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Effect of Eicosapentaenoic and Docosahexaenoic Acids Added to Statin Therapy on Coronary Artery Plaque in Patients With Coronary Artery Disease: A Randomized Clinical Trial

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Background—Although statins reduce cardiovascular events, residual risk remains. Therefore, additional modalities are needed to reduce risk. We evaluated the effect of eicosapentaenoic acid and docosahexaenoic acid in pharmacologic doses added to statin treatment on coronary artery plaque volume.

Methods and Results—A total of 285 subjects with stable coronary artery disease on statins were randomized to omega-3 ethyl-ester (1.86 g of eicosapentaenoic acid and 1.5 g of docosahexaenoic acid daily) or no omega-3 (control) for 30 months. Coronary plaque volume was assessed by coronary computed tomographic angiography. Mean (SD) age was 63.0 (7.7) years; mean low-density lipoprotein cholesterol \leq 80 mg/dL. In the intention-to-treat analysis, our primary endpoint, noncalcified plaque volume, was not different between groups ($P=0.14$) but approached significance in the per protocol analysis ($P=0.07$). When stratified by age in the intention-to-treat analysis, younger omega-3 subjects had significantly less progression of the primary endpoint, noncalcified plaque ($P=0.013$), and fibrous, calcified and total plaque. In plaque subtype analysis, controls had significant progression of fibrous plaque compared to no change in the omega-3 ethyl-ester group (median % change [interquartile range], 5.0% [−5.7, 20.0] versus −0.1% [−12.3, 14.5], respectively; $P=0.018$). Among those on low-intensity statins, omega-3 ethyl-ester subjects had attenuation of fibrous plaque progression compared to controls (median % change [interquartile range], 0.3% [−12.8, 9.0] versus 4.8% [−5.1, 19.0], respectively; $P=0.032$). In contrast, those on high-intensity statins had no difference in plaque change in either treatment arm.

Conclusions—High-dose eicosapentaenoic acid and docosahexaenoic acid provided additional benefit to statins in preventing progression of fibrous coronary plaque in subjects adherent to therapy with well-controlled low-density lipoprotein cholesterol levels. The benefit on low-intensity statin, but not high-intensity statin, suggests that statin intensity affects plaque volume.

Clinical Trial Registration—URL: <http://www.ClinicalTrials.gov>. Unique identifier: NCT01624727. (*J Am Heart Assoc.* 2017;6:e006981. DOI: 10.1161/JAHA.117.006981.)

Key Words: coronary computed tomography angiography • coronary plaque subtype • eicosapentaenoic acid • omega-3 fatty acids • plaque progression

Despite the significant reduction in cardiovascular events with statin therapy, those on statins still suffer from a high level of residual risk manifested as atherosclerotic plaque progression and cardiovascular events despite statin treatment to achieve target low-density-lipoprotein cholesterol

(LDL-C) reduction \leq 70 mg/dL.^{1–3} Therefore, additional modalities to reduce residual risk are needed. In the JELIS (Japan Eicosapentaenoic Lipid Intervention Study), addition of 1800 mg/day of open-label eicosapentaenoic acid (EPA) to low-intensity statin therapy conferred a significant 19%

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Clinical Perspective

What Is New?

- High dose eicosapentaenoic acid and docosahexaenoic acid (3.36 g daily) provided additional benefit to statins in preventing progression of fibrous coronary plaque over 30 months measured by coronary computed tomographic angiography in coronary artery disease subjects adherent to therapy with low-density lipoprotein cholesterol <80 mg/dL.
- Subjects aged <64.2 years had significantly less progression of noncalcified plaque (primary endpoint) and fibrous, calcified, and total plaque volume compared with older subjects.
- Eicosapentaenoic acid and docosahexaenoic acid prevented plaque progression in those on low-intensity statin, but not high-intensity statin.
- Musculoskeletal events, infectious diseases, and joint replacement were significantly lower with eicosapentaenoic acid and docosahexaenoic acid.

What Are the Clinical Implications?

- The benefit in younger subjects suggests that eicosapentaenoic acid and docosahexaenoic acid earlier in the course of disease may be beneficial.
- If high-intensity statin is not tolerated, adding high-dose eicosapentaenoic acid and docosahexaenoic acid to low-intensity statin may still prevent plaque progression.
- Past studies suggest that plaque volume predicts cardiovascular events, supporting the potential clinical importance of lack of plaque progression in the eicosapentaenoic acid/docosahexaenoic acid arm.
- The dose of 3.36 g is higher than can be achieved by consuming regular foods such as fish and higher than used in past trials with clinical end points.
- Eicosapentaenoic acid and docosahexaenoic acid may reduce musculoskeletal events and limit joint replacement.

reduction in major coronary events compared with statins alone, a finding suggesting that EPA added to low-intensity statin therapy can reduce residual risk.⁴

Omega-3 fatty acids are approved by the US Food and Drug Administration for lowering elevated levels of triglyceride, but their beneficial effect was independent of triglyceride lowering in the JELIS trial⁴; therefore, other mechanisms need to be explored. The aim of the current study was to determine whether high-dose, very-long-chain omega-3 polyunsaturated fatty acids—EPA and docosahexaenoic acid (DHA)—conferred additional benefit to statin treatment in preventing progression of coronary plaque volume compared with statin alone in patients with coronary artery disease (CAD). Coronary plaque volume was measured by coronary computed tomographic angiography (CCTA). We chose CCTA

because it is noninvasive, allows for examination of all coronary arteries in contrast to intravascular ultrasound, which examines only a culprit artery, and has been validated to detect progression of coronary plaque volume.^{5–8} Moreover, CCTA has shown attenuation of progression of coronary plaque by statin drugs.^{9–13}

Methods

Imaging methods, analytical methods, and study materials have been made available to other researchers for purposes of reproducing the results or replicating the procedures.^{14,15}

Study Design

The HEARTS (Slowing HEART Disease With Lifestyle and Omega-3 Fatty Acids) trial was a randomized, controlled, parallel clinical trial conducted at Beth Israel Deaconess Medical Center (Boston, MA). The protocol was approved by the Beth Israel Deaconess Medical Center Institutional Review Board, and all subjects signed informed consent. The hypothesis was that omega-3 ethyl-ester supplementation plus statin is superior to statin alone over 30 months in reducing progression of noncalcified coronary artery plaque measured by CCTA in patients with stable CAD.

Participants

Eligible participants were aged 21 to 80 years and had stable CAD defined as at least 1 of the following: $\geq 50\%$ stenosis in at least 1 coronary artery at cardiac catheterization; previous myocardial infarction (≥ 6 months previously) or percutaneous coronary intervention (≥ 6 months previously); coronary bypass surgery (≥ 12 months previously); abnormal exercise treadmill test (defined as at least 1 mm of horizontal or downsloping ST depression in at least 2 contiguous ECG leads) or an area of reversible ischemia on nuclear imaging; and pharmacologic stress or stress echocardiography with subsequent revascularization. Inclusion criteria also included a body mass index (BMI; weight in kilograms divided by height in meters squared) ≥ 27 kg/m² or a BMI of 25 to 26.9 with either an increased waist circumference or a history of at least 2 components of metabolic syndrome, which included triglyceride ≥ 150 mg/dL, high-density lipoprotein cholesterol <40 mg/dL if male or <50 mg/dL if female, glucose ≥ 100 mg/dL, or treated hypertension or blood pressure $\geq 130/85$ mm Hg.¹⁶ Additional inclusion criteria included stable use of 3-hydroxy-3-methylglutaryl-CoA reductase inhibitor (statin) and estimated creatinine clearance as measured by the Cockcroft-Gault equation ≥ 60 mL/min per 1.73 m². Exclusion criteria for CCTA were BMI >35 kg/m² (females) or >40 kg/m² (males), contraindication to iodinated contrast agents, and serum creatinine >1.5 mg/dL.

