Effect of Omega-3 Acid Ethyl Esters on Left Ventricular Remodeling After Acute Myocardial Infarction

The OMEGA-REMODEL Randomized Clinical Trial

BACKGROUND: Omega-3 fatty acids from fish oil have been associated with beneficial cardiovascular effects, but their role in modifying cardiac structures and tissue characteristics in patients who have had an acute myocardial infarction while receiving current guideline-based therapy remains unknown.

METHODS: In a multicenter, double-blind, placebo-controlled trial, participants presenting with an acute myocardial infarction were randomly assigned 1:1 to 6 months of high-dose omega-3 fatty acids (n=180) or placebo (n=178). Cardiac magnetic resonance imaging was used to assess cardiac structure and tissue characteristics at baseline and after study therapy. The primary study endpoint was change in left ventricular systolic volume index. Secondary endpoints included change in noninfarct myocardial fibrosis, left ventricular ejection fraction, and infarct size.

RESULTS: By intention-to-treat analysis, patients randomly assigned to omega-3 fatty acids experienced a significant reduction of left ventricular systolic volume index (–5.8%, *P*=0.017), and noninfarct myocardial fibrosis (–5.6%, *P*=0.026) in comparison with placebo. Per-protocol analysis revealed that those patients who achieved the highest quartile increase in red blood cell omega-3 index experienced a 13% reduction in left ventricular systolic volume index in comparison with the lowest quartile. In addition, patients in the omega-3 fatty acid arm underwent significant reductions in serum biomarkers of systemic and vascular inflammation and myocardial fibrosis. There were no adverse events associated with high-dose omega-3 fatty acid therapy.

CONCLUSIONS: Treatment of patients with acute myocardial infarction with high-dose omega-3 fatty acids was associated with reduction of adverse left ventricular remodeling, noninfarct myocardial fibrosis, and serum biomarkers of systemic inflammation beyond current guideline-based standard of care.

CLINICAL TRIAL REGISTRATION: URL: http://www.clinicaltrials.gov. Unique identifier: NCT00729430.

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Key Words: endomyocardial fibrosis ■ fatty acids, omega-3 ■ infarction ■ magnetic resonance imaging ■ ventricular remodeling

Clinical Perspective

What Is New?

- Large-scale randomized trials of patients with acute myocardial infarction have reported inconsistent mortality benefits from omega-3 fatty acids (1 g daily). Using cardiac MRI, the randomized, placebo-controlled OMEGA-REMODEL study (Omega-3 Acid Ethyl Esters on Left Ventricular Remodeling After Acute Myocardial Infarction) investigated for cardiac remodeling benefits from omega-3 fatty acids from fish oil (O-3FA) in patients with acute myocardial infarction who were receiving therapies per current treatment guidelines.
- In comparison with placebo, patients who received 4 g of O-3FA daily experienced significant improvement in both left ventricular end-systolic volume and a surrogate cardiac MRI measure of noninfarct myocardial fibrosis during the first 6 months of infarct healing.
- These remodeling benefits followed a dose-response relationship with the rise of the in vivo O-3FA levels quantified by the red blood cell index.

What Are the Clinical Implications?

- The OMEGA-REMODEL study provides randomized trial evidence that 4 g daily dose of O-3FA is a safe and effective treatment in improving cardiac remodeling in patients receiving current guideline-based post–myocardial infarction therapies.
- Given that the incidence of heart failure after acute myocardial infarction remains high despite current therapies, the cardiac remodeling benefits from O-3FA may translate to a significant clinical impact and warrants prospective clinical studies.

Preclinical cardiovascular benefits of omega-3 fatty acids from fish oil[1,2] (O-3FA) have been evaluated in large-scale clinical trials in patients suffering an acute myocardial infarction (MI).[3,4] The GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico)-Prevenzione open-label trial randomly assigned 11 324 patients to 1 g/d O-3FA versus placebo and observed a 20% mortality reduction for O-3FA therapy.[3] However, with advances in acute infarct care, the reported incremental benefits of O-3FA therapy have been inconsistent.[4] Cardiac MRI (CMR) offers accurate serial quantification of left ventricular (LV) structure and function, infarct size, and extracellular matrix expansion within noninfarcted myocardium.[5] The OMEGA-REMODEL trial (Omega-3 Acid Ethyl Esters on Left Ventricular Remodeling After Acute Myocardial Infarction) is a prospective, multicenter, double-blind, placebo-controlled trial designed to evaluate the hypothesis that 4 g/d O-3FA for 6 months after acute MI attenuates adverse LV remodeling beyond optimal standard of care.

METHODS

Patients

Patients were enrolled across 3 tertiary-care centers in Boston, MA (Brigham and Women's, Massachusetts General, and Beth Israel Deaconess Medical Center hospitals) who were >21 years of age and presented with an acute MI based on (1) symptoms consistent with an acute coronary syndrome, (2) serial Troponin T (or I) profile consistent with acute injury and peak level >0.5 ng/mL, and (3) significant angiographic coronary stenosis. Patient recruitment occurred between June 2008 and August 2012. Exclusion criteria included MI secondary to cardiac procedure, life expectancy <1 year, clinical indication for O-3FA treatment, active pregnancy, and absolute contraindications to CMR. All patients received standard medical therapy per discretion of the attending cardiologists. The institutional review board at each enrolling site approved the study and all patients provided informed consent.

Study Design and Randomization

The National Institutes of Health provided sole funding for this study, whereas GlaxoSmithKline (Research Triangle Park, NC) provided study medication (O-3FA and placebo). The investigational pharmacies of the enrolling centers randomly assigned patients 1:1 to either O-3FA or placebo using a 2×2 blocked randomization scheme for age (>70 years age) and anterior MI location in double-blinded fashion. Computer-generated randomization codes were used by the investigational pharmacies for blocked randomization. Pretreatment and post-treatment visits occurred at 14 to 28 days and 6 months after index acute MI, respectively. Study visits included collection of coronary risk profile, detailed events of index MI, adverse events, standardized lifestyle and dietary questionnaires, contrast-enhanced CMR, and blood samples. All procedures during study visits were conducted or overseen in person by a physician investigator.

Study Intervention and Monitoring

During the pretreatment visit, enrolled patients received 6-month supplies of study drug and were instructed to take four 1g capsules per day with meals. Study drug was either Lovaza, containing ethyl esters of eicosapentaenoic acid (EPA, ≈465 mg) and docosahexaenoic acid (DHA, ≈375 mg; GlaxoSmithKline) or placebo, containing corn oil (600 mg linoleic acid, no O-3FA, and <0.05% of transfatty acids). All patients received lifestyle counseling, including dietary recommendations for standard post-MI care,[6] but no specific recommendations were given with regard to dietary O-3FA intake. All patients were instructed to refrain from consuming over-the-counter fish oil products. Every 2 months during the 6-month study drug period, an investigator conducted scripted

telephone interviews with each patient and assessed for tolerance to study drug, adverse events, and pill counts.

Study Endpoints

The primary study endpoint was adverse LV remodeling measured as change in left ventricular end-systolic volume indexed to body surface area (LVESVI, mL/m^2) by CMR after 6 months of study therapy. Secondary endpoints included changes in (1) noninfarct myocardial fibrosis measured as the myocardial extracellular volume fraction remote from the acute infarction (ECV_{Remote}), (2) total infarct size, and (3) left ventricular ejection fraction (LVEF). Sudden cardiac death during follow-up was an additional secondary endpoint at trial commencement, but removal was recommended by the Data Safety and Monitoring Board because of the anticipated low number of events.

