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 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.

reclinical 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 1-g 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 trans fatty 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 toler-
ance to study drug, adverse events, and pill counts.

**Study Endpoints**

The primary study endpoint was adverse LV remodeling mea-
sured as change in left ventricular end-systolic volume indexed
to body surface area (LVESVI, mL/m²) 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 eje-
tion 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 Moni-
toring 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 myocard-
dial 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 enhance-
ment 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 val-
dues using ≥2 standard deviation criteria were then used in all
analyses. Short-axis late gadolinium enhancement and myocard-
dial T1 images were segmented as per the American Heart
Association 16-segment model.8 For each T1 Look-Locker
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Association 16-segment model.8 For each T1 Look-Locker

**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), neuro-
hormonal activation (N-terminal prohormone brain natriureti-
cepteptide, 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
fluence 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 quar-
tile), 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 ran-
dom, 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 mea-
surements. As a sensitivity analysis, the mixed models included
increasing levels of covariate adjustment; the initial model only
included the randomization group assignment, an indicator vari-
able 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 stan-
dard 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 fibro-
sis. 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 skew-
ness. 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 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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Omega-3 Fatty Acids (n=180)</th>
<th>Placebo (n=178)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>60±10</td>
<td>58±10</td>
<td>0.22</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>32 (18)</td>
<td>38 (21)</td>
<td>0.39</td>
</tr>
<tr>
<td>White race, n (%)</td>
<td>143 (81)</td>
<td>146 (82)</td>
<td>0.68</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29±5.4</td>
<td>29±5.6</td>
<td>0.92</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>2.0±0.23</td>
<td>2.0±0.22</td>
<td>0.82</td>
</tr>
<tr>
<td>Heart rate, bpm*</td>
<td>64 (60, 71)</td>
<td>66 (60, 71)</td>
<td>0.26</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>121±15</td>
<td>120±16</td>
<td>0.73</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>70±10</td>
<td>70±11</td>
<td>0.62</td>
</tr>
<tr>
<td><strong>Enrolling sites, n (%)</strong></td>
<td></td>
<td></td>
<td>0.57</td>
</tr>
<tr>
<td>Brigham and Women’s</td>
<td>115 (64)</td>
<td>109 (61)</td>
<td></td>
</tr>
<tr>
<td>Massachusetts General</td>
<td>38 (21)</td>
<td>33 (19)</td>
<td></td>
</tr>
<tr>
<td>Beth Israel Deaconess</td>
<td>27 (15)</td>
<td>36 (20)</td>
<td></td>
</tr>
<tr>
<td><strong>Index event</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI, n (%)</td>
<td>102 (57)</td>
<td>105 (59)</td>
<td>0.66</td>
</tr>
<tr>
<td>Anterior, n (%)</td>
<td>48 (27)</td>
<td>48 (27)</td>
<td>1.00</td>
</tr>
<tr>
<td>TIMI 3 flow achieved, n (%)</td>
<td>145 (91)</td>
<td>156 (91)</td>
<td>0.99</td>
</tr>
<tr>
<td>Troponin-T (peak), μmol/L*</td>
<td>2.8 (0.9, 9.1)</td>
<td>3.4 (0.8, 10.4)</td>
<td>0.72</td>
</tr>
<tr>
<td>Creatine kinase (peak), U/L*</td>
<td>786 (330, 1608)</td>
<td>693 (296, 1621)</td>
<td>0.74</td>
</tr>
<tr>
<td>Creatine kinase MB (peak), U/L</td>
<td>61 (26, 152)</td>
<td>61 (21, 148)</td>
<td>0.97</td>
</tr>
<tr>
<td>Hematocrit, %*</td>
<td>39 (36, 42)</td>
<td>40 (36, 43)</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Cardiovascular disease history</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina, n (%)</td>
<td>44 (25)</td>
<td>36 (20)</td>
<td>0.30</td>
</tr>
<tr>
<td>Peripheral vascular disease, n (%)</td>
<td>7 (4)</td>
<td>13 (7)</td>
<td>0.17</td>
</tr>
<tr>
<td>Myocardial infarction, n (%)</td>
<td>22 (12)</td>
<td>14 (8)</td>
<td>0.16</td>
</tr>
<tr>
<td>CABG, n (%)</td>
<td>24 (13)</td>
<td>11 (6)</td>
<td>0.02</td>
</tr>
<tr>
<td>PCI, n (%)</td>
<td>24 (13)</td>
<td>23 (13)</td>
<td>0.91</td>
</tr>
<tr>
<td>Congestive heart failure, n (%)</td>
<td>4 (2)</td>
<td>6 (3)</td>
<td>0.52</td>
</tr>
<tr>
<td>NYHA class, n (%)</td>
<td></td>
<td></td>
<td>0.37</td>
</tr>
<tr>
<td>1</td>
<td>167 (94)</td>
<td>160 (90)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>10 (5.5)</td>
<td>17 (9.5)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>134 (75)</td>
<td>120 (67)</td>
<td>0.10</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>46 (26)</td>
<td>45 (25)</td>
<td>0.90</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>118 (66)</td>
<td>112 (63)</td>
<td>0.51</td>
</tr>
<tr>
<td>Smoker (current), n (%)</td>
<td>23 (13)</td>
<td>36 (20)</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dual antiplatelet, n (%)†</td>
<td>174 (98)</td>
<td>174 (98)</td>
<td>1.00</td>
</tr>
<tr>
<td>β-Blocker, n (%)</td>
<td>163 (92)</td>
<td>164 (92)</td>
<td>0.85</td>
</tr>
<tr>
<td>Statin, n (%)</td>
<td>172 (97)</td>
<td>171 (96)</td>
<td>0.78</td>
</tr>
<tr>
<td>Calcium channel blocker, n (%)</td>
<td>16 (9)</td>
<td>10 (6)</td>
<td>0.22</td>
</tr>
<tr>
<td>ACE inhibitor or ARB, n (%)</td>
<td>134 (75)</td>
<td>127 (71)</td>
<td>0.40</td>
</tr>
</tbody>
</table>

(Continued)
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 intra-class 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>
<thead>
<tr>
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<th>Placebo (n=178)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldosterone antagonists, n (%)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0.91</td>
</tr>
<tr>
<td>Insulin, n (%)</td>
<td>18 (10)</td>
<td>15 (8)</td>
<td>0.57</td>
</tr>
<tr>
<td>Nitroglycerin, n (%)</td>
<td>25 (14)</td>
<td>19 (11)</td>
<td>0.33</td>
</tr>
<tr>
<td>Diuretics, n (%)</td>
<td>25 (14)</td>
<td>18 (10)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Continuous data are means±SD if normally distributed, otherwise median (25th, 75th percentile). \(\beta\)-Blocker is defined as \(\beta\)-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.
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

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Omega-3 Fatty Acids (n=180)</th>
<th>Placebo (n=178)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty acids (RBC % of total)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omega-3 index</td>
<td>5.5±1.8</td>
<td>5.7±1.7</td>
<td>0.45</td>
</tr>
<tr>
<td>DHA (C22:6n3)</td>
<td>4.7±1.3</td>
<td>4.9±1.4</td>
<td>0.29</td>
</tr>
<tr>
<td>EPA (C20:5n3)†</td>
<td>0.63 (0.47, 0.90)</td>
<td>0.64 (0.51, 0.89)</td>
<td>0.67</td>
</tr>
<tr>
<td>DPA (C22:5n3)</td>
<td>2.94±0.48</td>
<td>2.94±0.42</td>
<td>0.49</td>
</tr>
<tr>
<td>α-Linolenic (C18:3n3)</td>
<td>0.12±0.04</td>
<td>0.12±0.04</td>
<td>0.71</td>
</tr>
<tr>
<td>Arachidonic (C20:4n6)</td>
<td>17.1±1.7</td>
<td>17.2±1.5</td>
<td>0.69</td>
</tr>
<tr>
<td>Linoleic (C18:2n6)</td>
<td>9.5±1.5</td>
<td>9.4±1.5</td>
<td>0.30</td>
</tr>
<tr>
<td>Oleic (C18:1)</td>
<td>13.9±1.1</td>
<td>13.9±1.1</td>
<td>0.90</td>
</tr>
<tr>
<td>Inflammatory biomarkers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>405 (341, 522)</td>
<td>407 (340, 499)</td>
<td>0.83</td>
</tr>
<tr>
<td>hsCRP, mg/L*</td>
<td>2.6 (1.3, 8.5)</td>
<td>2.4 (1.0, 6.9)</td>
<td>0.22</td>
</tr>
<tr>
<td>Myeloperoxidase, ng/mL*</td>
<td>341 (265, 404)</td>
<td>324 (264, 386)</td>
<td>0.39</td>
</tr>
<tr>
<td>Lp-PLA2</td>
<td>171 (140, 200)</td>
<td>164 (135, 194)</td>
<td>0.25</td>
</tr>
<tr>
<td>Neurohormonal activation biomarkers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP, ng/L*</td>
<td>526 (244, 1086)</td>
<td>460 (224, 881)</td>
<td>0.27</td>
</tr>
<tr>
<td>Cystatin C, mg/dL*</td>
<td>1.0 (0.9, 1.2)</td>
<td>1.0 (0.9, 1.2)</td>
<td>0.52</td>
</tr>
<tr>
<td>GFR, mL/min per 1.73 m²*</td>
<td>82 (61, 101)</td>
<td>84 (66, 102)</td>
<td>0.54</td>
</tr>
<tr>
<td>Cardiac strain biomarkers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST2, ng/mL*</td>
<td>35 (27, 43)</td>
<td>36 (29, 43)</td>
<td>0.23</td>
</tr>
<tr>
<td>Galectin-3, ng/mL*</td>
<td>16 (12, 19)</td>
<td>15 (13, 18)</td>
<td>0.78</td>
</tr>
<tr>
<td>Lipid levels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>129 (107, 148)</td>
<td>127 (109, 151)</td>
<td>0.94</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>69 (54, 86)</td>
<td>66 (54, 84)</td>
<td>0.46</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>42 (36, 49)</td>
<td>42 (36, 50)</td>
<td>0.94</td>
</tr>
<tr>
<td>Triglycerides, mg/dL*</td>
<td>120 (64, 161)</td>
<td>121 (92, 183)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Continuous data are expressed as means±SD if normally distributed, otherwise median (25th, 75th percentile). DHA indicates docosahexanoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic 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.
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...
significant associations between change in O-3FA levels and noninfarct myocardial fibrosis, and an increase in LVEF, as well. There were no significant associations between change in O-3FA 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 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 analysis, there were no statistically significant associations between change in RBC levels of EPA 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.

