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**ORIGINAL RESEARCH**

# Regression of Coronary Fatty Plaque and Risk of Cardiac Events According to Blood Pressure Status: Data From a Randomized Trial of Eicosapentaenoic Acid and Docosahexaenoic Acid in Patients With Coronary Artery Disease

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**BACKGROUND:** Residual risk of cardiovascular events and plaque progression remains despite reduction in low-density lipoprotein cholesterol. Factors contributing to residual risk remain unclear. The authors examined the role of eicosapentaenoic acid and docosahexaenoic acid in coronary plaque regression and its predictors.

**METHODS AND RESULTS:** A total of 240 patients with stable coronary artery disease were randomized to eicosapentaenoic acid plus docosahexaenoic acid (3.36 g/d) or none for 30 months. Patients were stratified by regression or progression of coronary fatty plaque measured by coronary computed tomographic angiography. Cardiac events were ascertained. The mean±SD age was 63.0±7.7 years, mean low-density lipoprotein cholesterol level was <2.07 mmol/L, and median triglyceride level was <1.38 mmol/L. Regressors had a 14.9% reduction in triglycerides that correlated with fatty plaque regression ( $r=0.135$ ;  $P=0.036$ ). Compared with regressors, progressors had higher cardiac events (5% vs 22.3%, respectively;  $P<0.001$ ) and a 2.89-fold increased risk of cardiac events (95% CI, 1.1–8.0;  $P=0.034$ ). Baseline non-high-density lipoprotein cholesterol level <2.59 mmol/L (100 mg/dL) and systolic blood pressure <125 mmHg were significant independent predictors of fatty plaque regression. Normotensive patients taking eicosapentaenoic acid plus docosahexaenoic acid had regression of noncalcified coronary plaque that correlated with triglyceride reduction ( $r=0.35$ ;  $P=0.034$ ) and a significant decrease in neutrophil/lymphocyte ratio. In contrast, hypertensive patients had no change in noncalcified coronary plaque or neutrophil/lymphocyte ratio.

**CONCLUSIONS:** Triglyceride reduction, systolic blood pressure <125 mmHg, and non-high-density lipoprotein cholesterol <2.59 mmol/L were associated with coronary plaque regression and reduced cardiac events. Normotensive patients had greater benefit than hypertensive patients potentially due to lower levels of inflammation. Future studies should examine the role of inflammation in plaque regression.

**REGISTRATION:** URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT01624727.

**Key Words:** cardiovascular events ■ coronary computed tomographic angiography ■ coronary plaque regression ■ eicosapentaenoic acid ■ triglyceride

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## CLINICAL PERSPECTIVE

### What Is New?

- Predictors of regression of coronary fatty plaque include baseline levels of non-high-density lipoprotein cholesterol <2.59 mmol/L and systolic blood pressure <125 mmHg and reduction in triglyceride level over 30 months in patients with stable coronary artery disease with normal triglyceride levels on statin therapy randomized to high-dose eicosapentaenoic acid and docosahexaenoic acid.
- Regressors had a 4-fold lower risk of major adverse cardiovascular events.
- Normotensive patients taking eicosapentaenoic acid and docosahexaenoic acid had regression of noncalcified coronary plaque and reduction of triglyceride level and neutrophil/lymphocyte ratio compared with control, whereas hypertensive patients had no difference.

### What Are the Clinical Implications?

- The study supports the importance of maintaining a systolic blood pressure <125 mmHg and non-high-density lipoprotein cholesterol <2.59 mmol/L to reduce residual cardiovascular risk through coronary plaque regression.
- The association of triglyceride lowering with eicosapentaenoic acid plus docosahexaenoic acid and regression of coronary fatty plaque supports use of omega-3 fatty acids to reduce residual cardiovascular risk in patients with coronary artery disease with normal triglyceride levels on statin therapy.
- The study highlights the importance of maintaining optimal triglyceride levels, non-high-density lipoprotein cholesterol levels and systolic blood pressure, in addition to guideline-recommended low-density lipoprotein cholesterol levels, to regress coronary fatty plaque and thus optimize secondary prevention of cardiac events.

Low-density lipoprotein cholesterol (LDL-C) reduction has been the primary target to reduce the risk of cardiovascular disease (CVD) morbidity and mortality. However, despite maximal LDL-C reduction on statin therapy, significant residual risk for cardiovascular events remains,<sup>1-3</sup> and coronary artery disease (CAD) remains the leading cause of death in industrialized countries. Prior studies with coronary computed tomographic angiography (CCTA) and intravascular ultrasound have shown that progression of noncalcified coronary plaque is associated with higher rates of cardiovascular events,<sup>4-6</sup> and regression of plaque is associated with fewer events.<sup>3</sup> Identification of potential mechanisms contributing to cardiovascular events and plaque progression is important because it may allow modification and thus reduction of residual risk.

Omega-3 fatty acids are polyunsaturated fatty acids required in the diet to provide the very long-chain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) for metabolic structure and function. We previously reported that achieving an omega-3 fatty acid index  $\geq 4\%$  with 3.36 g daily of EPA plus DHA added to statin treatment prevented progression of noncalcified plaque over 30 months and that an index of 8.4% was associated with regression of noncalcified plaque in nondiabetic patients.<sup>7,8</sup> Fatty plaque is a lipid-rich plaque that is vulnerable to rupture, leading to thrombosis and acute coronary syndromes.<sup>9</sup> Therefore, we undertook a strategy to determine predictors of regression of fatty plaque to provide insight into factors that may affect residual risk on statin therapy. We stratified patients by regression or progression of fatty plaque using CCTA to measure plaque volumes in our 30-month randomized trial of EPA+DHA in patients with CAD taking statin therapy. Cardiac events were assessed. CCTA is noninvasive and allows for examination of all coronary arteries, in contrast to intravascular ultrasound imaging, which generally examines only a culprit artery and is invasive with inherent risks. CCTA has been validated to detect progression of coronary plaque volume<sup>10-13</sup> and has shown that statin therapy attenuates progression of coronary plaque.<sup>14-18</sup>

## Nonstandard Abbreviations and Acronyms

<b>DHA</b>	docosahexaenoic acid
<b>EPA</b>	eicosapentaenoic acid
<b>HEARTS</b>	Slowing Heart Disease With Lifestyle and Omega-3 Fatty Acids
<b>HU</b>	hounsfield units
<b>NLR</b>	neutrophil lymphocyte ratio
<b>SPRINT</b>	Systolic Blood Pressure Intervention Trial
<b>WHHL</b>	Watanabe heritable hyperlipidemic

## METHODS

### Study Design

The HEARTS (Slowing Heart Disease With Lifestyle and Omega-3 Fatty Acids) trial is a randomized clinical trial conducted at Beth Israel Deaconess Medical Center (BIDMC), Boston, MA. The BIDMC's institutional review board approved the protocol, and all patients signed informed consent. The effect of EPA+DHA on progression of coronary noncalcified plaque at 30-month follow-up is the primary end point and has been reported.<sup>19</sup> Prespecified secondary end

points include prevention of progression of albuminuria by EPA and DHA in diabetic patients<sup>20</sup>; effect of EPA and DHA on physical function, exercise, and joint replacement<sup>21</sup>; diastolic blood pressure (BP) as a predictor of noncalcified coronary plaque volume<sup>22</sup>; and effect of EPA and DHA on cognitive function.<sup>23,24</sup> The data that support the findings of this study are available from the corresponding author upon reasonable request. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) cohort reporting guidelines were used.

## Participants and Study Intervention

Participating patients were aged 37 to 80 years and had stable CAD as previously defined.<sup>19</sup> Patients were randomized to 1.86 g EPA and 1.5 g DHA or no EPA and DHA (control) for 30 months. All patients were recommended statin and aspirin and were instructed not to take over-the-counter omega-3 fatty acid supplementation.

## Data Collection

History, physical examination, BP, height, weight, and waist measurement were obtained at baseline and every 6 months. After a 12-hour fast, blood samples were obtained, and biochemical and lipid levels were measured at Quest Diagnostics (Cambridge, MA). High-sensitivity CRP (C-reactive protein), plasma EPA, DHA, and total fatty acids and small dense LDL-C were measured as previously described.<sup>7,25</sup> The plasma omega-3 fatty acid index was the percentage that EPA+DHA comprised total fatty acids.

## Cardiac Events

Cardiac events were reported every 3 months until the final visit at 30 months. Cardiac events included unstable angina, myocardial infarction (MI), percutaneous coronary intervention, and coronary artery bypass grafting. Unstable angina was defined as onset of angina at rest. MI was defined according to the Third Universal Definition of Myocardial Infarction.<sup>26</sup> Events were documented through review of medical records. Data were analyzed as time-to-first event.

