Omega-3 Fatty Acid Supplementation Does Not Reduce Risk of Atrial Fibrillation After Coronary Artery Bypass Surgery

A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

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Background—Omega-3 polyunsaturated fatty acids (n-3 PUFA) have been reported to reduce the risk of sudden cardiac death presumed to be due to fatal ventricular arrhythmias, but their effect on atrial arrhythmias is unclear.

Methods and Results—Patients (n=108) undergoing coronary artery bypass graft surgery were randomly assigned to receive 2 g/d n-3 PUFA or placebo (olive oil) for at least 5 days before surgery (median, 16 days; range, 12 to 21 days). Phospholipid n-3 PUFA were measured in serum at study entry and at surgery and in right atrial appendage tissue at surgery. Echocardiography was used to assess left ventricular function and left atrial dimensions. Postoperative continuous ECG monitoring (Lifecard CF) for 5 days or until discharge, if earlier, was performed with a daily 12-lead ECG and clinical review if patients remained in the hospital beyond 5 days. Lifecard recordings were analyzed for episodes of atrial fibrillation (AF) ≥30 seconds (primary outcome). Clinical AF, AF burden (% time in AF), hospital stay, and intensive care/high dependency care stay were measured as secondary outcomes. One hundred three patients completed the study (51 in the placebo group and 52 in the n-3 PUFA group). There were no clinically relevant differences in baseline characteristics between groups. n-3 PUFA levels were higher in serum and right atrial tissue in the active treatment group. There was no significant difference between groups in the primary outcome of AF (95% confidence interval [CI], −6% to 30%, P=0.28) in any of the secondary outcomes or in AF-free survival.

Conclusions—Omega-3 PUFA do not reduce the risk of AF after coronary artery bypass graft surgery.

Clinical Trial Registration—www.ukcrn.org.uk. Identifier: 4437. (Circ Arrhythm Electrophysiol. 2010;3:46-53.)

Key Words: n-3 PUFA • fish oil • coronary artery bypass graft surgery • atrial fibrillation • inflammation

Atrial fibrillation (AF) occurs frequently after cardiac surgery, with a reported incidence between 10% and 65%,1,2 and is most common on postoperative days 2 to 3.3 The explanation for the variation in incidence among studies probably relate to differences in patient profile, type of surgery, method of arrhythmia surveillance, and definition of arrhythmia. The development of AF may be associated with a longer hospital stay and has been shown to increase long-term mortality after adjustment for known associated risk factors.4 Although several interventions have been shown to reduce the risk of AF, none has proven sufficiently effective to be used routinely in this setting.5–8 One recent open-label study demonstrated a significant benefit with short-term supplementation of the omega-3 polyunsaturated fatty acids (n-3 PUFA) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in preventing AF after coronary artery bypass graft surgery (CABG).9 This interesting development, if corroborated by further studies with a more stringent design, would open a new therapeutic avenue. Hence, we designed a randomized, double-blind, placebo-controlled clinical trial to test the hypothesis that short-term n-3 PUFA supplementation would reduce the risk of AF after CABG. The major limitations of previous studies on postoperative AF and most studies using n-3 PUFA are the lack of robust monitoring for AF in the former and the lack of objective evidence of levels of n-3 PUFA in the latter, along with a possible confounding effect of dietary PUFA intake on these levels. We sought to address these issues by means of continuous monitoring of AF in the postoperative period and by quantifying serum and tissue levels of n-3 PUFA to assess if therapy had indeed altered the levels, along with a food frequency questionnaire to estimate the dietary intake of n-3 PUFA. We also estimated serum levels of C-reactive protein.
Materials and Methods

Study Design
This was a single-center, randomized, double-blind, placebo-controlled study investigating the effect of short-term n-3 PUFA supplementation in patients undergoing CABG (minimum treatment of 5 days and maximum 100 days before surgery followed by supplementation for the period of hospital stay after surgery). The study protocol was approved by the Medicines and Healthcare Regulatory Agency and the National Research Ethics Committee and registered with the European Clinical Trials database (EudraCT) as a clinical trial of an investigational medicinal product. The conduct of the study was approved by the Trent Multi-center Research Ethics Committee. A data monitoring committee was formed consisting 2 independent cardiologists and a statistician from within the study institution.