### 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

<table>
<thead>
<tr>
<th></th>
<th>LVESVI</th>
<th>Noninfarct Myocardial Fibrosis</th>
<th>Infarct Size</th>
<th>LVEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT analysis (GLMM*)</td>
<td>–5.8% (-10.3%, -1.1%)</td>
<td>–5.6% (-10.4%, -0.9%)</td>
<td>–3.4% (-17.8%, 13.6%)</td>
<td>2.4% (-0.4%, 5.2%)</td>
</tr>
<tr>
<td>( P = 0.017†, n=358 )</td>
<td>( P = 0.022†, n=358 )</td>
<td>( P = 0.68, n=358 )</td>
<td>( P = 0.094, n=358 )</td>
<td></td>
</tr>
<tr>
<td>Per-protocol analysis (t test)</td>
<td>–6.6% (-11.3%, -1.8%)</td>
<td>–5.5% (-10.4%, -0.6%)</td>
<td>–6.9% (-19.2%, 5.3%)</td>
<td>2.7% (-0.3%, 5.6%)</td>
</tr>
<tr>
<td>( P = 0.0068†, n=247 )</td>
<td>0.026†, n=171</td>
<td>0.27, n=254</td>
<td>0.073, n=247</td>
<td></td>
</tr>
<tr>
<td>O-3FA absolute change (95% CI)</td>
<td>–2.6 (-3.8, -1.4) mL/m², n=124 †</td>
<td>–1.3 (-2.5, -0.2)%, n=84 †</td>
<td>–1.3 (-2.6, 0.0)%, n=130</td>
<td>2.2 (1.3, 3.2)%, n=124 †</td>
</tr>
<tr>
<td>Placebo absolute change (95% CI)</td>
<td>–0.5 (-1.8, 0.9) mL/m², n=123</td>
<td>0.8 (-0.4, 2.1)%, n=87</td>
<td>–1.6 (-2.9, -0.4)% , n=124 †</td>
<td>0.7 (-0.5, 1.9)%, n=123</td>
</tr>
</tbody>
</table>

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.

### 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

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

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.
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 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**

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

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.
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 myocar-
dial 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. Numerous
studies have reported that improvement of LVESVI dur-
ing infarct convalescence remains the strongest favor-

**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.

**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 noninfarct 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. 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. The multicenter CAPRICORN (Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction) trial reported that carvedilol reduced all-cause post-MI mortality by 20%, whereas the echocardiographic substudy found only a 5.9% reduction of LV end systolic volume at 6 months. 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. 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. Furthermore, O-3FA treatment in this study reduced levels of serum ST, a biomarker that is upregulated in conditions of myocardial necrosis and dysfunction. ST antagonizes upregulation of interleukin-33, which has antihypertrophic and antiﬁbrotic effects. O-3FA treatment also has been shown to block directly cardiac fi broblast transformation, proliferation, and collagen synthesis through activation of the cyclic GMP/protein kinase G pathway. These mechanisms collectively may explain the attenuation of post-MI noninfarct myocardial ﬁ brosis 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 ﬁ ndings. 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 ﬁ brosis) 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 ﬁ rst 36 hours post-MI may have resulted in a more signiﬁ cant treatment beneﬁ t. 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 beneﬁ cial effect for high-dose O-3FA treatment on adverse LV remodeling after acute MI in patients receiving modern, guideline-based therapies. This ﬁ nding was supported by the attenuation of concurrent ﬁ brosis within noninfarcted myocardium and lower levels of systemic biomarkers of myocardial inﬂ ammation and cardiac ﬁ brosis.

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

**DISCLOSURES**
None.

**AFFILIATIONS**
From Noninvasive Cardiovascular Imaging Section, Cardiovascular Division, Department of Medicine and Department of Radiology, Brigham and Women’s Hospital, Boston, MA (B.H., S.A., R.S., S.A., D.M., J.H.F., R.B., M.S., M.J.H., R.Y.K.); Cardiovascular Division, Department of Medicine, Brigham and Women’s Hospital, Boston, MA (B.H., S.A., R.S., S.A., D.M., J.H.F., E.M.A., R.Y.K.); Department of Internal Medicine, Sanford School of Medicine, University of South Dakota, Sioux Fall (J.V.P., W.H.); Division of Cardiology, Department of Medicine, Massachusetts General Hospital, Boston (R.S., S.A.F.); Department of Radiology, Massachusetts General Hospital, Boston (H.L., B.B.G., U.F.); Cardiovascular Division, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA (E.A.); Health Diagnostic Laboratory, Inc., Richmond, VA (J.P.M.); and OmegaQuant Analytics, LLC, Sioux Falls, SD (W.H.).

**FOOTNOTES**
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Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz. Circulation is available at http://circ.ahajournals.org.
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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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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)

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

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

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

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.
Efeito dos Ésteres Etílicos do Ácido Ômega 3 no Remodelamento do Ventrículo Esquerdo Depois do Infarto Agudo do Miocárdio

O Ensaio Clínico Randomizado OMEGA-REMODEL

HISTÓRICO: Os ácidos graxos ômega 3 de óleo de peixe têm sido associados a efeitos cardiovasculares benéficos, mas seu papel na modificação das estruturas cardíacas e das características teciduais em pacientes que tiveram infarto agudo do miocárdio enquanto recebiam tratamento com base na diretriz atual permanece desconhecido.

MÉTODOS: Em um ensaio multicêntrico, duplo-cego e controlado por placebo, os participantes apresentando infarto agudo do miocárdio foram distribuídos aleatoriamente 1:1 para receber seis meses de ácidos graxos ômega 3 em alta dose (n = 180) ou placebo (n = 178). Ressonância magnética cardíaca foi usada para avaliar a estrutura cardíaca e as características teciduais no início do estudo e depois do tratamento. O desfecho primário do estudo foi a mudança no volume sistólico indexado do ventrículo esquerdo. Os desfechos secundários incluíam alteração na fibrose miocárdica em áreas sem infarto, fração de ejeção ventricular esquerda e tamanho do infarto.

RESULTADOS: Pela análise da intenção de tratar, os pacientes aleatoriamente distribuídos para os ácidos graxos ômega 3 apresentaram uma redução significativa do volume sistólico indexado do ventrículo esquerdo (−5,8%, p = 0,017) e fibrose miocárdica em áreas sem infarto (−5,6%, p = 0,026) em comparação com o placebo. A análise de acordo com o protocolo revelou que o quartil de pacientes que atingiram o maior aumento no índice de ômega 3 nos eritrócitos experimentaram uma redução de 13% no índice do volume sistólico ventricular esquerdo em comparação com aqueles do quartil mais baixo. Além disso, os pacientes do braço ácidos graxos ômega 3 sofreram reduções significativas nos biomarcadores séricos de infmação sistêmica e vascular e na fibrose miocárdica. Não houve eventos adversos associados à terapia de alta dose de ácidos graxos ômega 3.

CONCLUSÃO: O tratamento de pacientes com infarto agudo do miocárdio com alta dose de ácidos graxos ômega 3 foi associado a redução do remodelamento do ventrículo esquerdo, fibrose miocárdica em áreas sem infarto e biomarcadores séricos da inflamação sistêmica, em associação ao tratamento padrão da diretriz atual.

**Perspectiva Clínica**

**O Que Há de Novo?**

- Ensaios clínicos randomizados em larga escala com pacientes com infarto agudo do miocárdio relataram benefícios inconsistentes quanto à mortalidade com os usados ácidos graxos ômega 3 (1g diariamente). Utilizando a ressonância magnética (RM) cardíaca, o estudo randomizado e controlado por placebo Omega-3 Acid Ethyl Esters on Left Ventricular Remodeling After Acute Myocardial Infarction (OMEGA-REMODEL) investigou os benefícios dos ácidos graxos ômega 3 de óleo de peixe (O-3FA) no remodelamento cardíaco em pacientes com infarto agudo do miocárdio (IAM) que estavam sob tratamento de acordo com as diretrizes atuais.

- Em comparação com o placebo, os pacientes que receberam 4g de O-3FA diariamente apresentaram melhora significativa no volume sistólico final do ventrículo esquerdo e no desfecho secundário fibrose miocárdica em área sem infarto durante os primeiros seis meses de cicatrização do infarto mensurado pela RM cardíaca.

- Esses benefícios de remodelamento seguiram uma relação dose-resposta com o aumento dos níveis de óleo do O-3FA quantificado pelo índice de eritrócitos.

**Quais São as Implicações Clínicas?**

- O estudo OMEGA-REMODEL fornece evidências de ensaio randomizado de que uma dose diária de 4 g de 3FA-O é um tratamento seguro e eficaz na melhora do remodelamento cardíaco em pacientes recebendo terapias pós-infarto do miocárdio padrão.

- Uma vez que a incidência da insuficiência cardíaca depois do infarto do miocárdio permanece alta apesar das terapias atuais, os benefícios no remodelamento cardíaco do O-3FA representam um impacto clínico significativo e justificam estudos clínicos prospectivos.

Os benefícios cardiovasculares pré-clínicos dos ácidos graxos ômega 3 do óleo de peixe (O-3FA) foram avaliados em grandes ensaios clínicos em pacientes que sofreram um infarto agudo do miocárdio (IAM). O ensaio aberto Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico (GISSI)-Prevenzione determinou aleatoriamente 11.324 pacientes para 1 g/dia de O-3FA versus placebo e observou uma redução de 20% na mortalidade no tratamento com O-3FA. Com os avanços no tratamento do infarto agudo, no entanto, os benefícios adicionais relatados da terapia com O-3FA foram inconsistentes. A ressonância magnética (RM) cardíaca oferece uma quantificação exata da estrutura e da função ventricular esquerda (VE), do tamanho do infarto e da expansão da matriz extracelular no miocárdio sem infarto. O Omega-3 Acid Ethyl Esters on Left Ventricular Remodeling After Acute Myocardial Infarction (OMEGA-REMODEL) é um ensaio prospectivo, multicêntrico, duplo-cego e controlado por placebo desenhado para avaliar a hipótese de que 4 g/dia de O-3FA por seis meses pós-IAM, adicionalmente às terapias padronizadas pelas diretrizes, atenuam o remodelamento inadequado do VE.

**MÉTODOS**

**Pacientes**

Os pacientes foram inscritos em três centros de atendimento terciário em Boston, MA (Hospitals Brigham and Women’s, Massachusetts General, e Beth Israel Deaconess Medical Center), tinham > 21 anos de idade e diagnóstico de IAM com base em (1) sintomas consistentes com síndrome coronariana aguda, (2) medidas seriadas de troponina T (ou I) consistente com lesão aguda e nível de pico > 0,5 ng/ml e (3) estenose coronariana angiográfica significativa. O recrutamento de pacientes ocorreu entre junho de 2008 e agosto de 2012, e os critérios de exclusão incluíam IM secundário a procedimento cardíaco, expectativa de vida < 1 ano, indicação clínica para o tratamento com O-3FA, gravidez ativa e contraindicações absolutas à RM cardíaca. Todos os pacientes receberam o tratamento clínico padrão segundo o critério dos cardiologistas responsáveis pelo atendimento. O comitê de ética de cada instituição aprovou o estudo e todos os pacientes forneceram um termo de consentimento informado.

**Desenho e Randomização do Estudo**

O National Institutes of Health (NHI) concedeu um financiamento exclusivo para este estudo, enquanto a GlaxoSmithKline (Research Triangle Park, NC) forneceu a medicación para o estudo (O-3FA e placebo). As farmácias experimentais dos centros de inscrição distribuíram aleatoriamente os pacientes 1:1 para O-3FA ou placebo usando um esquema de randomização bloqued 2 × 2 por idade (> 70 anos de idade) e IM anterior de modo duplo-cego. Os códigos de randomização gerados por computador foram usados pelas farmácias experimentais para a randomização em blocos. As consultas pré-e pós-tratamento ocorreram de 14 a 28 dias e seis meses depois do IAM-índice, respectivamente.

As consultas do estudo incluíam coleta do perfil de risco coronariano, eventos detalhados do IM-índice, eventos adversos, padrão do estilo de vida e questionários alimentares, RM cardíaca realizada por contraste e amostras de sangue. Todos os procedimentos durante as consultas do estudo foram realizados ou supervisionados pessoalmente por um pesquisador clínico.