## Image Acquisition, Reconstruction, and Coronary Plaque Analysis

A 320-row detector scanner (Aquilion ONE, Toshiba Medical Systems) with prospective ECG gating was used for imaging at BIDMC. The protocol for plaque identification and quantification has been previously published.<sup>27,28</sup> Representative images of coronary artery segments demonstrating progression [A] and regression [B] of coronary plaque over 30 months are shown in the eFigure in Supplement 2 of Reference [28].

Three-dimensional reconstruction of CCTA images for coronary segment plaque volume analysis was performed with semiautomated software (SUREPlaque, version 6.3.2; Vital Images).<sup>12,29–31</sup> To exclude calcium-bloom artifact, segments with prior revascularization or significant calcification were excluded. To ensure measurement of the same segment at 30-month follow-up, branches or focal calcification served as fiducial markers. Two readers blinded to treatment allocation performed the plaque analyses independently. Hounsfield unit (HU) densities were used to classify plaque, with fatty plaque being  $-100$  to  $49$  HU, fibrous plaque,  $50$  to  $150$  HU, and calcified plaque  $>150$  HU. Noncalcified plaque was the sum of fatty and fibrous plaque. Indexed plaque volume was defined as plaque volume ( $\text{mm}^3$ ) divided by artery segment length (mm). The HEARTS trial was powered to detect a difference of 4% change in coronary plaque volume at 30 months using CCTA. Therefore, our cut point for separating those with progression versus regression of plaque took the 4% margin into account. Plaque regression was defined as  $\leq -2\%$  reduction in fatty plaque volume and progression as  $> +2\%$  increase in fatty plaque volume. A third group classified as “no change” included those with  $< -2\%$  reduction and up to  $+2\%$  plaque progression.

## Statistical Analysis

Patients were grouped according to change in coronary fatty plaque for the total group of patients regardless of treatment assignment. Categorical variables were expressed as counts and percentages. Normality tests were conducted using the Shapiro–Wilk test. Continuous variables were reported as the mean and SD for normally distributed variables or median and interquartile range [IQR] for nonnormally distributed variables. Continuous variables were compared using 2-tailed paired *t* tests and unpaired *t* tests at 30 months compared with baseline for normally distributed variables and Wilcoxon signed rank test and the Mann–Whitney *U* test for nonnormally distributed variables. Spearman correlation coefficients were determined. Hazard ratio (HRs) and 95% CIs for the association between plaque change and cardiovascular events were estimated using Cox proportional-hazard regression. Freedom from cardiovascular events in progressors versus regressors was graphed with a Kaplan–Meier plot. We then examined baseline variables predicting arithmetic change in fatty plaque from baseline to 30 months. The correlation coefficient, *r*, was used to measure the correlation between each continuous variable and arithmetic change in fatty plaque. The following discrete variables were also used to determine in univariate analyses whether they were associated with change in fatty plaque from baseline to 30 months: randomized treatment, sex, race,

**Table 1. Baseline Characteristics in the Regressor, No Change, and Progressor Groups**

	Regressors ≤-2% n=100	No change >-2% to +2% n=19	Progressors >+2% n=121	P value*
Demographic characteristics				
Age, mean (SD), y	62.8 (8.0)	62.7 (6.7)	63.2 (7.6)	0.70
Men, n (%)	84 (84.0)	15 (78.9)	105 (86.8)	0.63
Inclusion criteria (may have >1), n (%)				
History of MI	51 (51.0)	9 (47.4)	52 (43.0)	0.49
Percutaneous coronary intervention	64 (64.0)	10 (52.6)	76 (62.8)	0.64
Coronary artery bypass graft	27 (27.0)	3 (15.8)	29 (24.0)	0.57
Cardiovascular risk factors, n (%)				
Hypertension	84 (84.0)	14 (73.7)	102 (84.3)	0.50
Diabetes	31 (31.0)	6 (31.6)	31 (25.6)	0.64
Anthropometrics and BP, mean (SD)				
Weight, kg	91.5 (12.9)	89.4 (14.0)	91.8 (14.7)	0.87
BMI, kg/m <sup>2</sup>	30.4 (3.5)	29.8 (3.2)	31.0 (3.7)	0.20
Waist circumference, cm	105.7 (10.0)	102.8 (8.5)	107.9 (10.7)	0.22
Systolic BP, mmHg	122.9 (12.6)	122.2 (16.3)	125.8 (15.3)	0.13
Diastolic BP, mmHg	73.1 (9.4)	70.0 (8.1)	73.9 (10.3)	0.58
Medications, n (%)				
Statin	91 (91)	19 (100)	118 (97.5)	0.04
Aspirin	94 (94)	19 (100)	118 (97.5)	0.31
ACEI	54 (54)	8 (42.1)	69 (57.0)	0.47
ARB	14 (14)	4 (21.1)	28 (23.1)	0.22
Hydrochlorothiazide	23 (23)	4 (21.1)	18 (14.9)	0.30
Furosemide	7 (7)	1 (5.3)	11 (9.1)	0.77
Calcium channel blocker	30 (30)	1 (5.3)	27 (22.3)	0.055
β-Blocker	76 (76)	13 (68.4)	84 (69.4)	0.52
High-sensitivity CRP and CBC count				
High-sensitivity CRP, median [IQR], mg/L	0.9 [0.4–2.4]	0.6 [0.3–1.1]	0.8 [0.4–2.3]	0.42
WBC count, mean (SD), 10 <sup>9</sup> cells/L	6.4 (1.4)	6.1 (1.5)	7.0 (2.6)	0.019
Monocytes, mean (SD), cells/μL	510 (153)	522 (217)	545 (169)	0.11
Neutrophils, mean (SD), cells/μL	3976 (1243)	3624 (1284)	4384 (1574)	0.037
Lymphocytes, mean (SD), cells/μL	1656 (540)	1707 (546)	1849 (1915)	0.33
Platelets, mean (SD), cells/μL	191 (46)	200 (44)	190 (54)	0.91
Lipids, mean (SD), except triglyceride, non-HDL-C, small dense LDL-C, and remnant cholesterol, which are median [IQR]				
Total cholesterol, mmol/L	3.88 (0.92)	3.88 (0.80)	3.99 (0.96)	0.39
mg/dL	150.1±35.4	150.1±31.0	154.3±37.1	
Triglycerides, mmol/L	1.36 [1.01–1.90]	1.03 [0.82–1.58]	1.36 [0.89–2.00]	0.94
mg/dL	120.5 [89–168]	91 [73–140]	121 [79–177]	
HDL-C, mmol/L	1.22 (0.43)	1.29 (0.39)	1.21 (0.32)	0.75
mg/dL	47.2±16.8	49.7±14.9	46.6±12.4	
LDL-C, mmol/L	1.96 (0.63)	2.01 (0.61)	2.06 (0.77)	0.29
mg/dL	75.8±24.5	77.9±23.6	79.8±29.8	
Non-HDL-C, mmol/L	2.41 [1.99–3.00]	2.52 [2.12–2.90]	2.52 [2.17–3.08]	0.22
mg/dL	93.0 [77.0–116.0]	97.5 [82.0–112.0]	97.5 [84.0–119.0]	

(Continued)

**Table 1. Continued**

	Regressors ≤-2% n=100	No change >-2% to +2% n=19	Progressors >+2% n=121	P value*
Small dense LDL-C, mmol/L	0.54 [0.29–0.82]	0.57 [0.30–0.80]	0.53 [0.32–0.86]	0.16
mg/dL	20.7 [11.4–31.7]	21.9 [11.7–31.0]	20.5 [12.5–33.1]	
Remnant cholesterol, mmol/L	0.62 [0.47–0.87]	0.47 [0.39–0.72]	0.62 [0.41–0.91]	0.95
mg/dL	24.0 [18.0–33.5]	18.0 [15.0–28.0]	24.0 [16.0–35.0]	
Biochemical profile, mean (SD), except omega-3 fatty acid index and albumin-creatinine ratio, which are median [IQR]				
Glucose, mmol/L	5.9 (1.8)	6.2 (2.2)	5.8 (1.6)	0.86
mg/dL	105.9±32.1	111.7±39.2	105.2±29.5	
Hemoglobin A1c, %	6.1 (0.9)	6.2 (1.3)	6.2 (0.8)	0.72
Estimated creatinine clearance, mL/minute	100.2 (21.4)	98.5 (24.0)	103.4 (31.1)	0.40
Omega-3 fatty acid index %, median [IQR]	3.3 [2.6–4.4]	3.1 [2.46–3.6]	3.3 [2.5–4.3]	0.26
Albumin-creatinine ratio, µg/mg creatinine, median [IQR]	5.0 [2.5–11.5]	3.5 [1.9–4.0]	4.4 [2.9–9.0]	0.60

SI conversion factors: to convert cholesterol levels to mg/dL, divide by 0.0259; triglyceride level to mg/dL, divide by 0.0113; and glucose level to mg/dL, divide by 0.0555. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CBC, complete blood count; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; WBC, white blood cell.