Patients, Sample Collection, Surgery, and Clinical Monitoring
All patients over the age of 18 years, who were to undergo elective isolated CABG on cardiopulmonary bypass at University Hospital of South Manchester, United Kingdom, were eligible for inclusion in the study unless they had a previous or current history of any atrial arrhythmia, were taking any class 1 or class 3 antiarrhythmic drugs (Vaughan-Williams classification), or were taking or had been taking within the previous 3 months fish oil supplements. Patients were enrolled during a preadmission clinic visit, which typically took place 1 to 3 weeks before surgery. At enrollment, all participants gave written informed consent to take part in the study.

Study enrollment commenced in June 2007 and was completed in January 2009. A total of 108 patients were enrolled of 343 eligible patients as shown in Figure 1. Consecutive patients were randomly assigned, in a double-blind fashion, to receive 2 g/d of a commercially available n-3 PUFA preparation (Omacor; Pronova Biopharma, Lysaker, Norway) providing 85% to 88% EPA/DHA as a pure ethyl esters and in a ratio of 1.2:1 in addition to standard care (active treatment group) or 2 g/d placebo (olive oil) along with standard care (placebo group). Both n-3 PUFA and placebo were presented in identical 1-g capsules. Random assignment was based on a computer-generated randomization list obtained using blocks of size 4.

On enrollment and random assignment, a peripheral venous blood sample was collected and serum was prepared. All patients had a 2D echocardiographic evaluation for left ventricular (LV) systolic function and left atrial (LA) size, using standardized measurements. Patients were deemed to have LV dysfunction if they had an LV ejection fraction <55% and significant atrial dilation if the atrial AP diameter was $\geq 2.3$ cm$^2$/m$^2$ body surface area.

All participants had CABG surgery using a midline sternotomy incision on cardiopulmonary bypass. On the day of surgery, all patients had a second venous blood sampling, and serum was prepared. During surgery, a small sample of tissue from the right atrial appendage was obtained.

A heart rhythm monitor (Lifecard CF digital Holter recorder; Space Labs Healthcare, Wash) was attached to the patient’s chest in the immediate postoperative period in the cardiac intensive care to continuously record 2-lead ECG data for 5 postoperative days. If patients stayed in the hospital for longer than 5 days, a daily ECG was performed along with a daily clinical follow-up by a cardiologist.

On completion of recording, data from the Lifecard monitor was downloaded onto a Delmar Reynolds computer system (Space Labs Healthcare) and archived to a disk. At the end of the study, these data were analyzed by 2 independent experts using an automated arrhythmia diagnostic system (Pathfinder Digital; Space Labs Healthcare). The system divides the continuous ECG recording into 24-hour segments. The methods of AF identification were as follows: ECG recordings were loaded, and appropriate program sensitivity and detection were checked. Interpretation of whether any arrhythmia existed on each day was performed by analysis of peaks/troughs of the 24-hour trend graphs of heart rate, N-N intervals (the time intervals between consecutive normal beats, reflecting underlying sinus rhythm), and sNN50 (number of pairs of adjacent R-R intervals differing by $>50$ ms). If no arrhythmia was detected, it was recorded as 0 incidence of AF and 0% of recording spent in AF. If the interpretation was inconclusive or if an arrhythmia was thought to have occurred, then the entire 24-hour recording was scanned at an appropriate speed and episodes of AF >30 seconds were manually identified and appropriately labeled. The program then calculated the number of AF episodes marked and the percentage of recording in AF. All 12-lead ECGs were manually analyzed by a cardiologist. Patients continued to take n-3 PUFA or placebo in the postoperative period until discharge from the hospital. If patients were unable to take the capsules orally (3 patients in the active treatment arm and 2 patients in the control arm) in the immediate postoperative period, the contents of the capsules were mixed with the naso-gastric feed: this was carried out exclusively in the intensive care unit by the nurse in charge of patient care, without compromising the blinding process.