Cardiac MRI

CMR studies were performed using 3.0 Tesla scanners (Trio or Verio, Siemens, Erlangen, Germany). The CMR protocol consisted of cine function, native and postcontrast myocardial T1 mapping, and late gadolinium enhancement imaging. Myocardial T1 was measured using a look-locker gradient-echo sequence (3 short-axis locations centered midventricle) acquired before and 5, 15, and 25 minutes after administration of 0.1 mmol/kg intravenous gadolinium (Magnevist, Bracco). Image analyses using a commercial software (QMass, Medis Inc, Raleigh, NC) was performed blinded to clinical data, time order of CMR studies, and treatment assignment. Total infarct size was measured as infarct mass (in grams) and as percentage of total LV mass (from late gadolinium enhancement images). Infarct mass was similar between 2 criteria (≥2 standard deviations beyond mean remote myocardial signal intensity and full-width half-maximum)[7] and infarct mass values using ≥2 standard deviation criteria were then used in all analyses. Short-axis late gadolinium enhancement and myocardial T1 images were segmented as per the American Heart Association 16-segment model.[8] For each T1 Look-Locker acquisition, T1 was determined by nonlinear least-squares fitting of a parameterized representation of an inversion recovery [signal intensity=A–B·exp(–TI/T_1*)] to the measured average signal intensity values in myocardial segments. T1 was then calculated from the best-fit parameters with the correction formula $T_1=T_1^*\cdot(B/A-1)$.[9] We derived segmental extracellular volume fraction (ECV) by plotting the reciprocal of T1 ($R_1=1/T_1$) for myocardial segments against the simultaneously measured R1 in the blood pool, using both pre- and postcontrast measurements where R1 in the blood pool was <3.5 s^{-1}. R1 data pairs with higher values of R1 in the blood pool were excluded from a linear regression line fit to the R1 data to avoid an underestimation of ECV as conditions of fast water exchange may not be met.[10] ECV was calculated from the slope of the linear regression line, ie, the partition coefficient (λ), using the blood hematocrit (HCT): ECV=λ·(1–HCT).[11] ECV segments without matching late enhancement were averaged to yield the global ECV of the remote, noninfarcted myocardium (ECV_{Remote}).

Biomarkers and Omega-3 Fatty Acids

Blood samples were assayed for red blood cell (RBC) fatty acid levels (OmegaQuant Analytics, LLC, Sioux Falls, SD) and serum biomarkers (Health Diagnostic Laboratory, Inc, Richmond, VA) as follows: inflammation (C-reactive protein, myeloperoxidase, lipoprotein-associated phospholipase A2, fibrinogen), neurohormonal activation (N-terminal prohormone brain natriuretic peptide, cystatin C), and cardiac fibrosis (ST-2, galectin-3). RBC fatty acid composition, which has been shown to correlate with myocardial O-3FA levels and unbiased by recent dietary intake,[12,13] was evaluated by using gas chromatography by flame ionization detection. The omega-3 index was calculated from the sum of DHA and EPA and expressed as a percentage of total RBC fatty acids.

Statistical Analysis

Descriptive statistics were calculated by treatment arm using mean±standard deviation and median (first quartile, third quartile), for normal and skewed continuous variables, respectively. Categorical variables were presented as count (%) for each level. General linear mixed models were used to perform an intention-to-treat analysis that included patients missing follow-up visits for the primary and secondary endpoints.[14] Restricted maximum likelihood estimation produces unbiased estimates under the assumption the missing responses are missing at random, ie, the missing responses may be related to the observed responses, but are independent of the unobserved responses. This method alleviates the need for imputation. A compound symmetry correlation structure was used for the repeated measurements. As a sensitivity analysis, the mixed models included increasing levels of covariate adjustment; the initial model only included the randomization group assignment, an indicator variable for pre- or post-treatment visit, and their interaction. Age, sex, race, and clinical site were added to the model as fixed covariates, with CMR infarct size used to adjust for MI severity; RBC omega-3 index was included for pretreatment exposure to O-3FA. Finally, medication status, coronary risk factors, and heart rate were added to the model. Residual diagnostics were performed to verify model assumptions. A per-protocol analysis was also conducted for all patients who completed both study visits, and the changes in RBC levels of EPA and DHA (summed and individually) were used as biomarker-based measures of exposure to treatment. The changes in primary and secondary endpoints were regressed against the changes in RBC O-3FA levels (modeled separately as a continuous factor per 1 standard deviation increase and by quartiles using the first quartile as reference). In an exploratory analysis, fish oil randomization group assignment was used to predict changes in biomarkers of inflammation, neurohormonal activation, and cardiac fibrosis. All statistical analyses were performed using SAS (SAS Institutes, version 9.4, Cary, NC), and a *P* value of <0.05 was used to ascribe statistical significance.

Power/Sample Size

The primary endpoint, change in LVESVI, was modeled as a log-normal distribution because of expected positive skewness. The coefficient of variation for LV end systolic volume in studies of LV dysfunction was reported as 26%.[15] The correlation between measurements 6 months apart was assumed to be 0.7.[16,17] To have >80% power and detect a 5% mean within-patient change in LV end systolic volume using a 2-sided critical level of 0.05, a minimum of 129 patients were required in each arm. Estimating a 30% loss to follow-up and a 25%

noncompliance rate, the recruitment goal was 202 patients per arm (n=404).

RESULTS

Patients and Baseline Clinical Characteristics

Figure 1 illustrates study enrollment and randomization. Because of logistical issues, 3 patients deviated in study scheduling: 2 had a pretreatment visit at 5 days after index MI and 1 had a post-treatment visit at 9 months. Baseline demographics stratified by treatment arm are shown in Table 1. Overall, 91% of patients achieved Thrombolysis in Myocardial Infarction (TIMI) 3 flow within the infarct-related artery, and there was high adherence to all post-MI guideline-recommended[18] therapies. In the overall cohort, 73% of patients were