\*P value compares regressors with progressors.

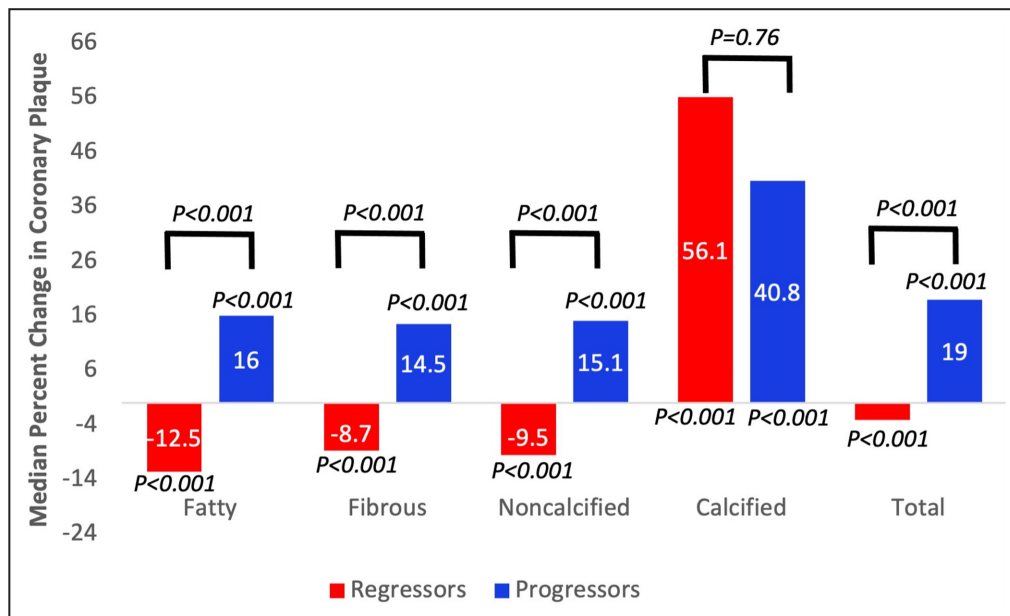
diabetes, and hypertension. Analysis of variance was used to assess the effect of each discrete variable on arithmetic change in fatty plaque. Analysis of covariance was used for multivariable-adjusted regression analyses. The final regression model was built using a stepwise backward procedure for variable selection with criterion  $P < 0.05$  for inclusion. A 2-sided  $P$  value  $\leq 0.05$  was considered statistically significant. Data analyses were performed using SPSS 20.0 (IBM) and

R programming version 4.2.2 (R Project for Statistical Computing).

## RESULTS

### Baseline Characteristics

A total of 285 patients with stable CAD were randomized to EPA+DHA (n=143) or none (n=142). Of these, 126 in



**Figure 1. Median percent change in coronary plaque subtypes for those with regression of plaque compared with progression.**

Regressors had a significant reduction in fatty, fibrous, noncalcified, and total plaque compared with progressors.

**Table 2. Median of Percent Change in Coronary Plaque in Regressors Compared With Progressors at 30-Month Follow-Up**

Plaque type	Regressors ≤-2% n=100		Progressors >+2% n=121		P value <sup>†</sup>
	Median of % change [IQR]	P value*	Median of % change [IQR]	P value*	
Fatty	-12.5 [-20.6 to -7.1]	<0.001	16.0 [8.0-32.6]	<0.001	<0.001
Fibrous	-8.7 [-19.5 to 1.4]	<0.001	14.5 [1.5-26.4]	<0.001	<0.001
Noncalcified	-9.5 [-19.3 to -4.0]	<0.001	15.1 [5.0-27.2]	<0.001	<0.001
Calcified	56.1 [-0.6 to 139.3]	<0.001	40.8 [0.81-18.4]	<0.001	0.76
Total	-3.0 [-13.7 to 6.3]	<0.001	19.0 [7.9-33.8]	<0.001	<0.001

IQR indicates interquartile range.

\*P value compares plaque volume at baseline with 30 months.

<sup>†</sup>P value compares regressors with progressors.

the EPA+DHA group and 114 in the control group had paired CCTA scans at baseline and 30-month follow-up and were included in the current analysis. The mean age was 63.0 years (SD, 7.7 years), and 15% were women. Table 1 describes baseline characteristics stratified by regression, no change, or progression of coronary fatty

plaque at 30 months. Compared with the regressor group, progressors were significantly more likely to be taking a statin (P=0.04) and have higher levels of white blood cell (WBC) and neutrophil counts (P=0.019 and P=0.037, respectively) at baseline. Of note, median high-sensitivity CRP values were ≤0.9 mg/L in each group.

**Table 3. Median Percent Change from Baseline at 30-Month Follow-Up**

Clinical variable	Regressors ≤-2% n=100	Progressors >+2% n=121	P value
	Median [IQR]	Median [IQR]	
Clinical variable			
Systolic BP	-4.2 [-11.7 to 5.4]	-4.8 [-11.2 to 3.3]	0.64
Diastolic BP	-4.5 [-14.1 to 1.7]	-4.7 [-11.1 to 2.2]	0.36
Waist circumference	0.5 [-3.2 to 4.2]	0.6 [-1.6 to 3.6]	0.54
Weight	-1.1 [-5.0 to 2.9]	-0.7 [-4.2 to 2.8]	0.82
Body mass index	-0.2 [-4.8 to 3.9]	0.3 [-3.4 to 3.9]	0.70
High-sensitivity CRP and CBC count			
High-sensitivity CRP	0.0 [-50.0 to 50.0]	0.0 [-56.4 to 75.8]	0.91
WBC count	-5.9 [-14.6 to 4.9]	-6.2 [-15.0 to 5.6]	0.78
Monocyte count	-5.7 [-17.8 to 13.6]	-8.0 [-20.6 to 7.0]	0.38
Neutrophil count	-4.1 [-19.8 to 11.6]	-7.3 [-20.6 to 8.8]	0.54
Lymphocyte count	-6.8 [-16.3 to 5.3]	-4.7 [-20.8 to 6.6]	0.96
Platelet count	-7.0 [-15.4 to 1.5]	-4.7 [-16.0 to 2.2]	0.87
Lipid profile			
Total cholesterol	-5.9 [-13.7 to 9.9]	-2.0 [-10.5 to 14.1]	0.16
Triglycerides	-14.9 [-31.3 to 6.3]	-2.8 [-25.1 to 15.1]	0.025
HDL-C	0.0 [-11.3 to 10.6]	-3.6 [-10.6 to 8.5]	0.79
LDL-C	-6.1 [-19.2 to 12.0]	1.6 [-17.8 to 30.1]	0.15
Small dense LDL-C	-12.2 [-39.8 to 40.7]	-13.0 [-38.0 to 38.3]	0.87
Non-HDL-C	-1.8 [-20.7 to 16.9]	-2.7 [17.3-19.2]	0.83
Remnant cholesterol	-12.9 [-30.4 to 5.0]	-3.3 [-27.3 to 15.4]	0.084
Biochemical profile			
Glucose	0.3 [-5.7 to 9.5]	1.6 [-6.7 to 11.3]	0.85
Hemoglobin A1c	0.0 [-3.2 to 3.6]	0.0 [-3.4 to 3.7]	0.87
Omega-3 fatty acid index	36.5 [-0.81 to 12.6]	18.5 [-1.2 to 94.4]	0.61
Creatinine clearance	-7.5 [-14.5 to 1.6]	-7.6 [-14.0 to 0.4]	0.84
Albumin-creatinine ratio	38.0 [-31.8 to 202.2]	12.0 [-33.7 to 78.1]	0.084

BP indicates blood pressure; CBC, complete blood count; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; and WBC, white blood cell.

