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Icosapent ethyl, a pure EPA omega-3 fatty acid: Effects on lipoprotein particle concentration and size in patients with very high triglyceride levels (the MARINE study)

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BACKGROUND: Icosapent ethyl (IPE; formerly AMR101) is a high-purity prescription form of eicosapentaenoic acid ethyl ester. In the MARINE study we evaluated the efficacy and safety of IPE in patients with very high triglycerides (TG; ≥500 mg/dL) and previously demonstrated significant reductions in TG levels with no significant increases in low-density lipoprotein (LDL) cholesterol levels.

OBJECTIVES: In this follow-up, exploratory analysis, we report the effects of IPE on lipoprotein particle concentration and size.

METHODS: MARINE was a phase 3, multicenter, placebo-controlled, randomized, double-blind, 12-week study. Hypertriglyceridemic patients (N = 229) were randomized to three treatment groups: IPE 4 g/day, IPE 2 g/day, or placebo. Lipoprotein particle concentrations and sizes were measured by nuclear magnetic resonance spectroscopy.

RESULTS: Compared with placebo, IPE 4 g/day significantly reduced median concentrations of large very-low-density lipoprotein (VLDL; -27.9%; $P = .0211$), total LDL (-16.3%; $P = .0006$), small LDL (-25.6%; $P < .0001$), and total high-density lipoprotein (HDL; -7.4%; $P = .0063$) particles and reduced VLDL particle size (-8.6%; $P = .0017$). In this patient population with TG ≥500 mg/dL, IPE did not significantly change the overall sizes of LDL or HDL particles.

CONCLUSION: IPE 4 g/day significantly reduced large VLDL, total LDL, small LDL, and total HDL particle concentrations and VLDL particle size in patients with TG ≥500 mg/dL. Changes in VLDL particle concentration and size reflect the TG-lowering effects of eicosapentaenoic acid. The reduction in LDL particle concentration with IPE is novel among ω-3 therapies and is consistent with the previously reported reduction in apolipoprotein B and lack of LDL-C increase with IPE in patients with very high TG levels. Clinical trial registration number: NCT01047683.

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Introduction

Hypertriglyceridemia is directly associated with an increased risk of atherosclerotic coronary heart disease (CHD).[1] Consumption of the marine ω-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) lowers triglyceride (TG) plasma levels.[2] However, TG-lowering therapies containing both EPA and DHA may increase low-density lipoprotein (LDL) cholesterol, especially in patients with marked elevations of TGs at baseline.[3] In previous smaller studies of patients with normal to moderately elevated TG levels, purified EPA reduced TG levels without increasing LDL cholesterol levels.[4–9]

Icosapent ethyl (IPE; Vascepa® [formerly AMR101]; Amarin, Bedminster, NJ) is a high-purity prescription form of EPA ethyl ester approved by the United States Food and Drug Administration as an adjunct to diet to reduce TG levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia. The MARINE study (Multi-Center, PlAcebo-Controlled, Randomized, Double-BlINd, 12-week study with an open-label Extension)[10] was the largest clinical trial of any ω-3 fatty acid agent in this particular patient population (N = 229) in which investigators evaluated the efficacy and safety of IPE in patients with very high TG levels (≥500 mg/dL and ≤2000 mg/dL). In this study, IPE significantly reduced TG levels (IPE 4 g/day: −33.1%; $P < .0001$) without increasing LDL cholesterol levels.[10] Among those with baseline TG levels >750 mg/dL, IPE 4 g/day reduced the placebo-adjusted TG levels by 45.4% (mean baseline TG level, 902.0 mg/dL; $P = .0001$).

LDL cholesterol is the primary treatment target for cholesterol-lowering therapy for prevention of CHD.[11] It is the consensus of many lipidologists that apolipoprotein B and lipoprotein particle concentration are also important factors influencing atherogenicity, as well as being potentially useful in the initial assessment and on-treatment lipid management of hypertriglyceridemic patients at increased CHD risk.[12] This exploratory analysis reports the effects of IPE on lipoprotein particle concentrations and sizes in patients with baseline TG levels ≥500 mg/dL.