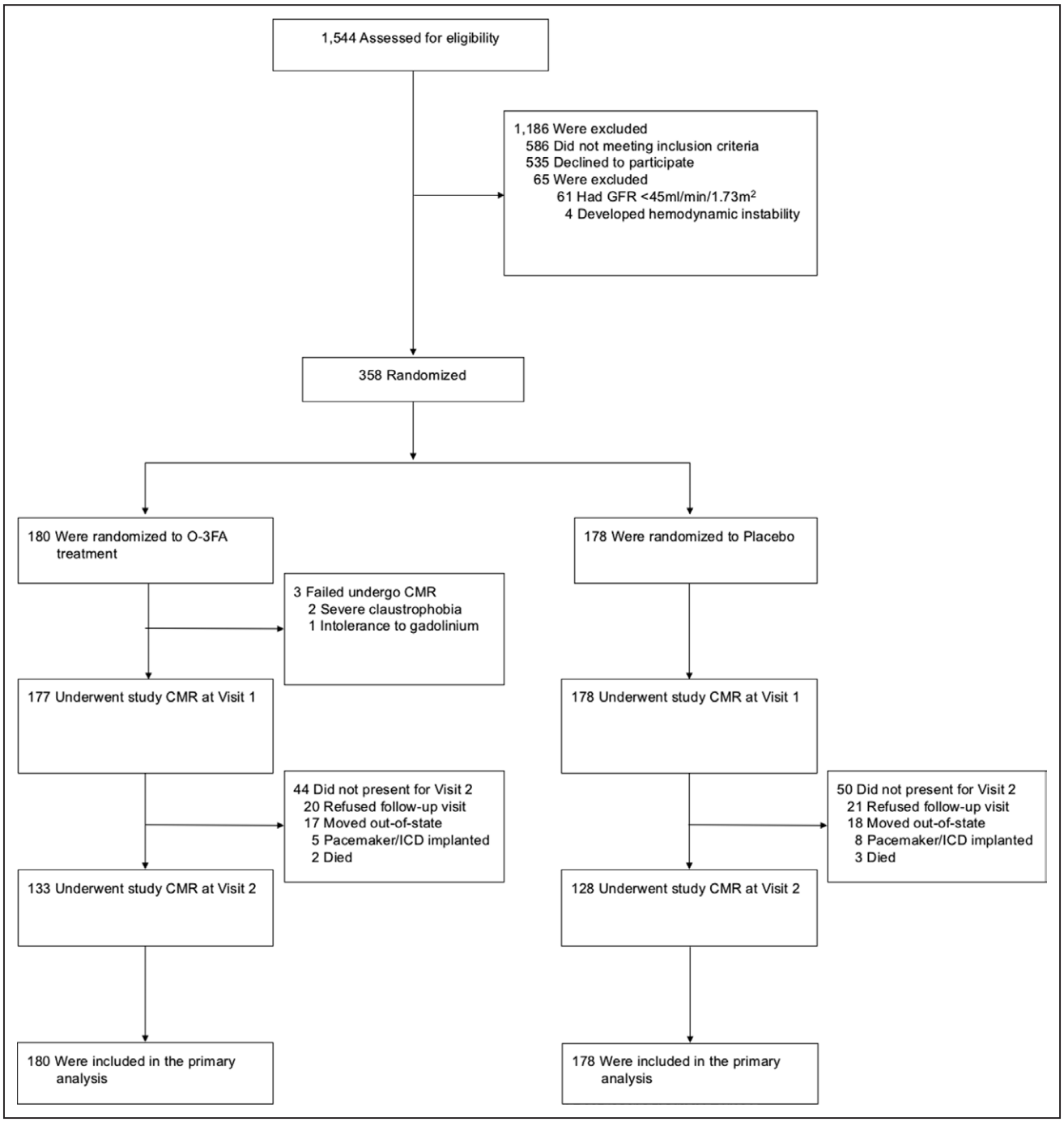

Figure 1. Enrollment and randomization.
The treatment duration was 6 months for both randomized arms (between study visit 1 and 2). CMR indicates cardiac magnetic resonance imaging; GFR, glomerular filtration rate; ICD, implantable cardioverter-defibrillator; and O-3FA, omega-3 fatty acids from fish oil.

Table 1. Baseline Characteristics of the Intention-to-Treat Population

Characteristic	Omega-3 Fatty Acids (n=180)	Placebo (n=178)	*P* Value
Demographics			
Age, y	60±10	58±10	0.22
Female sex, n (%)	32 (18)	38 (21)	0.39
White race, n (%)	143 (81)	146 (82)	0.68
Body mass index, kg/m^2	29±5.4	29±5.6	0.92
Body surface area, m^2	2.0±0.23	2.0±0.22	0.82
Heart rate, bpm*	64 (60, 71)	66 (60, 71)	0.26
Systolic BP, mm Hg	121±15	120±16	0.73
Diastolic BP, mm Hg	70±10	70±11	0.62
Enrolling sites, n (%)			0.57
Brigham and Women's	115 (64)	109 (61)	
Massachusetts General	38 (21)	33 (19)	
Beth Israel Deaconess	27 (15)	36 (20)	
Index event			
STEMI, n (%)	102 (57)	105 (59)	0.66
Anterior, n (%)	48 (27)	48 (27)	1.00
TIMI 3 flow achieved, n (%)	145 (91)	156 (91)	0.99
Troponin-T (peak), μmol/L*	2.8 (0.9, 9.1)	3.4 (0.8, 10.4)	0.72
Creatine kinase (peak), U/L*	786 (330, 1608)	693 (296, 1621)	0.74
Creatine kinase MB (peak), U/L	61 (26, 152)	61 (21, 148)	0.97
Hematocrit, %*	39 (36, 42)	40 (36, 43)	0.10
Cardiovascular disease history			
Angina, n (%)	44 (25)	36 (20)	0.30
Peripheral vascular disease, n (%)	7 (4)	13 (7)	0.17
Myocardial infarction, n (%)	22 (12)	14 (8)	0.16
CABG, n (%)	24 (13)	11 (6)	0.02
PCI, n (%)	24 (13)	23 (13)	0.91
Congestive heart failure, n (%)	4 (2)	6 (3)	0.52
NYHA class, n (%)			0.37
1	167 (94)	160 (90)	
2	10 (5.5)	17 (9.5)	
3	1 (0.5)	1 (0.5)	
Hypercholesterolemia, n (%)	134 (75)	120 (67)	0.10
Diabetes mellitus, n (%)	46 (26)	45 (25)	0.90
Hypertension, n (%)	118 (66)	112 (63)	0.51
Smoker (current), n (%)	23 (13)	36 (20)	0.06
Medications			
Dual antiplatelet, n (%)†	174 (98)	174 (98)	1.00
β-Blocker, n (%)	163 (92)	164 (92)	0.85
Statin, n (%)	172 (97)	171 (96)	0.78
Calcium channel blocker, n (%)	16 (9)	10 (6)	0.22
ACE inhibitor or ARB, n (%)	134 (75)	127 (71)	0.40

(*Continued*)

Table 1. Continued

Characteristic	Omega-3 Fatty Acids (n=180)	Placebo (n=178)	*P* Value
Aldosterone antagonists, n (%)	0 (0)	1 (1)	0.91
Insulin, n (%)	18 (10)	15 (8)	0.57
Nitroglycerin, n (%)	25 (14)	19 (11)	0.33
Diuretics, n (%)	25 (14)	18 (10)	0.33

Continuous data are means±SD if normally distributed, otherwise median (25th, 75th percentile). β-Blocker is defined as β-adrenergic receptor antagonist, and statin is defined as hydroxymethylglutaryl-coenzyme A reductase inhibitor. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CABG, coronary artery bypass grafting; MB, MB isoenzyme of creatine kinase; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST-segment–elevation myocardial infarction; and TIMI, Thrombolysis in Myocardial Infarction.

*Natural logarithm transformation was used to improve normality and homoscedasticity of residuals, before performing Student *t* tests.