**Intervenção e Monitoramento do Estudo**

Durante as consultas pré-tratamento, os pacientes inscritos receberam suplementos do fármaco de estudo para seis meses e foram instruídos a tomar quatro cápsulas de 1 g ao dia junto com as refeições. O fármaco de estudo era o Lovaza, contendo óleo de peixe exclusivo para este estudo, enquanto a GlaxoSmithKline (Research Triangle Park, NC) forneceu a medicação para o estudo (O-3FA e placebo). Os códigos de randomização gerados por computador foram usados pelas farmácias experimentais para a randomização em blocos. As consultas pré-e pós-tratamento ocorreram de 14 a 28 dias e seis meses depois do IAM-índice, respectivamente.

Como os benefícios cardiovasculares pré-clínicos dos ácidos graxos ômega 3 de óleo de peixe (O-3FA) foram avaliados em grandes ensaios clínicos em pacientes que sofreram um infarto agudo do miocárdio (IAM), foi realizado um ensaio aberto Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico (GISSI)-Prevenzione aleatoriamente 11.324 pacientes para 1 g/dia de O-3FA versus placebo e observou uma redução de 20% na mortalidade no tratamento com O-3FA. Com os avanços no tratamento do infarto agudo, os benefícios adicionais relatados da terapia com O-3FA foram inconsistentes. A ressonância magnética (RM) cardíaca oferece uma quantificação exata da estrutura e da função ventricular esquerda (VE), do tamanho do infarto e da expansão da matriz extracelular no miocárdio sem infarto. O Omega-3 Acid Ethyl Esters on Left Ventricular Remodeling After Acute Myocardial Infarction (OMEGA-REMODEL) é um ensaio prospectivo, multicêntrico, duplo-cego e controlado por placebo desenhado para avaliar a hipótese de que 4 g/dia de O-3FA por seis meses pós-IAM, adicionalmente às terapias padronizadas pelas diretrizes, atenuam o remodelamento inadequado do VE.
seis meses de utilização do fármaco do estudo, a cada dois meses um investigador realizou entrevistas por telefone com cada paciente e avaliou a tolerância ao fármaco, os efeitos adversos e a contagem dos comprimidos.

Desfechos do Estudo
O desfecho primário do estudo foi o remodelamento inadequado do VE medida como mudança no volume sistólico final do ventrículo esquerdo indexado à área de superfície corporal (VSFVE, ml/m²) por RM cardíaca depois dos seis meses de tratamento do estudo. Os desfechos secundários incluíam mudanças (1) na fibrose miocárdica em área sem infarto medida como fração do volume extracelular miocárdico em área remota do infarto agudo (VEC₉₀₀₉₀), (2) no tamanho total do infarto e (3) na fração de ejeção do ventrículo esquerdo (FEVE). A morte cardíaca súbita durante o acompanhamento foi um desfecho secundário adicional no início do ensaio, porém a remoção foi recomendada pelo Data Safety and Monitoring Board devido ao baixo número esperado de eventos desse tipo.

Ressonância Magnética Cardíaca
Os estudos de RM cardíaca foram realizados usando-se scanners 3.0 Tesla (Trio ou Verio, Siemens, Erlangen, Germany). O protocolo da RM cardíaca consistia em sequência cine, mapeamento miocárdico nativo e pós-contrastante em T1 e imagem de realce tardio por gadolinio. O T1 miocárdico foi medido utilizando-se uma sequência gradiente-eco de Look-Locker (três localizações de eixo curto centradas no meio do ventrículo) adquirido antes e 5, 15 e 25 minutos depois da administração de 0,1 mmol/kg de gadolinio por via intravenosa (Magnevist, Bracco). As análises de imagem realizadas mediante um software comercial (QMass, Medis Inc, Raleigh, NC) foram “cegas” aos dados clínicos, à ordem temporal dos estudos da RM cardíaca e à atribuição de tratamento. O tamanho total do infarto foi medido como massa infartada (em gramas) e percentual total da massa do VE (a partir de imagens de realce tardio com gadolinio). A massa infartada era semelhante entre dois critérios (≥ 2 desvios padrão além da intensidade do sinal miocárdico remoto médio e largura à meia altura), e os valores da massa infartada usando-se os critérios de ≥ 2 desvios padrão foram usados em todas as análises. As imagens com realce tardio com gadolinio de eixo curto e do T1 miocárdico foram segmentadas de acordo com o modelo de 16 segmentos da American Heart Association (AHA). Para cada aquisição Look-Locker do T1, o T1 foi determinado por ajuste não linear de mínimos quadrados de uma representação parametrizada de uma regressão inversa (intensidade do sinal = A – B·exp[–TI/T1*]) aos valores de intensidade do sinal miocárdico remoto no segmento do miocárdio. O T1 foi calculado a partir dos parâmetros de melhor ajuste com a fórmula de correção T1 = T1*·(B/A–1). Derivamos a fração de volume extracelular (VEC) traçando a recepção de TI (R = 1/T1) para os segmentos do miocárdico contra o R1 simultaneamente medido no pool de sangue, usando medidas pré e pós-contrastante em que o R1 no pool de sangue era < 3,5 s⁻¹. Pares de dados de R1 com valores de R1 mais elevados no pool de sangue foram excluídos de uma linha de ajuste da regressão linear para os dados de R1 para evitar a subestimação do VEC, já que as condições de troca rápida de água podem não ser atendidas. O VEC foi calculado a partir da inclinação da linha de regressão linear, ou seja, o coeficiente de partição (α), usando-se o hematocrito do sangue (HCT): VEC = λ·(1 – HCT). Os segmentos VEC sem combinar o realce tardio foram calculadas para se obter o VEC global do miocárdio sem infarto remoto (VEC₉₀₀₉₀).  

Biomarcadores e Ácidos Graxos Ômega 3
Amostras de sangue foram analisadas quanto a níveis de ácidos graxos nos eritrócitos (OmegaQuant Analytics, LLC, Sioux Falls, SD) e biomarcadores séricos (Health Diagnostic Laboratory, Inc, Richmond, VA) conforme a seguinte: inflamação (proteína C reativa, mieloperoxidase, lipoproteína associada à fosfolipase A₂, fibrinogênio), ativação neuro-hormonal (peptídeo natriurético cerebral do pró-hormônio N terminal, cistatina C) e fibrose cardíaca (ST-2, galectina-3). A composição de ácidos graxos dos eritrócitos, que mostrou estar relacionada com os níveis miocárdicos de O-3FA e ser alterada por ingestão alimentar recente, foi avaliada por meio de cromatografia gasosa por detecção de ionização de chamas. O índice de ômega 3 foi calculado a partir da soma de DHA e EPA e expresso como um percentual do total de ácidos graxos eritrócitos.

Análise Estatística
As estatísticas descritivas foram calculadas pela fase de tratamento usando-se média ± desvio padrão e mediana (primeiro quartil, terceiro quartil) para as variáveis contínuas normais e enviesadas, respectivamente. As variáveis categóricas foram apresentadas como contagem (%) para cada nível. Os modelos lineares lineares gerais foram utilizados para realizar uma análise com intenção de tratar que incluiu os pacientes sem consultas de acompanhamento para os desfechos primários e secundários. A estimativa da probabilidade máxima restrita produz estimativas imparciais sob a suposição de que as respostas faltantes estão ausentes na randomização, ou seja, as respostas faltantes podem estar relacionadas com as respostas observadas, mas são independentes das respostas não observadas. Este método diminui a necessidade de atribuição. Uma estrutura de correlação da simetria composta foi usada para medidas repetidas. Como uma análise de sensibilidade, os modelos mistos incluíam níveis crescentes de ajuste covariável; o modelo inicial incluia apenas a atribuição do grupo de randomização, um indicador variável para a consulta pré ou pós-tratamento e sua interação. Idade, sexo, raça e local foram adicionados ao modelo como covariables fixas, com o tamanho do infarto na RM cardíaca sendo usado para ajustar a gravidade do IM; o índice de ômega 3 dos eritrócitos foi incluído para exposição pré-tratamento ao O-3FA. Por fim, o status da medição, os fatores de risco coronarianos e a frequência cardíaca foram adicionados ao modelo. Os diagnósticos residuais foram realizados para verificar as suposições do modelo. Uma análise por protocol também foi realizada em todos os pacientes que completaram ambas as consultas de estudo, e as alterações nos níveis eritrócitos de EPA e DHA (somados e individualmente) foram usadas como biomarcadores da exposição ao tratamento. As alterações nos desfechos primário e secundário foram comparadas com as alterações nos níveis de O-3FA dos eritrócitos (modeladas separadamente como um fator contínuo, de acordo com um aumento do desvio padrão e por quartis usando-se o primeiro quartil como referência). Em uma análise exploratória, a atribuição do grupo de randomização do óleo de peixe foi usada para prever alterações nos biomarcadores de inflamação, ativação neuro-hormonal e fibrose cardíaca. Todas as análises estatísticas foram realizadas utilizando-se o SAS (SAS Institutes, versão 9.4, Cary, NC) e um valor de p < 0,05 foi usado para atribuir a significância estatística.

Tamanho da Amostra/Poder
O desfecho primário, a alteração no VSFVE, foi adaptado como uma distribuição normal de registro devido à assimetria positiva. O coeficiente de variação para o volume sistólico
final do VE em estudos de disfunção ventricular esquerda foi relatado como 26%, e a correlação entre as medidas com seis meses de diferença foi considerada de 0,7. Para ter > 80% de poder e detectar 5% de média da alteração do volume sistólico final VE no paciente usando-se um nível crítico para as duas extremidades de 0,05, foi necessário um mínimo de 129 pacientes em cada braço. Estimando-se uma perda de 30% no acompanhamento e uma taxa de não conformidade de 25%, a meta de recrutamento era de 202 pacientes por braço (n = 404).