A further blood sample was collected on the 3rd postoperative day (48 to 72 hours after completion of surgery); serum was prepared and used to measure concentrations of CRP. Formal participation in the study ended at hospital discharge. However, any hospital admission in the 4 weeks after surgery was evaluated for potential study-related complications.

Clinical Outcomes
The primary outcome measure was any AF $\geq 30$ seconds in the Lifecard monitor recordings. Secondary outcomes were clinically recognized AF (as documented by the treating clinicians in the patients clinical records), AF burden (defined as the percent of time
Table 1. Characteristics of Patients in Each Treatment Group

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 51)</th>
<th>n-3 PUFA (n = 52)</th>
<th>% (n)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>82% (42)</td>
<td>77% (40)</td>
<td></td>
</tr>
<tr>
<td><strong>Age (y)</strong></td>
<td>68 (64–73)</td>
<td>64 (58–71)</td>
<td></td>
</tr>
<tr>
<td><strong>Body mass index (kg/m²)</strong></td>
<td>27.2 (24.9–30.2)</td>
<td>28.3 (26.1–31.5)</td>
<td></td>
</tr>
<tr>
<td><strong>β-blockers</strong></td>
<td>82% (42)</td>
<td>88% (46)</td>
<td></td>
</tr>
<tr>
<td><strong>ACE inhibitors/ARB</strong></td>
<td>88% (45)</td>
<td>79% (41)</td>
<td></td>
</tr>
<tr>
<td><strong>Calcium antagonists</strong></td>
<td>26% (13)</td>
<td>19% (10)</td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>98% (50)</td>
<td>96% (51)</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>10% (8)</td>
<td>13% (7)</td>
<td></td>
</tr>
<tr>
<td><strong>COPD</strong></td>
<td>10% (5)</td>
<td>8% (4)</td>
<td></td>
</tr>
<tr>
<td><strong>Renal impairment</strong></td>
<td>8% (4)</td>
<td>6% (3)</td>
<td></td>
</tr>
<tr>
<td><strong>Previous myocardial infarction</strong></td>
<td>28% (14)</td>
<td>23% (12)</td>
<td></td>
</tr>
<tr>
<td><strong>Echo LV function, low, %</strong></td>
<td>8% (4)</td>
<td>10% (5)</td>
<td></td>
</tr>
<tr>
<td><strong>Echo LA size, dilated, cm²</strong></td>
<td>6% (3)</td>
<td>4% (2)</td>
<td></td>
</tr>
<tr>
<td><strong>Postoperative inotropes</strong></td>
<td>53% (27)</td>
<td>58% (30)</td>
<td></td>
</tr>
<tr>
<td><strong>No. of vessels grafted</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8% (4)</td>
<td>6% (3)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>39% (20)</td>
<td>33% (17)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>49% (25)</td>
<td>56% (29)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4% (2)</td>
<td>6% (3)</td>
<td></td>
</tr>
<tr>
<td><strong>Bypass time, min</strong></td>
<td>72 (34, 245)</td>
<td>88 (25, 245)</td>
<td></td>
</tr>
<tr>
<td><strong>Cross-clamp time, min</strong></td>
<td>50 (20, 130)</td>
<td>61 (19, 126)</td>
<td></td>
</tr>
</tbody>
</table>

IQR indicates interquartile range; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blockers; COPD, chronic obstructive pulmonary disease.

*Unless otherwise indicated.