†Dual-antiplatelet therapy included aspirin plus either clopidogrel or prasugrel.

treated with an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker, in comparison with 89% of those who had suffered an anterior ST-segment–elevation myocardial infarction (83% in placebo group and 94% in omega-3 group, *P*=0.20). Baseline CMR characteristics stratified by treatment arm are shown in Table 2, whereas both fatty acid and biomarker levels are shown in Table 3. Median infarct size (13 g and 11% total LV mass) were similar in both treatment arms. In comparison with published values from healthy controls,[19,20] pretreatment noninfarct myocardial fibrosis of the total cohort was significantly higher (33.8±5.3, n=358 versus 24.8±2.0, n=14, *P*<0.0001),[20] whereas pretreatment mean O-3FA values were similar to those in the Framingham Offspring cohort.[21] We examined test-retest reproducibility for measuring infarct size by late gadolinium enhancement in 38 randomly selected patients and found a high intraclass correlation of 0.94 (95% confidence interval [CI], 0.88–0.97). We also have shown high intraclass correlation for intraobserver, interobserver, and test-retest variability for ECV measurements.[22]

Table 2. Baseline CMR Characteristics of the Intention-to-Treat Population

Characteristic	Omega-3 Fatty Acids (n=180)	Placebo (n=178)	*P* Value
LVESVI, mL/m^2*	37 (30, 45)	35 (27, 82)	0.29
ECV_{Remote}, %†	34.3±5.6	33.3±4.9	0.11
Infarct size, grams, using 2SD*	13 (6, 23)	13 (6, 24)	0.43
Infarct size, grams, using FWHM*	13 (6, 22)	12 (5, 23)	0.45
LVEF, %	54±9	54±10	0.48
LVEDVI, mL/m^2	84±20	82±21	0.45
RVEF, %	53±6	53±8	0.85
RVESVI, mL/m^2	33±9	34±11	0.48
RVEDVI, mL/m^2	71±17	72±19	0.41
Infarct percent, %LV mass, using 2SD*	11 (6, 21)	12 (5, 21)	0.62
Infarct percent, %LV mass, using FWHM*	12 (6, 19)	11 (5, 20)	0.65
LV mass index, g/m^2	60±14	59±15	0.34
LV mass/volume, g/mL	0.74±0.18	0.74±0.20	0.95

Continuous variables are expressed as means±SD if normally distributed, otherwise median (25th, 75th percentile). CMR indicates cardiac magnetic resonance imaging; FWHM, full-width half-maximum; LV, left ventricular; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; RVEDVI, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; RVESVI, right ventricular end-systolic volume index; and SD, standard deviation.

*Natural logarithm transformation was used to improve normality and homoscedasticity of residuals, before performing Student *t* tests.

†ECV_{Remote} was the extracellular volume fraction of myocardium remote from the infarction, an estimate of noninfarct myocardial fibrosis.

Table 3. Baseline Omega-3 Fatty Acid and Biomarker Levels of Intention-to-Treat Population

Characteristic	Omega-3 Fatty Acids (n=180)	Placebo (n=178)	*P* Value
Fatty acids (RBC % of total)			
Omega-3 index	5.5±1.8	5.7±1.7	0.45
DHA (C22:6n3)	4.7±1.3	4.9±1.4	0.29
EPA (C20:5n3)†	0.63 (0.47, 0.90)	0.64 (0.51, 0.89)	0.67
DPA (C22:5n3)	2.94±0.48	2.94±0.42	0.49
α-Linolenic (C18:3n3)	0.12±0.04	0.12±0.04	0.71
Arachidonic (C20:4n6)	17.1±1.7	17.2±1.5	0.69
Linoleic (C18:2n6)	9.5±1.5	9.4±1.5	0.30
Oleic (C18:1)	13.9±1.1	13.9±1.1	0.90
Inflammatory biomarkers			
Fibrinogen, g/L	405 (341, 522)	407 (340, 499)	0.83
hsCRP, mg/L*	2.6 (1.3, 8.5)	2.4 (1.0, 6.9)	0.22
Myeloperoxidase, ng/mL*	341 (265, 404)	324 (264, 386)	0.39
Lp-PLA2	171 (140, 200)	164 (135, 194)	0.25
Neurohormonal activation biomarkers			
NT-proBNP, ng/L*	526 (244, 1086)	460 (224, 881)	0.27
Cystatin C, mg/dL*	1.0 (0.9, 1.2)	1.0 (0.9, 1.2)	0.52
GFR, mL/min per 1.73 m^2*	82 (61, 101)	84 (66, 102)	0.54
Cardiac strain biomarkers			
ST2, ng/mL*	35 (27, 43)	36 (29, 43)	0.23
Galectin-3, ng/mL*	16 (12, 19)	15 (13, 18)	0.78
Lipid levels			
Total cholesterol, mg/dL	129 (107, 148)	127 (109, 151)	0.94
LDL-C, mg/dL	69 (54, 86)	66 (54, 84)	0.46
HDL-C, mg/dL	42 (36, 49)	42 (36, 50)	0.94
Triglycerides, mg/dL*	120 (84, 161)	121 (92, 183)	0.26

Continuous data are expressed as means±SD if normally distributed, otherwise median (25th, 75th percentile). DHA indicates docosahexanoic acid; DPA, docosapentaenoic acid; EPA, eicosapentanoic acid; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; Lp-PLA2, lipoprotein-associated phospholipase A2; NT-proBNP, N-terminal prohormone brain natriuretic peptide; and RBC, red blood cell.

*Natural logarithm transformation was used to improve normality and homoscedasticity of residuals, before performing Student *t* tests.

Treatment Effects

Based on pill counts, compliance to study drug was 96% in both O-3FA and placebo groups (*P*=0.86). Changes in RBC fatty acid levels are shown in Figure 2. Patients who received O-3FA treatment experienced marked increases in RBC levels of EPA, DHA, and omega-3 index in addition to a decrease in arachidonic acid in comparison with placebo (all *P*<0.0001). The greatest impact of O-3FA treatment was on RBC EPA and omega-3 index, which were increased by 256% and 81%, respectively. Figure 3 illustrates the primary and secondary endpoints stratified by treatment assignment. Patients who received O-3FA experienced a mean reduction of LVESVI by 5.4%, in comparison with a mean 1.2% expansion in the placebo group (*P*=0.0068). O-3FA patients experienced a mean regression of noninfarct myocardial fibrosis by 2.1%, in comparison with a mean 3.4% progression in the placebo group (*P*=0.026). There was a marginally significant difference toward improved LVEF in the O-3FA–treated group (4.8±11.3% versus 2.1±12.2%, *P*=0.073). Although both groups experienced a reduction of infarct size, these reductions were not statistically different between the groups (–8.8±39.9% versus –1.9±57.7%, *P*=0.27). Intention-to-treat and per-protocol analyses for the mean effects of O-3FA on the primary and secondary endpoints are shown in Table 4. In comparison with placebo, O-3FA treatment was associated with a