Randomization and Study Intervention

Randomization was computer allocated in blocks of 4 and stratified by presence or absence of diabetes mellitus. The trial protocol included a screening visit, baseline visit, and follow-up visits at 6 weeks and 3, 6, 9, 12, 18, 24, and 30 months. A detailed history, physical examination, height, weight, and waist measurement, blood pressure measurement, ECG, and ascertainment of medications were obtained at each visit. Blood samples were obtained after a 12-hour fast, and plasma and serum were prepared. Glucose, hemoglobin A1c, chemical profile, total white blood cell count, absolute neutrophil, lymphocyte, monocyte, and platelet counts and lipid panel were measured at Quest Diagnostics (Cambridge, MA). High-sensitivity C-reactive protein was measured by immunoturbidimetric assays using an automated, standardized, high-throughput method with coefficient of variation below 5% at Boston Heart Diagnostics (a College of American Pathologists-accredited, Clinical Laboratory Improvement Amendments-certified clinical laboratory; Framingham, MA). CCTA was performed at baseline and repeated at 30 months. Adverse events were assessed by questionnaires at follow-up visits.

Participants were randomly assigned to receive either open-label, omega-3 ethyl esters prepared from fish oil (Lovaza) in the form of 4 capsules daily or no Lovaza (termed control) for 30 months. All subjects were on a stable dose of a statin for at least 3 months. Subjects in the omega-3 ethyl-ester group received 3.36 g of Lovaza as 4 soft gels. Each 1000-mg capsule of Lovaza contains at least 900 mg of the ethyl esters of omega-3 fatty acids with EPA (465 mg) and DHA (375 mg) for a total daily dose of 1.86 g of EPA and 1.5 g of DHA, a dose higher than the amount of omega-3 fatty acids that can be derived from dietary intake. The GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico)-prevention study¹⁷ and the GISSI heart failure trial¹⁸ used 1 g of omega-3 fatty acid daily (\approx 850 mg of EPA and DHA) and had a reduction in cardiovascular events. Subsequent trials used the same dose, but had negative outcomes possibly attributed to increased use of cardioprotective medications that were not available when GISSI was done.^{19–21} Therefore, we used a higher dose of 3.36 g of EPA and DHA daily. Controls were instructed not to take over-the-counter omega-3 fatty acid supplementation. A detailed medication list was obtained during each visit to screen for compliance with omega-3 ethyl-ester and the use of over-the-counter omega-3 fatty acids. Lovaza was provided by GlaxoSmithKline (Research Triangle Park, NC).

Image Acquisition and Reconstruction

Imaging was performed at Beth Israel Deaconess Medical Center using a 320-row detector scanner (Aquilion ONE; Toshiba Medical Systems, Otawara, Japan) with prospective

ECG gating. The protocol for performance of CCTA, plaque identification, and quantification has been previously published^{14,15} with image acquisition details and references in Appendix 1 in Supplement 2 of Hauser et al.¹⁵

Coronary Plaque Analysis

CCTA images underwent 3-dimensional reconstruction for coronary segment plaque volume analysis using semiautomated software (SUREPlaque, version 6.3.2; Vital Images, Minnetonka, MN).^{7,22–24} Representative images have been previously published (Supplement 2 in Hauser et al).¹⁵ Segments with past revascularization or significant calcification causing calcium-bloom artifact were excluded. Branches or focal calcification served as fiducial markers to ensure measurement of the same segment at 30-month follow-up. Plaque analysis was performed independently by 2 readers blinded to treatment allocation. Noncalcified plaque, the sum of fatty and fibrous plaque, was based on Hounsfield unit densities of fatty (-100 to 49 Hounsfield units) and fibrous plaque (50 – 150 Hounsfield units). Calcified plaque was ≥ 150 Hounsfield units. Plaque volumes were indexed to the length of the plaque lesion; indexed plaque volume was defined as plaque volume (mm^3) divided by artery segment length (mm).

Statistical Analysis

The primary outcome was percent change in indexed volume of noncalcified coronary plaque, the sum of fatty and fibrous plaque, at 30-month follow-up compared with baseline. A prespecified per-protocol analysis of primary and secondary outcomes was done in those who adhered to treatment. Given that biological mechanisms for formation of fatty and fibrous plaque may differ, prespecified secondary outcomes included assessing changes in fatty and fibrous plaques individually as well as calcified and total plaque volumes. Sample size for the primary outcome was estimated based on data from the single longitudinal CCTA study at the time showing a mean (SD) 24% (13%) reduction in coronary plaque volume with statin treatment in 27 patients.⁹ Given the lack of data on the effect of omega-3 fatty acid on coronary plaque, we powered the study to detect a 4% reduction (one sixth that of statins) in plaque volume in the omega-3 ethyl-ester group compared with no change in controls. Therefore, a total of 111 subjects completing the trial in each treatment group were required to achieve 80% power with a type I error of 0.05. The analysis was performed following intention-to-treat and per-protocol principles. Subgroup analyses stratified by age, BMI, triglyceride, and LDL-C \leq and $>$ than the median was performed. Subgroup analyses were also performed for sex, diabetes mellitus status, and statin intensity. Categorical variables

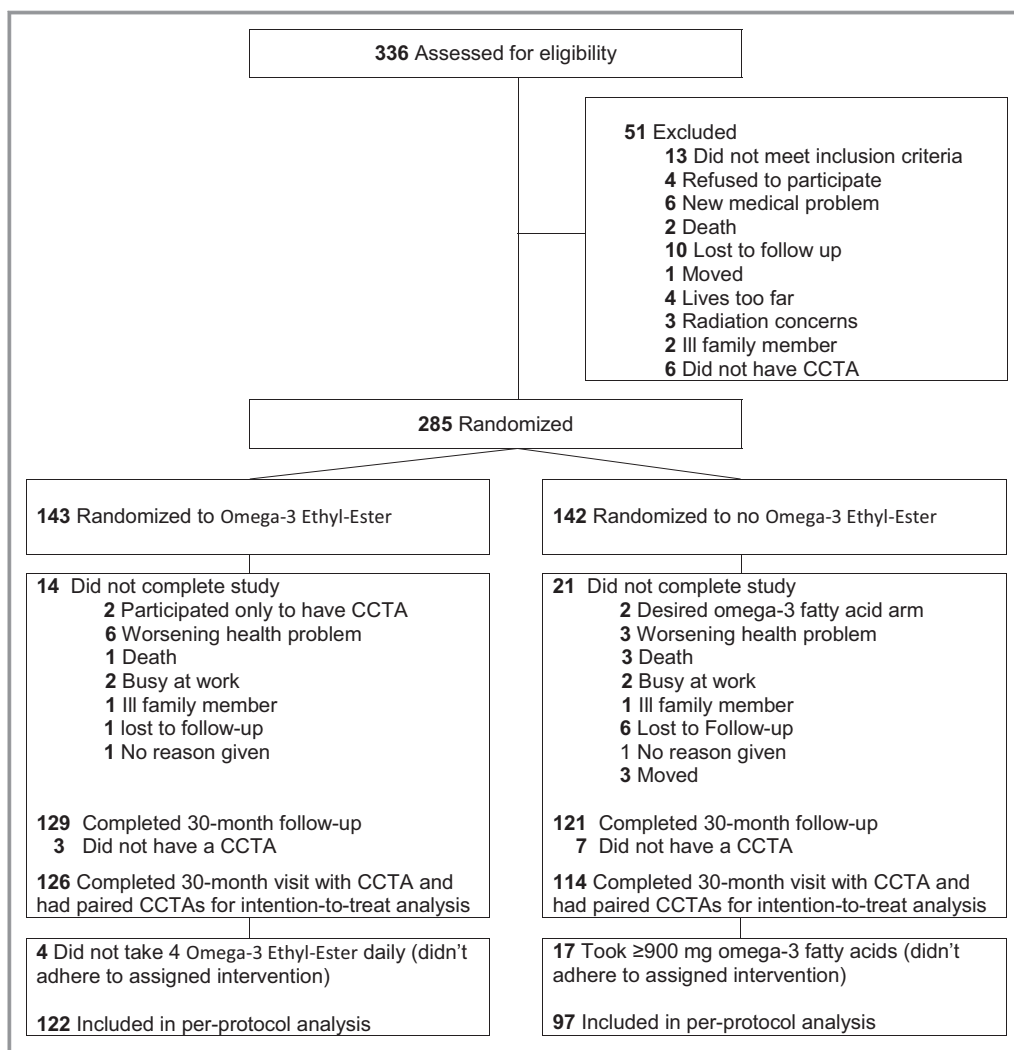


Figure. Consolidated standards of reporting trials diagram. CCTA indicates coronary computed tomographic angiography.