Table 2. Duration of Therapy and Clinical Outcome Measures

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 51)</th>
<th>n-3 PUFA (n = 52)</th>
<th>% (n)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of AF in Lifecard monitor, % (n)</td>
<td>43% (22)</td>
<td>56% (29)</td>
<td>0.28*</td>
<td></td>
</tr>
<tr>
<td>Clinical AF, % (n)</td>
<td>35% (18)</td>
<td>42% (22)</td>
<td>0.60*</td>
<td></td>
</tr>
<tr>
<td>AF burden, % hours</td>
<td>9.6 (4–20)</td>
<td>13.2 (5–30)</td>
<td>0.49†</td>
<td></td>
</tr>
<tr>
<td>Hospital stay, d</td>
<td>7 (6–10)</td>
<td>8.5 (6–12)</td>
<td>0.49†</td>
<td></td>
</tr>
<tr>
<td>ICU/HDU stay, d</td>
<td>1 (1–2)</td>
<td>1 (1–2)</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>Duration of therapy, d</td>
<td>17 (12–20)</td>
<td>16.5 (13–21)</td>
<td>...</td>
<td></td>
</tr>
</tbody>
</table>

Values are median (IQR) for continuous variables.

ICU indicates intensive care unit; HDU, high-dependency unit.

*χ² test; †Mann–Whitney U test.

Dietary Intake of n-3 PUFA

On recruitment, all patients were provided with a self-administered food frequency questionnaire listing commonly consumed food items that are considered to be sources of marine n-3 fatty acids. All 103 patients who completed the study responded to this questionnaire, providing an estimate of their weekly intake of marine n-3 PUFA, and participants were advised not to change their dietary habits during the study period.

Sample Size Calculation

The average incidence of AF after CABG in the authors’ institution is approximately 50%, which is within the range of previously reported values.1,2 Hence, sample size was calculated with an expected incidence of postoperative AF of 50% in the control group and a relative risk reduction of 55% by n-3 PUFA in accordance with the study by Calo et al.8 This gave a sample size of 54 patients in each group (108 in all), with 80% power to detect a significant difference using simple χ² test with the conventional 5% significance level.

Statistical Analysis

All data were analyzed by a qualified statistician. All analyses were done on an intention-to-treat basis. Comparisons between groups were made using χ², Student t test, and Mann–Whitney U tests as appropriate. Differences in AF-free survival were assessed using Kaplan–Meir analysis. Cox proportional hazards regression analysis was performed to assess the confounding effect of baseline patient characteristics. Variable selection was done using a stepwise selection process. All analysis was carried out using SPSS Version 15.0. In all cases, a value of P <0.05 was taken to indicate statistical significance. All continuous variables are reported as median with interquartile ranges (25th to 75th percentiles).

Results

Patient Characteristics

Of the 108 patients recruited into the study, 103 completed the study. Fifty-one patients were randomly assigned to receive placebo, and 52 received n-3 PUFA. Of the 5 patients who did not complete the study, 2 died awaiting surgery (both were in the placebo arm), 2 had their surgery cancelled, and 1 withdrew consent. There were no clinically relevant differences between the 2 groups with respect to baseline variables such as demographics, comorbidities, and other likely confounding factors, as shown in Table 1.

The median duration of therapy before surgery was 17 days12–20 in the placebo group and 16.5 days13–21 in the n-3 PUFA group, as shown in Table 2.

a given patient is in AF), length of stay in the hospital, and length of stay in the intensive care or high-dependency care unit.

Laboratory Measurements

All serum and tissue samples were stored at −80°C until analysis. Serum CRP concentrations were measured by a previously validated technique of particle-enhanced immuno-turbidimetric assay (Modular P600, Roche Diagnostics, Mannheim, Germany) using ruthenium electrochemiluminescence to obtain a signal.12,13