Methods

MARINE was a phase 3, multicenter, placebo-controlled, randomized, double-blind, 12-week study that evaluated the efficacy and safety of IPE in patients with very high TG levels (≥500 mg/dL and ≤2000 mg/dL). Details of the MARINE study design and methods were reported elsewhere.[10] In summary, following a 4- to 6-week lead-in period of diet, lifestyle, medication stabilization, and washout of prohibited lipid-altering medication, patients aged >18 years of age entered a 2- to 3-week TG-qualifying period. Patients with qualifying TG levels (≥500 mg/dL and ≤2000 mg/dL) entered the 12-week

double-blind treatment period and were randomized to receive either IPE 4 g/day, IPE 2 g/day, or matched placebo (Fig. 1).[10] Prohibited lipid-altering therapies that required a washout period included fibrates, niacins, and ω-3 fish oils. Ezetimibe monotherapy or statins with or without ezetimibe could be continued throughout the study (unless the investigator elected to washout these therapies at study entry) as long as no change was made in statin type or dose. Other prohibited concomitant agents included drugs for weight loss, human immunodeficiency virus protease inhibitors, cyclophosphamide, isotretinoin, and systemic corticosteroids. The remaining key exclusion criteria were history of pancreatitis; untreated hypothyroidism; known nephrotic range (>3 g/day) proteinuria; history of stroke, myocardial infarction, life-threatening arrhythmia, or coronary vascularization within 6 months before screening; body mass index >45 kg/m²; weight change >3 kg during the lead-in period; hemoglobin A_{1c} >9.5%; thyroid-stimulating hormone >1.5 × upper limit of normal; thyroid hormone therapy not stable for ≥6 weeks before screening; alanine aminotransferase or aspartate aminotransferase >3 × upper limit of normal; unexplained creatine kinase concentration >3 × upper limit of normal; or creatine kinase elevation attributable to known muscle disease.

Lipoprotein measurements

All lipoprotein particle concentration and size assessments were obtained from fasting blood samples which were collected into tubes containing ethylenediaminetetraacetic acid and plasma was isolated via centrifugation (1200g for 15 minutes) and stored at −20°C or lower. Lipoprotein particle concentration and size were measured by nuclear magnetic resonance (NMR) spectroscopy[13] at LipoScience, Inc. (Raleigh, NC) using the LipoScience, Inc. LipoProfile-3 algorithm. Concentrations of the following subclasses were analyzed in this study: small LDL (18.0–20.5 nm), large LDL (20.5–23.0 nm), intermediate-density lipoprotein (IDL; 23.0–29.0 nm), large high-density lipoprotein (HDL; 9.4–14.0 nm), medium HDL (8.2–9.4 nm), small HDL (7.3–8.2 nm), large very-low-density lipoprotein (VLDL; >60 nm), medium VLDL (42–60 nm), and small VLDL (29–42 nm). VLDL, LDL, and HDL subclasses of different size were quantified from the amplitudes of their spectroscopically distinct lipid methyl group NMR signals as previously described.[13]

Statistical methods

This was an exploratory analysis of IPE 4 and 2 g/day (vs placebo) on lipoprotein particle concentrations and sizes. Efficacy analyses included the intent-to-treat (ITT) population, defined as all randomized patients who had a baseline efficacy measurement, received ≥1 dose of study drug, and had ≥1 postrandomization efficacy measurement. Because of the lack of a normal distribution of the lipoprotein particle parameters, medians and interquartile
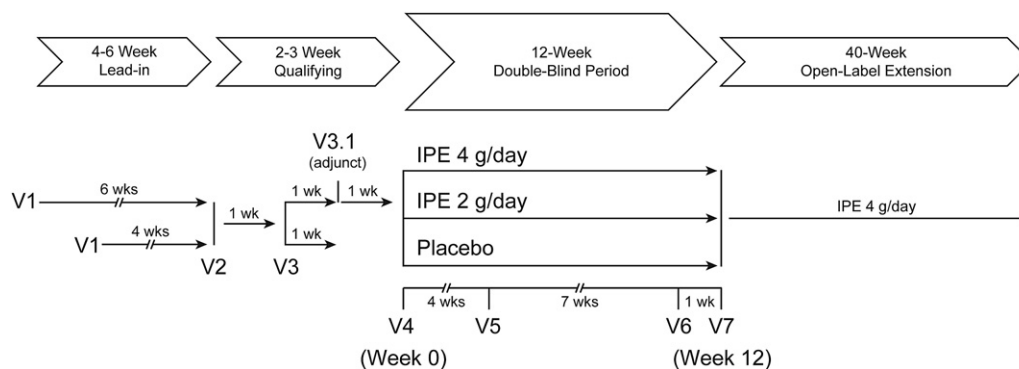
Figure 1   Study design. Eligible patients entered 4- to 6-week lead-in period (6-week washout period for patients receiving lipid-altering therapy, 4 weeks for patients not receiving lipid-altering therapy), followed by qualifying TG measurements at visits 2 and 3. If TG levels were not within the inclusion range, an additional week was allowed for another measurement (adjunct visit 3.1). Qualifying patients were randomized at Visit 4 and entered the double-blind 12-week safety and efficacy measurement phase.[10] IPE, icosapent ethyl.