were expressed as counts and percentages. Normality tests were conducted using the Shapiro–Wilk test. Continuous variables were reported as the mean and SD or 95% confidence interval (CI) for normally distributed variables or median and interquartile range [IQR] for non-normally distributed variables. Plaque volumes and % change were not normally distributed and therefore are reported as median [IQR]. Continuous variables were compared using unpaired (between-group comparisons) and paired *t* tests (within-group comparisons) for normally distributed variables or the Mann–Whitney *U* test (between-group comparisons) and Wilcoxon signed-rank test (within group comparisons) for non-normally distributed variables. Correlations were determined using Pearson correlation coefficient for normally distributed variables or Spearman’s rank correlation coefficient for non-normally distributed variables. A 2-sided $P \leq 0.05$ was considered statistically significant. Ninety-five percent CIs around estimated mean differences between treatment

groups for change in baseline biochemical and anthropometric data are reported. Comparisons of coronary plaque subtypes were a prespecified secondary analysis; therefore, *P* values were not adjusted. Data analyses were performed using SPSS software (version 20.0; IBM Corp, Armonk, NY).

Results

Demography and Study Adherence

Of 336 subjects screened, 285 underwent baseline CCTA evaluation and were randomized to omega-3 ethyl-ester ($n=143$) or no omega-3 ethyl-ester ($n=142$; Figure). Fourteen of those receiving omega-3 ethyl-ester and 21 of those not receiving omega-3 ethyl-ester discontinued the intervention and did not have 30-month follow-up. Reasons for discontinuation are shown in Figure. Of those 250 subjects with 30-month follow-up, 10 did not have a 30-month CCTA scan,

the majority attributed to developing an allergy to iodinated contrast material over the 30-month follow-up. Of the remaining 240 subjects, 126 in the omega-3 ethyl-ester group and 114 in control had paired CCTA scans and were included in the intention-to-treat analysis for the primary end point. In the per-protocol analysis, we excluded 17 controls who took ≥ 900 mg of omega-3 fatty acids and 4 subjects in the omega-3 ethyl-ester group who did not take daily omega-3 ethyl-ester.

Clinical and Laboratory Outcomes

Baseline characteristics are shown in Table 1. Mean (SD) age was 63.0 (7.7) years and 15% were women. Tables 2 and 3 show baseline values of clinical and laboratory variables and % change from baseline at 30-month follow-up in the control and omega-3 ethyl-ester groups according to the intention-to-treat and per-protocol analyses, respectively. In both analyses at 30-month follow-up (Tables 2 and 3), mean LDL-C was similar between the 2 groups (for intention-to-treat: mean [SD], 77.5 mg/dL [28.3] versus 80.5 mg/dL [33.7]; $P=0.46$). In the intention-to-treat analysis (Table 2), those receiving omega-3 ethyl-ester had a significant reduction in triglyceride level (median [IQR], 123.0 mg/dL [81.5, 178.5] to 102.0 mg/dL [67.5, 146.8]; paired $P<0.001$) whereas controls had no significant change (median [IQR], 117.0 mg/dL [83.0, 161.5] to 113.0 mg/dL [78.5, 169.8]; paired $P=0.70$); the % change between the 2 groups was significant (median % change [IQR], -14.3% [$-32.1, 9.5$] versus -2.2% [$-19.4, 16.1$], respectively; $P=0.003$). No significant difference was observed in the % change of high-sensitivity C-reactive protein in the controls compared with the omega-3 ethyl-ester group (mean difference, 53.4%; 95% CI, -42.2 to 149.1; $P=0.27$). There were no other significant between-group differences.

Coronary Plaque Outcomes

The intraobserver and interobserver agreement indexes were 0.99 and 0.98, respectively, showing excellent correlation between readings. Table 4 reports the changes in coronary plaque volume. No significant differences were observed at baseline in the volume of fatty, fibrous, noncalcified, calcified, and total coronary plaque between the 2 treatment groups. For our primary end point of noncalcified plaque, which is the sum of fatty and fibrous plaque, the difference between control and omega-3 ethyl-ester groups was not significant at 30-month follow-up in the intention-to-treat analysis (median % change [IQR], 4.5% [$-6.1, 15.8$] versus -2.4% [$-9.8, 16.7$], respectively; between-group, $P=0.14$), but approached significance in the per-protocol analysis (median % change [IQR], 4.4% [$-5.9, 16.0$] versus -2.7% [$-10.3, 16.4$], respectively; between-group, $P=0.072$). Because the mechanism for

development of fatty and fibrous plaque may differ, we also analyzed results for these subtypes. The difference between control and omega-3 ethyl-ester groups for fibrous plaque approached significance for the intention-to-treat analysis (median % change [IQR], 4.6% [$-8.0, 18.5$] versus 0.1% [$-12.2, 14.9$], respectively; between-group, $P=0.063$) and was significant for the per-protocol analysis (median % change [IQR], 5.0% [$-5.7, 20.0$] versus -0.1% [$-12.3, 14.5$], respectively; between-group, $P=0.018$). There was no difference in % change in total, fatty, or calcified plaque between the omega-3 ethyl-ester and control groups.

We next did a post-hoc subgroup analysis according to statin intensity. High-intensity statin includes atorvastatin ≥ 40 mg, rosuvastatin ≥ 20 mg, and simvastatin 80 mg. Table 5 shows the baseline characteristics in those on low-intensity statin compared with those on a high-intensity statin. In Table 6, in the intention-to-treat analysis, those on omega-3 ethyl-ester on low-intensity statins had attenuation of fibrous plaque progression compared with controls on low-intensity statin (median % change [IQR], 0.3% [$-12.8, 9.0$] versus 4.8% [$-5.1, 19.0$], respectively; $P=0.032$). This difference remained significant in the per-protocol analysis ($P=0.023$). In contrast, in the high-intensity statin group, no difference in plaque change was observed in either treatment arm.

In subgroup analyses, there was no significant difference stratified by BMI, triglyceride, and LDL-C \leq and $>$ than the median and for analyses stratified by sex and diabetes mellitus status. Table 7 shows that omega-3 subjects with age \leq the median had significantly lower plaque volume, including the primary end point, noncalcified plaque.

In the omega-3 ethyl-ester group, there was no correlation between triglyceride reduction and % change in fibrous plaque in either the intention-to-treat ($r=0.094$; $P=0.29$) or per-protocol analyses ($r=0.108$; $P=0.24$).

Adverse Events

No significant differences were observed in incidence of adverse events between the 2 treatment groups, with the exception of a significantly lower incidence of serious musculoskeletal events in the omega-3 ethyl-ester group compared with control (5 versus 14 events, respectively; $P=0.034$; Table 8). Of these, 11 control subjects had total knee or hip replacements compared with only 1 in the omega-3 ethyl-ester group. Furthermore, the incidence of nonserious musculoskeletal adverse events was also significantly lower in the omega-3 ethyl-ester group compared with control (43 versus 64 events; $P=0.008$). No significant differences in serious and nonserious musculoskeletal adverse events were observed in those on low- versus high-intensity statins. Finally, a significantly lower incidence of nonserious infectious