**Table 4. Correlation Between Percent Change in Lipids and Coronary Plaque at 30-Month Follow-Up**

Percent change in lipids	Percent change in coronary plaque									
	Fatty		Fibrous		Noncalcified		Calcified		Total	
	r	P value	r	P value	r	P value	r	P value	r	P value
Total cholesterol	0.049	0.46	-0.006	0.93	0.021	0.76	-0.050	0.45	0.016	0.81
LDL-C	0.045	0.51	0.038	0.57	0.048	0.47	-0.016	0.81	0.046	0.49
HDL-C	-0.037	0.57	-0.155	0.016	-0.134	0.039	0.042	0.52	-0.052	0.42
Triglyceride	0.135	0.036	0.116	0.07	0.146	0.024	-0.045	0.49	0.080	0.22
Small dense LDL-C	0.007	0.92	0.021	0.76	0.020	0.77	-0.067	0.33	-0.014	0.84
Non-HDL-C	0.011	0.88	0.012	0.86	0.010	0.88	-0.033	0.63	-0.099	0.89
High-sensitivity CRP	0.006	0.93	0.028	0.68	0.026	0.70	-0.001	0.99	-0.012	0.86
Remnant cholesterol	0.105	0.11	0.108	0.10	0.123	0.06	-0.033	0.61	0.075	0.25

CRP indicates C-reactive protein; HDL-C, high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol.

### Regression and Progression of Coronary Plaque

Figure 1 (data in Table 2) reports that regressors had significant regression of fatty (median, -12.5% [IQR, -20.6 to -7.1],  $P < 0.001$ ), fibrous (-8.7% [IQR, -19.5 to 1.4],  $P < 0.001$ ), noncalcified (-9.5% [IQR, -19.3 to -4.0],  $P < 0.001$ ), and total coronary (-3.0% [IQR, -13.7 to 6.3],  $P < 0.001$ ) plaque, whereas progressors had significant progression of fatty (16% [IQR, 8.0-32.6],  $P < 0.001$ ), fibrous (14.5% [IQR, 1.5-26.4],  $P < 0.001$ ), noncalcified (15.1% [IQR, 5.0-27.2],  $P < 0.001$ ), calcified (40.8% [IQR, 0.8-118.4],  $P < 0.001$ ), and total coronary (19.0% [IQR, 7.9-33.8],  $P < 0.001$ ) plaque. The percent change in fatty, fibrous, noncalcified, and total plaque was significantly different between the regressors and progressors at 30-month follow-up ( $P < 0.001$  for all).

### Percent Change in Characteristics at 30-Month Follow-Up

Table 3 reports median percent change in characteristics from baseline at 30-month follow-up for regressors compared with progressors. Regressors had a median reduction (-14.9% [IQR, -31.3 to 6.3]) in triglyceride level (from a median of 1.35-1.22 mmol/L; 120-108 mg/dL) compared with no significant change (-2.8% [IQR, -25.1 to 15.1]) in progressors (between-group  $P = 0.025$ ). Otherwise, there were no significant differences.

### Correlations Between Changes in Lipids and Coronary Plaque

The percent change in triglyceride level was significantly positively correlated with the percent change in fatty and noncalcified plaque ( $r = 0.135$  [ $P = 0.036$ ] and  $r = 0.146$  [ $P = 0.024$ ], respectively) (Table 4). The percent change in plasma omega-3 fatty acid index was inversely correlated with triglyceride change in the total group of regressors and progressors ( $r = -0.274$

[ $P < 0.001$ ]) and in those with regression ( $r = -0.384$  [ $P < 0.001$ ]) (data not shown).

### Cardiac Events in Progressors and Regressors

Table 5 reports the cardiac events stratified by progression or regression of coronary plaque. Compared with progressors, regressors had significantly fewer total cardiac events (22.3% vs 5.0%,  $P < 0.001$ ), percutaneous coronary interventions (15.7% vs 3.0%,  $P = 0.002$ ), and unstable angina (21.5% vs 3.0%,  $P < 0.001$ ). Figure 2 shows the Kaplan-Meier plot for freedom from cardiovascular events. Those with progression of plaque had a 2.89-fold increased risk of events (95% CI, 1.1-8.0;  $P = 0.034$ ).

### Baseline Predictors of Change in Fatty Plaque

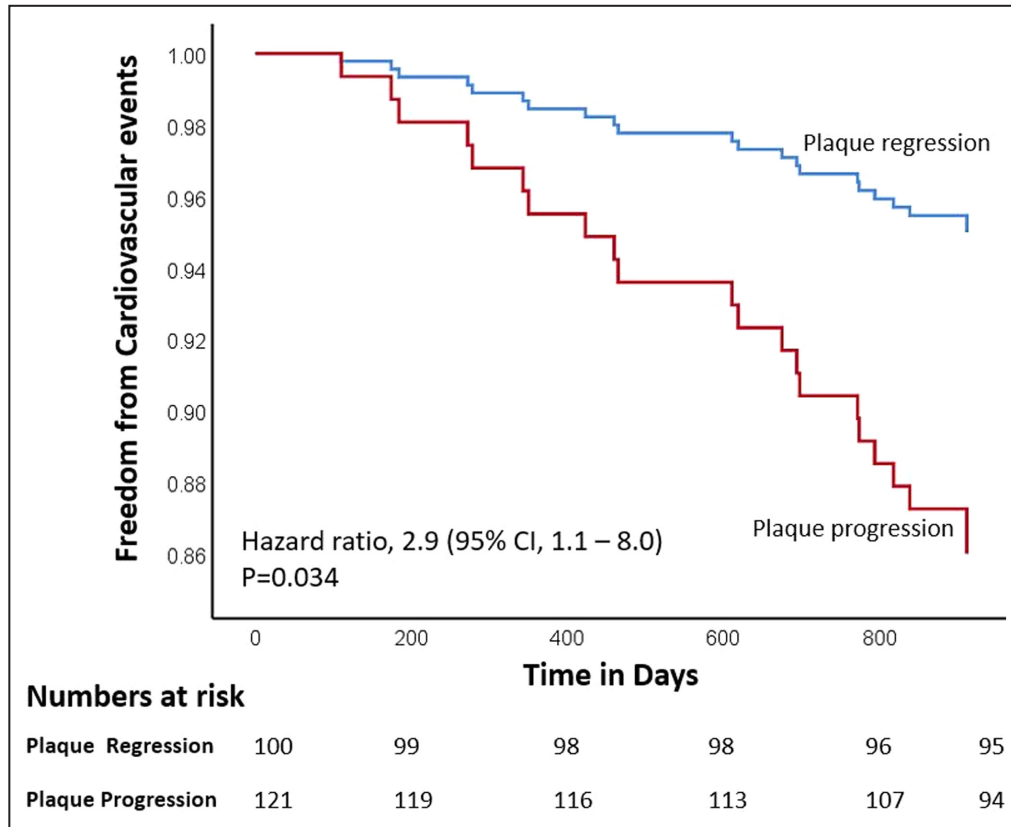
The univariate analysis for baseline predictors of change in fatty plaque is shown in Table 6. After multivariate adjustment including the treatment arm, non-HDL-C level  $< 2.59$  mmol/L and systolic BP  $< 125$  mm Hg

**Table 5. Cardiac Events Stratified by Progression or Regression of Coronary Fatty Plaque**

	Progressors n=121	Regressors n=100	P value
Percutaneous coronary intervention, n (%)	19 (15.7)	3 (3)	0.002
Unstable angina, n (%)	26 (21.5)	3 (3)	<0.001
Myocardial infarction, n (%)	2 (1.65)	0 (0)	0.50
Coronary artery bypass graft, n (%)	2 (1.65)	0 (0)	0.50
Total incident cardiac events, n (%)*	27 (22.3)	5 (5)	<0.001

\*Total incident events include percutaneous coronary intervention, nonfatal myocardial infarction, and coronary artery bypass graft or unstable angina. The total incident cardiac events is less than the sum of individual events because some patients had more than 1 event.





**Figure 2.** Kaplan–Meier plot for freedom from cardiovascular events over 30 months in patients with coronary plaque regression compared with those with coronary plaque progression. Those with plaque progression had a 2.9-fold higher rate of cardiovascular events compared with those with plaque regression.

were significant independent predictors of coronary fatty plaque regression: the regression coefficient for systolic BP was 0.03 (95% CI, 0.012–0.048;  $P=0.001$ ) and for non-HDL-C was 0.014 (95% CI, 0.006–0.022;  $P=0.002$ ).

### Results Stratified by BP Status

A significant interaction term between randomization treatment arm and hypertension status was noted in the prediction of noncalcified ( $P=0.044$ ) and total ( $P=0.008$ ) plaque. Therefore, we stratified the analysis based on BP status. Table 7 reports baseline characteristics stratified by BP status. Compared with normotensive patients, hypertensive patients were significantly younger and had significantly higher baseline coronary artery calcium score, higher systolic BP, lower creatinine clearance, higher level of monocytes, and higher use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and hydrochlorothiazide. Median baseline coronary artery calcium for normotensive patients was 213.3 (IQR, 42.2–630.2) and for hypertensive patients was 475.5 (IQR, 154.9–1156.3) (between-group  $P=0.003$ ).