The fatty acid compositions of serum phosphatidyl-choline (PC), the major circulating phospholipid, and of atrial tissue PC and phosphatidyl-ethanolamine (PE) were determined using gas chromatography. In brief, total lipid was extracted from serum or homogenized atrial tissue using chloroform/methanol (2:1 vol/vol). PC and for atrial tissue PE were isolated from the total lipid extract using aninopropylsilica solid-phase extraction columns; PC was eluted with chloroform/methanol (3:2 vol/vol) and PE with methanol. Fatty acid methyl esters were prepared from the isolated PC and PE fractions by incubation with methanol containing 2% sulfuric acid for 2 hours at 50°C. Fatty acid methyl esters were extracted using hexane and then separated on a Hewlett Packard 6890 gas chromatograph. Running conditions were as described elsewhere.14 The fatty acid methyl esters were identified by comparison with standards run previously, and data are expressed as percentage of total fatty acids present in the PC or PE fraction.

Running conditions were as described elsewhere.14 The fatty acid methyl esters were identified by comparison with standards run previously, and data are expressed as percentage of total fatty acids present in the PC or PE fraction.
Primary Outcome
The overall incidence of AF in the 5 days after CABG surgery (as estimated by continuous ECG monitoring) was 49.5% (51 patients of 103 had at least 1 episode of AF ≥30 seconds). Postoperative AF was observed in 43% of the placebo group and 56% of the n-3 PUFA group, with a difference of 13% between the 2 groups (95% confidence interval [CI], −6% to 30%; χ² test; P=0.28), as summarized in Table 2.

The Kaplan-Meier actuarial estimates of the occurrence of the primary end point of AF ≥30 seconds after CABG are shown in Figure 2. There was no significant difference in the AF-free distribution between the 2 groups (log rank test; P=0.26).

AF occurred most commonly between 40 to 80 hours after surgery (59%). There were no new episodes of clinical AF after 5 days of surgery (after the period of continuous monitoring).

Cox proportional hazards regression analysis to assess the confounding effect of baseline patient characteristics on the relationship between n-3 PUFA therapy and AF showed age and number of vessels grafted as the only variables of importance in univariate analysis; multivariate analysis, adjusting for these differences, confirmed that n-3 PUFA therapy had no effect on the incidence of AF, as shown in Table 3.

Secondary Outcomes
Clinical AF
The overall incidence of clinical AF as documented by the clinicians involved in the patients’ care in the postoperative period was 38.8%, with no difference between groups (35% in the placebo group versus 42% in the n-3 PUFA group; χ² test; P=0.60).

AF Burden
There was no difference in percentage of time in AF for each patient who recorded AF in the Lifecard monitor (AF burden) between groups (9.6 [4 to 20] [% hours] in the placebo group versus 13.2 [5 to 30] in the n-3 PUFA group; Mann–Whitney U test; P=0.49).

Hospital Stay and Intensive Care Unit/High-Dependency Unit Stay
Length of hospital stay was not different between groups, with a median hospital stay of 7 days (6 to 10 days) for the

Table 3. Risk of AF Using Univariate and Multivariate Cox Proportional Hazard Regression Models

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group, PUFA</td>
<td>1.37 (0.79, 2.30)</td>
<td>1.48 (0.84, 2.60); P=0.18</td>
</tr>
<tr>
<td>Sex, male</td>
<td>0.74 (0.39, 1.41)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>1.03 (1.001, 1.06)</td>
<td>1.04 (1.002, 1.07); P=0.036</td>
</tr>
<tr>
<td>β-blockers</td>
<td>0.79 (0.39, 1.63)</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors/ARB</td>
<td>0.52 (0.27, 1.02)</td>
<td></td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>0.95 (0.49, 1.85)</td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>0.72 (0.10, 5.18)</td>
<td></td>
</tr>
<tr>
<td>Echo LV function, low</td>
<td>1.32 (0.56, 3.10)</td>
<td></td>
</tr>
<tr>
<td>Echo LA size, dilated</td>
<td>1.09 (0.34, 3.50)</td>
<td></td>
</tr>
<tr>
<td>Postoperative inotropes</td>
<td>0.96 (0.55, 1.66)</td>
<td></td>
</tr>
<tr>
<td>No. of vessels grafted</td>
<td>1.56 (1.03, 2.36)</td>
<td>1.51 (0.99, 2.30); P=0.055</td>
</tr>
<tr>
<td>Bypass time, 10 min</td>
<td>1.03 (0.97, 1.09)</td>
<td></td>
</tr>
<tr>
<td>Cross-clamp time, 10 min</td>
<td>1.05 (0.95, 1.15)</td>
<td></td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blockers.

