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Icosapent ethyl (eicosapentaenoic acid ethyl ester): Effects on remnant-like particle cholesterol from the MARINE and ANCHOR studies

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ABSTRACT

Background and aims: Remnant-like particle cholesterol (RLP-C) is atherogenic and may increase atherosclerotic cardiovascular disease risk. Icosapent ethyl is a high-purity prescription eicosapentaenoic acid ethyl ester (approved as an adjunct to diet to reduce triglyceride [TG] levels in adult patients with TGs ≥500 mg/dL [≥5.65 mmol/L] at 4 g/day). In the MARINE and ANCHOR studies, icosapent ethyl reduced TG and other atherogenic lipid parameter levels without increasing low-density lipoprotein cholesterol (LDL-C) levels. This exploratory analysis evaluated the effects of icosapent ethyl on calculated and directly measured RLP-C.

Methods: MARINE (TGs ≥500 and ≤2000 mg/dL [≥5.65 mmol/L and ≤22.6 mmol/L]) and ANCHOR (TGs ≥200 and <500 mg/dL [≥2.26 and <5.65 mmol/L] despite statin-controlled LDL-C) were phase 3, 12-week, double-blind studies that randomized adult patients to icosapent ethyl 4 g/day, 2 g/day, or placebo. This analysis assessed median percent change from baseline to study end in directly measured (immunoseparation assay) RLP-C levels (MARINE, n = 218; ANCHOR, n = 252) and calculated RLP-C levels in the full populations.

Results: Icosapent ethyl 4 g/day significantly reduced directly measured RLP-C levels −29.8% ($p = 0.004$) in MARINE and −25.8% ($p = 0.0001$) in ANCHOR *versus* placebo, and also reduced directly measured RLP-C levels to a greater extent in subgroups with higher *versus* lower baseline TG levels, in patients receiving statins *versus* no statins (MARINE), and in patients receiving medium/higher-intensity *versus* lower-intensity statins (ANCHOR). Strong correlations were found between calculated and directly measured RLP-C for baseline, end-of-treatment, and percent change values in ANCHOR and MARINE (0.73–0.92; $p < 0.0001$ for all).

Conclusions: Icosapent ethyl 4 g/day significantly reduced calculated and directly measured RLP-C levels *versus* placebo in patients with elevated TG levels from the MARINE and ANCHOR studies.

1. Introduction

Triglyceride (TG)-rich apolipoprotein B (ApoB)-containing lipoproteins released from the intestine or liver undergo lipolysis at the surface of endothelial cells, creating TG-poor and cholesterol-rich remnant particles (e.g., chylomicron remnants in the non-fasting state and dense subfractions of very-low-density lipoprotein [VLDL] and intermediate-density lipoprotein in the fasting and non-fasting states) [1,2]. An indirect approximation of remnant lipoprotein cholesterol (RLP-C) levels can be readily achieved by subtracting the cholesterol carried by low-density lipoproteins (LDL-C) from the cholesterol carried by all atherogenic lipoproteins, as reflected by non-high-density lipoprotein cholesterol (non-HDL-C), which in turn is calculated by subtracting high-density

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lipoprotein cholesterol (HDL-C) from total cholesterol (TC) (i.e., RLP-C = TC − [HDL-C] − [LDL-C]) [3]. More direct measures of RLP-C levels include immunoseparation and vertical auto profile testing [4]. Direct isolation of remnants allows for a more accurate measurement of the atherogenic cholesterol within the TG-rich lipoprotein subpopulation than calculated RLP-C, but such direct measures are not readily available to practicing clinicians [5].

High RLP-C levels appear to be a risk factor for atherosclerotic cardiovascular disease in patients with coronary artery disease, diabetes, or metabolic syndrome, as well as those on statin therapy [6–10]. Overall, current evidence suggests that elevated remnant cholesterol levels are one of the causal factors of residual ischemic heart disease risk [3] and cardiovascular disease [11].

Icosapent ethyl (Vascepa®; Amarin Pharma Inc., Bedminster, NJ, USA) is a high-purity prescription form of eicosapentaenoic acid (EPA) ethyl ester approved by the US Food and Drug Administration as an adjunct to diet to reduce TG levels in adult patients with severe hypertriglyceridemia (≥500 mg/dL [≥5.65 mmol/L]) at a dose of 4 g/day [12]. Two randomized, double-blind, placebo-controlled, multicenter, phase 3 studies (MARINE and ANCHOR) demonstrated the efficacy and safety of icosapent ethyl 2 g/day and 4 g/day. In both studies, icosapent ethyl 4 g/day significantly reduced TG levels and improved other lipid parameters including non-HDL-C and ApoB, without raising LDL-C levels compared with placebo [13,14]. To gain a better understanding of the lipid effects of icosapent ethyl, this exploratory analysis evaluated the impact of icosapent ethyl on directly measured and calculated RLP-C levels in patients from the MARINE and ANCHOR studies.