ranges were calculated for each treatment group at baseline and week 12. Subjects with missing baseline or week 12 measurements, as the result of either missing laboratory samples or unreportable values, were excluded from this analysis. The percent change from baseline was computed by dividing the week 12 change from baseline by the baseline value, multiplied by 100. If the baseline value was zero, then the NMR LipoProfile minimum value for the end point was used as the divisor. Only three end points included patients with zero baseline values: particle concentration for large LDL (111 patients; minimum value 1.0 nmol/L), small VLDL (2 patients; minimum value 0.1 nmol/L), and large HDL (2 patients; minimum value 0.1 μmol/L), compared with a total of 177 patients in the data set. The median difference of each lipoprotein particle variable (percent change from baseline) between each IPE treatment group and the placebo group was evaluated with a nonparametric test using the Hodges-Lehmann medians of the differences between treatment groups and the Wilcoxon rank-sum test. For exploratory efficacy parameters, including lipoprotein particle size and concentration, it was prespecified that no adjustments were to be made for

multiplicity, and that significance was defined as a P value of ≤.05. All statistical analyses were carried out using SAS 9.2 software.

Results

In total, 224 patients were included in the ITT population of the MARINE study; 177 of these had evaluable samples for lipoprotein particle analysis with 61, 63, and 53 patients in the IPE 4 g/day, IPE 2 g/day, and placebo groups, respectively. The analysis of LDL particle size contained 60 patients in the IPE 4 g/day group. Baseline demographics were comparable among treatment groups (Table 1) and were similar to those reported for the overall randomized MARINE population.[10] The majority of patients were white, overweight men who were ≤65 years of age. The median baseline TG levels were 652, 620, and 629 mg/dL, and the median baseline LDL cholesterol levels were 98, 86, and 92 mg/dL for the IPE 4 g/day, IPE 2 g/day, and placebo groups, respectively (Table 2). These baseline lipid levels were similar to those reported

Table 1   Baseline characteristics

Characteristic	IPE 4 g/day (n = 61)	IPE 2 g/day (n = 63)	Placebo (n = 53)	Total (N = 177)
Age, mean (SD), y	52.1 (9.6)	53.7 (9.2)	53.9 (7.9)	53.2 (9.0)
Age ≤65 y, n (%)	55 (90)	58 (92)	51 (96)	164 (93)
Male, n (%)	46 (75)	48 (76)	39 (74)	133 (75)
White, n (%)	53 (87)	56 (89)	51 (96)	160 (90)
Weight, mean (SD), kg	92.8 (17.1)	92.8 (15.4)	93.5 (17.8)	93.0 (16.6)
BMI, mean (SD), kg/m^2	30.7 (4.1)	30.9 (4.2)	30.8 (4.4)	30.8 (4.2)
Diabetes mellitus, n (%)	18 (29.5)	17 (27.0)	16 (30.2)	51 (28.8)
High risk for CVD,* n (%)	32 (52.5)	37 (59.7)	30 (56.6)	99 (56.3)†
Apo B, mean (SD), mg/dL	126.1 (28.4)	121.9 (28.8)	122.3 (32.8)	123.5 (29.8)

Apo B, apolipoprotein B; BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; IPE, icosapent ethyl; ITT, intent-to-treat; SD, standard deviation.

Values are reported for patients from the MARINE ITT population for whom lipoprotein particle measurements were taken.

*High CVD risk: patients with clinical CHD or clinical CHD risk equivalents (10-year risk ≥20%) as defined by the National Cholesterol Education Program Adult Treatment Panel III guidelines.[33]

†N = 176.