RESULTADOS

Pacientes e Características Clínicas Basais

A Figura 1 ilustra o recrutamento e a randomização do estudo. Devido a questões logísticas, três pacientes apresentaram desvios no protocolo do estudo: dois tiveram uma consulta pré-tratamento cinco dias depois do IM-índice e um teve uma consulta pós-tratamento no nono mês. Os dados demográficos basais estratificados pela fase de tratamento são mostrados na Tabela 1. No geral, 91% dos pacientes atingiram o fluxo TIMI 3 na artéria relacionada ao infarto e houve alta adesão a todas as terapias recomendadas pelas diretrizes pós-IM. Na coorte geral, 73% dos pacientes foram tratados com um inibidor da enzima conversora da angiotensina (IECA) ou um bloqueador do receptor de angiotensina II (BRA II), em comparação com 89% dos indivíduos que sofreram um IAM com supradesnível do segmento ST (83% no grupo placebo e 94% no grupo ômega 3, p = 0,20). As características basais da RM cardíaca estratificadas pelo braço de tratamento são mostradas na Tabela 2, ao passo que ambos os níveis de ácidos graxos e biomarcadores estão na Tabela 3.
Heydari et al

### Tabela 1. Características Básicas da População com Intenção de Tratar

<table>
<thead>
<tr>
<th>Característica</th>
<th>Ócidos Graxos Ômega 3 (n = 180)</th>
<th>Placebo (n = 178)</th>
<th>Valor de p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dados demográficos</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idade, anos</td>
<td>60 ± 10</td>
<td>58 ± 10</td>
<td>0,22</td>
</tr>
<tr>
<td>Sexo feminino, n (%)</td>
<td>32 (18)</td>
<td>38 (21)</td>
<td>0,39</td>
</tr>
<tr>
<td>Raça branca, n (%)</td>
<td>143 (81)</td>
<td>146 (82)</td>
<td>0,68</td>
</tr>
<tr>
<td>Índice de massa corporal, kg/m²</td>
<td>29 ± 5,4</td>
<td>29 ± 5,6</td>
<td>0,92</td>
</tr>
<tr>
<td>Área de superfície corporal, m²</td>
<td>2 ± 0,23</td>
<td>2 ± 0,22</td>
<td>0,82</td>
</tr>
<tr>
<td>Frequência cardíaca, bpm*</td>
<td>64 (60, 71)</td>
<td>66 (60, 71)</td>
<td>0,26</td>
</tr>
<tr>
<td>PA sistólica, mmHg</td>
<td>121 ± 15</td>
<td>120 ± 16</td>
<td>0,73</td>
</tr>
<tr>
<td>PA diastólica, mmHg</td>
<td>70 ± 10</td>
<td>70 ± 11</td>
<td>0,62</td>
</tr>
<tr>
<td>Locais de recrutamento, n (%)</td>
<td></td>
<td></td>
<td>0,57</td>
</tr>
<tr>
<td>Brigham and Women’s</td>
<td>115 (64)</td>
<td>109 (61)</td>
<td></td>
</tr>
<tr>
<td>Massachusetts General</td>
<td>38 (21)</td>
<td>33 (19)</td>
<td></td>
</tr>
<tr>
<td>Beth Israel Deaconess</td>
<td>27 (15)</td>
<td>36 (20)</td>
<td></td>
</tr>
<tr>
<td><strong>Índice do evento</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI, n (%)</td>
<td>102 (57)</td>
<td>105 (59)</td>
<td>0,66</td>
</tr>
<tr>
<td>Anterior, n (%)</td>
<td>48 (27)</td>
<td>48 (27)</td>
<td>1,00</td>
</tr>
<tr>
<td>Fluxo 3 da TIMI atingido, n (%)</td>
<td>145 (91)</td>
<td>156 (91)</td>
<td>0,99</td>
</tr>
<tr>
<td>Troponina T (pico), μmol/l*</td>
<td>2,8 (0,9; 9,1)</td>
<td>3,4 (0,8; 10,4)</td>
<td>0,72</td>
</tr>
<tr>
<td>Creatina quinase (pico), U/l†</td>
<td>786 (330, 1,608)</td>
<td>693 (296, 1,621)</td>
<td>0,74</td>
</tr>
<tr>
<td>Creatina quinase MB (pico), U/l</td>
<td>61 (26, 152)</td>
<td>61 (21, 148)</td>
<td>0,97</td>
</tr>
<tr>
<td>Hematócrito, %*</td>
<td>39 (36, 42)</td>
<td>40 (36, 43)</td>
<td>0,10</td>
</tr>
<tr>
<td><strong>Histórico de doença cardiovascular</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina, n (%)</td>
<td>44 (25)</td>
<td>36 (20)</td>
<td>0,30</td>
</tr>
<tr>
<td>Doença vascular periférica, n (%)</td>
<td>7 (4)</td>
<td>13 (7)</td>
<td>0,17</td>
</tr>
<tr>
<td>Infarto do miocárdio, n (%)</td>
<td>22 (12)</td>
<td>14 (8)</td>
<td>0,16</td>
</tr>
<tr>
<td>Revascularização miocárdica, n (%)</td>
<td>24 (13)</td>
<td>11 (6)</td>
<td>0,02</td>
</tr>
<tr>
<td>ICP, n (%)</td>
<td>24 (13)</td>
<td>23 (13)</td>
<td>0,91</td>
</tr>
<tr>
<td>Insuficiência cardíaca congestiva, n (%)</td>
<td>4 (2)</td>
<td>6 (3)</td>
<td>0,52</td>
</tr>
<tr>
<td>Classe NYHA, n (%)</td>
<td></td>
<td></td>
<td>0,37</td>
</tr>
<tr>
<td>1</td>
<td>167 (94)</td>
<td>160 (90)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>10 (5,5)</td>
<td>17 (9,5)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1 (0,5)</td>
<td>1 (0,5)</td>
<td></td>
</tr>
<tr>
<td>Hipercolesterolemia, n (%)</td>
<td>134 (75)</td>
<td>120 (67)</td>
<td>0,10</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>46 (26)</td>
<td>45 (25)</td>
<td>0,90</td>
</tr>
<tr>
<td>Hipertensão, n (%)</td>
<td>118 (66)</td>
<td>112 (63)</td>
<td>0,51</td>
</tr>
<tr>
<td>Fumante (atual), n (%)</td>
<td>23 (13)</td>
<td>36 (20)</td>
<td>0,06</td>
</tr>
<tr>
<td><strong>Medicamentos</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplaquetário duplo, n (%)†</td>
<td>174 (98)</td>
<td>174 (98)</td>
<td>1</td>
</tr>
<tr>
<td>Betabloqueador, n (%)</td>
<td>163 (92)</td>
<td>164 (92)</td>
<td>0,85</td>
</tr>
<tr>
<td>Estatina, n (%)</td>
<td>172 (97)</td>
<td>171 (96)</td>
<td>0,78</td>
</tr>
<tr>
<td>Bloqueador do canal de cálcio, n (%)</td>
<td>16 (9)</td>
<td>10 (6)</td>
<td>0,22</td>
</tr>
<tr>
<td>Inibidor de ECA ou BRA, n (%)</td>
<td>134 (75)</td>
<td>127 (71)</td>
<td>0,40</td>
</tr>
</tbody>
</table>
média do infarto (13 g e 11% de massa VE total) era semelhan-
te em ambos os braços do tratamento. Em comparação com
os valores previamente publicados, a fibrose miocárdica
em áreas sem infarto pré-tratamento da coorte total foi signi-
ficativamente maior (33,8 ± 5,3, n = 358 versus 24,8 ± 2, n
= 14, p < 0,0001), enquanto a média dos valores de O-3FA
pré-tratamento foram semelhantes na coorte de Framingham
Offspring. Examinamos a reprodutibilidade do teste-reteste
para a medição do tamanho do infarto por realce tardio com
gadolinio em 38 pacientes aleatoriamente selecionados e des-
cobrimos uma alta correlação intraclasse de 0,94 (intervalo de
confiança [IC] de 95%, 0,88-0,97). Também mostramos a alta
correlação intraclasse para intraobservador, interobservador e
a variabilidade teste-reteste para as medições de VEC.22

**Efeitos do Tratamento**

Com base na contagem de comprimidos, a adesão ao fárma-
co do estudo foi de 96% nos grupos O-3FA e placebo (p = 0,86). As alterações nos níveis de ácidos graxos dos eritróc-
tos são mostradas na Figura 2. Os pacientes que receberam
o tratamento com O-3FA tiveram aumentos acentuados nos
niveis de EPA, DHA e do índice do ômega 3 nos eritrócitos,

### Tabela 1. Continuação

<table>
<thead>
<tr>
<th>Característica</th>
<th>Ácidos Graxos Ómega 3 (n = 180)</th>
<th>Placebo (n = 178)</th>
<th>Valor de p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antagonistas da aldosterona, n (%)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0,91</td>
</tr>
<tr>
<td>Insulina, n (%)</td>
<td>18 (10)</td>
<td>15 (8)</td>
<td>0,57</td>
</tr>
<tr>
<td>Nitroglicerina, n (%)</td>
<td>25 (14)</td>
<td>19 (11)</td>
<td>0,33</td>
</tr>
<tr>
<td>Diuréticos, n (%)</td>
<td>25 (14)</td>
<td>18 (10)</td>
<td>0,33</td>
</tr>
</tbody>
</table>

Os dados contínuos são média ± DP se distribuídos normalmente; caso contrário, medianas (25º, 75º percentil). O betabloqueador é definido como antagonista do receptor beta-adrenérgico, e a estatina, como inibidor da coenzima hidroximetilglutaril reductase A. ECA, enzima convertera da angioten-
sina; BRA, bloqueador do receptor de angiotensina; PA, pressão arterial; MB, isoenzima MB da creatina quinase; NYHA, New York Heart Association; IC, intervenção coronariana percutânea; DP, desvio padrão; STEMI, infarto agudo do miocárdio com supradesnivel do segmento ST; TIMI, trombose
no infarto do miocárdio. O logaritmo natural de transformação foi utilizado para melhorar a normalidade e homocedasticidade de resíduos antes de executar os testes t de Student.
1 A terapia antiplaquetária dupla inclui aspirina e clopidogrel ou prasugrel.

### Tabela 2. Características Basais da RM cardíaca da População com Intenção de Tratar

<table>
<thead>
<tr>
<th>Característica</th>
<th>Ácidos Graxos Ómega 3 (n = 180)</th>
<th>Placebo (n = 178)</th>
<th>Valor de p</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSFVE, ml/m²*</td>
<td>37 (30, 45)</td>
<td>35 (27, 82)</td>
<td>0,29</td>
</tr>
<tr>
<td>VEC (remoto), %†</td>
<td>34,3 ± 5,6</td>
<td>33,3 ± 4,9</td>
<td>0,11</td>
</tr>
<tr>
<td>Tamanho do infarto, gramas, usando 2DP*</td>
<td>13 (6, 23)</td>
<td>13 (6, 24)</td>
<td>0,43</td>
</tr>
<tr>
<td>Tamanho do infarto, gramas, usando FWHM*</td>
<td>13 (6, 22)</td>
<td>12 (5, 23)</td>
<td>0,45</td>
</tr>
<tr>
<td>FEVE, %</td>
<td>54 ± 9</td>
<td>54 ± 10</td>
<td>0,48</td>
</tr>
<tr>
<td>VDFVE, ml/m²</td>
<td>84 ± 20</td>
<td>82 ± 21</td>
<td>0,45</td>
</tr>
<tr>
<td>FEVD, %</td>
<td>53 ± 6</td>
<td>53 ± 8</td>
<td>0,85</td>
</tr>
<tr>
<td>VSFVD, ml/m²</td>
<td>33 ± 9</td>
<td>34 ± 11</td>
<td>0,48</td>
</tr>
<tr>
<td>VDFVD, ml/m²</td>
<td>71 ± 17</td>
<td>72 ± 19</td>
<td>0,41</td>
</tr>
<tr>
<td>Percentual do infarto, % de massa VE, usando 2DP*</td>
<td>11 (6, 21)</td>
<td>12 (5, 21)</td>
<td>0,62</td>
</tr>
<tr>
<td>Percentual do infarto, % de massa VE, usando FWHM*</td>
<td>12 (6, 19)</td>
<td>11 (5, 20)</td>
<td>0,65</td>
</tr>
<tr>
<td>Índice de massa VE, g/m²</td>
<td>60 ± 14</td>
<td>59 ± 15</td>
<td>0,34</td>
</tr>
<tr>
<td>Massa/volume VE, g/ml</td>
<td>0,74 ± 0,18</td>
<td>0,74 ± 0,20</td>
<td>0,95</td>
</tr>
</tbody>
</table>

