorvastatin 40 to 80 mg, simvastatin 80 mg, simvastatin 40 to 80 mg plus ezetimibe 5 to 10 mg.

<sup>‡</sup> n = 120 for the icosapent ethyl 4 g/day group and n = 115 for the placebo group.

Table 2

Effects of icosapent ethyl 4 g/day on lipids/lipoproteins, apolipoproteins, and markers of oxidation and inflammation in patients from ANCHOR ITT population with baseline hsCRP  $\geq 2.0$  mg/L

Parameter	Icosapent ethyl 4 g/day			Placebo			Median difference in % change from baseline, icosapent ethyl 4 g/day vs placebo, %, p value
	Baseline	End of treatment	Change from baseline, %	Baseline	End of treatment	Change from baseline, %	
<b>Lipids/Lipoproteins</b>							
TG (mg/dl) (primary efficacy variable)							
n = 126, 120	267.8 (97.0)	220.8 (110.0)	-16.6 (32.3)	267.5 (86.8)	280.5 (118.8)	+5 (44.4)	-19.9, <0.0001
LDL-C (mg/dl)							
n = 126, 119	81.0 (23.0)	83.5 (34.0)	+2.8 (28.9)	84.0 (24.0)	88.0 (28.0)	+9.2 (36.1)	-5.0, 0.1162
Non-HDL-C (mg/dl)							
n = 126, 120	128.5 (29.0)	125.0 (41.0)	-4.5 (22.0)	131.5 (29.0)	136.0 (42.5)	+9.7 (32.7)	-12.3, <0.0001
TC (mg/dl)							
n = 126, 120	167.0 (37.0)	166.0 (41.0)	-2.6 (15.8)	170.0 (34.0)	182.5 (47.5)	+9.2 (24.0)	-11.1, <0.0001
HDL-C (mg/dl)							
n = 126, 120	36.5 (12.0)	36.0 (13.0)	-2.1 (18.8)	39.0 (11.0)	39.0 (15.5)	+5.6 (19.6)	-5.2, 0.0042
VLDL-C (mg/dl)							
n = 126, 119	45.5 (20.0)	38.0 (20.0)	-11.8 (49.2)	42.0 (21.0)	49.0 (29.0)	+11.1 (63.4)	-21.0, <0.0001
VLDL-TG (mg/dl)							
n = 126, 119	196.5 (92.0)	154.5 (100.0)	-18.7 (52.4)	190.0 (95.0)	205.0 (129.0)	+4.6 (67.2)	-22.9, <0.0001
RLP-C (mg/dl)*							
n = 43, 40	14.0 (5.0)	10.0 (6.0)	-26.3 (45.0)	14.0 (6.0)	13.0 (5.0)	+3.8 (67.8)	-23.0, 0.0125
<b>Apolipoproteins</b>							
Apo B (mg/dl)†							
n = 120, 115	93.0 (21.5)	93.5 (24.5)	-0.5 (15.4)	91.0 (23.0)	99.0 (22.0)	+6.5 (26.4)	-7.4, 0.0021
Apo C-III (mg/dl)†							
n = 114, 106	15.4 (5.0)	14.0 (5.0)	-7.7 (28.1)	15.1 (4.4)	16.2 (5.6)	+6.8 (33.4)	-16.0, <0.0001
<b>Markers of Oxidation and Inflammation</b>							
Ox-LDL (U/L)*							
n = 46, 39	54.1 (14.8)	54.1 (17.2)	-2.9 (20.9)	53.3 (16.0)	62.4 (17.9)	+14.7 (25.6)	-13.7, 0.0020
Lp-PLA <sub>2</sub> (ng/ml)							
n = 120, 113	184.5 (54.5)	163.0 (59.0)	-13.3 (16.3)	192.0 (61.0)	203.0 (74.0)	+7.3 (24.6)	-19.6, <0.0001
hsCRP (mg/L)							
n = 120, 115	3.9 (3.2)	3.7 (3.6)	-10.5 (70.1)	4.6 (4.4)	5.4 (7.2)	+8.0 (77.3)	-17.9, 0.0213
IL-6 (pg/ml)							
n = 46, 38	3.4 (2.8)	2.8 (2.5)	-1.6 (57.9)	4.2 (2.7)	4.0 (4.2)	-1.7 (66.6)	-4.2, 0.7463
ICAM-1 (ng/ml)							
n = 46, 38	288.5 (107.0)	300.5 (116.0)	+3.3 (12.1)	304.5 (130.0)	307.5 (149.0)	+2.2 (12.9)	+1.1, 0.5621