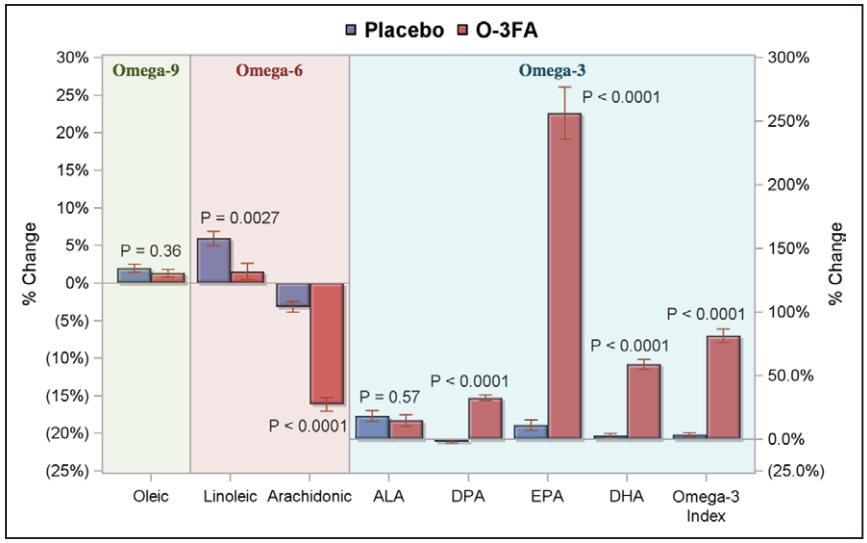

Figure 2. Percent change of fatty acid levels from baseline to post-treatment.
Percent changes from baseline to post-treatment levels of red blood cell fatty acid levels are shown for the omega-3 fatty acid–treated group (red bars) and placebo arm (blue bars). *P* values are for comparisons of percent change in red blood cell fatty acid levels between the randomized treatment arms. ALA indicates α-linolenic acid; DHA, docosahexanoic acid; DPA, docosapentaenoic acid; EPA, eicosapentanoic acid; and O-3FA, omega-3 fatty acids from fish oil.

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mean –5.8% (95% CI, –10.3% to –1.1%; *P*=0.017) and –6.6% (95% CI, –11.3% to –1.8%; *P*=0.007) reduction in LVESVI by intention-to-treat and per-protocol analyses, respectively. In addition, O-3FA treatment was associated with a significant reduction of noninfarct myocardial fibrosis. In comparison with placebo, O-3FA treatment was associated with a mean –5.6% (95% CI, –10.4% to –0.9%; *P*=0.022) and –5.5% (95% CI, –10.4% to –0.6%; *P*=0.026) reduction in noninfarct myocardial fibrosis by intention-to-treat and per-protocol analyses, respectively. There was no significant effect of O-3FA treatment on change in infarct size or LVEF in the intention-to-treat or per-protocol analyses. To remove the potential confounding effect of previous MIs, we performed similar intention-to-treat and per-protocol analyses after excluding 36 patients with a history of previous MI. As shown in online-only Data Supplement Table I, O-3FA treatment was associated with a strong and significant reduction of LVESVI and noninfarct myocardial fibrosis in both intention-to-treat and per-protocol analyses in the 322 patients without a history of previous MI.

Additional covariate adjustment of O-3FA effects on primary and secondary outcome measures are shown in online-only Data Supplement Table II. LVESVI reduction by O-3FA therapy remained significant when adjusted for fixed covariates, including age, sex, race, enrolling site, pretreatment omega-3 index, and pretreatment log transformed infarct mass by CMR (model 1, –5.4% relative change from pretreatment, *P*=0.03). The effect of O-3FA on change in LVESVI remained significant when guideline-based standard post-MI medical therapies, coronary risk factors, body mass index, and baseline heart rate were added to model 1 (model 2, –5.7% relative change from pretreatment, *P*=0.021). Noninfarct myocardial fibrosis also was significantly reduced by O-3FA treatment after covariate adjustment for baseline characteristics, O-3FA

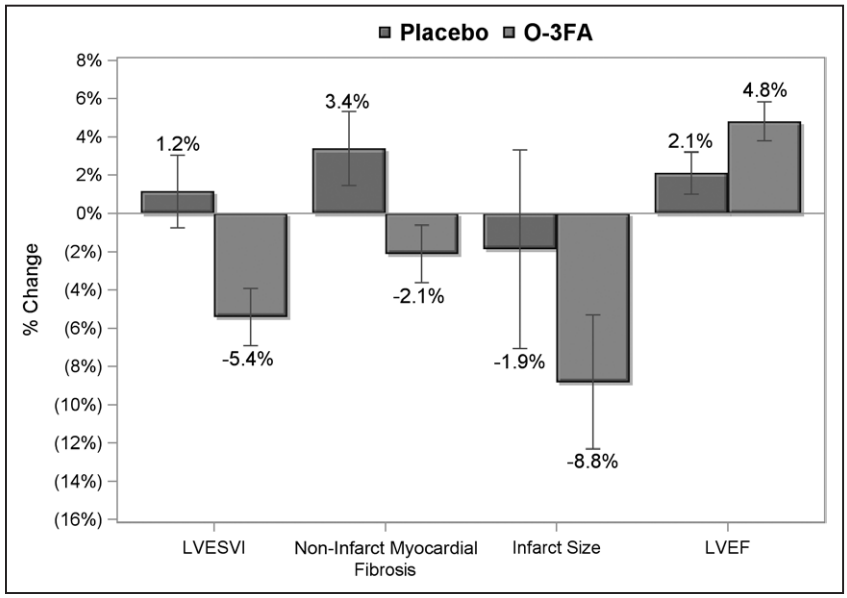

Figure 3. Percent change of primary and secondary endpoints post-treatment.
Percent changes from baseline to post-treatment of the primary and secondary endpoints are shown for the omega-3 fatty acid–treated group (red bars) and placebo arm (blue bars). LVEF indicates left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; and O-3FA, omega-3 fatty acids from fish oil.

Table 4. Six-Month Effect (95% CI) of 4 g/d O-3FA Treatment Versus Placebo in Post-MI Patients by Intention-to-Treat Analysis

	LVESVI	Noninfarct Myocardial Fibrosis	Infarct Size	LVEF
ITT analysis (GLMM*)	-5.8% (-10.3%, -1.1%) P=0.017‡, n=358	–5.6% (–10.4%, –0.9%) *P*=0.022‡, n=358	–3.4% (–17.8%, 13.6%) *P*=0.68, n=358	2.4% (–0.4%, 5.2%) *P*=0.094, n=358
Per-protocol analysis (*t* test†)	–6.6% (–11.3%, –1.8%) *P*=0.0068‡, n=247	–5.5% (–10.4%, –0.6%) *P*=0.026‡, n=171	–6.9% (–19.2%, 5.3%) *P*=0.27, n=254	2.7% (–0.3%, 5.6%) *P*=0.073, n=247
O-3FA absolute change (95% CI)	–2.6 (–3.8, –1.4) mL/m^2, n=124‡	–1.3 (–2.5, –0.2)%, n=84‡	–1.3 (–2.6, 0.0)%, n=130	2.2 (1.3, 3.2)%, n=124‡
Placebo absolute change (95% CI)	–0.5 (–1.8, 0.9) mL/m^2, n=123	0.8 (–0.4, 2.1)%, n=87	–1.6 (–2.9, –0.4)%, n=124‡	0.7 (–0.5, 1.9)%, n=123

The paired absolute changes are calculated on raw data without any transformations. CI indicates confidence interval; GLMM, general linear mixed model; ITT, intention-to-treat; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; MI, myocardial infarction; and O-3FA, omega-3 fatty acids from fish oil.

*The general linear mixed model produces unbiased estimates for responses with missing data (see Statistical Analysis). LVESVI and infarct size were natural logarithm transformed to reduce skewness and heteroscedasticity of residuals. Estimates are relative changes.