Table 1. Baseline Characteristics in the Control and Omega-3 Ethyl-Ester Groups

	Intention-to-Treat		Per-Protocol	
	Controls (n=114)	Omega-3 Ethyl-Ester (n=126)	Controls (n=97)	Omega-3 Ethyl-Ester (n=122)
Demographic characteristics				
Age, mean±SD, y	63.5±7.6	62.5±7.8	62.6±7.5	62.4±7.8
Male sex, n (%)	97 (85.1)	107 (84.9)	84 (86.6)	104 (85.2)
Inclusion criteria (may have more than 1), n (%)				
History of MI	50 (43.9)	62 (49.2)	47 (48.5)	60 (49.2)
History of PCI	69 (60.5)	81 (64.3)	59 (60.8)	77 (63.1)
History of CABG	35 (30.7)	24 (19.0)	26 (26.8)	23 (18.9)
Cardiovascular risk factors, n (%)				
Hypertension	101 (88.6)	99 (78.6)	87 (89.7)	96 (78.7)
Diabetes mellitus	34 (29.8)	34 (27.0)	27 (27.8)	33 (27.0)
Anthropometric and blood pressure, mean±SD				
Weight, kg	90.8±14.0	92.2±13.8	91.2±13.9	92.5±13.7
Body mass index, kg/m ² *	30.5±3.5	30.8±3.7	30.5±3.5	30.9±3.8
Waist circumference, cm	106.2±10.2	106.9±10.6	106.6±10.3	106.9±10.7
Systolic BP, mm Hg	124.5±14.0	124.2±14.7	124.1±13.9	124.3±14.8
Diastolic BP, mm Hg	73.3±9.6	73.3±10.0	73.3±9.8	73.3±10.1
Biochemical profile, mean±SD				
Glucose, mg/dL (mmol/L)	107.4±35.4 (6.0±2.0)	104.7±27.2 (5.8±1.5)	106.2±32.2 (5.9±1.8)	104.6±27.3 (5.8±1.5)
HbA1c, % (mmol/mol)	6.2±1.0 (44.0±10.0)	6.1±0.8 (43.0±9.0)	6.2±1.0 (44.0±10.0)	6.1±0.8 (43.0±9.0)
hs-CRP, mg/L (nmol/L)	1.7±2.4 (16.2±22.9)	1.9±2.4 (18.1±22.9)	1.8±2.5 (17.1±23.8)	2.0±2.4 (19.1±22.9)
Lipids, mean±SD				
Total cholesterol, mg/dL (mmol/L)	151.0±37.5 (3.9±1.0)	153.2±34.5 (4.0±0.9)	152.2±38.4 (3.9±1.0)	153.7±34.6 (4.0±0.9)
Triglyceride, median [IQR], mg/dL (mmol/L)	117.0 [83.0, 161.5] (1.3 [0.9, 1.8])	123.0 [81.5, 178.5] (1.4 [0.9, 2.0])	116.0 [84.0, 163.5] (1.3 [1.0, 1.9])	122.0 [81.5, 176.5] (1.4 [0.9, 2.0])
HDL-C, mg/dL (mmol/L)	46.9±14.9 (1.2±0.4)	47.3±14.2 (1.2±0.4)	47.2±15.5 (1.2±0.4)	47.6±14.3 (1.2±0.4)
LDL-C, mg/dL (mmol/L)	77.5±27.5 (2.0±0.7)	78.5±27.0 (2.0±0.7)	78.1±28.4 (2.0±0.7)	79.1±27.2 (2.1±0.7)
Complete blood count, mean±SD				
WBC, 10 ⁹ cells/L	6.5±1.8	6.8±2.4	6.6±1.8	6.8±2.4
Monocytes, cells/μL	536.7±169.2	521.4±165.3	538.3±176.7	516.0±157.3
Neutrophils, cells/μL	4125.0±1592.9	4179.8±1289.4	4153.2±1608.1	4155.2±1275.6
Lymphocytes, cells/μL	1620.7±509.2	1880.9±1882.6	1649.4±531.1	1884.3±1912.2
Platelets, cells/μL	191.5±45.6	191.0±53.9	194.7±44.5	190.5±54.5
Medication, n (%)				
Statin	107 (93.9)	121 (96.0)	91 (93.8)	117 (95.9)
Aspirin	110 (96.5)	121 (96.0)	93 (95.9)	117 (95.9)
ACE-I	63 (55.3)	68 (54.0)	53 (54.6)	66 (54.1)
ARB	25 (21.9)	21 (16.7)	21 (21.6)	20 (16.4)

Continued

Table 1. Continued

	Intention-to-Treat		Per-Protocol	
	Controls (n=114)	Omega-3 Ethyl-Ester (n=126)	Controls (n=97)	Omega-3 Ethyl-Ester (n=122)
Hydrochlorothiazide	23 (20.2)	22 (17.5)	21 (21.6)	21 (17.2)
Furosemide	12 (10.5)	7 (5.6)	9 (9.3)	7 (5.7)
Calcium-channel blocker	28 (24.6)	30 (23.8)	23 (23.7)	30 (24.6)
Beta blockers	85 (74.6)	88 (69.8)	73 (75.3)	86 (70.5)

ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CABG, coronary artery bypass grafting; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; WBC, white blood cell count.

*Calculated as weight in kilograms divided by height in meters squared.

disease events was observed in those taking omega-3 ethyl-ester.

Discussion

In the current randomized controlled trial, we examined whether omega-3 ethyl-ester added to statin therapy in patients with CAD reduced progression of coronary plaque volume compared with statin alone. In the intention-to-treat analysis, no difference was observed in our primary endpoint, noncalcified plaque volume, between the 2 treatment groups. However, when stratified by age, younger subjects had significant benefit, a finding suggesting that initiation of treatment earlier in the course of disease may be beneficial. Because this is a post-hoc analysis, it is hypothesis generating and should be examined further in future studies.

Because we were interested in the biological effect of omega-3 ethyl-ester, we also performed a per-protocol analysis in which our primary end point approached significance ($P=0.072$), a finding suggesting that adherence to treatment assignment is important. Only 4 subjects randomized to omega-3 ethyl-ester did not tolerate and stopped; however, 17 controls took ≥ 900 mg of over-the-counter omega-3 fatty acid daily. Thus, a limitation of our trial is the open-label nature, which gave subjects knowledge of their assignment and allowed controls to “drop-in” and perhaps affected the outcome.

Noncalcified plaque is the sum of fatty and fibrous plaque. Because the mechanisms for development of these 2 plaque subtypes may differ, we also analyzed results for subtypes in a prespecified subtype analysis. In the intention-to-treat analysis, the difference in fibrous plaque approached significance ($P=0.063$). Interestingly, in the per-protocol analysis, control subjects had significant progression of fibrous plaque compared with no change in those taking omega-3 ethyl-ester ($P=0.018$), a finding supporting a potential biological effect of omega-3 ethyl-ester with adherence to treatment assignment. This difference was observed in the setting of statin therapy, with a mean LDL-C of 77.5 mg/dL in the control group and 80.5 mg/dL in the omega-3 ethyl-ester group.

In a post hoc subgroup analysis of statin intensity, among those on low-intensity statin, controls had significant progression of fibrous plaque volume whereas those receiving high-dose omega-3 ethyl-esters had no change (median % change [IQR], 4.8% [−5.1, 19.0] versus 0.3% [−12.8, 9.0], respectively; $P=0.032$). Similar changes were noted in noncalcified plaque, with a trend toward significance ($P=0.062$). In contrast, in the high-intensity statin group, no difference in plaque change was observed in either treatment arm. Therefore, omega-3 ethyl-ester supplementation prevented progression of fibrous plaque in those on low-intensity statin therapy, but not in those on high-intensity statin. Clinical trials of the effect of omega-3 fatty acids on cardiovascular events have shown conflicting results with those preceding the statin era showing benefit,^{17,18} whereas those conducted during the statin era, with the exception of JELIS, have not (reviewed in de Lorgeril et al).¹⁹ The Omega and Alpha Omega trials were conducted in post-myocardial infarction patients, but showed no benefit.^{20,21} A total of 81.5% of patients were receiving statins in the Omega Trial²⁰ and 85% of patients were receiving statins in the Alpha Omega Trial.²¹ In an analysis of statin users and nonusers in the Alpha Omega Trial, no benefit of omega-3 fatty acids was observed on reduction of cardiovascular events among statin users (13% versus 15%, respectively). In contrast, among statin nonusers, 9% of those receiving omega-3 fatty acids had cardiovascular events compared with 18% of those not receiving omega-3 fatty acids (hazard ratio, 0.46; 95% CI, 0.21–1.01; $P=0.051$).²⁵ As noted earlier, the JELIS trial reported that addition of 1800 mg/day of open-label EPA to low-intensity statin therapy conferred a significant 19% reduction in major coronary events compared with low-intensity statin alone, a finding suggesting that high-dose EPA added to low-intensity statin therapy can reduce residual risk.⁴ These findings, coupled with our results, suggest that statin use and dose may be important factors affecting clinical outcomes and plaque volume. Further studies should investigate the mechanism of how statins interact with omega-3 fatty acids. This may be an important pharmacological issue because higher intensity statin therapy