*Multivariate model contains only treatment group together with significant independent predictors (P<0.10).
placebo group and 8.5 days (6 to 12 days) for the n-3 PUFA group (Mann–Whitney U test;  P = 0.49). Similarly, the length of stay in intensive care/high dependency care was not different with a median ICU/HDU stay of 1 day (1 to 2 days) for the placebo group and 1 day (1 to 2 days) for the n-3 PUFA group.

CRP Concentration

CRP concentrations were measured in serum samples collected within 24 hours of surgery and on day 3 (48 to 72 hours) after surgery. There were no clinically relevant differences in CRP at either time point between the 2 groups, as shown in Table 4.

n-3 PUFA Content of Serum and Right Atrial Appendage Tissue

Serum PC EPA and DHA did not differ between the 2 groups at study entry and did not change in the placebo group. However, both EPA and DHA in serum PC increased significantly in the n-3 PUFA group and were higher at surgery in the n-3 PUFA group than in the placebo group. Importantly, PC and PE EPA and DHA in atrial tissue collected at surgery were higher in the n-3 PUFA group than in the placebo group, as summarized in Table 5.

Dietary n-3 PUFA Intake

Evaluation of baseline dietary n-3 PUFA intake, at study entry, showed that patients in the placebo group had a median daily EPA + DHA intake of 118 mg (range, 31 to 431 mg) and those in the n-3 PUFA group had a median daily intake of 131 mg (range, 24 to 524 mg).

Postoperative Complications

Three patients were hospitalized (2 in the placebo group and 1 in the active treatment group) in the 4 weeks after discharge with complications that were deemed unrelated to study participation. Two patients (1 in each group) had skin infection over the vein graft site and 1 (placebo group) had noncardiac chest pain.

Discussion

In this study, we demonstrate that short-term therapy with n-3 PUFA raises levels of EPA and DHA in serum and atrial tissue phospholipids but does not reduce the incidence of AF after CABG. The 95% CI for the primary end point of AF ≥ 30 seconds (range, –6 to 30) suggests that the maximum benefit that could have been derived by n-3 PUFA therapy is 6%. It was also found that by continuous monitoring of the ECG, the overall incidence of significant AF episodes (defined as any AF ≥ 30 seconds) was higher than most previously published reports. However, the incidence of clinically recognized AF and AF burden were not altered by n-3 PUFA supplementation. There were no significant differences in any of the secondary outcomes measured. These findings contrast with those of Calo et al,9 showing a significant reduction in AF after CABG.

An important difference between our study and that of Calo et al is the method of evaluating the occurrence of AF and its burden. We used continuous ECG monitoring for 5 days after surgery, recording and analyzing every heart beat in this period with a cutoff value of ≥30 seconds of AF as opposed to 5 minutes of AF in the study by Calo et al. Thus, unsurprisingly, the overall incidence of AF in the current cohort was much higher than in the previous study: in the current study, routine clinical surveillance identified a much lower incidence of AF than that identified using continuous ECG monitoring. This may partly explain the different findings between the 2 studies. In addition, there were significant differences in concomitant drug therapy between the current study and that of Calo et al.9 In our study, 85% of patients were taking β-blockers and 98% were taking statins as their standard therapy compared with 57.5% and 56.9%, respectively, in the study by Calo et al.9 These 2 agents have been reported to reduce the incidence of AF after CABG.5,7 There were no significant differences in the use of these agents between the 2 groups in either study. However, the optimal use of these agents in the current study could have offset any beneficial effects that n-3 PUFA might have on the incidence of AF. There were also significant differences in the rates of prior myocardial infarction and off-pump CABG (both higher in Calo et al), and these might have resulted in different responses to therapy.