Table 8 reports changes at 30-month follow-up for characteristics stratified by BP status. Both normotensive and hypertensive patients taking EPA+DHA had a significant reduction in triglyceride level compared with their respective control groups (20.7% vs 11.5%, respectively) (graphed in Figure 3). Normotensive patients taking EPA+DHA had a 2.2% reduction in WBC count compared with a significant 16% increase in control for a mean difference of 18.2% ( $P=0.013$ ) (Table 8). Figure 3 reports that normotensive patients taking EPA+DHA also had a reduction in neutrophil count (mean  $-6.2\%$  [95% CI,  $-15.9$  to  $3.5$ ]) compared with a significant 30.4% increase (95% CI, 0.84–59.9) in control for a 36.6% difference ( $P=0.022$ ), suggesting lower levels of inflammation in the normotensive patients taking EPA and DHA. Hypertensive patients had no difference in WBC or neutrophil count by treatment assignment (Figure 3). When examined by neutrophil/lymphocyte ratio (NLR), Table 9 reports that normotensive patients taking EPA+DHA had a significant reduction in NLR ( $2.64\pm 0.87$  at baseline vs  $2.39\pm 1.03$  at 30-month follow-up,  $P=0.024$ ), whereas normotensive patients taking control had an increase that approached significance:  $2.09\pm 0.85$  at baseline versus  $2.47\pm 0.96$  at

**Table 6. Univariate Analysis for Baseline Factors Predicting Change in Coronary Fatty Plaque at 30-Month Follow-Up**

Variable	Correlation coefficient, <i>r</i>	<i>P</i> value
Systolic BP	0.167	0.010
Apolipoprotein B	0.169	0.011
Non-HDL-C	0.158	0.017
Diastolic BP	0.108	0.094
Percent small dense LDL-C	0.109	0.10
Neutrophil count	0.056	0.39
DHA	0.053	0.44
Triglyceride level	0.052	0.44
WBC count	0.050	0.44
Waist circumference	0.049	0.45
Body mass index	0.042	0.51
LDL-C	0.040	0.54
Hemoglobin A1c	0.039	0.54
EPA	0.040	0.56
Albumin-creatinine ratio	0.018	0.78
Omega-3 fatty acid index	0.014	0.83
Monocyte count	0.011	0.87
Lymphocyte count	-0.008	0.90
Platelet count	0.005	0.94
Age	0.003	0.96

BP indicates blood pressure; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and WBC, white blood cell.

30-month follow-up ( $P=0.064$ ). In contrast, hypertensive patients taking EPA+DHA had no significant difference. No other changes between normotensive and hypertensive patients taking EPA+DHA were noted.

Figure 4 (data in Table 10) shows changes in coronary plaque volume at 30-month follow-up stratified by BP status. Compared with control, normotensive patients taking EPA+DHA had regression of fibrous ( $P=0.008$ ), noncalcified ( $P=0.008$ ), and total ( $P=0.003$ ) plaque. In contrast, there was no difference in percent change in any of the plaque subtypes in hypertensive patients taking EPA+DHA compared with control. These findings suggest that the effect of EPA+DHA supplementation is modified by BP status, and normotensive patients may have greater benefit. The change in noncalcified plaque volume correlated positively with the change in triglyceride level in normotensive patients ( $r=0.35$  [ $P=0.034$ ]).

## DISCUSSION

### Predictors of Regression of Coronary Fatty Plaque: Triglyceride Reduction

Assessing factors associated with plaque volume and composition has significant prognostic implications. Several studies with CCTA have shown that a higher

volume of noncalcified plaque and total plaque is associated with higher rates of cardiac death, MI, and coronary revascularization<sup>4</sup> and higher rates of acute coronary syndrome.<sup>5,6</sup> Furthermore, progression of plaque atheroma volume measured by intravascular ultrasound is an independent predictor of a composite of cardiac death, MI, and coronary revascularization ( $P<0.002$ ), and regression is associated with fewer events.<sup>3</sup> Because fatty plaque is more prone to rupture and lead to thrombosis and acute coronary syndrome than fibrous or calcified plaque,<sup>9</sup> we examined fatty plaque separately. In the current trial of patients with CAD taking optimal statin therapy and mean LDL-C  $<2.07$  mmol/L (80 mg/dL), those with regression of fatty plaque had significantly fewer cardiovascular events and significantly lower triglyceride levels at 30 months. This reduction in triglyceride level likely represents treatment effect from EPA+DHA added to statins and was positively and significantly correlated with reduction in coronary fatty plaque ( $r=0.135$  [ $P=0.036$ ]). These findings suggest that plaque composition and regression of fatty plaque predict cardiovascular events and support the potential clinical importance of regression of coronary plaque volume. To our knowledge, the current study is the first to report on coronary fatty plaque by CCTA separately from other plaque types.

A systematic review and meta-regression analysis of randomized controlled trials reported on the association between triglyceride lowering and reduction of cardiovascular risk across multiple lipid-lowering therapeutic classes.<sup>32</sup> The meta-regression predicted that lowering triglyceride levels to 0.79 mmol/L (70 mg/dL) (1 mmol/L lower than average baseline triglycerides in the trials included) would have reduced events by 16%, assuming a linear relationship between triglyceride reduction and events at lower triglyceride levels. Taken together, the current findings suggest that in the setting of optimal statin treatment with LDL-C  $<2.07$  mmol/L (80 mg/dL) and low high-sensitivity CRP, a reduction in triglyceride level from a level usually considered to be in the normal range is associated with regression of fatty plaque volume, which, in turn, is associated with a reduction in cardiovascular events.

Prior studies examining the relationship between triglyceride levels and regression or progression of coronary plaque have been limited. A meta-analysis of 4957 patients with CAD from 9 clinical trials reported on the relationship between achieved triglyceride levels and non-HDL-C with change in coronary atheroma volume using intravascular ultrasound to measure coronary atheroma volume.<sup>33</sup> The rate of atheroma progression started to increase as triglyceride levels increased  $>1.24$  mmol/L (110 mg/dL) in the setting of LDL-C  $<1.81$  mmol/L (70 mg/dL) ( $P<0.001$ ).<sup>33</sup> In the current study, plaque regression occurred with a median 14.9% reduction in triglyceride level from a baseline

**Table 7. Baseline Characteristics Stratified by BP Status**

	Hypertensive (n=200)	Normotensive (n=40)	P value
Demographic characteristics			
Age, mean±SD, y	58.3±8.0	63.9±7.3	<0.001
Male sex, n (%)	165 (84.6)	33 (80.5)	0.51
Inclusion criteria (may have >1), n (%)			
History of MI	84 (43.1)	21 (51.2)	0.45
History of PCI	116 (59.5)	27 (65.9)	0.52
History of CABG	50 (25.6)	6 (14.6)	0.26
Cardiovascular risk factors, n (%)			
History of diabetes	54 (27.7)	9 (22.0)	0.45
Coronary calcium score, median [IQR]			
Baseline CAC score, Agatston units	475.5 [154.9–1156.3]	213.3 [42.2–630.2]	0.003
Plaque volume, mm <sup>3</sup> /mm, median [IQR]			
Fatty	8.7 [5.3–13.7]	10.6 [6.1–15.1]	0.25
Fibrous	15.9 [9.2–23.4]	20.0 [10.6–25.4]	0.14
Noncalcified	24.9 [14.3–36.6]	30.8 [16.4–40.8]	0.16
Total plaque	33.1 [18.1–47.2]	37.3 [22.3–51.0]	0.22
Anthropometrics and BP, mean±SD			
Weight, kg	91.5±13.7	89.1±13.6	0.15
BMI, kg/m <sup>2</sup>	30.7±3.5	30.0±3.5	0.13
Waist circumference, cm	106.8±10.4	104.1±9.0	0.061
Systolic BP, mmHg	125.8±13.6	117.4±15.8	<0.001
Diastolic BP, mmHg	73.7±9.8	71.8±9.3	0.13
Biochemical profile, mean±SD, except high-sensitivity CRP and omega-3 fatty acid index, which are median [IQR]			
Glucose, mmol/L	5.76±1.54	5.69±1.47	0.79
mg/dL	103.8±27.8	102.6±26.4	
Hemoglobin A1c, %	5.8±0.80	6.1±1.1	0.81
Creatinine clearance, mL/min	99.7±26.6	109.9±26.4	0.025
High-sensitivity CRP, mg/L	0.80 [0.40–2.7]	0.70 [0.40–1.1]	0.20
Omega-3 fatty acid Index	3.29 [2.60–4.16]	2.99 [2.33–4.22]	0.39
Lipid levels, mean±SD, except triglyceride, which is median [IQR]			
HDL-C, mmol/L	1.23±0.40	1.22±0.24	0.79
mg/dL	47.4±15.3	47.0±9.4	
LDL-C, mmol/L	2.01±0.68	2.04±0.81	0.84
mg/dL	77.8±26.3	78.8±31.4	
Total cholesterol, mmol/L	3.94±0.92	3.88±1.00	0.70
mg/dL	152.4±35.5	150.0±38.7	
Triglyceride, median [IQR], mmol/L	1.33 [0.94–1.89]	1.29 [0.80–1.72]	0.33
mg/dL	118.0 [83.0–167.0]	114.0 [71.3–152.3]	
CBC, mean±SD			
WBCs, 10 <sup>9</sup> cells/L	6.7±2.3	6.3±1.3	0.29
Monocytes, cells/μL	540±167	482±160	0.044
Neutrophils, cells/μL	4206±1512	3960±1184	0.33
Lymphocytes, cells/μL	1757±1537	1699±424	0.81
Platelets, cells/μL	191±51	196±47	0.54
Medications, n (%)			
Statin	185 (94.9)	38 (92.7)	0.58
Aspirin	184 (94.4)	41 (100)	0.12
ACEI	116 (59.5)	15 (36.6)	0.007