Table 2. Percent Change From Baseline at 30-Month Follow-Up in the Control and Omega-3 Ethyl-Ester Groups in the Intention-to-Treat Analysis

	Control (n=114)		Omega-3 Ethyl-Ester (n=126)		Differences in % Change	
	Baseline Value Mean±SD	% Change From Baseline Mean (95% CI)	Baseline Value Mean±SD	% Change From Baseline Mean (95% CI)	Mean (95% CI)	P Value*
Clinical parameters						
Systolic BP, mm Hg	124.5±14.0	-2.7 (-5.2, -0.1)	124.2±14.7	-3.0 (-5.2, -0.9)	0.4 (-2.9, 3.7)	0.82
Diastolic BP, mm Hg	73.3±9.6	-4.4 (-6.5, -2.2)	73.3±10.0	-4.3 (-6.4, -2.2)	-0.1 (-3.1, 2.9)	0.96
Waist circumference, cm	106.2±10.2	0.3 (-0.6, 1.3)	106.9±10.6	7.6 (-6.6, 21.8)	-7.3 (-22.1, 7.5)	0.92
Weight, kg	90.8±14.0	-1.4 (-2.5, -0.3)	92.2±13.8	-0.9 (-2.2, 0.4)	-0.5 (-2.2, 1.2)	0.58
Body mass index, kg/m ²	30.5±3.5 [†]	-0.7 (-1.8, 0.4)	30.8±3.7 [†]	1.9 (-2.4, 6.2)	-2.6 (-7.2, 2.1)	0.28
Biochemical profile						
Glucose, mg/dL (mmol/L)	107.4±35.4 (6.0±2.0)	7.5 (1.2, 13.8)	104.7±27.2 (5.8±1.5)	8.2 (0.0, 16.4)	-0.7 (-11.2, 9.7)	0.89
HbA1c, % (mmol/mol)	6.2±1.0 (44.0±10.0)	1.7 (-0.1, 3.5)	6.1±0.8 (43.0±9.0)	1.4 (-0.2, 3.0)	0.3 (-2.1, 2.7)	0.82
hs-CRP, mg/L (nmol/L)	1.7±2.4 (16.2±22.9)	119.9 (35.8, 204.0)	1.9±2.4 (18.1±22.9)	66.4 (13.5, 119.5)	53.4 (-42.2, 149.1)	0.27
Lipid profile						
Total cholesterol, mg/dL (mmol/L)	151.0±37.5 (3.9±1.0)	0.9 (-2.3, 4.2)	153.2±34.5 (4.0±0.9)	0.7 (-3.7, 5.2)	0.2 (-5.3, 5.6)	0.26
Triglyceride, mg/dL [‡] (mmol/L)	117.0 [83.0, 161.5] (1.3 [0.9, 1.8])	-2.2 [-19.4, 16.1]	123.0 [81.5, 178.5] (1.4 [0.9, 2.0])	-14.3 [-32.1, 9.5]	17.2 (6.3, 28.0)	0.003
HDL-C, mg/dL (mmol/L)	46.9±14.9 (1.2±0.4)	-2.3 (-5.4, 0.9)	47.3±14.2 (1.2±0.4)	1.9 (-1.6, 5.4)	-4.2 (8.9, 0.6)	0.22
LDL-C, mg/dL (mmol/L)	77.5±27.5 (2.0±0.7)	3.7 (-1.8, 9.1)	78.5±27.0 (2.0±0.7)	7.8 (0.1, 15.5)	-4.1 (-13.5, 5.3)	0.76
Complete blood count						
WBC, 10 ⁹ cells/L	6.5±1.8	-2.5 (-6.7, 1.6)	6.81±2.4	-4.7 (-8.5, -0.9)	2.2 (-3.4, 7.8)	0.64
Monocytes, cells/μL	536.7±169.2	-5.3 (-9.9, -0.8)	521.4±165.3	-2.1 (-6.9, 2.7)	-3.2 (-9.8, 3.4)	0.20
Neutrophils, cells/μL	4125.0±1592.9	2.2 (-4.4, 8.8)	4179.8±1289.4	-3.7 (-9.2, 1.7)	6.0 (-2.5, 14.4)	0.23
Lymphocytes, cells/μL	1620.7±509.3	-5.6 (-9.5, -1.8)	1880.9±1882.6	-2.9 (-6.7, 0.9)	-2.8 (-8.2, 2.7)	0.23
Platelets, cells/μL	191.5±45.6	-6.1 (-9.2, -3.0)	191.0±53.9	22.7 (-11.9, 57.4)	-28.8 (-63.6, 6.0)	0.57

BP indicates blood pressure; CI, confidence interval; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; WBC, white blood cell count.

*P values calculated using *t* test (except triglycerides where a Mann-Whitney *U* test was used).

[†]Calculated as weight in kilograms divided by height in meters squared.

[‡]Values represented as median [interquartile range].

is more likely to have adverse side effects, particularly on muscle and joint symptoms, whereas omega-3 fatty acids actually reduce such symptoms as shown by the significantly lower incidence of both serious and nonserious musculoskeletal adverse events in the present study. Remarkably, 11 of the 14 serious musculoskeletal events in the control group were total knee or hip replacements attributed to progressive pain and/or arthritis whereas there was only 1 in the omega-3 ethyl-ester group. This was an unexpected finding, which may be a consequence of more-limited symptoms and/or decreased progression of arthritis. Joint replacement is an

expensive procedure; therefore, further studies should examine the effect of high-dose omega-3 ethyl-ester on joint symptoms given that prevention of joint replacement could be a huge cost-savings to the healthcare system.

Elevated levels of triglyceride are associated with increasing risk of coronary heart disease.²⁶ As expected, triglyceride levels were significantly reduced in the omega-3 ethyl-ester group compared with the control group. This reduction was not correlated with change in volume of fibrous plaque, and our subgroup analysis showed no difference in outcome when stratified by triglyceride levels above and below the median,

Table 3. Percent Change From Baseline at 30-Month Follow-Up in the Control and Omega-3 Ethyl-Ester Groups in the Per-Protocol Analysis