There is a considerable volume of evidence showing that n-3 PUFA reduce the risk of sudden cardiac death, particularly after myocardial infarction. Because the most common cause of death after an myocardial infarction is serious ventricular arrhythmia, it has been postulated that n-3 PUFA reduce the risk of such arrhythmias. However, studies designed to investigate a direct antiarrhythmic effect have shown mixed results,19–21 with meta-analyses uniformly showing a lack of benefit.22–24 Similarly, epidemiological studies on the effect of n-3 PUFA in the incidence of AF have also shown mixed results.25–27 Experiments on whole-heart animal models and single ventricular myocytes report that n-3

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**Table 4. CRP Concentrations in the 2 Groups**

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Placebo (n = 51)</th>
<th>n-3 PUFA (n = 52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 24 h of surgery, mg/L</td>
<td>32 (2–49)</td>
<td>28.5 (15–38)</td>
</tr>
<tr>
<td>Day 3 after surgery, mg/L</td>
<td>188 (79–226)</td>
<td>187.5 (132–229)</td>
</tr>
</tbody>
</table>

Values are median (IQR).

**Table 5. Serum and Atrial Tissue Phospholipid n-3 PUFA Content**

<table>
<thead>
<tr>
<th>Fatty Acid</th>
<th>Time Point</th>
<th>Placebo</th>
<th>n-3 PUFA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum EPA</td>
<td>Study entry</td>
<td>1.76 (1.49)</td>
<td>1.51 (0.98)</td>
<td>NS</td>
</tr>
<tr>
<td>Serum EPA</td>
<td>Surgery</td>
<td>1.53 (0.74)</td>
<td>2.78 (1.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum DHA</td>
<td>Study entry</td>
<td>3.82 (1.38)</td>
<td>3.79 (1.37)</td>
<td>NS</td>
</tr>
<tr>
<td>Serum DHA</td>
<td>Surgery</td>
<td>4.19 (1.29)</td>
<td>5.49 (1.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tissue PC EPA</td>
<td>Surgery</td>
<td>0.69 (0.30)</td>
<td>1.23 (0.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tissue PC DHA</td>
<td>Surgery</td>
<td>3.3 (1.1)</td>
<td>4.5 (1.6)</td>
<td>0.007</td>
</tr>
<tr>
<td>Tissue PE EPA</td>
<td>Surgery</td>
<td>1.73 (0.73)</td>
<td>2.7 (1.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Tissue PE DHA</td>
<td>Surgery</td>
<td>11.6 (3.7)</td>
<td>14.3 (3.9)</td>
<td>0.037</td>
</tr>
</tbody>
</table>

Values are mean (SD), percent of total fatty acids.
*Student t test, unpaired.
PUFA result in a shortening of the effective refractory period and action potential duration.\textsuperscript{28–30} Interestingly, this change is the hallmark of tachycardia remodeling (atrial electric remodeling), which favors initiation and maintenance of AF.\textsuperscript{31–33} In keeping with this, one study, in an atrial tachycardia pacing model of AF, reported that n-3 PUFA pretreatment did not have a beneficial influence on parameters of atrial electric remodeling or the duration of AF induced by pacing,\textsuperscript{34} whereas other animal studies have shown beneficial changes in atrial electrophysiological properties, rendering the animal less susceptible to pacing-induced AF.\textsuperscript{35,36} In addition, animal work and clinical reports have shown that n-3 PUFA may have a proarrhythmic effect, with an increased risk of reentrant arrhythmias.\textsuperscript{20,37,38}