†The per-protocol analysis only included patients that attended both visits. No transformations were required; instead, Satterthwaite approximation was used for heteroscedasticity. Estimates are relative changes.

‡Values are statistically significant.

levels, and infarct size (model 1, –5.0% relative change from baseline, *P*=0.046). However, after adjusting for standard post-MI medical therapies, there was only a nonstatistically significant trend for the treatment effect of O-3FA on noninfarct myocardial fibrosis (model 2, –4.7% relative change from baseline, *P*=0.067).

A dose-response relationship for O-3FA treatment was evaluated further in the subgroup of patients who completed both study visits per protocol (Table 5). Change in mean RBC levels of omega-3 index, DHA, and EPA were used as individual biomarkers of exposure to the intervention. For every 1 standard deviation increase in the mean RBC levels of omega-3 index and DHA there were significant reductions in LVESVI and noninfarct myocardial fibrosis, and an increase in LVEF, as well. There were no significant associations between change in O-3FA levels and reduction of infarct size. Increases of mean RBC levels of EPA were only associated with a decrease in LVESVI. The strength of the associations between mean RBC levels of omega-3 index and DHA on the primary and secondary endpoints were evaluated using quartile analysis for the percent change in RBC omega-3 index levels (Figure 4). In comparison with the first quartile as reference, there was a graded significant change in LVESVI (linear trend *P*<0.0001) and LVEF (linear trend *P*=0.016), but not for either noninfarct myocardial fibrosis or infarct size.

Effects of O-3FA Treatment on Biomarkers

By intention-to-treat analysis (Table 6), O-3FA treatment was associated with an 8.1% and 7.9% reduction in myeloperoxidase and ST2, respectively. By per-protocol

Table 5. Mean Percent Change in Primary and Secondary Endpoints per 1 SD Change in RBC Omega-3 Fatty Acids After 6 Months of Treatment

	LVESVI* n=227	Noninfarct Myocardial Fibrosis n=157	Infarct Size* n=232	LVEF n=227
Δ Omega-3 index (% RBC FA) (per 1 SD=2.6%)	–4.6% (–6.9%, –2.2%) *P*=0.0002†	–1.0% (–1.9%, –0.1%) *P*=0.039†	2.5% (–5.7%, 11.3%) *P*=0.56	1.1% (0.3%, 1.9%) *P*=0.0087†
Δ DHA (% RBC FA) (per 1 SD=1.6%)	–5.2% (–7.5%, –2.8%) *P*<0.0001†	–1.1% (–2.1%, –0.2%) *P*=0.013†	1.0% (–7.0%, 9.7%) *P*=0.81	1.2% (0.4%, 2.0%) *P*=0.0031†
Δ EPA (% RBC FA) (per 1 SD=1.1%)	–3.1% (–5.5%, –0.6%) *P*=0.015†	–0.5% (–1.5%, 0.4%) *P*=0.25	4.4% (–3.9%, 13.4%) *P*=0.31	0.7% (–0.1%, 1.5%) *P*=0.078

DHA indicates docosahexaenoic acid; EPA, eicosapentaenoic acid; FA fatty acid; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; RBC, red blood cell; and SD, standard deviation.

*Natural logarithm transformation was used to improve normality and/or homoscedasticity of residuals.

†Values are statistically significant.

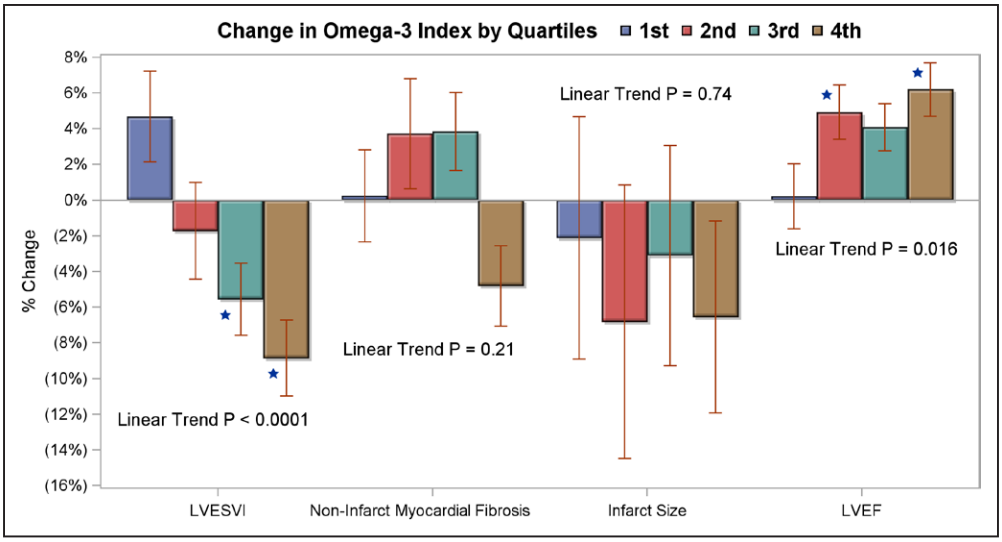

Figure 4. Comparison of percent change in study endpoints with quartiles of change in omega-3-index post-treatment for patients that completed both study visits.

Percent changes from pretreatment to post-treatment of LVESVI, noninfarct myocardial fibrosis, and LVEF versus quartile changes of the red blood cell omega-3 index levels for all patients who completed both study visits (n=227). The quartiles for change in the red blood cell omega-3 index were –0.6% to 0.5%, 0.5 to 2.6%, 2.6 to 5.8%, and >5.8%. The 5th and 95th percentiles for change in the omega-3 index were –1.0% and 6.8%, respectively. **P* value <0.05 compared with first quartile (reference); linear trend *P* values also are reported. LVEF indicates left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; and O-3FA, omega-3 fatty acids from fish oil.

analysis (Table 6), O-3FA treatment still was associated with similar reductions of myeloperoxidase and ST2 (9.3% and 8.3%, respectively). Figure 5 displays significant dose-response relationships between quartile increase of omega-3 index and progressive reductions of ST2, lipoprotein-associated phospholipase A2, and serum triglycerides. In O-3FA treated patients, reduction of ST2 demonstrated a strong correlation with reduction of noninfarct myocardial fibrosis (Figure 6, r=0.65, P<0.0001).

Patient Outcomes and Study Safety

The most common side effect in this study was nausea, which was reported in 5.9% of the O-3FA–treated arm and 5.4% of the placebo arm (P=0.11). Only 4.8% of O-3FA–treated patients reported a fishy taste, which compared with 1.1% in placebo patients (P=0.04). No patient experienced significant bleeding related to study drug. There were 3 (2%) and 8 (4%) deaths in placebo and O-3FA patients, respectively (P=0.22). Among the 11 patients who died, 8 who received fish oil treatment died at a median time of 24 months (range, 12–37 months) after study enrollment. None of these 8 patients experienced any bleeding during the 6 months of fish oil treatment or experienced any drop in hematocrit during subsequent clinical visits. One O-3FA–treated patient experienced tongue swelling 1 month after enrollment that necessitated study drug termination, which resulted in resolution of the patient's symptoms.