(Continued)

**Table 7. Continued**

	Hypertensive (n=200)	Normotensive (n=40)	P value
ARB	40 (20.5)	3 (7.3)	0.047
Hydrochlorothiazide	43 (22.1)	0 (0)	<0.001
Furosemide	17 (8.7)	1 (2.4)	0.17
Calcium channel blocker	56 (28.7)	0 (0)	0.051
β-Blocker	144 (73.8)	22 (53.7)	0.12

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass graft; CBC, complete blood count; CAC, coronary artery calcium; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; and WBC, white blood cell.

median of 1.35 to 1.22 mmol/L (120–108 mg/dL) in the setting of baseline mean LDL-C <2.07 mmol/L (80 mg/dL). This decrease in triglycerides was the only predictor of change in fatty plaque among the lipids and suggests that the reduction in triglycerides may have contributed to plaque regression. It is important to note that the median baseline level of triglycerides was already <1.69 mmol/L (150 mg/dL), which is the current recommended goal by the American Heart Association/American College of Cardiology.<sup>34</sup> The current finding suggests that lower levels of triglycerides than currently recommended may be beneficial.

### Baseline Predictors of Fatty Plaque Regression

We also examined baseline predictors of coronary fatty plaque regression at 30 months. Both non-HDL-C level <2.59 mmol/L and systolic BP <125 mmHg were significant independent predictors. Of 9361 patients in SPRINT (Systolic Blood Pressure Intervention Trial), those randomized to intensive BP lowering had a significant reduction in mortality and cardiovascular events compared with the usual care group.<sup>35</sup> On the basis of these results, the recommended systolic BP level was lowered from 140 mmHg to 130 mmHg.<sup>36,37</sup> The benefit of SBP <125 mmHg associated with regression of coronary plaque in the current report may be one explanation for lower CVD events in SPRINT.

The current findings also report that baseline non-HDL-C <2.59 mmol/L was an independent predictor of fatty plaque regression and a more important predictor than baseline levels of LDL-C, triglycerides, or remnant cholesterol. Non-HDL-C is total cholesterol minus HDL-C, which is the sum of very low-density lipoprotein cholesterol, intermediate-density lipoprotein cholesterol, and LDL-C. Therefore, non-HDL-C includes the cholesterol in all of the atherogenic apolipoprotein B-containing lipoproteins: triglyceride-enriched lipoproteins, chylomicrons, chylomicron remnants, very low-density lipoprotein and very low-density lipoprotein remnants, intermediate-density lipoprotein, LDL, and lipoprotein (a), and this may explain the greater

predictive value of non-HDL-C compared with LDL-C. Elevated levels of non-HDL-C have been reported to be predictive of CVD and CVD mortality, similar to apolipoprotein B and as good as, or better than, that of LDL-C.<sup>38–41</sup> During a median follow-up of 6.1 years in 302 430 individuals without CVD from 68 long-term prospective studies in North America and Europe, the HR for nonfatal MI and coronary heart disease death for triglycerides was 1.37 (95% CI, 1.31–1.42) after adjustment for nonlipid risk factors.<sup>42</sup> However, the HR for triglycerides was reduced to 0.99 (95% CI, 0.94–1.05) after further adjustment for HDL-C and non-HDL-C. After adjustment for nonlipid risk factors, the HR for coronary heart disease with non-HDL-C was 1.56 (95% CI, 1.47–1.66) and remained significant at 1.50 (95% CI, 1.39–1.61) after adjustment for HDL-C and log triglyceride. The better prediction of coronary heart disease risk and future cardiovascular events with non-HDL-C than LDL-C or triglyceride level is probably due to the inclusion of all apolipoprotein B-containing lipoproteins in non-HDL-C.

### Outcomes in Normotensive Compared With Hypertensive Patients

When stratified by BP status, important findings emerge. Normotensive patients taking EPA+DHA had regression of noncalcified plaque compared with control, whereas there was no difference in hypertensive patients. Moreover, compared with patients taking control, normotensive patients taking EPA+DHA had a significant reduction in neutrophil count and NLR, whereas hypertensive patients did not. Furthermore, the reduction in triglycerides correlated with the change in noncalcified plaque in normotensive patients. These findings suggest that the effect of EPA+DHA supplementation is modified by hypertension status, and normotensive patients may have greater benefit. When baseline characteristics of the regressors and progressors were compared, the progressors had significantly higher levels of WBC and neutrophil counts, markers of inflammation; thus, these findings suggest that progressors had a higher level of inflammation at baseline.

**Table 8. Percent Change in Characteristics at 30-Month Follow-Up in the Control and EPA+DHA Groups Stratified by BP Status**