Apo B = apolipoprotein B; Apo C-III = apolipoprotein C-III; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; ICAM-1 = intercellular adhesion molecule-1; IL-6 = interleukin-6; ITT = intent-to-treat; LDL-C = low-density lipoprotein cholesterol; Lp-PLA<sub>2</sub> = lipoprotein-associated phospholipase A<sub>2</sub>; non-HDL-C = non-high-density lipoprotein cholesterol; ox-LDL = oxidized low-density lipoprotein; RLP-C = remnant lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides; VLDL-C = very low-density lipoprotein cholesterol; VLDL-TG = very low-density lipoprotein triglycerides.

Data are presented as medians (interquartile ranges) for end point values. Median differences in percent changes from baseline versus placebo are Hodges-Lehmann medians. Patient numbers are presented as the number of patients in the icosapent ethyl 4 g/day group and the placebo group, respectively.

\* RLP-C and ox-LDL were measured in approximately the first 35% of patients randomized in the ANCHOR study.

† Apo B and Apo C-III were measured in the subgroup of all patients with available archived plasma samples from the ANCHOR study.<sup>13</sup>

In patients with hsCRP  $\geq 2.0$  mg/L at baseline, and compared with placebo, icosapent ethyl 4 g/day significantly reduced the primary endpoint of fasting TG by 19.9% ( $p < 0.0001$ ; Table 2, Figure 1), as well as non-HDL-C, total cholesterol, HDL-C, very low-density lipoprotein cholesterol, very low-density triglycerides, and RLP-C as compared with placebo ( $p$  values ranging from 0.0125 to  $<0.0001$ ), without increasing LDL-C ( $p = 0.1162$ ; Table 2, Figure 1). Apolipoproteins (apolipoprotein B and apolipoprotein C-III) and markers of oxidation and inflammation (hsCRP, ox-LDL, and Lp-PLA<sub>2</sub>) also significantly decreased with icosapent ethyl 4 g/day as compared with

placebo ( $p$  values ranging from 0.0213 to  $<0.0001$ ; Table 2, Figure 1). Changes in IL-6 and intercellular adhesion molecule-1 were small and statistically insignificant when compared with placebo (Table 2, Figure 1). Icosapent ethyl 4 g/day significantly increased mean EPA in plasma and red blood cells (Table 3).

As with the overall ANCHOR population, the safety profile of icosapent ethyl 4 g/day was similar to placebo in this subgroup analysis of patients with baseline hsCRP  $\geq 2.0$  mg/L (Table 4). In this subgroup analysis of patients with baseline hsCRP  $\geq 2.0$  mg/L, the only TEAE reported in  $\geq 3\%$  of patients receiving icosapent ethyl 4 g/day was