As variáveis contínuas são expressas como médias ± DP se normalmente distribuídas; caso contrário, como medianas (25º, 75º percentil). RM, ressonância magnética; FWHM, largura à meia altura; VE, ventricular esquerdo; VDFVE, índice do volume diastólico final ventricular esquerdo; FEVE, fração de ejeção ventricular esquerda; VSFVE, índice do volume sistólico final ventricular esquerdo; VDFVE, índice do volume diastólico final ventricular direito; FRVD, fração de ejeção ventricular direita; VSFVD, índice do volume sistólico final ventricular direito; DP, desvio padrão.
1 O logaritmo natural de transformação foi utilizado para melhorar a normalidade e a homocedasticidade de resíduos antes de executar os
testes t de Student.
1 O VEC (remoto) era a fração de volume extracelular do miocárdio remoto do infarto, uma estimativa de fibrose miocárdica sem infarto.
além de uma diminuição do ácido araquidônico em comparação com o placebo (todos os p < 0,0001). O maior impacto do tratamento com O-3FA ocorreu no EPA e no índice de ômega 3 dos eritrócitos, que sofreram aumentos de 256% e 81%, respectivamente. A Figura 3 ilustra os desfechos primário e secundário estratificados pela atribuição do tratamento. Os pacientes que receberam O-3FA experimentaram uma redução média de 5,4% no VSFVE em comparação com uma elevação média de 1,2% no grupo placebo (p = 0,0068). Os pacientes do O-3FA apresentaram 2,1% de regressão média da fibrose miocárdica sem infarto em comparação com uma progressão média de 3,4% no grupo placebo (p = 0,026). Havia uma diferença não significativa quanto à melhora na FEVE no grupo tratado com O-3FA (4,8 ± 11,3% versus 2,1 ± 12,2%, p = 0,073). Embora ambos os grupos apresentassem reduções do tamanho do infarto, elas não foram estatisticamente diferentes entre os grupos (–8,8 ± 39,9% versus –1,9 ± 57,7%, p = 0,27). As análises por protocol e intenção de tratar dos efeitos médios do O-3FA nos desfechos primário e secundário são mostrados na Tabela 4. Em comparação com o placebo, o tratamento com O-3FA foi associado a uma média de –5,8% (IC 95%, –10,3% a –1,1%; p = 0,017) e redução de –6,6% (IC 95%, –11,3% a –1,8%; p = 0,007) no VSFVE por análises por protocol e de intenção de tratar, respectivamente. Além disso, o tratamento com O-3FA foi associado a significativa redução da fibrose miocárdica sem infarto. Em comparação com o placebo, o tratamento com O-3FA foi associado a uma média de –5,6% (IC 95%, –10,4% a –0,9%; p = 0,026) e –5,5% (IC 95%, –10,4% a –0,6%; p = 0,026) de redução na fibrose miocárdica sem infarto por análises de intenção de tratar e por protocolo.

### Tabela 3. Ácidos Graxos Ômega 3 Basais e Níveis dos Biomarcadores da População com Intenção de Tratar

<table>
<thead>
<tr>
<th>Característica</th>
<th>Ácidos Graxos Ômega 3 (n = 180)</th>
<th>Placebo (n = 178)</th>
<th>Valor de p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Índice de ômega 3</td>
<td>5,5 ± 1,8</td>
<td>5,7 ± 1,7</td>
<td>0,45</td>
</tr>
<tr>
<td>DHA (C22:6n3)†</td>
<td>4,7 ± 1,3</td>
<td>4,9 ± 1,4</td>
<td>0,29</td>
</tr>
<tr>
<td>EPA (C20:5n3)†</td>
<td>0,63 (0,47; 0,90)</td>
<td>0,64 (0,51; 0,89)</td>
<td>0,67</td>
</tr>
<tr>
<td>DPA (C22:5n3)†</td>
<td>2,94 ± 0,48</td>
<td>2,94 ± 0,42</td>
<td>0,49</td>
</tr>
<tr>
<td>Alfa-linolênico (C18:3n3)</td>
<td>0,12 ± 0,04</td>
<td>0,12 ± 0,04</td>
<td>0,71</td>
</tr>
<tr>
<td>Araquidônico (C20:4n6)</td>
<td>17,1 ± 1,7</td>
<td>17,2 ± 1,5</td>
<td>0,69</td>
</tr>
<tr>
<td>Linoleico (C18:2n6)</td>
<td>9,5 ± 1,5</td>
<td>9,4 ± 1,5</td>
<td>0,30</td>
</tr>
<tr>
<td>Oleico (C18:1)</td>
<td>13,9 ± 1,1</td>
<td>13,9 ± 1,1</td>
<td>0,90</td>
</tr>
</tbody>
</table>

### Biomarcadores inflamatórios

<table>
<thead>
<tr>
<th>Biomarcador</th>
<th>Média ± DP</th>
<th>Média ± DP</th>
<th>Valor de p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogênio, g/l</td>
<td>405 (341, 522)</td>
<td>407 (340, 499)</td>
<td>0,83</td>
</tr>
<tr>
<td>PCR-as, mg/l†</td>
<td>2,6 (1,3; 8,5)</td>
<td>2,4 (1; 6,9)</td>
<td>0,22</td>
</tr>
<tr>
<td>Mieloperoxidase, ng/ml†</td>
<td>341 (265, 404)</td>
<td>324 (264, 386)</td>
<td>0,39</td>
</tr>
<tr>
<td>Lp-PLA2</td>
<td>171 (140, 200)</td>
<td>164 (135, 194)</td>
<td>0,25</td>
</tr>
</tbody>
</table>

### Biomarcadores de ativação neuro-hormonal

<table>
<thead>
<tr>
<th>Biomarcador</th>
<th>Média ± DP</th>
<th>Média ± DP</th>
<th>Valor de p</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT-proBNP, ng/l*</td>
<td>526 (244, 1086)</td>
<td>460 (224, 881)</td>
<td>0,27</td>
</tr>
<tr>
<td>Cistatina C, mg/dl*</td>
<td>1 (0,9, 1,2)</td>
<td>1 (0,9, 1,2)</td>
<td>0,52</td>
</tr>
<tr>
<td>TFG, ml/min por 1,73 m2*</td>
<td>82 (61, 101)</td>
<td>84 (66, 102)</td>
<td>0,54</td>
</tr>
</tbody>
</table>

### Biomarcadores da tensão cardíaca

<table>
<thead>
<tr>
<th>Biomarcador</th>
<th>Média ± DP</th>
<th>Média ± DP</th>
<th>Valor de p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST2, ng/ml*</td>
<td>35 (27, 43)</td>
<td>36 (29, 43)</td>
<td>0,23</td>
</tr>
<tr>
<td>Galectina-3, ng/ml*</td>
<td>16 (12, 19)</td>
<td>15 (13, 18)</td>
<td>0,78</td>
</tr>
</tbody>
</table>

### Níveis lipídicos

<table>
<thead>
<tr>
<th>Biomarcador</th>
<th>Média ± DP</th>
<th>Média ± DP</th>
<th>Valor de p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colesterol total, mg/dl</td>
<td>129 (107, 148)</td>
<td>127 (109, 151)</td>
<td>0,94</td>
</tr>
<tr>
<td>LDL-C, mg/dl</td>
<td>69 (54, 86)</td>
<td>66 (54, 84)</td>
<td>0,46</td>
</tr>
<tr>
<td>HDL-C, mg/dl</td>
<td>42 (36, 49)</td>
<td>42 (36, 50)</td>
<td>0,94</td>
</tr>
<tr>
<td>Triglicerídeos, mg/dl*</td>
<td>120 (84, 161)</td>
<td>121 (92, 183)</td>
<td>0,26</td>
</tr>
</tbody>
</table>

Os dados contínuos são expressos como média ± DP se normalmente distribuídos; caso contrário, como medianas (25º, 75º percentil). DHA, ácido docosaexaenoico; DPA, ácido docosapentaenoico; EPA, ácido eicosapentaenoico; TFG, taxa de filtração glomerular; HDL-C, colesterol da lipoproteína de alta densidade; PCR-as, proteína C reativa de alta sensibilidade; LDL-C, colesterol da lipoproteína de baixa densidade; LP-PLA2, lipoproteína associada à fosfolipase A2; NT-proBNP, fragmento N-terminal do pró-peptídeo natriurético cerebral. *O logaritmo natural de transformação foi utilizado para melhorar a normalidade e a homocedasticidade de resíduos antes de executar os testes t de Student.
respectivamente. Não houve efeito significativo do tratamento com O-3FA na alteração do tamanho do infarto ou FEVE nas análises com intenção de tratar ou per protocol. Para remover o possível efeito de confusão dos IMs prévios, realizamos análises semelhantes com intenção de tratar e per protocol depois da exclusão de 36 pacientes com histórico de IM prévio. Como mostrado nos Dados Complementares somente on-line da Tabela I, o tratamento com O-3FA foi associado a significativa redução do VSFVE e da fibrose miocárdica sem infarto nas análises de intenção para tratar e per protocol em 322 pacientes sem histórico de IM prévio.

O ajuste covariável adicional dos efeitos do O-3FA nas medidas dos desfechos primários e secundários é mostrado nos Dados Complementares somente on-line da Tabela II. A redução do VSFVE pela terapia com O-3FA permaneceu significativa quando ajustada para as covariables fixas, incluindo idade, sexo, raça, local de inscrição, índice de ômega 3 pré-tratamento e massa infartada com registro pré-tratamento transformado por RM cardíaca (modelo 1, alteração relativa de –5,4%, p = 0,03). O efeito do O-3FA na redução do VSFVE permaneceu significativo quando os tratamentos clínicos pós-IM padrão com base nas diretrizes, os fatores de risco coronarianos, o índice de massa corporal e a frequência cardíaca basal foram adicionados ao modelo 1 (modelo 2, alteração relativa pré-tratamento de –5,7%, p = 0,021). A fibrose miocárdica sem infarto também foi significativamente reduzida pelo tratamento com O-3FA após o ajuste da covariable para as características basais dos níveis de O-3FA e pelo tamanho do infarto (modelo 1, alteração relativa basal de –5%, p = 0,046). Entretanto, posteriormente ao ajuste para as terapias médicas padrão pós-IM, houve apenas uma tendência não estatisticamente significativa para o efeito do O-3FA no tratamento da fibrose miocárdica sem infarto (modelo 2, –4,7% alteração basal relativa, p = 0,067).

**Figura 2. Alteração percentual dos níveis basais de ácidos graxos para o pós-tratamento.**
As alterações do percentual dos níveis basais pós-tratamento do ácidos graxos ômega 3 e ômega 6 para o pós-tratamento são mostradas para os grupos tratados com ácidos graxos ômega 3 (barras vermelhas) e placebo (barras azuis). Os valores de p são para comparações da alteração percentual dos níveis de ácidos graxos ômega 3 e ômega 6 nos grupos tratados e não tratados.

**Figura 3. Alteração percentual dos desfechos primário e secundário pós-tratamento.**
As alterações percentuais basais dos desfechos primário e secundário pós-tratamento são mostradas para os grupos tratados com ácidos graxos ômega 3 (barras vermelhas) e placebo (barras azuis). FEVE, fração de ejeção ventricular esquerda; VSFVE, índice do volume sistólico final ventricular esquerda; O-3FA, ácidos graxos ômega 3 do óleo de peixe.
DP nos Ácidos graxos Ômega 3 Eritrocitários Depois de seis Meses de tratamento (Figura 4). Em comparação com o primeiro quartil como alteração percentual nos níveis do índice do ômega 3 eritrocitário foi avaliada usando-se a análise de quartil para o ômega 3 eritrocitário e o DHA nos desfechos primário e secundário foram associados somente a uma diminuição do VSFVE. A alteração nos níveis de O-3FA e a redução do tamanho do infarto eram logaritmos naturais transformados para reduzir a distorção e a heterocedasticidade dos resíduos. As estimativas são alterações relativas. 