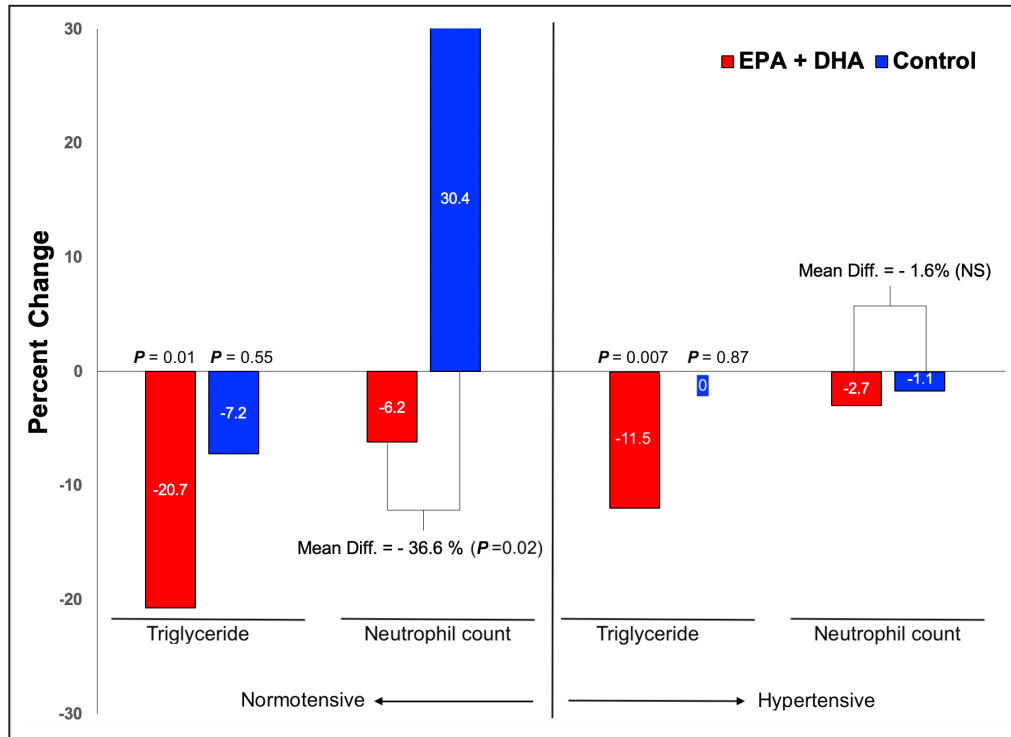
	Hypertensive			Normotensive			P value*	Mean difference in % change	P value*
	Percent change from baseline			Percent change from baseline					
	Controls (n=101)	EPA+DHA (n=99)	Mean difference in % change	Controls (n=13)	EPA+DHA (n=27)	Mean difference in % change			
Anthropometrics and BP, mean (95% CI)									
Weight	-1.5 (-2.7 to -0.37)	-0.82 (-2.2 to 0.61)	0.72 (-1.1 to 2.6)	0.66 (-1.7 to 3.0)	0.51 (-2.3 to 3.4)	-0.14 (-4.5 to 4.3)	0.44	0.95	
BMI†	-0.88 (-2.1 to 0.29)	-0.34 (-1.7 to 1.0)	0.42 (-1.4 to 2.2)	1.2 (-1.4 to 3.8)	10.2 (-8.8 to 29.2)	9.0 (-18.7 to 36.7)	0.64	0.51	
Waist, cm	1.3 (0.26 to 2.3)	0.90 (-0.24 to 2.0)	-0.47 (-2.0 to 1.0)	2.2 (0.43 to 4.0)	3.1 (0.86 to 5.3)	0.85 (-2.6 to 4.3)	0.54	0.62	
Systolic BP	-0.52 (-3.2 to 2.2)	0.010 (-2.1 to 2.2)	0.57 (-2.9 to 4.1)	2.6 (-5.9 to 11.1)	-0.21 (-4.5 to 4.1)	-2.8 (-11.1 to 5.4)	0.75	0.49	
Diastolic BP	-4.1 (-6.4 to -1.7)	-3.0 (-5.7 to -0.34)	1.0 (-2.5 to 4.6)	1.4 (-3.2 to 6.1)	1.2 (-3.6 to 6.0)	-0.23 (-6.7 to 6.2)	0.57	0.95	
Biochemical profile, mean (95% CI), except high-sensitivity CRP and omega-3 fatty acid index, which are median [IQR]									
Glucose	5.4 (0.91-10.0)	9.0 (2.9-15.0)	3.5 (-3.9 to 11.0)	-2.1 (-11.8 to 7.6)	4.7 (-1.4 to 10.8)	6.8 (-3.9 to 17.6)	0.35	0.21	
Hemoglobin A1c	1.97 (-0.24 to 3.8)	0.55 (-0.8 to 1.9)	-0.21 (-2.9 to 2.4)	-0.81 (-3.1 to 1.5)	2.9 (-0.72 to 6.6)	3.8 (-1.8 to 9.3)	0.88	0.18	
Creatinine clearance	-7.56 (-10.7 to -4.4)	-5.3 (-8.4 to -2.3)	2.2 (-2.1 to 6.6)	-5.9 (-15.8 to 4.0)	-2.0 (-9.2 to 5.2)	3.9 (-8.9 to 16.6)	0.31	0.54	
High-sensitivity CRP	0 [-50.0 to 88.0]	-13.3 [-50.0 to 33.2]	0.80	33.3 [-20.5 to 482.7]	0 [-40.5 to 141.1]	0.55	0.13	0.34	
Omega-3 fatty acid Index	1.39 [-9.27 to 13.69]	95.33 [51.89-159.16]	96.72‡	9.54 [3.94-21.17]	134.50 [42.98-175.46]	124.96‡	<0.001	0.001	
Lipid levels, mean (95% CI), except triglyceride, which is median [IQR]									
HDL-C	-3.4 (-6.7 to -0.01)	2.2 (-2.1 to 6.5)	5.6 (0.18-10.9)	1.8 (-7.2 to 10.8)	-1.1 (-7.2 to 4.9)	-2.9 (-13.3 to 7.4)	0.043	0.57	
LDL-C	5.0 (-2.1 to 12.2)	6.9 (-2.2 to 16.1)	1.9 (-9.6 to 13.4)	4.8 (-8.4 to 18.1)	13.1 (-3.5 to 29.7)	8.3 (-16.9 to 33.5)	0.75	0.51	
Total cholesterol	1.6 (-2.5 to 5.7)	0.32 (-4.9 to 5.6)	-1.25 (-7.8 to 5.3)	1.5 (-6.7 to 9.7)	2.3 (-7.2 to 11.9)	0.84 (-13.8 to 15.5)	0.71	0.91	
Triglycerides	0.0 [-17.5 to 50.9]	-11.5 [-33.7 to 13.1]	-4.2‡	-7.2 [-29.8 to 16.6]	-20.7 [-32.5 to -1.5]	-14.1‡	0.011	0.32	
CBC, mean (95% CI)									
WBC count	-4.5 (-8.7 to -0.35)	-5.4 (-10.0 to -0.75)	-0.89 (-7.1 to 5.3)	16.0 (2.0 to 30.1)	-2.2 (-9.8 to 5.4)	-18.2 (-32.6 to -4.0)	0.78	0.013	
Monocytes	-7.1 (-11.6 to -2.7)	-4.7 (-9.1 to -0.30)	2.4 (-3.8 to 8.6)	12.9 (-5.8 to 31.6)	3.4 (-11.8 to 18.7)	-9.5 (-34.6 to 15.6)	0.44	0.45	
Neutrophils	-1.1 (-7.4 to 5.2)	-2.7 (-9.5 to 4.0)	-1.6 (-10.8 to 7.5)	30.4 (0.84 to 59.9)	-6.2 (-15.9 to 3.5)	-36.6 (-67.2 to -6.0)	0.73	0.022	
Lymphocytes	-6.1 (-10.3 to -2.0)	-5.4 (-9.7 to -1.1)	0.80 (-5.2 to 6.7)	3.6 (-8.8 to 15.9)	5.8 (-3.2 to 14.8)	2.3 (-12.9 to 17.4)	0.80	0.77	
Platelets	-6.9 (-10.2 to -3.6)	32.0 (-14.2 to 78.2)	38.9 (-7.5 to 83.5)	-0.28 (-9.2 to 8.7)	-3.1 (-7.7 to 1.5)	-2.8 (-11.5 to 5.9)	0.087	0.52	

BMI indicates body mass index; BP, blood pressure; CBC, complete blood count; CRP, C-reactive protein; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; and WBC, white blood cell.

\*P values calculated using t test except for triglycerides and high-sensitivity CRP, where a Mann-Whitney U test was used.

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

‡Median of difference in percent change; therefore, no 95% CI can be calculated.



**Figure 3. Effect of EPA plus DHA on triglyceride level and neutrophil count in normotensive and hypertensive patients.**

Normotensive patients taking EPA+DHA had a reduction in neutrophil count (mean -6.2% [95% CI, -15.9 to 3.5]) compared with a significant 30.4% increase (95% CI, 0.84–59.9) in control for a 36.6% difference (P=0.022), suggesting lower levels of inflammation in the normotensive patients taking EPA and DHA. Hypertensive patients had no difference in neutrophil count by treatment assignment. Both triglycerides and neutrophil count are markers of inflammation. Diff indicates difference; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; and NS, nonsignificant.

The total WBC count has been reported to predict the incidence of CAD and mortality in patients without CAD and mortality in patients with CAD.<sup>43</sup> In a meta-analysis of 7 large studies including 5337 patients without CAD, a 1.4-fold increased risk of CAD (95% CI, 1.3–1.5) was observed with a high baseline WBC count, comparable to that of high-sensitivity CRP (relative risk, 1.45 [95% CI, 1.25–1.68]).<sup>44,45</sup> Whether higher levels of inflammation lessen response to omega-3 fatty acid supplementation should be examined in future studies. If this were the case, higher levels of omega-3 fatty acid supplementation should be examined to determine whether higher levels would improve outcome.

The current finding of a benefit on “NLR” in normotensive patients lends further support to a role of inflammation. Inflammation has been established to play a role in the development of cardiovascular events through its involvement in the pathogenesis and progression of atherosclerosis via various possible mechanisms.<sup>46</sup> The NLR reflects a dynamic relationship between neutrophils and lymphocytes and is a sensitive marker of inflammation.<sup>47</sup> Neutrophils secrete proinflammatory mediators that may cause vascular wall degeneration,<sup>48</sup> while lymphocytes regulate the