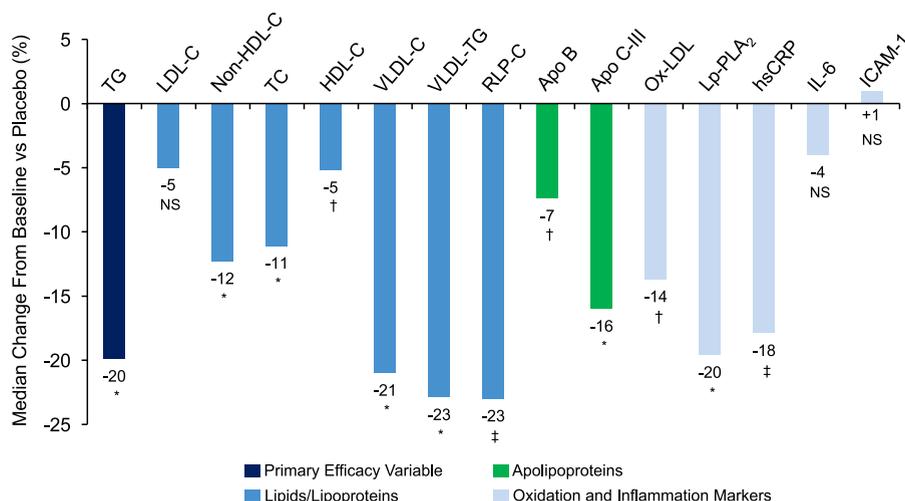


Figure 1. Change in levels of lipids/lipoproteins, apolipoproteins, and markers of oxidation and inflammation (patients from the ANCHOR ITT population with baseline hsCRP  $\geq 2.0$  mg/L). Values represent median of difference in percent change from baseline to week 12 for icosapent ethyl 4 g/day versus placebo. \* $p < 0.0001$ ; † $p < 0.01$ ; ‡ $p < 0.05$ ; NS, not significant versus placebo. Apo B = apolipoprotein B; Apo C-III = apolipoprotein C-III; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; ICAM-1 = intercellular adhesion molecule-1; IL-6 = interleukin-6; ITT = intent-to-treat; LDL-C = low-density lipoprotein cholesterol; Lp-PLA<sub>2</sub> = lipoprotein-associated phospholipase A<sub>2</sub>; non-HDL-C = non-high-density lipoprotein cholesterol; ox-LDL = oxidized low-density lipoprotein; RLP-C = remnant lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides; VLDL-C = very low-density lipoprotein cholesterol; VLDL-TG = very low-density lipoprotein triglycerides.

Table 3

Change in plasma and RBC EPA in patients from ANCHOR ITT population with baseline hsCRP  $\geq 2.0$  mg/L\*

Parameter	Icosapent ethyl 4 g/day			Placebo			Change from baseline, LS mean, icosapent ethyl 4 g/day vs placebo, %, p value
	Baseline, mean (SD)	End of treatment, mean (SD)	Change from baseline, LS mean (SE)	Baseline, mean (SD)	End of treatment, mean (SD)	Change from baseline, LS mean (SE)	
Plasma EPA, $\mu\text{g/ml}$ n = 41, 38	29.4 (20.4)	179.1 (72.9)	+157.0 (8.7)	25.5 (14.8)	29.7 (13.1)	+11.9 (8.8)	+637.0, <0.0001
RBC EPA, $\mu\text{g/ml}$ n = 39, 35	11.2 (5.5)	67.2 (29.3)	+57.6 (3.4)	10.0 (6.2)	9.0 (4.4)	+1.0 (3.5)	+631.6, <0.0001

EPA = eicosapentaenoic acid; hsCRP = high-sensitivity C-reactive protein; ITT = intent-to-treat; LS = least squares; RBC = red blood cell; SD = standard deviation; SE = standard error.

Patient numbers are presented as the number of patients in the icosapent ethyl 4 g/day group and the placebo group, respectively.

\* Includes only patients with available EPA data at both baseline and week 12; EPA was measured in approximately the first 216 ANCHOR patients with complete sample datasets as prespecified.

Table 4

Adverse events in patients from the ANCHOR safety population with baseline hsCRP  $\geq 2.0$  mg/L

Preferred Term	Patients With TEAEs	
	Icosapent ethyl 4 g/day (n = 131)	Placebo (n = 124)
Any TEAE	60 (45.8%)	60 (48.4%)
Nausea*	3 (2.3%)	3 (2.4%)
Diarrhea*	5 (3.8%)	8 (6.5%)
Nasopharyngitis*	1 (0.8%)	6 (4.8%)
Arthralgia*, †	3 (2.3%)	0 (0.0%)

hsCRP = high-sensitivity C-reactive protein; TEAE = treatment-emergent adverse event.