As alterações absolutas emparelhadas são calculadas em dados brutos sem quaisquer transformações. IC, intervalo de confiança; MMLG, modelo misto linear geral; ITT, intenção de tratar; FEVE, fração de ejeção ventricular esquerda; VSFVE, índice do volume sistólico final ventricular esquerdo; IM, infarto do miocárdio; O-3FA, ácidos graxos ômega 3 do óleo de peixe. 

Uma relação dose-resposta para o tratamento com O-3FA foi avaliada posteriormente no subgrupo de pacientes que completaram ambas as consultas do estudo de acordo com o protocolo (Tabela 5). Alterações nos níveis médios do índice de ômega 3 eritrocitário, DHA e EPA foram usadas como biomarcadores individuais da exposição para a intervenção. Para cada aumento de um desvio padrão nos níveis eritrocitários médios do índice de ômega 3 e DHA houve reduções significativas no VSFVE e na fibrose miocárdica sem infarto, além de um aumento na FEVE. Não houve associações significativas entre a alteração nos níveis de O-3FA e a redução do tamanho do infarto. Os aumentos nos níveis médios de eritrócitos do EPA foram associados somente a uma diminuição do VSFVE. A capacidade das associações entre os níveis médios do índice de ômega 3 eritrocitário e o DHA nos desfechos primário e secundário foi avaliada usando-se a análise de quartil para a alteração percentual nos níveis do índice do ômega 3 eritrocitário (Figura 4). Em comparação com o primeiro quartil como referência, houve uma alteração significativa avaliada no VSFVE (tendência linear p = 0,0001) e na FEVE (tendência linear p = 0,016), mas não na fibrose miocárdica sem infarto ou no tamanho do infarto.

| Tabela 4. Efeito de 4 g/d em Seis Meses (IC 95%) de Tratamento com O-3FA Versus Placebo em Pacientes Pós-IM para Análises com Intenção de Tratar |
|------------------|----------------|------------------|----------------|----------------|
|                   | VSFVE           | Fibrose Miocárdica Sem Infarto | Tamanho do Infarto | FEVE           |
| Análise ITT (MMLG*) | -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 |
| Análise de acordo com o protocolo (teste f) | -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 |
| Alteração absoluta do O-3FA (IC 95%) | -2,6 (-3,8, -1,4) ml/m², 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† |
| Alteração absoluta do placebo (IC 95%) | -0,5 (-1,8, 0,9) ml/m², 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 |

†Os valores são estatisticamente significativos.
‡Os valores são estatisticamente significativos.

As alterações absolutas emparelhadas são calculadas em dados brutos sem quaisquer transformações. IC, intervalo de confiança; MMLG, modelo misto linear geral; ITT, intenção de tratar; FEVE, fração de ejeção ventricular esquerda; VSFVE, índice do volume sistólico final ventricular esquerdo; IM, infarto do miocárdio; O-3FA, ácidos graxos ômega 3 do óleo de peixe.

| Tabela 5. Alteração Percentual nos Desfechos Primário e Secundários de acordo com a Mudança de 1 DP nos Ácidos Graxos Ômega 3 Eritrocitários Depois de Seis Meses de Tratamento |
|------------------|----------------|------------------|----------------|----------------|
|                   | VSFVE* n = 227 | Fibrose Miocárdica Sem Infarto n = 157 | Tamanho do Infarto* n = 232 | FEVE n = 227 |
| Índice Δ de ômega 3 (% AG eritrocitário) (de acordo com 1 DP = 2,6%) | -4,6% (-6,9%, -2,2%) p = 0,0002‡ | -1% (-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 (% AG eritrocitário) (de acordo com 1 DP = 1,6%) | -5,2% (-7,5%, -2,8%) p < 0,00011‡ | -1,1% (-2,1%, -0,2%) p = 0,013† | 1% (-7%, 9,7%) p = 0,81 | 1,2% (0,4%, 2%) p = 0,0031† |
| Δ EPA (% AG eritrocitário) (de acordo com 1 DP = 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, ácido docosaeaxenoico; EPA, ácido eicosapentaenoico; AG, ácido graxo; FEVE, fração de ejeção ventricular esquerda; VSFVE, índice do volume sistólico final ventricular esquerdo; DP, desvio padrão.

* A transformação do logaritmo natural foi usada para melhorar a normalidade e/ou a homocedasticidade dos resíduos.

†Os valores são estatisticamente significativos.
com a redução da fibrose miocárdica sem infarto (Figura 6, r = 0,65, p < 0,0001).

Resultados do Paciente e Segurança do Estudo
O efeito colateral mais comum neste estudo foi a náusea, que foi relatada em 5,9% no grupo de tratamento com o O-3FA e 5,4% no grupo placebo (p = 0,11). Somente 4,8% dos pacientes tratados com O-3FA relataram sentir gosto de peixe, em comparação com 1,1% tratado com placebo (p = 0,04). Nenhum paciente sofreu hemorragia considerável relacionada com o fármaco de estudo. Houve três (2%) e oito (4%) mortes entre os pacientes tratados com placebo e com O-3FA, respectivamente (p = 0,22). Entre esses 11 pacientes, oito que receberam tratamento com óleo de peixe morreram, em média, nos 24 meses (intervalo, 12-37 meses) depois da entrada no estudo. Nenhum desses oito pacientes teve algum tipo de sangramento durante os seis meses de tratamento com óleo de peixe ou apresentou alguma queda no hematocrito durante as consultas médicas subsequentes. Um paciente tratado com O-3FA apresentou um edema na língua um mês depois de inscrito, o que exigiu a interrupção do fármaco do estudo, resultando na resolução do sintoma.

DISCUSSÃO
Em comparação com o placebo, o tratamento com alta dose de O-3FA durante os primeiros seis meses pós-IAM resultou em reduções significativas do VSFVE e da fibrose miocárdica sem infarto em pacientes revascularizados que estão recebendo tratamento médico padrão com base nas diretrizes. Observamos que o grau de redução do VSFVE correlacionado com o grau de incorporação do O-3FA na membrana do eritrócito, sugerindo que o índice de ômega 3 eritrocitário pode servir como um marcador útil da eficácia do tratamento. Os resultados foram altamente sugestivos de uma relação dose-resposta com os pacientes no quartil mais alto do índice de ômega 3, demonstrando a maior redução no remodelamento adverso (redução de 13% do VSFVE). O tratamento com O-3FA também foi associado a significativa diminuição dos biomarcadores de

Tabela 6. Efeito do Tratamento com 4g/d de O-3Fa em Seis Meses Versus Placebo em Biomarcadores Séricos em Pacientes Pós-IM

<table>
<thead>
<tr>
<th>Resposta do Registro</th>
<th>Análise ITT n = 358</th>
<th>Valor de p</th>
<th>Análise de Acordo com o Protocolo n = 216</th>
<th>Valor de p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCR-as</td>
<td>–25</td>
<td>0,089</td>
<td>–24</td>
<td>0,095</td>
</tr>
<tr>
<td>Mieloperoxidase</td>
<td>–8,1</td>
<td>0,058</td>
<td>–9,3</td>
<td>0,034</td>
</tr>
<tr>
<td>LpPLA2</td>
<td>–3,2</td>
<td>0,25</td>
<td>–4,1</td>
<td>0,14</td>
</tr>
<tr>
<td>Fibrinogênio</td>
<td>–3,6</td>
<td>0,29</td>
<td>–9,7</td>
<td>0,27</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>–6,6</td>
<td>0,50</td>
<td>–6,2</td>
<td>0,54</td>
</tr>
<tr>
<td>Cistatina C</td>
<td>2,3</td>
<td>0,24</td>
<td>2,1</td>
<td>0,29</td>
</tr>
<tr>
<td>ST2</td>
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<td>0,030</td>
<td>–8,3</td>
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</tr>
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<td>Galectina-3</td>
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<td>0,12</td>
</tr>
<tr>
<td>Triglicerídeos</td>
<td>–4,4</td>
<td>0,40</td>
<td>–3,9</td>
<td>0,48</td>
</tr>
</tbody>
</table>

Os valores da análise são demonstrados como %. PCR-as, proteína C reativa de alta sensibilidade; ITT, intenção de tratar; LP-PLA2, lipoproteína associada à fosfolipase A2; NT-proBNP, fragmento N-terminal do pró-peptídeo natriurético cerebral.
inflamação (mieloperoxidase, lipoproteína associada à fosfolipase A2) e fibrose miocárdica (ST2). Estamos, portanto, especulando que o tratamento com O-3FA proporciona a melhora já mencionada no remodelamento do VE e na fibrose miocárdica sem infarto por meio da supressão da inflamação nos níveis sistêmico e miocárdico durante a fase cicatrização pós-IAM.

Semelhante ao ensaio OMEGA, os pacientes do estudo atual apresentavam alta adesão aos tratamentos pós-IM com base nas diretrizes atuais, incluindo revascularização coronariana percutânea de emergência. Ao contrário do OMEGA e de outros ensaios pós-IM com O-3FA, o estudo atual usou uma dose quatro vezes maior de O-3FA que mais se assemelha àquelas administradas em estudos transicionais com animais relatando efeitos cardiovasculares benéficos. Inúmeros estudos relataram que a melhora do VSFVE durante a convalescença do infarto continua sendo um preditor de risco altamente favorável, paralelo à redução das taxas de mortalidade pós-IM, servindo como uma via mecanista comum para diferentes classes terapêuticas que reduzem a incidência de mortalidade, morte súbita cardíaca e insuficiência cardíaca. No su-bestudo ecocardiográfico do ensaio Survival and Ventricular Enlargement (SAVE), embora o captopril tenha reduzido a expansão sistólica final do VE pós-IM em apenas 4%, ele foi associado a uma redução de 45% na mortalidade dos pacientes. O ensaio multicêntrico Carvediol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) relatou que o car-

**Figura 5.** Comparação da alteração percentual em biomarcadores sistêmicos com quartis da alteração no índice de ômega 3 pós-tratamento para pacientes que concluíram ambas as consultas do estudo.

Alterações percentuais do pré-tratamento ao pós-tratamento dos biomarcadores sistêmicos versus as alterações do quartil dos níveis de índice de ômega 3 para todos os pacientes que concluíram ambas as consultas do estudo (n = 227). Os quartis para alteração no índice eritrocitário de ômega 3 foram –0,6% a 0,5%, 0,5 a 2,6%, 2,6 a 5,8%, e > 5,8%. O 5º e o 95º percentis para alteração no índice de ômega 3 foram –1% e 6,8%, respectivamente. *p < 0,05 em comparação com o primeiro quartil (referência), os valores de p da tendência linear também são relatados. PCR-CS, proteína C reativa de alta sensibilidade; Lp-PLA2, lipoproteína associada à fosfolipase A2; MPO, mieloperoxidase; NT-proBNP, fragmento N-terminal do pró-peptídeo natriurético cerebral.