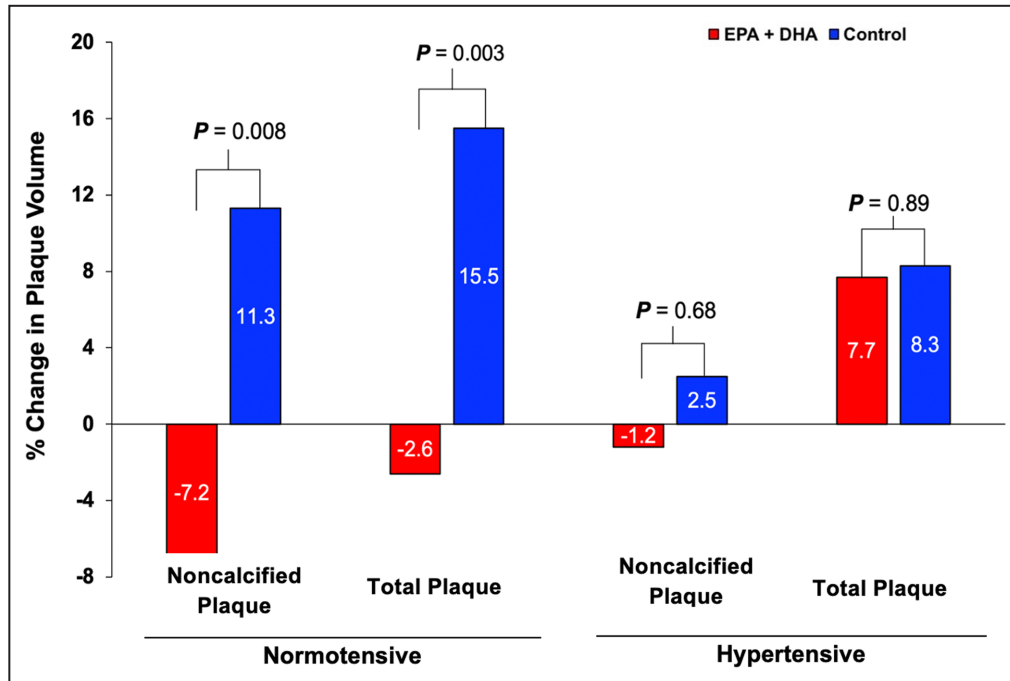
inflammatory response through T-regulatory lymphocytes and have an antiatherosclerotic effect.<sup>49</sup>

NLR is inexpensive and readily available from a complete blood cell count. It positively correlates with CRP levels<sup>50,51</sup> and could serve as a potential surrogate marker for CRP.<sup>51</sup> In certain instances, NLR is better at predicting outcomes, such as bacteremia or the severity of community-acquired pneumonia, than CRP.<sup>52,53</sup> NLR also has advantages as it is not influenced by physiological conditions such as dehydration

**Table 9. Effect of EPA+DHA on Neutrophil Lymphocyte Ratio in Normotensive and Hypertensive Patients**

Neutrophil lymphocyte ratio			
	Baseline, mean±SD	30 months, mean±SD	P value
Normotensive patients			
EPA+DHA	2.64±0.87	2.39±1.03	0.024
Control	2.09±0.85	2.47±0.96	0.064
Hypertensive patients			
EPA+DHA	2.76±1.36	2.72±1.50	0.25
Control	2.93±1.50	2.95±1.61	0.58

DHA indicates docosahexaenoic acid; and EPA, eicosapentaenoic acid.



**Figure 4.** EPA and DHA are associated with regression of noncalcified and total plaque in normotensive but not hypertensive patients. The change in noncalcified plaque correlated positively with the change in triglyceride level in normotensive patients ( $r=0.35$  [ $P=0.034$ ]). DHA indicates docosahexaenoic acid; and EPA, eicosapentaenoic acid.

and exercise, conditions that affect the absolute numbers of individual cell types.<sup>54</sup>

In a systematic review and meta-analysis, NLR has been found to be significantly associated with CVD outcomes including CAD, acute coronary syndrome, stroke,

and composite cardiovascular events.<sup>55</sup> Moreover, NLR is independently and significantly associated with an increased risk of all-cause mortality, cardiovascular mortality, and other mortality (but not cancer mortality) and is thus considered a strong and independent

**Table 10.** Percent Change in Coronary Plaque in EPA+DHA and Control Groups Stratified by BP Status

	Controls (n=13)	EPA+DHA (n=27)	P value
	Percent change, median [IQR]	Percent change, median [IQR]	
<b>Normotensive</b>			
Fatty	11.9 [-11.9 to 47.0]	0.22 [-17.3 to 13.1]	0.11
Fibrous	13.2 [-3.5 to 34.0]	-7.6 [-20.7 to 2.6]*	0.008
Noncalcified	11.3 [3.8-28.6]	-7.2 [-19.9 to 5.8]†	0.008
Calcified	96.3 [-5.2 to 131.2]	7.7 [-28.8 to 79.0]	0.096
Total	15.5 [4.0-50.0]	-2.6 [-15.4 to 12.5]	0.003
	Controls n=101	EPA+DHA n=99	P value
	Percent change, median [IQR]	Percent change, median [IQR]	
<b>Hypertensive</b>			
Fatty	2.7 [-10.1 to 14.5]	0.81 [-9.2 to 23.7]	0.45
Fibrous	3.6 [-10.6 to 17.2]	1.2 [-10.5 to 15.5]	0.58
Noncalcified	2.5 [-6.9 to 13.3]	-1.2 [-10.1 to 15.2]	0.68
Calcified	47.4 [3.1-146.8]	51.4 [2.4-139.6]	0.98
Total	8.3 [-4.2 to 25.1]	7.7 [-2.0 to 20.9]	0.89

BP indicates blood pressure; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; and IQR, interquartile range.

\*Within-group P value=0.012.

†Within-group P value=0.092.

risk indicator for mortality in the elderly population.<sup>56</sup> Therefore, the beneficial effect of EPA+DHA on NLR in the current report would potentially predict a beneficial effect on CVD outcomes.

Potential mechanisms for the lower response to omega-3 fatty acids in hypertensive patients in the current report could be due to the association of hypertension with endothelial dysfunction, which is involved in the initiation and development of vascular inflammation and characterized by vasoconstriction, cell proliferation, and shifting toward a proinflammatory and prothrombotic state, leading to increased cardiovascular risk and atherosclerosis.<sup>57</sup> A basic study that lends support to potential differential findings by BP status is that of Ning et al,<sup>58</sup> who generated hypertension in Watanabe heritable hyperlipidemic (WHHL) rabbits by surgically removing 1 kidney and partially ligating the other renal artery. Forty percent of the small arteries and arterioles in hypertensive WHHL rabbits were completely occluded compared with 5% in normotensive WHHL rabbits.<sup>58</sup> Moreover, these coronary lesions in hypertensive WHHL rabbits were accompanied by an increased number of macrophages and smooth muscle cells compared with normotensive WHHL rabbits. Lipid levels were similar in both rabbits. Compared with the normotensive WHHL group, aortic intimal lesions of hypertensive WHHL rabbits were 1.6-fold higher in the aortic arch and 1.4-fold higher in the thoracic and abdominal aorta with an 8.5-fold increase in aortic macrophages ( $P < 0.01$ ) and a higher frequency of intraplaque hemorrhage and vulnerable plaques.<sup>58</sup> Five of 7 hypertensive WHHL rabbits had transmural MIs compared with none of the 7 normotensive WHHL rabbits; all hypertensive WHHL rabbits died within 34 to 56 weeks compared with no normotensive WHHL rabbits. These results indicate that hypertension induced in WHHL rabbits may not only enhance the development of atherosclerosis but also destabilize the plaques and increase cardiac death compared with normotensive rabbits.<sup>58</sup>

## Strengths and Limitations

The strengths of the current study include the use of CCTA to measure atherosclerotic plaque subtypes, the randomization to high-dose EPA+DHA, 30-month follow-up, and the significant reduction in cardiovascular events noted in those with regression of coronary fatty plaque. All CCTA results were read by a core team that allows consistency in measurement. Generalizability is limited to patients with clinical CAD.

## CONCLUSIONS

Patients with regression of coronary fatty plaque had 4-fold fewer cardiac events. Triglyceride reduction with

EPA+DHA at 30 months correlated positively with coronary fatty plaque regression. Baseline levels of non-HDL-C level  $< 2.59$  mmol/L and systolic BP  $< 125$  mmHg were significant independent predictors of coronary fatty plaque regression. Normotensive patients taking EPA+DHA compared with control had regression of noncalcified coronary plaque, which correlated with a decrease in triglyceride level; they also had a significant decrease in neutrophil and WBC count and NLR, all markers of inflammation. In contrast, hypertensive patients had no change in coronary plaque or NLR. Thus, normotensive patients show greater benefit than hypertensive patients, which may be due to lower levels of inflammation. Future studies should examine the role of EPA+DHA in inflammation further. Taken together, the current results suggest that SBP  $< 125$  mmHg and non-HDL-C  $< 2.59$  mmol/L would be predicted to prevent progression of fatty plaque and potentially lead to regression, thus possibly decreasing the risk of CVD events and reducing residual risk in statin-treated patients. The study highlights the importance of maintaining optimal levels of triglycerides, non-HDL-C, and systolic BP, in addition to guideline-recommended LDL-C levels, to reduce cardiac events and regress coronary fatty plaque.

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### Disclosures

None.

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