\* TEAEs (irrespective of causality) occurring in  $\geq 3\%$  of all patients in the entire safety population of the ANCHOR study (in any treatment group).<sup>9</sup>

† Most commonly reported adverse event listed in the icosapent ethyl prescribing information.<sup>26</sup>

diarrhea, occurring in 5 (3.8%) patients compared with 8 (6.5%) patients in the placebo group (Table 4). In the overall ANCHOR population, diarrhea, nausea, nasopharyngitis, and arthralgia were the most commonly reported TEAEs (occurring in  $\geq 3\%$  of any treatment group), and arthralgia was the only of these TEAEs that occurred with higher frequency in the icosapent ethyl treatment groups than in the placebo group.<sup>9</sup> These TEAEs occurred at similar rates in this subgroup analysis of patients with baseline hsCRP  $\geq 2.0$  mg/L (icosapent ethyl 4 g/day vs placebo groups, respectively: nausea [2.3% vs 2.4%], nasopharyngitis [0.8% vs 4.8%], and arthralgia [2.3% vs 0%]) (Table 4). One patient each in the icosapent ethyl 4 g/day and placebo groups discontinued due to an AE (icosapent ethyl 4 g/day: subarachnoid hemorrhage, ruptured cerebral aneurysm, and brain edema; placebo: headache), none of which were considered related to study drug by the treating investigator.

## Discussion

This post hoc analysis of statin-treated patients with high CV risk, TG 200 to 499 mg/dl, and hsCRP  $\geq$  2.0 mg/L at baseline suggests icosapent ethyl 4 g/day significantly reduces TG and other atherogenic and inflammatory parameters without increasing LDL-C versus placebo. Results are generally similar to those in the entire ANCHOR population.<sup>9,10,12,13</sup> Icosapent ethyl 4 g/day also demonstrated similar improvement in TG and other atherogenic/inflammatory parameters in other ANCHOR subpopulations including diabetes mellitus,<sup>15</sup> women,<sup>18</sup> chronic kidney disease,<sup>19</sup> and women with diabetes mellitus.<sup>20</sup>

EPA is incorporated into cell membranes and atherosclerotic plaque, where it alters cellular inflammation, oxidation, and signaling pathways that promote atherosclerosis.<sup>8,21</sup> Prior studies suggest that purified EPA may have anti-inflammatory effects in addition to improving lipid levels in patients with high CV risk.<sup>8,10,21</sup> EPA treatment has been associated with improvements in several markers of inflammation, including the ratio of EPA to arachidonic acid (EPA/AA), ox-LDL, Lp-PLA<sub>2</sub>, adiponectin, IL-6, IL-10, monocyte chemoattractant protein-1, and pentraxin-3, a marker of local arterial inflammation.<sup>8,10,21</sup> In the overall ANCHOR population, icosapent ethyl 4 g/day significantly improved hsCRP, Lp-PLA<sub>2</sub>, ox-LDL, and the EPA/AA ratio.<sup>10,22</sup> Although EPA lowered hsCRP in the ANCHOR and MARINE trials (MARINE included patients with TG 500 to 2000 mg/dl with or without statin therapy), similar hsCRP reductions were not observed in trials evaluating EPA and DHA mixtures in patients with high or very high TG.<sup>10,23–25</sup>

Previous reports support icosapent ethyl as having safety and tolerability similar to that of placebo.<sup>9,14</sup> In pooled analyses of randomized, double-blind icosapent ethyl clinical trials including the ANCHOR study, the only AE reported in >2% of patients and at a rate greater than placebo was arthralgia (reported in 2.3% of patients receiving icosapent ethyl vs 1.0% of patients receiving placebo).<sup>26</sup> Safety data in the present post hoc subanalysis of patients from ANCHOR with hsCRP  $\geq$  2.0 mg/L at baseline were consistent with the safety profile of icosapent ethyl and data from the overall ANCHOR population.<sup>9</sup>