**Figura 6.** Gráfico de dispersão da alteração percentual do biomarcador sérico ST2 versus alteração percentual da fibrose miocárdica sem infarto pós-tratamento.

Alteração percentual basal a partir do pós-tratamento do biomarcador sérico ST2 correlacionada com a alteração percentual da fibrose miocárdica sem infarto seis meses depois do tratamento com altas doses de ácidos graxos ômega 3 do óleo de peixe. O valor de p é para o coeficiente de correlação de Pearson.
vediol reduziu a mortalidade por todas as causas pós-IM em 20%, ao passo que o subestudo ecocardiográfico encontrou uma redução de apenas 5,9% do volume sistólico final VE em seis meses. Supomos que a melhora observada no remodelamento adverso do VE no miocárdio sem infarto. No período inicial depois do IAM, as alterações inflamatórias no miocárdio não infartado contribuem para as mudanças fibróticas, enquanto o aumento do estresse da parede e a tensão biomecânica nas fases posteriores contribuem para a hipertrofia miocitária adicional e a expansão da matriz extracelular. Os resultados deste ensaio demonstram mecanismos potenciais pelos quais o O-3FA pode atenuar esses processos adversos. Nossa observação de que o tratamento com O-3FA foi associado à redução da inflamação é consistente com os estudos translacionais que mostraram diminuição das citocinas inflamatórias pela exposição ao O-3FA do miocárdio animal e humano pós-infarto. Além disso, o tratamento com O-3FA neste estudo reduziu os níveis séricos de ST, um biomarcador que é suprarregulado em condições de necrose e disfunção miocárdica. O ST2 antagoniza a suprarregulação da interleucina-33, que tem efeitos anti-hipertróficos e antifibróticos. O tratamento com O-3FA também mostrou bloquear diretamente a transformação dos fibroblastos cardíacos, a proliferação e a síntese de colágeno por meio da ativação da via do monofosfato de guanosina cíclico (GMPc)/proteína quinase G. Coletivamente, esses mecanismos podem explicar a atenuação da fibrose miocárdica sem infarto pós-IM e do remodelamento adverso do VE pelo tratamento com altas doses de O-3FA descoberta neste ensaio.

Este estudo teve várias limitações. Primeiro, apesar dos esforços dos seus pesquisadores, uma proporção substancial de pacientes não poderia retornar para a consulta de acompanhamento pós-tratamento. Embora a distribuição tenha sido realizada de maneira relativamente uniforme em ambos os braços do tratamento, ainda é incerto se isso causou algum viés para os principais achados do estudo. Segundo, as fórmulas comerciais de óleos de peixe estão amplamente disponíveis, portanto a suplementação, pelos próprios pacientes, sem prescrição médica não poderia ser eliminada de maneira confiável e pode ter influenciado nossos resultados. No entanto, a relação dose-resposta entre o tratamento com O-3FA e os principais desfechos do estudo apoiam fortemente nossa análise por intenção de tratar. Por fim, as mudanças percentuais absolutas do VSFVE e da fração do volume extracelular (uma substituta da fibrose miocárdica sem infarto) do tratamento com O-3FA, iniciado duas a quatro semanas pós-IM, foram apenas modestas em comparação com o tratamento clínico fundamentado nas diretrizes. O início precoce do O-3FA durante os primeiros dias pós-IM pode ter resultado em benefício mais significativo para o tratamento. Um ensaio prospectivo seria necessário para determinar o efeito da terapia inicial com O-3FA na melhora do remodelamento cardíaco, das características do tecido do miocárdio e dos resultados clínicos.

Em conclusão, nosso estudo demonstrou um efeito benéfico do tratamento com altas doses de O-3FA no remodelamento adverso do VE pós-IM em pacientes recebendo terapias com base nas diretrizes atuais. Este achado foi confirmado pela atenuação da fibrose concomitante no miocárdio sem infarto e pelos níveis mais baixos dos biomarcadores sistêmicos de inflamação miocárdica e fibrose cardiaca.

**FONTES DE FINANCIAMENTO**

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**DIVULGAÇÕES**

Nenhuma.

**AFI利亚ÇÕES**

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**NOTAS DE RODAPÉ**

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**REFERÊNCIAS**

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급성 심근경색증 환자에서 고용량 오메가-3 지방산은 좌심실 재형성( Remodeling)을 감소시켜준다: The OMEGA-REMODEL 무작위 임상연구

나승운 교수 고려대학교 구로병원 순환기내과

초록

배경

어유(fish oil)에서 추출한 오메가-3 지방산(omega-3 fatty acid)은 심혈관에 여러 가지 긍정적인 효과가 있다고 알려져 있다. 그러나 급성 심근경색증으로 치료된 환자에게서 심장 구조와 조직 특성에 어떤 영향을 줄 수 있는지에 대해서는 잘 알려져 있지 않다.

방법

본 연구는 단기간, 이중맹검, 위약 대조연구로서, 급성 심근경색증 환자들을 6개월 동안 고용량 오메가-3 지방산(180mg)과 위약 투여군(178mg)으로 1:1 무작위 배정하여 관찰하였다. 치료 전과 후의 심장 구조와 조직 특성은 심장 자기공명영상 등을 이용해 비교하였다. 일차 종료점은 좌심실 수축용적지수(left ventricular systolic volume index)의 변화이며, 이차 종료점에는 비정상 부위 심근섬유화(noninfarct myocardial fibrosis), 좌심실 구혈률(left ventricular ejection fraction) 그리고 심근경색 크기의 변화가 포함되었다.

결과

치료 의향(intention-to-treat, ITT) 분석 결과, 오메가-3 지방산을 투여한 군에서 좌심실 수축용적지수는 위약 대비 5.8% 감소하였고(P=0.017), 비정상 부위 심장섬유화도 5.6% 감소하여 (P=0.026) 심장기능의 변화를 보여주었다. 특히, 프로토플론 수용 집단(per protocol, PP) 분석에서 약국 오메가-3지수를 4분 위로 나누었을 때, 증가된 가장 높은 분위수가 가장 낮은 분위수 대비 좌심실 수축용적지수가 13% 감소한 것으로 나타났다. 그 외에도 오메가-3 지방산 투여군은 전신 및 혈관 염증 그리고 심근섬유화의 생물지표(biomarker)도 유의하게 개선시키는 것으로 관찰되었다. 고용량 오메가-3 지방산치료와 관련된 부작용은 보고되지 않았다.

결론

급성 심근경색증 환자에서 고용량 오메가-3 지방산치료는 가이드라인에 기초한 표준치료와는 다른 결과, 좌심실 재형성을 줄여준다면 아니라, 비정상 부위 심근섬유화와 전신 염증의 생물 지표를 개선시키는 것과 연관이 있었다.
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.
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 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.

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 mg/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 1 g 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, 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

Preclinical cardiovascular benefits of omega-3 fatty acids from fish oil1-2 (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.
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/m²) 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/T1)]\(^*\) to the measured average signal intensity values in myocardial segments. T1 was then calculated from the best-fit parameters with the correction formula T1 = T1\(^*\)·(B/A−1).\(^9\) We derived segmental extracellular volume fraction (ECV) by plotting the reciprocal of T1 (R1 = 1/T1) 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, i.e., 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, i.e., 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%
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 therapies. In the overall cohort, 73% of patients were noncompliance rate, the recruitment goal was 202 patients per arm (n=404).
### Table 1. Baseline Characteristics of the Intention-to-Treat Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Omega-3 Fatty Acids (n=180)</th>
<th>Placebo (n=178)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>60±10</td>
<td>58±10</td>
<td>0.22</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>32 (18)</td>
<td>38 (21)</td>
<td>0.39</td>
</tr>
<tr>
<td>White race, n (%)</td>
<td>143 (81)</td>
<td>146 (82)</td>
<td>0.68</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>29±5.4</td>
<td>29±5.6</td>
<td>0.92</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>2.0±0.23</td>
<td>2.0±0.22</td>
<td>0.82</td>
</tr>
<tr>
<td>Heart rate, bpm*</td>
<td>64 (60, 71)</td>
<td>66 (60, 71)</td>
<td>0.26</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>121±15</td>
<td>120±16</td>
<td>0.73</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>70±10</td>
<td>70±11</td>
<td>0.62</td>
</tr>
<tr>
<td><strong>Enrolling sites, n (%)</strong></td>
<td></td>
<td></td>
<td>0.57</td>
</tr>
<tr>
<td>Brigham and Women’s</td>
<td>115 (64)</td>
<td>109 (61)</td>
<td></td>
</tr>
<tr>
<td>Massachusetts General</td>
<td>38 (21)</td>
<td>33 (19)</td>
<td></td>
</tr>
<tr>
<td>Beth Israel Deaconess</td>
<td>27 (15)</td>
<td>36 (20)</td>
<td></td>
</tr>
<tr>
<td><strong>Index event</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI, n (%)</td>
<td>102 (57)</td>
<td>105 (59)</td>
<td>0.66</td>
</tr>
<tr>
<td>Anterior, n (%)</td>
<td>48 (27)</td>
<td>48 (27)</td>
<td>1.00</td>
</tr>
<tr>
<td>TIMI 3 flow achieved, n (%)</td>
<td>145 (91)</td>
<td>156 (91)</td>
<td>0.99</td>
</tr>
<tr>
<td>Troponin-T (peak), μmol/L*</td>
<td>2.8 (0.9, 9.1)</td>
<td>3.4 (0.8, 10.4)</td>
<td>0.72</td>
</tr>
<tr>
<td>Creatine kinase (peak), U/L*</td>
<td>786 (330, 1608)</td>
<td>693 (296, 1621)</td>
<td>0.74</td>
</tr>
<tr>
<td>Creatine kinase MB (peak), U/L</td>
<td>61 (26, 152)</td>
<td>61 (21, 148)</td>
<td>0.97</td>
</tr>
<tr>
<td>Hematocrit, %*</td>
<td>39 (36, 42)</td>
<td>40 (36, 43)</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Cardiovascular disease history</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina, n (%)</td>
<td>44 (25)</td>
<td>36 (20)</td>
<td>0.30</td>
</tr>
<tr>
<td>Peripheral vascular disease, n (%)</td>
<td>7 (4)</td>
<td>13 (7)</td>
<td>0.17</td>
</tr>
<tr>
<td>Myocardial infarction, n (%)</td>
<td>22 (12)</td>
<td>14 (8)</td>
<td>0.16</td>
</tr>
<tr>
<td>CABG, n (%)</td>
<td>24 (13)</td>
<td>11 (6)</td>
<td>0.02</td>
</tr>
<tr>
<td>PCI, n (%)</td>
<td>24 (13)</td>
<td>23 (13)</td>
<td>0.91</td>
</tr>
<tr>
<td>Congestive heart failure, n (%)</td>
<td>4 (2)</td>
<td>6 (3)</td>
<td>0.52</td>
</tr>
<tr>
<td>NYHA class, n (%)</td>
<td></td>
<td></td>
<td>0.37</td>
</tr>
<tr>
<td>1</td>
<td>167 (94)</td>
<td>160 (90)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>10 (5.5)</td>
<td>17 (9.5)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>134 (75)</td>
<td>120 (67)</td>
<td>0.10</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>46 (26)</td>
<td>45 (25)</td>
<td>0.90</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>118 (66)</td>
<td>112 (63)</td>
<td>0.51</td>
</tr>
<tr>
<td>Smoker (current), n (%)</td>
<td>23 (13)</td>
<td>36 (20)</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dual antiplatelet, n (%)†</td>
<td>174 (98)</td>
<td>174 (98)</td>
<td>1.00</td>
</tr>
<tr>
<td>β-Blocker, n (%)</td>
<td>163 (92)</td>
<td>164 (92)</td>
<td>0.85</td>
</tr>
<tr>
<td>Statin, n (%)</td>
<td>172 (97)</td>
<td>171 (96)</td>
<td>0.78</td>
</tr>
<tr>
<td>Calcium channel blocker, n (%)</td>
<td>16 (9)</td>
<td>10 (6)</td>
<td>0.22</td>
</tr>
<tr>
<td>ACE inhibitor or ARB, n (%)</td>
<td>134 (75)</td>
<td>127 (71)</td>
<td>0.40</td>
</tr>
</tbody>
</table>