Table 2 Median percent change from baseline to study end in lipid end points

	IPE 4 g/day (n = 61)			IPE 2 g/day (n = 63)			Placebo (n = 53)			Median placebo-adjusted percent change from baseline	
	Baseline value (IQR)	End-of-treatment value (IQR)	Change from baseline, % (IQR)	Baseline value (IQR)	End-of-treatment value (IQR)	Change from baseline, % (IQR)	Baseline value (IQR)	End-of-treatment value (IQR)	Change from baseline, % (IQR)	IPE 4 g/day vs placebo, %, P	IPE 2 g/day vs placebo, %, P
TG, mg/dL	652.0 (210.0)	486.5 (293.5)	−26.4 (35.3)	620.5 (272.5)	589.0 (394.5)	−7.0 (48.7)	629.0 (309.5)	659.5 (443.0)	6.4 (44.3)	−27.7, <.0001	−12.7, .0642
LDL-C, mg/dL	98.0 (43.0)	90.0 (54.0)	−6.5 (37.6)	86.0 (62.0)	94.0 (59.0)	−2.9 (33.0)	92.0 (59.0)	80.0 (50.0)	0.0 (41.8)	−6.7, .1992	0.5, .8614
HDL-C, mg/dL	29.0 (10.0)	26.0 (12.0)	−4.5 (21.7)	28.0 (7.0)	30.0 (10.0)	3.3 (28.0)	28.0 (8.0)	28.0 (10.0)	0.0 (25.0)	−5.9, .0891	0.9, .7456

HDL-C, high-density lipoprotein cholesterol; IPE, icosapent ethyl; IQR, interquartile range; ITT, intention-to-treat; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.
Data are presented as median (IQR) for end-point values. Median placebo-adjusted percent changes are Hodges-Lehmann medians. Values are reported for patients from the MARINE ITT population for whom lipoprotein particle measurements were taken.

for the MARINE ITT population.[10] The effects of IPE on the efficacy end points of TG, LDL cholesterol, and HDL cholesterol in the patient groups of this analysis (Table 2) were similar to those of the MARINE ITT population.[10]

Lipoprotein particle concentrations

Table 3 contains the median placebo-adjusted changes in lipoprotein particle concentrations. By study end and compared with placebo, IPE 4 g/day significantly reduced the concentration of large VLDL particles (−27.9%; $P = .0211$) and increased the concentration of medium VLDL particles (+28.0%, $P = .0238$) with no significant change in median concentration of total VLDL particles (+9.3%, $P = .2262$). IPE 2 g/day did not significantly change total, small, medium, or large VLDL particle concentration. IPE 4 g/day reduced total LDL particle concentration (which included IDL particles, small LDL particles, and large LDL particles) by 16.3% ($P = .0006$). IPE 2 g/day did not significantly change total LDL particle concentration (−1.1%, $P = .8202$). IPE 4 g/day and 2 g/day both significantly reduced small LDL particle concentration by 25.6% ($P < .0001$) and 12.8% ($P = .0274$), respectively, with no significant changes in concentrations of large LDL or IDL particles. LDL particle concentration declined numerically more in statin-treated patients (4 g/day [n = 16], −30.2%, $P = .1079$; 2 g/day [n = 15], −22.1%, $P = .2120$) than among those not receiving statins (4 g/day [n = 45], −13.2%, $P = .0054$; 2 g/day [n = 48], +1.7%, $P = .7176$). However, the number of patients receiving statins was small and statistical significance was not achieved for the decreases observed in this group.

IPE 4 g/day significantly reduced total HDL particle concentration (−7.4%, $P = .0063$); IPE 2 g/day did not (−3.0%, $P = .2701$). Neither dose of IPE significantly changed concentrations of large, medium, or small HDL particles.

The concentration of all LDL and VLDL particles correlated with apolipoprotein B concentration at Week 12 ($R^2 = .623$, $P < .0001$; Fig. 2).

Lipoprotein particle sizes

Table 4 contains the median placebo-adjusted changes in lipoprotein particle size for IPE. At study end and compared with placebo, IPE 4 g/day significantly decreased VLDL particle size (−8.6%, $P = .0017$). IPE 2 g/day also decreased VLDL particle size, although not significantly (−4.0%, $P = .0734$). Neither IPE dose significantly changed LDL or HDL particle size.