	Control (n=97)		Omega-3 Ethyl-Ester (n=122)		Differences in % Change	
	Baseline Value Mean±SD	% Change From Baseline Mean (95% CI)	Baseline Value Mean±SD	% Change From Baseline Mean (95% CI)	Mean (95% CI)	P Value*
Clinical parameters						
Systolic BP, mm Hg	124.1±13.9	-2.7 (-5.5, 0.1)	124.3±14.8	-3.0 (-5.2, -0.8)	0.3 (-3.2, 3.8)	0.86
Diastolic BP, mm Hg	73.3±9.8	-4.2 (-6.7, -1.8)	73.3±10.1	-4.3 (-6.5, -2.2)	0.1 (-3.1, 3.3)	0.95
Waist circumference, cm	106.6±10.3	0.4 (-0.6, 1.5)	106.9±10.7	8.0 (-6.7, 22.6)	-7.5 (-23.7, 8.6)	0.88
Weight, kg	91.2±13.9	-1.4 (-2.7, -0.2)	92.5±13.7	-0.9 (-2.2, 0.5)	-0.6 (-2.4, 1.3)	0.54
BMI, kg/m ²	30.5±3.5 [†]	-0.7 (-2.0, 0.5)	30.8±3.7 [†]	2.0 (-2.4, 6.5)	-2.8 (-7.8, 2.3)	0.28
Biochemical profile						
Glucose, mg/dL (mmol/L)	106.2±32.2 (5.9±1.8)	9.2 (2.0, 16.4)	104.6±27.3 (5.8±1.5)	8.3 (-0.1, 16.7)	0.9 (-10.5, 12.3)	0.88
HbA1c, % (mmol/mol)	6.2±1.0 (44.0±10.0)	1.7 (-0.4, 3.7)	6.1±0.8 (43.0±9.0)	1.6 (-0.1, 3.2)	0.1 (-2.5, 2.7)	0.80
hs-CRP, mg/L (nmol/L)	1.8±2.5 (17.1±23.8)	80.1 (22.0, 138.1)	2.0±2.4 (19.1±22.9)	60.8 (7.0, 114.7)	19.2 (-60.4, 98.9)	0.63
Lipid profile						
Total cholesterol, mg/dL (mmol/L)	152.2±38.4 (3.9±1.0)	0.8 (-2.9, 4.5)	153.7±34.6 (4.0±0.9)	0.5 (-4.1, 5.0)	0.3 (-5.7, 6.3)	0.29
Triglyceride, mg/dL [‡] (mmol/L)	116.0 [85.0, 163.0] (1.3 [1.0, 1.9])	0.9 [-18.3, 17.2]	122.0 [82.0, 175.0] (1.4 [0.9, 2.0])	-13.9 [-31.2, 10.4]	18.9 (7.2, 30.6)	0.003
HDL, mg/dL (mmol/L)	47.2±15.5 (1.2±0.4)	-3.5 (-6.9, -0.1)	47.6±14.3 (1.2±0.4)	1.6 (-1.9, 5.1)	-5.1 (-10.0, -0.2)	0.13
LDL, mg/dL (mmol/L)	78.1±28.4 (2.0±0.7)	3.8 (-2.3, 9.9)	79.1±27.2 (2.1±0.7)	6.6 (-1.2, 14.5)	-2.9 (-12.7, 7.0)	0.65
Complete blood count						
WBC, 10 ⁹ cells/L	6.6±1.8	-3.7 (-7.5, 0.2)	6.8±2.4	-4.8 (-8.7, -0.9)	1.1 (-4.5, 6.6)	0.74
Monocytes, cells/μL	538.3±176.7	-7.0 (-11.7, -2.2)	516.0±157.3	-1.8 (-6.7, 3.1)	-5.1 (-12.1, 1.8)	0.078
Neutrophils, cells/μL	4153.2±1608.1	1.7 (-5.1, 8.5)	4155.2±1275.6	-3.7 (-9.3, 1.9)	5.3 (-3.3, 14.0)	0.26
Lymphocytes, cells/μL	1649.4±531.1	-6.9 (-10.6, -3.2)	1884.3±1912.2	-3.0 (-6.9, 0.9)	-3.9 (-9.3, 1.5)	0.16
Platelets, cells/μL	194.7±44.5	-6.5 (-9.4, -3.5)	190.5±54.5	23.6 (-12.2, 59.4)	-30.1 (-66.0, 5.8)	0.68

BMI indicates body mass index; BP, blood pressure; CI, confidence interval; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; WBC, white blood cell count.

*P values calculated using *t* test (except triglycerides where a Mann-Whitney *U* test was used).

[†]Calculated as weight in kilograms divided by height in meters squared.

[‡]Values represented as median [interquartile range].

findings suggesting that other mechanisms account for the benefit. Atherosclerosis is a disease of chronic inflammation in the arterial wall characterized by upregulation of vascular cell adhesion molecules, which promote monocyte infiltration into the subendothelial space where differentiation to macrophages occurs.²⁷ These macrophages take up oxidized apolipoprotein B-containing LDL particles, a process leading to foam cell and fatty streak formation, the precursor of advanced atherosclerotic lesions. Potential beneficial effects of EPA on atherosclerotic plaque include anti-inflammatory

and antioxidant effects, decreased adhesion of monocytes to the endothelium, decreased macrophage and foam cell accumulation in fatty streaks, and increased thickness of the fibrous cap overlying lipid-rich plaque^{28–30} (reviewed in Nelson et al).³¹ EPA and DHA are also converted to specialized proresolving lipid mediators, with EPA and DHA being the respective precursors of the E-series and D-series resolvins.³² The resolvins have been shown to stimulate the resolution of acute inflammation by stopping further neutrophil recruitment to inflamed tissues and stimulating

Table 4. Percent Change in Plaque Volume at 30-Month Follow-Up Compared to Baseline in the Control and Omega-3 Ethyl-Ester Groups for the Intention-to-Treat and Per-Protocol Analyses

Plaque Volume*	Controls		Omega-3 Ethyl-Ester		% Change From Baseline		
	Baseline Value Median [IQR]	30-Month Value Median [IQR]	Baseline Value Median [IQR]	30-Month Value Median [IQR]	Controls Median [IQR]	Omega-3 Ethyl-Ester Median [IQR]	P Value [†]
Intention-to-treat							
	(n=114)		(n=126)				
Fatty	8.6 [5.1, 14.0]	8.6 [5.3, 13.7]	9.4 [4.9, 14.7]	9.3 [5.5, 14.8]	2.9 [−9.8, 15.1]	0.8 [−10.4, 20.1]	0.94
Fibrous	15.1 [8.7, 23.0]	15.9 [9.2, 23.5]	17.5 [9.5, 25.5]	16.1 [9.7, 24.3]	4.6 [−8.0, 18.5]	0.1 [−12.2, 14.9]	0.063
Noncalcified	23.7 [14.3, 36.8]	24.7 [14.5, 36.6]	26.4 [14.3, 39.7]	25.7 [15.0, 39.9]	4.5 [−6.1, 15.8]	−2.4 [−9.8, 16.7]	0.14
Calcified	3.6 [1.3, 7.3]	6.2 [2.6, 10.3]	5.0 [2.4, 8.7]	6.4 [3.3, 10.3]	57.4 [4.3, 146.6]	39.1 [−5.2, 118.1]	0.18
Total	28.1 [16.6, 44.3]	33.8 [18.1, 46.5]	33.2 [17.9, 47.0]	33.4 [19.1, 50.5]	10.0 [−3.1, 25.9]	6.5 [−6.9, 19.2]	0.11
Per-protocol							
	(n=97)		(n=122)				
Fatty	9.6 [5.1, 14.1]	9.6 [5.3, 14.2]	9.7 [4.9, 15.0]	9.3 [5.5, 14.8]	0.2 [−8.9, 13.0]	0.4 [−10.6, 20.0]	0.99
Fibrous	16.0 [9.0, 23.5]	17.1 [9.3, 23.9]	17.7 [9.5, 25.7]	16.1 [9.7, 24.3]	5.0 [−5.7, 20.0]	−0.1 [−12.3, 14.5]	0.018
Noncalcified	26.9 [14.3, 37.2]	26.0 [14.9, 36.9]	27.1 [14.3, 40.0]	25.7 [15.0, 39.9]	4.4 [−5.9, 16.0]	−2.7 [−10.3, 16.4]	0.072
Calcified	3.7 [1.5, 7.6]	6.3 [3.0, 10.5]	5.1 [2.6, 8.7]	6.4 [3.7, 10.3]	59.2 [6.2, 154.1]	39.1 [−3.8, 121.4]	0.16
Total	30.9 [16.4, 45.7]	34.6 [18.6, 47.2]	33.9 [17.9, 47.4]	33.4 [19.3, 51.3]	9.9 [−3.3, 27.1]	6.3 [−7.4, 18.7]	0.087

*Plaque volume expressed as mm³/mm.[†]P values calculated using a Mann–Whitney U test.