(Continued)
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>
<thead>
<tr>
<th>Characteristic</th>
<th>Omega-3 Fatty Acids (n=180)</th>
<th>Placebo (n=178)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVESVI, mL/m²*</td>
<td>37 (30, 45)</td>
<td>35 (27, 82)</td>
<td>0.29</td>
</tr>
<tr>
<td>ECVRemote, %†</td>
<td>34.3±5.6</td>
<td>33.3±4.9</td>
<td>0.11</td>
</tr>
<tr>
<td>Infarct size, grams, using 2SD*</td>
<td>13 (6, 23)</td>
<td>13 (6, 24)</td>
<td>0.43</td>
</tr>
<tr>
<td>Infarct size, grams, using FWHM*</td>
<td>13 (6, 22)</td>
<td>12 (5, 23)</td>
<td>0.45</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>54±9</td>
<td>54±10</td>
<td>0.48</td>
</tr>
<tr>
<td>LVEDVI, mL/m²</td>
<td>84±20</td>
<td>82±21</td>
<td>0.45</td>
</tr>
<tr>
<td>RVEF, %</td>
<td>53±6</td>
<td>53±8</td>
<td>0.85</td>
</tr>
<tr>
<td>RVESVI, mL/m²</td>
<td>33±9</td>
<td>34±11</td>
<td>0.48</td>
</tr>
<tr>
<td>RVEDVI, mL/m²</td>
<td>71±17</td>
<td>72±19</td>
<td>0.41</td>
</tr>
<tr>
<td>Infarct percent, %LV mass, using 2SD*</td>
<td>11 (6, 21)</td>
<td>12 (5, 21)</td>
<td>0.62</td>
</tr>
<tr>
<td>Infarct percent, %LV mass, using FWHM*</td>
<td>12 (6, 19)</td>
<td>11 (5, 20)</td>
<td>0.65</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>60±14</td>
<td>59±15</td>
<td>0.34</td>
</tr>
<tr>
<td>LV mass/volume, g/mL</td>
<td>0.74±0.18</td>
<td>0.74±0.20</td>
<td>0.95</td>
</tr>
</tbody>
</table>

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; RVESVI, right ventricular end-systolic volume index; RVEDVI, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; and SD, standard deviation.

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

†ECVRemote was the extracellular volume fraction of myocardium remote from the infarction, an estimate of noninfarct myocardial fibrosis.
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 \((P<0.0001)\). 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 \((4.8\pm11.3\% \text{ versus } 2.1\pm12.2\%, P=0.073)\). Although both groups experienced a reduction of infarct size, these reductions were not statistically different between the groups \((-8.8\pm39.9\% \text{ versus } -1.9\pm57.7\%, P=0.27)\). 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

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Omega-3 Fatty Acids ((n=180))</th>
<th>Placebo ((n=178))</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty acids (RBC % of total)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omega-3 index</td>
<td>5.5\pm1.8</td>
<td>5.7\pm1.7</td>
<td>0.45</td>
</tr>
<tr>
<td>DHA (C22:6n3)</td>
<td>4.7\pm1.3</td>
<td>4.9\pm1.4</td>
<td>0.29</td>
</tr>
<tr>
<td>EPA (C20:5n3)†</td>
<td>0.63 (0.47, 0.90)</td>
<td>0.64 (0.51, 0.89)</td>
<td>0.67</td>
</tr>
<tr>
<td>DPA (C22:5n3)</td>
<td>2.94\pm0.48</td>
<td>2.94\pm0.42</td>
<td>0.49</td>
</tr>
<tr>
<td>(\alpha)-Linolenic (C18:3n3)</td>
<td>0.12\pm0.04</td>
<td>0.12\pm0.04</td>
<td>0.71</td>
</tr>
<tr>
<td>Arachidonic (C20:4n6)</td>
<td>17.1\pm1.7</td>
<td>17.2\pm1.5</td>
<td>0.69</td>
</tr>
<tr>
<td>Linoleic (C18:2n6)</td>
<td>9.5\pm1.5</td>
<td>9.4\pm1.5</td>
<td>0.30</td>
</tr>
<tr>
<td>Oleic (C18:1)</td>
<td>13.9\pm1.1</td>
<td>13.9\pm1.1</td>
<td>0.90</td>
</tr>
<tr>
<td>Inflammatory biomarkers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen, g/L</td>
<td>405 (341, 522)</td>
<td>407 (340, 499)</td>
<td>0.83</td>
</tr>
<tr>
<td>hsCRP, mg/L*</td>
<td>2.6 (1.3, 8.5)</td>
<td>2.4 (1.0, 6.9)</td>
<td>0.22</td>
</tr>
<tr>
<td>Myeloperoxidase, ng/mL*</td>
<td>341 (265, 404)</td>
<td>324 (264, 386)</td>
<td>0.39</td>
</tr>
<tr>
<td>Lp-PLA2</td>
<td>171 (140, 200)</td>
<td>164 (135, 194)</td>
<td>0.25</td>
</tr>
<tr>
<td>Neurohormonal activation biomarkers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP, ng/mL*</td>
<td>526 (244, 1086)</td>
<td>460 (224, 881)</td>
<td>0.27</td>
</tr>
<tr>
<td>Cystatin C, mg/dL*</td>
<td>1.0 (0.9, 1.2)</td>
<td>1.0 (0.9, 1.2)</td>
<td>0.52</td>
</tr>
<tr>
<td>GFR, mL/min per 1.73 m(^2)*</td>
<td>82 (61, 101)</td>
<td>84 (66, 102)</td>
<td>0.54</td>
</tr>
<tr>
<td>Cardiac strain biomarkers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST2, ng/mL*</td>
<td>35 (27, 43)</td>
<td>36 (29, 43)</td>
<td>0.23</td>
</tr>
<tr>
<td>Galectin-3, ng/mL*</td>
<td>16 (12, 19)</td>
<td>15 (13, 18)</td>
<td>0.78</td>
</tr>
<tr>
<td>Lipid levels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>129 (107, 148)</td>
<td>127 (109, 151)</td>
<td>0.94</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>69 (54, 86)</td>
<td>66 (54, 84)</td>
<td>0.46</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>42 (36, 49)</td>
<td>42 (36, 50)</td>
<td>0.94</td>
</tr>
<tr>
<td>Triglycerides, mg/dL*</td>
<td>120 (84, 161)</td>
<td>121 (92, 183)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Continuous data are expressed as means\(\pm\)SD if normally distributed, otherwise median (25th, 75th percentile). DHA indicates docosahexanoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic 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.
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 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, eicosapentaenoic acid; and O-3FA, omega-3 fatty acids from fish oil.

**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.
significant associations between change in O-3FA levels and noninfarct myocardial fibrosis, and an increase in LVEF, as well. There were no significant reductions in LVESVI and noninfarct myocardial fibrosis. The changes in RBC levels of omega-3 index and DHA there were significant for the treatment effect of O-3FA treatment on biomarkers. Increases of 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 (Table 4).

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.

### 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

<table>
<thead>
<tr>
<th></th>
<th>LVESVI*</th>
<th>Noninfarct Myocardial Fibrosis</th>
<th>Infarct Size</th>
<th>LVEF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=227</td>
<td>n=157</td>
<td>n=232</td>
<td>n=227</td>
</tr>
<tr>
<td><strong>ITT analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(GLMM*)</td>
<td>-5.8% (-10.3%, -1.1%) ( P=0.017 )‡, n=358</td>
<td>-5.6% (-10.4%, -0.9%) ( P=0.022 )‡, n=358</td>
<td>-3.4% (-17.8%, 13.6%) ( P=0.68 ), n=358</td>
<td>2.4% (-0.4%, 5.2%) ( P=0.094 ), n=358</td>
</tr>
<tr>
<td><strong>Per-protocol analysis</strong> (t test)</td>
<td>-6.6% (-11.3%, -1.8%) ( P=0.0068 ), n=247</td>
<td>-5.5% (-10.4%, -0.6%) ( P=0.026 ), n=171</td>
<td>-6.9% (-19.2%, 5.3%) ( P=0.27 ), n=254</td>
<td>2.7% (-0.3%, 5.6%) ( P=0.073 ), n=247</td>
</tr>
<tr>
<td><strong>O-3FA absolute change</strong> (95% CI)</td>
<td>-2.6 (-3.8, -1.4) mL/m², n=124‡</td>
<td>-1.3 (-2.5, -0.2%), n=84‡</td>
<td>-1.3 (-2.6, 0.0%), n=130</td>
<td>2.2 (1.3, 3.2%), n=124‡</td>
</tr>
<tr>
<td><strong>Placebo absolute change</strong> (95% CI)</td>
<td>-0.5 (-1.8, 0.9) mL/m², n=123</td>
<td>0.8 (-0.4, 2.1%), n=87</td>
<td>-1.6 (-2.9, -0.4%), n=124‡</td>
<td>0.7 (-0.5, 1.9%), n=123</td>
</tr>
</tbody>
</table>

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.

#### 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

<table>
<thead>
<tr>
<th></th>
<th>LVESVI*</th>
<th>Noninfarct Myocardial Fibrosis</th>
<th>Infarct Size*</th>
<th>LVEF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=277</td>
<td>n=157</td>
<td>n=232</td>
<td>n=227</td>
</tr>
<tr>
<td><strong>∆ Omega-3 index (% RBC FA)</strong> (per 1 SD=2.6%)</td>
<td>-4.6% (-6.9%, -2.2%) ( P=0.0002 )†</td>
<td>-1.0% (-1.9%, -0.1%) ( P=0.039 )†</td>
<td>2.5% (-5.7%, 11.3%) ( P=0.56 )</td>
<td>1.1% (0.3%, 1.9%) ( P=0.0087 )†</td>
</tr>
<tr>
<td><strong>∆ DHA (% RBC FA)</strong> (per 1 SD=1.6%)</td>
<td>-5.2% (-7.5%, -2.8%) ( P=0.0001 )†</td>
<td>-1.1% (-2.1%, -0.2%) ( P=0.013 )†</td>
<td>1.0% (-0.7%, 9.7%) ( P=0.81 )</td>
<td>1.2% (0.4%, 2.0%) ( P=0.0031 )†</td>
</tr>
</tbody>
</table>
| **∆ 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.
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 comparison 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**

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

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.
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, 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. Numerous studies have reported that improvement of LVESVI during infarct convalescence remains the strongest favor-
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 sub-study 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 non-infarcted 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, guideline-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.

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**DISCLOSURES**
None.

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**FOOTNOTES**
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