Discussion

This exploratory analysis of the MARINE study was the largest of any ω-3 fatty acid study to report lipoprotein particle data for patients with very high TG (≥500 mg/dL)

Table 3 Median percent change from baseline to study end in lipoprotein particle concentrations

	IPE 4 g/day (n = 61)			IPE 2 g/day (n = 63)			Placebo (n = 53)			Median placebo-adjusted percent change from baseline	
	Baseline value (IQR)	End-of-treatment value (IQR)	Change from baseline, % (IQR)	Baseline value (IQR)	End-of-treatment value (IQR)	Change from baseline, % (IQR)	Baseline value (IQR)	End-of-treatment value (IQR)	Change from baseline, % (IQR)	IPE 4 g/day vs placebo, %, P	IPE 2 g/day vs placebo, %, P
Total VLDL, nmol/L	166.2 (85.2)	200.3 (150.5)	15.2 (58.6)	165.5 (88.9)	190.1 (121.3)	13.1 (55.4)	161.8 (71.6)	169.1 (87.0)	1.2 (37.1)	9.3, .2262	5.4, .4644
Large VLDL, nmol/L	33.3 (26.8)	21.2 (27.9)	−24.5 (75.5)	33.2 (31.2)	29.9 (29.2)	−2.5 (69.0)	33.1 (23.5)	35.6 (34.4)	2.5 (80.7)	−27.9, .0211	−8.4, .4313
Medium VLDL, nmol/L	80.6 (68.6)	106.8 (95.2)	36.4 (89.7)	76.9 (52.2)	93.8 (89.2)	18.8 (69.8)	74.5 (55.0)	86.0 (40.3)	6.3 (72.1)	28.0, .0238	9.3, .4152
Small VLDL, nmol/L	56.1 (30.6)	52.5 (55.1)	4.3 (119.1)	41.3 (48.8)	53.9 (49.8)	12.7 (133.2)	48.8 (35.3)	45.5 (50.7)	−10.4 (76.2)	2.9, .8624	22.9, .1155
Total LDL, nmol/L	1418 (544.0)	1419 (718.0)	−0.1 (27.5)	1374 (556.0)	1464 (810.0)	12.6 (28.7)	1310 (462.0)	1452 (679.0)	14.4 (31.7)	−16.3, .0006	−1.1, .8202
IDL, nmol/L	160.0 (130.0)	185.0 (217.0)	19.2 (120.2)	121.0 (153.0)	144.0 (201.0)	0.8 (190.8)	174.0 (239.0)	154.0 (161.0)	−14.2 (92.6)	26.6, .1156	25.3, .1111
Large LDL,* nmol/L	7.0 (65.0)	64.0 (174.0)	187.1 (7770.3)	9.0 (116.0)	51.0 (181.0)	0.0 (1527.3)	3.0 (73.0)	21.0 (158.0)	52.3 (1335.1)	40.0, .3351	0.0, .8540
Small LDL, nmol/L	1132 (486.0)	998.0 (568.0)	−9.7 (33.8)	1155 (481.0)	1100 (724.0)	9.5 (29.8)	1001 (476.0)	1171 (524.0)	14.6 (38.6)	−25.6, <.0001	−12.8, .0274
Total HDL, μmol/L	34.3 (8.7)	30.8 (9.1)	−7.1 (17.2)	34.7 (8.9)	33.4 (7.1)	−3.3 (19.6)	32.9 (10.0)	33.9 (9.1)	−0.7 (12.7)	−7.4, .0063	−3.0, .2701
Large HDL, μmol/L	2.2 (1.4)	2.3 (1.3)	9.0 (69.3)	2.1 (1.9)	2.3 (2.0)	0.0 (85.6)	2.2 (1.6)	2.5 (3.0)	0.0 (89.3)	9.7, .3724	2.0, .8418
Medium HDL, μmol/L	10.8 (9.2)	8.4 (5.3)	−18.3 (81.6)	10.0 (7.9)	8.7 (7.3)	3.9 (68.7)	10.8 (8.3)	10.1 (9.3)	−12.6 (89.7)	−14.9, .1223	−4.2, .6415
Small HDL, μmol/L	20.6 (7.2)	21.6 (8.9)	−5.1 (34.6)	22.1 (8.1)	21.5 (6.7)	−3.2 (34.4)	18.8 (6.6)	17.9 (10.9)	−1.7 (37.1)	1.8, .8247	3.4, .5756

HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; IPE, icosapent ethyl; IQR, interquartile range; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.
Data are presented as median (IQR) for end point values. Median placebo-adjusted percent changes are Hodges-Lehmann medians.
*For large LDL particle concentration, 111 of 177 patients had a baseline value of zero. For these patients (if the week 12 value was >0), the percent change from baseline was calculated by use of the minimum value for large LDL particle concentration (1 nmol/L) instead of the zero baseline. These patients had high percent change values leading to a very large IQR value.
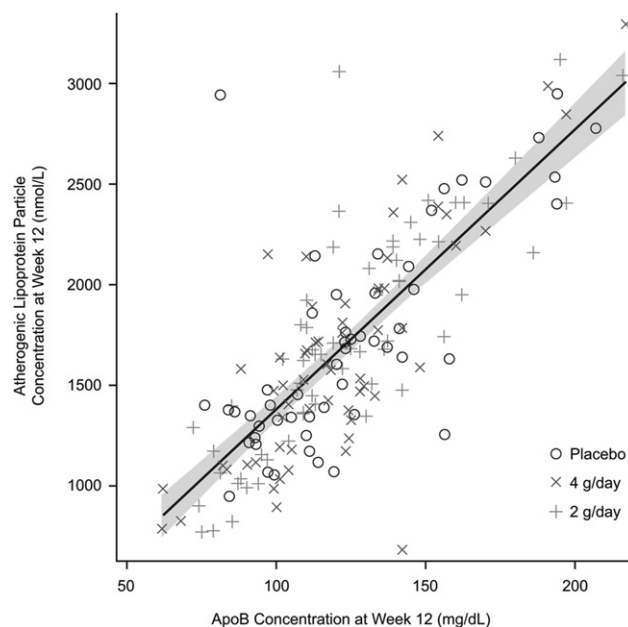

Figure 2 The atherogenic lipoprotein particle concentration correlated with apolipoprotein B (ApoB) at week 12 (N = 177; R^2 = .623; $P < .0001$). The atherogenic particle concentration consisted of all VLDL and LDL particles.

and was conducted to examine the effects of IPE, a high-purity prescription form of EPA ethyl ester, on lipoprotein particle concentrations and sizes. In this analysis, IPE 4 g/day significantly reduced the particle concentrations of large VLDL by 27.9%, total LDL by 16.3%, small LDL by 25.6%, and total HDL by 7.4% compared with placebo in patients with very high TG levels (≥500 and ≤2000 mg/dL) and significantly reduced VLDL particle size by 8.6%. The reduction in total LDL particle concentration with IPE 4 g/day is consistent with the previously reported reduction in apolipoprotein B levels.[10] The reduction in apolipoprotein B, as well as the reduction in VLDL particle size, is consistent with the lipoprotein- and TG-lowering effects of IPE.[3]

IPE did not significantly increase LDL cholesterol levels in the patient population with very high TG levels,[10] which is unique given that other TG-lowering agents such as fibrates and fish oil therapies containing both EPA and DHA increase LDL cholesterol levels, sometimes substantially.[3,14] These findings are supported by a recent literature review that found that DHA treatment was more often associated with increases in LDL cholesterol than EPA treatment,[15] as well as by a meta-analysis of 21 randomized clinical trials that concluded that although EPA and DHA both reduced TG, DHA significantly increased HDL cholesterol and LDL cholesterol, whereas EPA nonsignificantly reduced LDL cholesterol and caused a nonsignificant increase in HDL cholesterol.[16] This lack of LDL cholesterol increase observed for IPE may correlate with the reduction in LDL particle concentration observed in this analysis. In contrast to IPE, a prescription EPA and DHA combination was reported to produce reductions in IDL and small LDL

Table 4 Median percent change from baseline to study end in lipoprotein particle size (nm)

	IPE 4 g/day (n = 61*)			IPE 2 g/day (n = 63)			Placebo (n = 53)			Median placebo-adjusted percent change from baseline	
	Baseline value (IQR)	End-of-treatment value (IQR)	Change from baseline, % (IQR)	Baseline value (IQR)	End-of-treatment value (IQR)	Change from baseline, % (IQR)	Baseline value (IQR)	End-of-treatment value (IQR)	Change from baseline, % (IQR)	IPE 4 g/day vs placebo, %, P	IPE 2 g/day vs placebo, %, P
VLDL	62.3 (12.3)	55.7 (13.1)	−8.6 (19.6)	64.9 (12.3)	60.6 (16.4)	−3.4 (14.9)	66.8 (15.7)	65.7 (15.0)	−1.05 (12.1)	−8.6, .0017	−4.0, .0734
LDL	19.6 (0.2)	19.7 (0.6)	0.0 (2.6)	19.6 (0.3)	19.6 (0.5)	0.0 (2.1)	19.6 (0.2)	19.6 (0.3)	0.0 (1.0)	0.5, .4219	0.0, .8695
HDL	8.9 (0.4)	8.9 (0.4)	1.1 (4.3)	8.8 (0.4)	8.9 (0.4)	0.0 (3.4)	8.9 (0.4)	8.9 (0.4)	0.0 (3.3)	1.1, .1152	0.0, .7390