As observed in clinical trials in the statin-treated population, elevated hsCRP appears to be a marker of patients at higher risk of coronary events,<sup>4–7</sup> and the inflammation pathway is being evaluated as a potential therapeutic target for atherosclerotic CVD.<sup>7</sup> The recent Canakinumab Antiinflammatory Thrombosis Outcome Study in statin-treated patients with persistent hsCRP  $\geq$  2.0 mg/L adds support for the hypothesis that inflammation plays a role in atherothrombosis and is a modifiable risk factor, showing improved hsCRP and a reduction in CV events in patients treated with canakinumab, an anti-inflammatory therapy targeted at a cytokine upstream of hsCRP in the inflammatory cascade.<sup>7</sup>

CV outcomes data of pure EPA in statin-treated patients with high residual CV risk and elevated hsCRP have not been reported. In the recently completed Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT; NCT01492361), icosapent ethyl 4 g/day resulted in a significant reduction in major adverse CV

events compared with placebo (hazard ratio, 0.75; 95% confidence interval, 0.68 to 0.83;  $p < 0.001$ ) over a median follow-up time of 4.9 years.<sup>27</sup> In REDUCE-IT, loghsCRP decreased by a median of 21.8% ( $p < 0.0001$ ) from baseline to the year 2 in the icosapent ethyl 4 g/day group and by 0.0% ( $p = 0.9203$ ) in the placebo group, resulting in a 22.5% median between-group decrease for icosapent ethyl 4 g/day versus placebo ( $p < 0.0001$ ). In REDUCE-IT, reductions in hsCRP levels may have contributed to the observed CV risk reduction. Based on REDUCE-IT results, the American Diabetes Association recommends that icosapent ethyl be considered for reducing CV risk in statin-treated patients with controlled LDL-C, TG 135 to 499 mg/dl, diabetes, and atherosclerotic CV disease or other cardiac risk factors (Level A recommendation).<sup>28</sup>

The strength of the findings from these analyses in statin-treated patients with hsCRP  $\geq$  2.0 mg/L and high TG at baseline is limited due to the modest sample size and the post hoc nature of the analysis. In addition, although icosapent ethyl 4 g/day improved CV risk parameters in this subgroup of patients with hsCRP  $\geq$  2.0 mg/L from the ANCHOR study, the study was not designed to determine effects on CV events. Prospectively designed CV outcomes studies are needed to ascertain whether these changes will translate into lower CVD morbidity and mortality.

## Disclosures

Dr Miller discloses serving as advisor and steering committee member (REDUCE-IT) for Amarin Pharma Inc. Dr Ballantyne discloses the following relations: has received research grants (paid to institution, not individual) from Akcea, Amarin Pharma Inc, Amgen, Esperion, Novartis, Regeneron, and Sanofi-Synthelabo; and has received honoraria from Akcea, Amarin Pharma Inc, Amgen, AstraZeneca, Eli Lilly, Esperion, Matinas BioPharma Inc, Merck, Novartis, Pharmam Inc, Regeneron, and Sanofi-Synthelabo. Dr Bays discloses the following relations: has received research grants from Acasti, Akcea, Amarin Pharma Inc, Amgen, AstraZeneca, Esperion, LIB Therapeutics, MedImmune, Merck, Omthera, Pfizer, Regeneron, and Sanofi; has served as a consultant/advisory board member for Aegerion, Amarin Pharma Inc, Amgen, Esperion, Regeneron, and Sanofi; and has served as a speaker for Acasti, Amgen, Kowa, Regeneron, and Sanofi. Dr Granowitz, Mr Doyle, Dr Juliano, and Dr Philip disclose employment with and stock ownership in Amarin Pharma Inc.

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