IQR indicates interquartile range.

nonphlogistic infiltration of monocytes, which differentiate into resolution macrophages.³³ These resolution macrophages then phagocytize and clear apoptotic neutrophils and debris, a process termed efferocytosis, which is a key step in resolution and prevention of chronic inflammation.^{33,34} Recent research has shown that omega-3 fatty acids may hasten the resolution of inflammation when converted to resolvins.^{32,33} Formation of fibrous tissue is an end stage of the chronic inflammatory process with the recruitment of collagen to form a scar. The formation of resolvins from EPA and DHA leads to resolution of inflammation and, by hastening resolution, may cause less fibrosis. Therefore, the conversion of EPA and DHA to their downstream products may account for a beneficial effect on inflammation, leading to a decrease in fibrotic plaque. In a recent study, EPA and DHA have been shown to reduce myocardial fibrosis. EPA and DHA supplementation for 6 months in post-myocardial infarction patients was associated with a favorable effect on left ventricular remodeling and a significant reduction in noninfarct myocardial fibrosis measured by cardiac magnetic resonance imaging (mean reduction, −5.6%; 95% CI, −10.4% to −0.9%; $P=0.022$) compared with placebo.³⁵ In a subset of 6 patients from the current study, several resolvins, which have been shown to be present in healthy subjects,^{36–38} were absent or present at low levels in CAD patients not on omega-3 ethyl-ester; the resolvins were restored or their level

increased in those receiving omega-3 ethyl-ester.³⁹ The stimulation of resolution of infection and inflammation by resolvins (the downstream products of EPA and DHA) may be responsible for the significantly lower rate of nonserious infectious disease events in the omega-3 group.^{40,41} Future studies should examine whether conversion of EPA and DHA to resolvins is responsible for these beneficial effects.

Several randomized controlled trials have reported a beneficial relationship between EPA and DHA levels and atherosclerosis (reviewed in Nelson et al).³¹ In a study of 81 subjects with type 2 diabetes mellitus, those randomized to open-label, purified EPA (1800 mg/day) had a significant annual decrease in mean and maximum carotid intima-media thickness compared with those on no EPA.⁴² In the Estrogen Replacement and Atherosclerosis Trial, 228 women were randomized to either 0.625 mg of conjugated equine estrogen, 0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate, or placebo.⁴³ After 3.2-year follow-up, those with phospholipid DHA levels above the median had less atherosclerosis progression as measured with coronary angiography. Two studies in Japanese patients have shown a significant additional benefit of EPA (1800 mg/day) added to statin therapy compared with statin alone on coronary plaque volume, as measured with integrated backscatter intravascular ultrasound.^{44,45} In a post-hoc analysis of 50 diabetics who were randomized to pravastatin or

Table 5. Baseline Characteristics for the Total Group Stratified by Statin Intensity

	Low-Intensity Statin (n=114)	High-Intensity Statin (n=126)	P Value
Controls	53 (46.5%)	61 (48.4%)	0.766
Omega-3 ethyl-ester	61 (53.5%)	65 (51.6%)	
Demographic characteristics			
Age, mean±SD, y	62.8±7.9	63.1±7.5	0.819
Male sex, n (%)	97 (85.1%)	107 (84.9%)	0.971
Inclusion criteria (may have more than 1), n (%)			
History of MI	45 (39.5%)	67 (53.2%)	0.034
History of PCI	62 (54.4%)	88 (69.8%)	0.014
History of CABG	32 (28.1%)	27 (21.4%)	0.233
Cardiovascular risk factors, n (%)			
Hypertension	91 (79.8%)	109 (86.5%)	0.165
Diabetes mellitus	33 (28.9%)	35 (27.8%)	0.841
Anthropometric and blood pressure, mean±SD			
Weight, kg	91.4±13.2	91.6±14.5	0.898
Body mass index, kg/m ² *	30.6±3.3	30.7±3.9	0.951
Waist circumference, cm	106.0±9.9	107.1±10.7	0.436
Systolic BP, mm Hg	124.1±14.2	124.5±14.5	0.826
Diastolic BP, mm Hg	73.7±9.8	72.9±9.8	0.519
Biochemical profile, mean±SD			
Glucose, mg/dL (mmol/L)	104.4±31.2 (5.8±1.7)	107.5±31.5 (6.0±1.8)	0.440
HbA1c, % (mmol/mol)	6.1±0.8 (43.2±6.4)	6.2±1.0 (44.3±8.5)	0.345
hs-CRP, mg/L (nmol/L)	1.8±2.5 (17.1±23.8)	1.8±2.3 (1.8±17.1)	0.983
Lipids, mean±SD			
Total cholesterol, mg/dL (mmol/L)	154.3±36.1 (4.0±0.9)	150.3±35.7 (3.9±0.9)	0.390
Triglyceride, median [IQR], mg/dL (mmol/L)	120.0 [83.0, 171.0] (1.4 [0.9, 1.9])	120.0 [79.0, 167.0] (1.4 [0.9, 1.9])	0.941
HDL-C, mg/dL (mmol/L)	46.9±14.8 (1.2±0.4)	47.2±14.3 (1.2±0.4)	0.890
LDL-C, mg/dL (mmol/L)	80.1±27.3 (2.1±0.7)	76.1±27.0 (2.0±0.7)	0.259
Complete blood count, mean±SD			
WBC, 10 ⁹ cells/L	6.4±1.4	6.9±2.6	0.088
Monocytes, cells/μL	521.7±160.6	535.0±173.0	0.538
Neutrophils, cells/μL	4031.9±1202.5	4264.0±1620.1	0.213
Lymphocytes, cells/μL	1644.5±526.4	1859.4±1881.1	0.240
Platelets, cells/μL	192.7±44.1	189.9±55.0	0.658
Medication, n (%)			
Statin	103 (90.4%)	126 (100%)	0.002
Aspirin	111 (97.4%)	120 (95.2%)	0.386
ACE-I	59 (51.8%)	72 (57.1%)	0.402

Continued

Table 5. Continued

	Low-Intensity Statin (n=114)	High-Intensity Statin (n=126)	P Value
ARB	16 (14.0%)	30 (23.8%)	0.055
Hydrochlorothiazide	21 (18.4%)	24 (19.0%)	0.901
Furosemide	9 (7.9%)	10 (7.9%)	0.990
Calcium-channel blocker	25 (21.9%)	33 (26.2%)	0.441
Beta blockers	82 (71.9%)	91 (72.2%)	0.960

ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CABG, coronary artery bypass grafting; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; WBC, white blood cell count.

*Calculated as weight in kilograms divided by height in meters squared.

pitavastatin after percutaneous intervention and followed for 8 months, only low DHA levels remained significantly associated with atheroma progression measured by intravascular ultrasound after multivariate regression analysis.⁴⁶ Moreover, subjects with plaque regression had regression of only the fibrous component. None of the other plaque components changed significantly, findings similar to the current study, which detected a significant difference in fibrous plaque. This study did not randomize subjects to EPA and/or DHA. To our knowledge, the current study is the first randomized trial showing a benefit of high-dose EPA and DHA added to statin therapy on the progression of coronary plaque volumes

measured by CCTA. Taken together, the results of these past studies, along with our results, suggest that EPA and DHA affect plaque composition and volume. Although our trial was not designed to assess cardiovascular events, it is worth noting that several studies assessing coronary plaque subtypes with CCTA have shown that higher volume of total noncalcified plaque and total plaque volume are associated with higher rates of cardiac death, myocardial infarction, and coronary revascularization⁴⁷ and higher rates of acute coronary syndrome.^{48,49} Furthermore, evidence from intravascular ultrasound studies shows that progression of plaque atheroma volume is independently associated with higher rates of a

Table 6. Percent Change in Plaque Volume at 30-Month Follow-Up in Control and Omega-3 Ethyl-Ester Groups According to Intensity of Statin