HDL, high-density lipoprotein; IPE, icosapent ethyl; IQR, interquartile range; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.
Data are presented as median (IQR) for end point values. Median placebo-adjusted percent changes are Hodges-Lehmann medians.
* n = 60 for LDL.

particle concentrations and increases in large LDL particle concentrations while leaving the concentration of total LDL particles unchanged.[17] Further research is needed to gain a better understanding of the mechanism of action of IPE relative to combination EPA and DHA agents.

Organizations such as the American Diabetes Association and the American College of Cardiology have suggested the clinical use of apolipoprotein B and LDL particle concentration to help assess residual cardiovascular risk and aid in treatment strategies for patients with dyslipidemia.[18] LDL particle concentration as measured by NMR,[19–21] as well as studies of apolipoprotein B, a surrogate marker of LDL particle concentration,[22] are significant predictors of cardiovascular risk. The significant reduction in the concentration of total LDL particles in this analysis, along with the previously reported reduction of apolipoprotein B by IPE in the MARINE study,[10] may therefore have clinical significance.

Similar to this current analysis with IPE, in a previous study of a prescription EPA and DHA combination, investigators showed a reduction in HDL particle concentration that was due primarily to reduction in medium but not small or large HDL particle concentration.[17] The clinical significance of the reduction in HDL particle number is unknown. However, irrespective of potential effects of omega-3 fatty acids on HDL particle number, clinical trials support the cardiovascular benefits of EPA and DHA combination, as well as EPA alone.[23–25] This finding has presumably contributed to recommendations that HDL subfraction measurement not be recommended for initial assessment or on-treatment management of cardiovascular risk.[12]

Some studies have suggested that smaller LDL particles are more atherogenic than larger LDL particles[26–28] and that LDL particle size is inversely related to on-treatment TG levels.[17,29] The lack of change in LDL particle size observed in this analysis was expected because changes in LDL particle size occur most often at TG threshold levels between 100 and 250 mg/dL,[17,29,30] which were levels largely unachieved due to the very high TG entry criteria ($\geq$500 mg/dL). Although baseline lipoprotein particle size may assist in CHD risk assessment, virtually no data exist to support that therapeutic changes in lipoprotein particle size improve CHD outcomes, and the totality of CHD outcomes evidence suggests that lipid-altering therapy might best be focused toward reducing LDL cholesterol, apolipoprotein B, non-HDL cholesterol, and LDL particle number.[31] As with HDL subfraction monitoring, no CHD outcomes data exist to support LDL subfraction monitoring for CHD risk assessment or for on-treatment monitoring of cardiovascular risk.[12] Although definitive CHD outcome data are likewise lacking, assessment of LDL particle number is sometimes recommended for the initial management of cardiovascular risk in certain patient populations, such as those with discordantly elevated LDL particle number[12] due to the stronger association of LDL particle number than LDL cholesterol with risk of CVD events in these patients.[19]

Although neither the MARINE study nor the present analysis assessed CHD outcomes, in previous study, authors supported that a strategy of EPA therapy has the potential to reduce CHD events.[32] Regarding IPE, the evidence to date suggests that this agent significantly lowers TG and apolipoprotein B levels without increasing LDL cholesterol.[10] The ongoing Reduction of Cardiovascular Events With EPA-Intervention (REDUCE-IT; NCT1492361) study will evaluate the effect of IPE on prevention of a first major cardiovascular event in approximately 8000 patients with hypertriglyceridemia at high risk for cardiovascular events, and will provide important information about the utility of IPE for therapy in patients at risk for cardiovascular disease.

Conclusions

In this 12-week study of patients with TG levels ≥500 and ≤2000 mg/dL, IPE 4 g/day significantly reduced large VLDL, total LDL, small LDL, and total HDL particle concentrations and VLDL particle size. The reduction in LDL particle concentration observed with IPE therapy is novel among ω-3 therapies and is consistent with the previously reported reduction in apolipoprotein B concentration and lack of LDL cholesterol concentration increase in patients with very high TG levels treated with IPE.

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