DISCUSSION

In compared with placebo, high-dose O-3FA treatment during the first 6 months after acute MI resulted in significant reductions of LVESVI and noninfarct myocardial fibrosis in revascularized acute MI patients who are receiving standard guideline-based medical care. We observed

Table 6. Six-Month Effect of 4 g/d O-3FA Treatment Versus Placebo on Serum Biomarkers in Post-MI Patients

Log Response	ITT Analysis n=358	*P* Value	Per Protocol Analysis n=216	*P* Value
hsCRP	–25	0.089	–24	0.095
Myeloperoxidase	–8.1	0.058	–9.3	0.034
LpPLA2	–3.2	0.25	–4.1	0.14
Fibrinogen	–3.6	0.29	–9.7	0.27
NT-proBNP	–6.6	0.50	–6.2	0.54
CystatinC	2.3	0.24	2.1	0.29
ST2	–7.9	0.030	–8.3	0.026
Galectin-3	–4.6	0.10	–4.5	0.12
Triglycerides	–4.4	0.40	–3.9	0.48

Analysis values are stated as %. hsCRP indicates high-sensitivity C-reactive protein; ITT, intention-to-treat; Lp-PLA2, lipoprotein-associated phospholipase A2; and NT-proBNP, N-terminal prohormone brain natriuretic peptide.

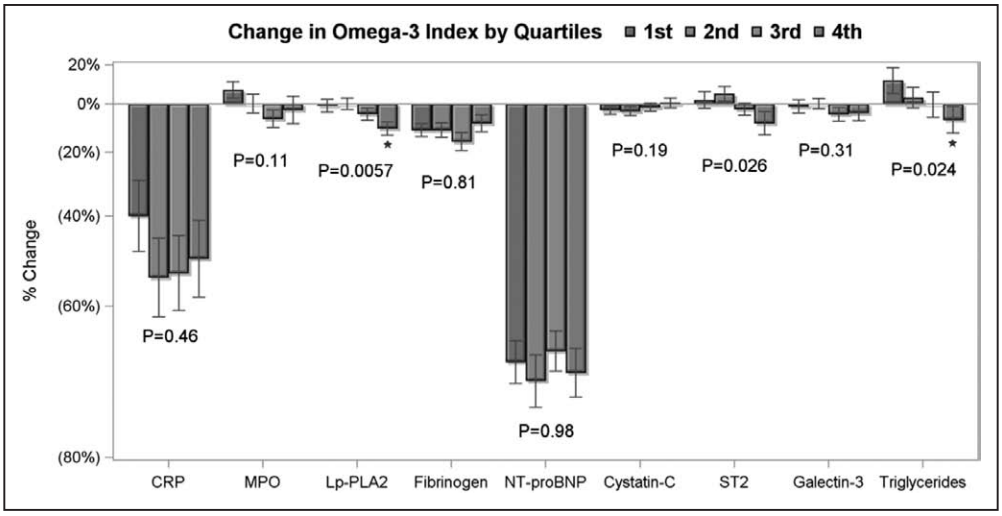

Figure 5. Comparison of percent change in systemic biomarkers with quartiles of change in omega-3-index post-treatment for patients that completed both study visits.
Percent changes from pretreatment to post-treatment of systemic biomarkers versus quartile changes of the red blood cell omega-3 index levels for all patients who completed both study visits (n=227). The quartiles for change in the red blood cell omega-3 index were –0.6% to 0.5%, 0.5 to 2.6%, 2.6 to 5.8%, and >5.8%. The 5th and 95th percentiles for change in the omega-3 index were –1.0% and 6.8%, respectively. **P* value <0.05 in comparison with first quartile (reference), linear trend *P* values also are reported. CRP indicates high-sensitivity C-reactive protein; Lp-PLA2, lipoprotein-associated phospholipase A2; MPO, myeloperoxidase; and NT-proBNP, N-terminal of the prohormone brain natriuretic peptide.

that the degree of LVESVI reduction correlated with the degree of O-3FA incorporation into the RBC membrane suggesting RBC omega-3 index may serve as a useful marker of treatment efficacy. The results were highly suggestive of a dose-response relationship with patients in the highest omega-3 index quartile demonstrating the greatest reduction in adverse remodeling (13% reduction of LVESVI). O-3FA treatment also was associated with a significant reduction of both biomarkers of inflammation (myeloperoxidase, lipoprotein-associated phospholipase A2) and myocardial fibrosis (ST2). We therefore speculate that O-3FA treatment provides the aforementioned improvement in LV remodeling and noninfarct myocardial fibrosis through suppression of inflammation at both systemic and myocardial levels during the convalescent healing phase after acute MI.

Similar to the OMEGA trial,[4] patients in the current study had high adherence to current guideline-based post-MI treatments, including emergent percutaneous coronary revascularization. Contrary to the OMEGA and other O-3FA post-MI trials, the current study used a 4-fold higher dose of O-3FA that more closely resembles the doses administered in translational animal studies reporting beneficial cardiovascular effects.[23] Numerous studies have reported that improvement of LVESVI during infarct convalescence remains the strongest favor-

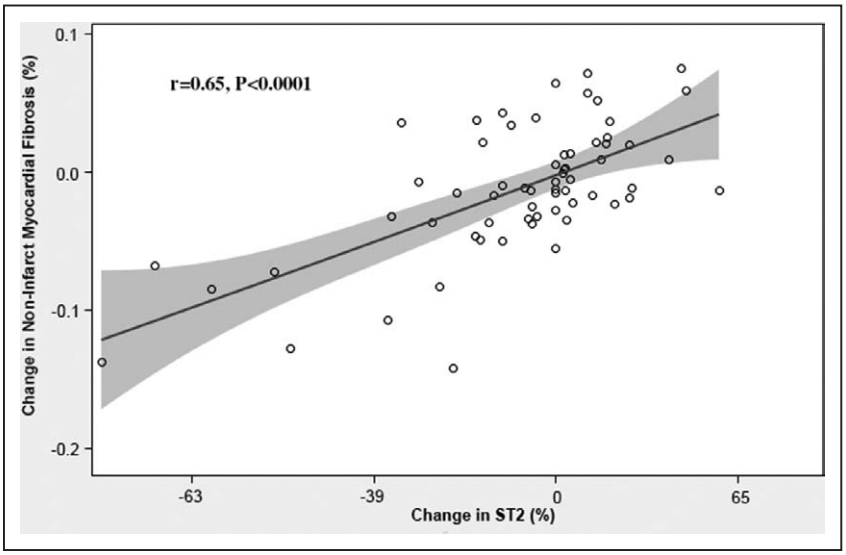

Figure 6. Scatter plot of percent change in serum biomarker ST2 versus percent change of noninfarct myocardial fibrosis post-treatment.
Percent change from baseline to post-treatment of the serum biomarker ST2 correlated against percent change in non-infarct myocardial fibrosis after 6 months of treatment with high-dose omega-3 fatty acids from fish oil. *P* value is for Pearson correlation coefficient.

able risk predictor, parallels reduction of post-MI mortality rates, and serves as a common mechanistic pathway for different classes of therapies that reduce mortality, sudden cardiac death, and heart failure incidence.[24–26] In the echocardiographic substudy of the SAVE (Survival and Ventricular Enlargement) Trial, although captopril only reduced post-MI LV end-systolic expansion by 4%, it was associated with a 45% reduction of patient mortality.[27] The multicenter CAPRICORN (Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction) trial reported that carvedilol reduced all-cause post-MI mortality by 20%,[28] whereas the echocardiographic substudy found only a 5.9% reduction of LV end systolic volume at 6 months.[29] We hypothesize that the observed improvement in adverse LV remodeling by 5.7% beyond the current guideline-based post-MI therapies may be clinically relevant and requires prospective evaluation in trials adequately powered to assess the therapeutic effects of high-dose O-3FA on patient outcomes.