	On Low-Intensity Statin			On High-Intensity Statin		
	Control	Omega-3 Ethyl-Ester	P Value*	Control	Omega-3 Ethyl-Ester	P Value*
	% Change Median [IQR]	% Change Median [IQR]		% Change Median [IQR]	% Change Median [IQR]	
Intention-to-treat						
	(n=53)	(n=61)		(n=61)	(n=65)	
Fatty	4.6 [−7.6, 15.3]	−2.3 [−10.4, 13.2]	0.289	0.2 [−10.0, 15.1]	5.0 [−9.8, 24.8]	0.286
Fibrous	4.8 [−5.1, 19.0]	0.3 [−12.8, 9.0]	0.032	3.9 [−9.8, 18.5]	0.0 [−11.8, 20.1]	0.596
Noncalcified	5.0 [−4.9, 15.3]	−2.9 [−11.1, 10.7]	0.062	3.1 [−7.3, 19.7]	0.6 [−9.3, 21.6]	0.820
Calcified	65.1 [3.4, 154.7]	37.5 [−6.9, 118.1]	0.261	54.7 [4.6, 130.7]	40.9 [−2.7, 122.2]	0.456
Total	10.1 [−3.1, 24.3]	5.0 [−11.1, 16.4]	0.066	8.9 [−1.9, 28.6]	8.4 [−3.9, 22.7]	0.556
Per-protocol						
	Control (n=44)	Omega-3 Ethyl-Ester (n=60)		Control (n=53)	Omega-3 Ethyl-Ester (n=62)	
Fatty	2.9 [−7.6, 11.3]	−2.9 [−10.5, 12.9]	0.453	0.0 [−9.8, 16.0]	3.6 [−11.1, 24.3]	0.497
Fibrous	4.6 [−2.8, 20.5]	0.0 [−12.9, 8.6]	0.023	7.3 [−8.9, 20.0]	−0.1 [−12.2, 18.7]	0.297
Noncalcified	3.9 [−5.3, 14.3]	−3.5 [−11.5, 8.8]	0.078	4.4 [−6.2, 24.0]	−2.4 [−9.7, 20.6]	0.459
Calcified	67.5 [9.0, 161.5]	34.6 [−7.3, 118.3]	0.156	54.7 [4.6, 139.3]	41.8 [0.2, 128.4]	0.591
Total	10.0 [−3.4, 24.3]	4.7 [−12.0, 16.3]	0.068	8.9 [−2.9, 30.8]	8.7 [−5.6, 22.6]	0.473

*P value compares control with omega-3 ethyl-ester group. IQR indicates interquartile range.

Table 7. Percent Change in Plaque Volume at 30-Month Follow-Up Compared With Baseline in the Control and Omega-3 Ethyl-Ester Groups for the Intention-to-Treat and Per-Protocol Analyses Stratified by Age (\leq or $>$ Than the Median)

Plaque Volume*	Age \leq Median			Age $>$ Median		
	Control	Omega-3 Ethyl-Ester	P Value [†]	Control	Omega-3 Ethyl-Ester	P Value [†]
	% Change Median [IQR]	% Change Median [IQR]		% Change Median [IQR]	% Change Median [IQR]	
Intention-to-treat[‡]						
	(n=55)	(n=65)		(n=59)	(n=61)	
Fatty	2.6 [−7.7, 23.2]	−0.2 [−12.2, 10.8]	0.339	4.9 [−9.9, 13.3]	4.5 [−10.2, 28.3]	0.190
Fibrous	7.3 [−5.8, 20.3]	−1.8 [−16.1, 8.4]	0.010	3.9 [−10.7, 17.7]	2.9 [−9.8, 23.2]	0.948
Noncalcified	7.6 [−6.5, 18.2]	−4.9 [−11.7, 8.7]	0.013	2 [−5.8, 13.9]	3.9 [−8.1, 25.6]	0.591
Calcified	63.6 [0.8, 156.5]	18.3 [−20.7, 111]	0.044	52.2 [8.1, 133.4]	56 [12.8, 135.2]	0.698
Total	10.1 [−0.5, 29.5]	1.4 [−12.3, 14.9]	0.003	9.9 [−3.5, 23]	10.8 [0.1, 26.4]	0.341
Per-protocol[§]						
	(n=49)	(n=61)		(n=48)	(n=61)	
Fatty	3 [−7.1, 23.4]	−2 [−12.2, 9.9]	0.135	−0.7 [−10.1, 8.4]	3.1 [−10.7, 28.3]	0.117
Fibrous	7.3 [−5.5, 22.3]	−3.2 [−16.5, 8.4]	0.003	4.2 [−10.3, 18.4]	1.2 [−9.8, 22.2]	0.723
Noncalcified	8.5 [−6.1, 19.7]	−5.1 [−12.5, 8.7]	0.004	1.9 [−5.9, 13.3]	−0.1 [−8.8, 25.6]	0.665
Calcified	45 [−7, 142.7]	18.3 [−19.4, 111]	0.120	64.8 [18, 161.5]	59.6 [12.8, 138.9]	0.750
Total	10.1 [0, 42.8]	1.4 [−13.3, 14.9]	0.004	8.9 [−3.9, 25.1]	10 [−0.9, 25.2]	0.534

*Plaque volume expressed as mm³/mm.

[†]P values calculated using a Mann–Whitney U test comparing % change in the 2 treatment groups.

[‡]Median [IQR] age is 64.2 [58.6, 68.3] years for intention-to-treat.

[§]Median [IQR] age is 63.7 [58.5, 68.0] years for per-protocol.

IQR indicates interquartile range.

composite of cardiac death, myocardial infarction, and coronary revascularization ($P<0.002$) and regression is associated with fewer events.³ Taken together, these findings suggest that plaque composition and volume predict cardiovascular events and support the potential clinical importance of lack of progression of plaque volume observed in the omega-3 ethyl-ester arm in the current trial.

No significant differences in adverse events were observed in those receiving omega-3 ethyl-ester compared with control, with the exception of a significantly lower rate of both serious and nonserious musculoskeletal adverse events and nonserious infectious diseases in those receiving omega-3 ethyl-ester. These findings support the safety of the intervention. In past studies, DHA raised LDL-C levels whereas EPA did not.^{50,51} In the current study of EPA plus DHA, there was no difference in LDL-C levels in the omega-3 versus no omega-3 groups; therefore, high-dose EPA plus DHA had no effect on LDL-C.

Major strengths of the current study are the randomized controlled design and high-dose of EPA and DHA (3.36 g). A limitation is that the 30-month duration may not be long enough to observe the full effect of EPA and DHA supplementation given that atherosclerosis is a long-term process. We hypothesize that longer duration of follow-up would result in a

larger difference between the 2 treatment groups. Limitations of the study also include the open-label study design as noted earlier; however, our primary outcome, plaque ascertainment, was blinded and therefore should not be affected by knowledge of treatment assignment. Although we consider it unlikely, we cannot rule out subtle effects on the randomized treatments attributed to the knowledge of treatment assignment by the principal investigator and participants.

In conclusion, high-dose omega-3 ethyl-ester provided additional benefit to statin treatment in preventing progression of fibrous coronary plaque volume over 30 months compared with a statin alone in subjects who adhered to treatment assignment and in the setting of well-controlled LDL-C levels. Moreover, the benefit was not correlated with triglyceride reduction. The benefit on low-intensity statin, but not high-intensity statin, suggests that statin intensity affects plaque volume. These findings support future trials examining mechanisms for beneficial effects of high-dose omega-3 fatty acids on plaque progression beyond triglyceride lowering.

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Table 8. Adverse Events

	Omega-3 Ethyl-Ester (n)	Control (n)	P Value*
Serious adverse events			
Cardiac	41	35	0.424
Atypical chest pain	5	6	0.768
Vascular	4	4	1.000
Neurological	5	8	0.409
Pulmonary	0	3	0.100
Gastrointestinal	17	17	1.000
Endocrine	2	0	0.498
Musculoskeletal	5	14	0.034
Infectious disease	6	8	0.595
Genitourinary	5	1	0.214
Psychiatric	2	1	1.000
HEENT	1	0	1.000
Nonserious adverse events			
Cardiac	27	19	0.262
Atypical chest pain	9	8	1.000
Dental	10	9	1.000
Vascular	3	1	0.623
Neurological	8	9	0.807
Rheumatological	4	5	0.748
Pulmonary	15	16	0.851
Gastrointestinal	32	25	0.377
Musculoskeletal	43	64	0.008
Infectious disease	47	63	0.049
Genitourinary	16	6	0.063
Hematological	2	2	1.000
Skin	25	14	0.117
HEENT	23	29	0.360
Endocrine	8	5	0.572
Psychiatric	1	2	0.620

HEENT indicates head, eye, ear, nose, and throat.

*P values calculated using chi-square or Fisher's exact, where appropriate.

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Disclosures

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