2. Materials and methods

2.1. Study design

Details of the MARINE and ANCHOR studies have been published previously [13,14]. Briefly, both studies included a 4–6 week lead-in period of diet, lifestyle, and medication stabilization with washout of prohibited lipid-altering medications. Both studies randomized patients aged >18 years with qualifying lipid levels (TGs ≥500 and ≤2000 mg/dL [≥5.65 and ≤22.6 mmol/L] in MARINE; statin-stabilized TGs ≥200 and <500 mg/dL [≥2.26 and <5.65 mmol/L] and LDL-C ≥40 and <100 mg/dL [≥1.04 and <2.59 mmol/L] in ANCHOR) to receive icosapent ethyl 4 g/day, icosapent ethyl 2 g/day, or matching placebo during a 12-week double-blind treatment period. The MARINE study permitted, but did not require stable statin therapy with or without ezetimibe. Enrollment in the ANCHOR study required patients to be at high risk of cardiovascular disease as defined by the National Cholesterol Education Program Adult Treatment Panel III guidelines [15] and on a stable statin dose (atorvastatin, rosuvastatin, or simvastatin with or without ezetimibe) prior to baseline initiation of icosapent ethyl or placebo. The protocols for each study were approved by the appropriate institutional review boards, and all patients provided written informed consent before enrollment [13,14].

2.2. Assessments and measurements

The MARINE and ANCHOR studies measured serum RLP-C as a prespecified exploratory endpoint using an immunoseparation assay from Polymedco (Cortlandt, NY, USA) on a Daytona chemistry analyzer (Randox Laboratories, Crumlin, UK) [16–18]. A central laboratory measured other lipid parameters as previously described, including LDL-C measurements by preparative ultracentrifugation (beta-quantification) [13,19]. Plasma lipid parameter evaluations included patients from the intent-to-treat population, defined as all randomized patients who had a baseline TG measurement, received ≥1 dose of the study drug, and had ≥1 post-randomization efficacy measurement.

2.3. Statistical analysis

Medians and interquartile ranges of RLP-C were calculated for each treatment group at baseline and at week 12, and for the percent changes from baseline. The median differences in percent changes from baseline for RLP-C were estimated between the icosapent ethyl and placebo groups using the Hodges-Lehmann method, with the Wilcoxon rank sum test used to calculate p values. Subgroup analyses were conducted by baseline TG level in each study, by statin use in the MARINE study, and by the statin intensity (lower vs medium/higher) in the ANCHOR study. This post hoc analysis computed Pearson correlation coefficients to assess the relationships between calculated RLP-C and directly measured RLP-C for baseline, week 12, and percent change from baseline values. Each analysis utilized pooled data from the icosapent ethyl treatment and placebo groups. A p value of 0.05 was the prespecified alpha for significance for exploratory endpoints in the MARINE and ANCHOR studies and was used in all analyses, including post hoc analyses in this report. The formula of RLP-C (TC − [HDL-C] − [LDL-C]; LDL-C being measured or calculated) was employed for correlation analyses involving calculated RLP-C levels [3]. For these RLP-C calculations, LDL-C was either directly measured by preparative ultracentrifugation (beta-quantification) or, when applicable, calculated. When calculated LDL-C was included in the RLP-C equation, the Friedewald equation (LDL-C = TC − [HDL-C] − [TG/5]) was applied, but only for patients with TG levels <400 mg/dL (<4.52 mmol/L) [20]. When applicable, resulting calculated RLP-C values are reported for both LDL-C methods.

3. Results

3.1. Patients

Baseline demographics and lipid parameters were comparable among treatment groups within each study (Table 1). In MARINE, 57 of 229 patients (25%) were receiving statin therapy, whereas in ANCHOR, all 702 patients were on statins, of whom 654 (93%) were on medium- or higher-intensity statin regimens (definitions of medium- and higher-intensity statin regimens are listed in the legend of Table 2). An immunoseparation assay was used to assess total RLP-C levels in MARINE and ANCHOR. In MARINE, RLP-C measurements were available from 218 patients (95% of study cohort); in ANCHOR, as prespecified in the study protocol, RLP-C measurements were to be conducted in (approximately) the first 240 patients enrolled (actual n = 252; 36% of study cohort).

Within each study, treatment groups showed comparable median baseline levels of TGs, non-HDL-C, LDL-C, VLDL-C, VLDL-TG, and ApoB in the subset of patients with RLP-C measurements (Table 1) as well as in the intent-to-treat populations of each study [13,14]. Each study also had comparable median RLP-C levels at baseline across treatment groups, ranging from 43.0 to 47.0 mg/dL (1.11–1.22 mmol/L) in MARINE and from 13.5 to 15.0 mg/dL (0.35–0.39 mmol/L) in ANCHOR (Table 2).

3.2. MARINE

At the approved dose of 4 g/day, icosapent ethyl significantly reduced median levels of directly measured RLP-C by −29.8% ($p = 0.004$) (Fig. 1 and Table 2) *versus* placebo. When evaluated by statin use, icosapent ethyl 4 g/day significantly reduced directly measured RLP-C levels by −21.4% in patients not receiving statins