The acute loss of myocardium post-MI leads to a complex set of neurohormonal, genetic, and mechanical factors that can trigger adverse LV remodeling within remote noninfarcted myocardium.[30] In the early period after MI, inflammatory changes within the noninfarcted myocardium contribute to fibrotic changes, whereas increased wall stress and biomechanical strain in later phases contribute to additional myocyte hypertrophy and extracellular matrix expansion. The results of this trial demonstrate potential mechanisms by which O-3FA may attenuate these adverse processes. Our observation that O-3FA treatment was associated with a reduction of inflammation are consistent with translational studies that have shown a reduction of inflammatory cytokines by O-3FA exposure in animal and human myocardium postinfarction.[31–33] Furthermore, O-3FA treatment in this study reduced levels of serum ST, a biomarker that is upregulated in conditions of myocardial necrosis and dysfunction.[34] ST2 antagonizes upregulation of interleukin-33, which has antihypertrophic and antifibrotic effects.[35,36] O-3FA treatment also has been shown to block directly cardiac fibroblast transformation, proliferation, and collagen synthesis through activation of the cyclic GMP/protein kinase G pathway.[37] These mechanisms collectively may explain the attenuation of post-MI noninfarct myocardial fibrosis and adverse LV remodeling by high-dose O-3FA treatment found in this trial.

This study has several limitations. First, despite efforts of the study investigators, a substantial proportion of patients could not return for the post-treatment follow-up visit. Although this was distributed relatively evenly in both treatment arms, it remains uncertain whether this caused any bias to the main study findings. Second, commercial forms of fish oils are widely available and, therefore, over-the-counter fish oil supplementation by patients could not be eliminated reliably and may have biased our results. However, the dose-response relationship between O-3FA therapy and our main study endpoints strongly supported our intention-to-treat analysis. Finally, the absolute percent changes of LVESVI and extracellular volume fraction (a surrogate of noninfarct myocardial fibrosis) from O-3FA treatment, started at 2 to 4 weeks post-MI, were only modest in comparison with guideline clinical care. Earlier initiation of O-3FA during the first days post-MI may have resulted in a more significant treatment benefit. A prospective trial would be necessary to determine the effect of earlier O-3FA therapy on improving cardiac remodeling, myocardial tissue characteristics, and clinical outcomes.

In conclusion, our study demonstrated a beneficial effect for high-dose O-3FA treatment on adverse LV remodeling after acute MI in patients receiving modern, guidelines-based therapies. This finding was supported by the attenuation of concurrent fibrosis within noninfarcted myocardium and lower levels of systemic biomarkers of myocardial inflammation and cardiac fibrosis.

SOURCES OF FUNDING

The National Heart, Lung, and Blood Institute of the National Institutes of Health funded this study.

DISCLOSURES

None.

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FOOTNOTES

Received October 15, 2015; accepted May 18, 2016.

Guest Editor for this article was Eric R. Bates, MD.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.115.019949/-/DC1.

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Effect of Omega-3 Acid Ethyl Esters on Left Ventricular Remodeling After Acute Myocardial Infarction: The OMEGA-REMODEL Randomized Clinical Trial

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Circulation. 2016;134:378-391
doi: 10.1161/CIRCULATIONAHA.115.019949
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

Supplemental Table 1. Six-month Effect (95% CI) of 4 g/d Lovaza Treatment versus Placebo in Post MI Patients (Excluding 36 Patients with History of Prior MI at Baseline)

	LVESVI	Non-Infarct Myocardial Fibrosis	Infarct Size	LVEF
ITT Analysis (GLMM†)	**-7.2% (-11.9%, -2.2%)** **P = 0.0056**, N = 322	**-5.9% (-10.9%, -0.9%)** **P = 0.020**, N = 322	-4.6% (-20.0%, 13.7%) P = 0.60, N = 322	2.8% (-0.2%, 5.7%) P = 0.073, N = 322
Per Protocol Analysis (t-test‡)	**-7.7% (-12.8%, -2.7%)** **P = 0.0028**, N = 221	**-5.4% (-10.6%, -0.3%)** **P = 0.036**, N = 152	-8.2% (-21.4%, 5.0%) P = 0.22, N = 228	2.8% (-0.4%, 6.0%) P = 0.083, N = 221

ITT was defined as intention-to-treat, LVEF left ventricular ejection fraction, and LVESVI left ventricular end-systolic volume index.

† The general linear mixed model (GLMM) produces unbiased estimates for responses with missing data (see statistical analysis). LVESVI and Infarct Size were natural logarithm transformed to reduce skewness and/or heteroscedasticity of residuals. Estimates are relative changes.

‡ The per protocol analysis only included patients that attended both visits. No transformations were required, instead Satterthwaite approximation was used for heteroscedasticity. Estimates are relative changes.

Supplemental Table 2. Adjusted Analysis for Six-month Effect (95% CI) of 4 g/d Lovaza Treatment versus Placebo in Post MI Patients by Intention-to-treat Analysis

	LVESVI†	Non-Infarct Myocardial Fibrosis	Infarct Size†¶	LVEF
Model 0*	**-5.8% (-10.3%, -1.1%) P=0.017**	**-5.6% (-10.4%, -0.9%) P=0.022**	-3.4% (-17.8%, 13.6%) P=0.68	2.4% (-0.4%, 5.2%) P=0.094
Model 1Φ	**-5.4% (-10.1%, -0.6%) P=0.030**	**-5.0% (-10.1%, 0.0%) P=0.046**	1.9% (-13.2%, 19.7%) P=0.81	2.0% (-0.9%, 5.0%) P=0.16
Model 2§	**-5.7% (-10.4%, -0.9%) P=0.021**	-4.7% (-9.7%, 0.3%) P=0.067	2.2% (-13.3%, 20.3%) P=0.80	2.2% (-0.7%, 5.2%) P=0.14

LVEF left ventricular ejection fraction, and LVESVI left ventricular end-systolic volume index.

*Model 0 (N=358) demonstrates unadjusted analysis of O-3FA treatment versus placebo for the primary and secondary study endpoints

ΦModel 1 (N=354) demonstrates Model 0 adjusted for fixed covariates, including age, gender, race, enrolling site, pre-treatment omega-3 index, and pre-treatment log transformed infarct mass.

§Model 2 (N=326) demonstrates Model 1 additionally adjusted for medical therapy (renin-angiotensin system blockade, β-adrenergic–receptor antagonists, dual antiplatelet therapy, hydroxymethylglutaryl–coenzyme A reductase inhibitors), and baseline coronary heart disease risk factors (diabetes mellitus, hypertension, hypercholesterolemia, body mass index, active smoking, and heart rate.)

¶Infarct mass (pre-treatment) was not included in these models.

†Natural logarithm transformation was used to improve normality and/or homoscedasticity of residuals.