In animal experiments, it has been shown that the electrophysiological effects of fish oils applied to ventricular myocytes in suspension vary significantly from those of the membrane incorporated n-3 PUFA,\textsuperscript{30} and this has been reflected by a variable effect of acute (often intravenous) versus chronic (dietary supplementation) administration of n-3 PUFA on cardiac arrhythmias in human beings. In a clinical setting, this would have a bearing on the dose, duration, and method of administration of n-3 PUFA and the consequent variation in circulating and tissue levels of n-3 PUFA. The complex interaction between circulating and tissue levels of these fatty acids, the effect of stress on free fatty acid release from adipocytes, and the resulting changes in the electrophysiology of cardiomyocytes are not well understood and may explain much of the diversity in the outcome of clinical studies. In the current study, both the serum and tissue levels of n-3 PUFA were measured. To our knowledge, this is the first time that tissue levels of n-3 PUFA have been measured in a clinical study evaluating the antiarrhythmic potential of these fatty acids.

Many studies have reported increased EPA and DHA in plasma or serum lipids after supplementation of the diet with n-3 PUFA.\textsuperscript{39} The increment in these fatty acids seen in the current study in serum phospholipids (86% increase in EPA and 45% increase in DHA) is consistent with existing data. However, the current study also shows higher EPA and DHA in phospholipids of atrial tissue after supplementation with n-3 PUFA for a relatively short period of time. The higher EPA and DHA content of atrial phospholipids after n-3 PUFA supplementation observed in the current study supports the observation of Metcalfe et al\textsuperscript{40} that these fatty acids, even with short-term supplementation, are readily incorporated into this tissue.

There are emerging data supporting a link between inflammation and AF\textsuperscript{10,41} and an association between measured serum or plasma inflammatory markers and the risk of developing AF.\textsuperscript{10,42} The marker that has been shown to be reliable and reproducible in this setting is CRP.\textsuperscript{43} The peak incidence of postoperative AF (day 3) has been shown to correlate with peak elevation of CRP\textsuperscript{44} and n-3 PUFA have been shown to possess anti-inflammatory properties by reducing the production of inflammatory cytokines.\textsuperscript{11} In the current study, CRP was measured within 24 hours of surgery and at the third day after surgery and was found not to be affected by n-3 PUFA. This may be because the dose of n-3 PUFA used was below the threshold dose required to influence inflammation.\textsuperscript{44,45}

In conclusion, n-3 PUFA given at a dose of 2 g/d increased the n-3 PUFA content of atrial tissue but did not reduce the incidence of AF in the 5 days after CABG. In addition, there appeared to be a trend toward more AF in the n-3 PUFA group. Larger randomized studies are needed to clarify this issue.

### Study Limitations

An important limitation of a study with a relatively small sample size is the fact that subtle benefits may not become apparent. However, given the fact that the 95% CI suggests a trend toward harm in the n-3 PUFA group, it is very unlikely that the lack of benefit seen in our study is a function of low power. Another potential limitation relating to the blinding process is the fact that fish oils have a taste and flavor that makes them recognizable to the patients. However, none of the trial participants disclosed such knowledge to the investigators, and therefore the blinding of the investigators was not compromised at any stage.

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### Disclosures

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**CLINICAL PERSPECTIVE**

Omega-3 polyunsaturated fatty acids (n-3 PUFA) of marine origin (fish oils) have been shown to reduce the risk of sudden cardiac death after myocardial infarction. This has evoked considerable interest in the possible antiarrhythmic effects of n-3 PUFA. Animal experiments have shown several potential antiarrhythmic properties of n-3 PUFA; however, clinical studies on ventricular arrhythmias have shown mixed results. Atrial fibrillation (AF) is a common arrhythmia and is associated with increased morbidity and mortality. Drug therapy of AF is limited, mainly because of the proarrhythmic properties of most antiarrhythmic agents, and there is a need to identify safe and effective drugs. Epidemiological studies evaluating the benefit of dietary fish intake on the risk of developing AF have shown conflicting results, but 1 clinical trial with open-label n-3 PUFA supplementation for a short duration has reported considerable reduction in the incidence of AF after coronary artery bypass surgery. This, if supported by further studies, would open a new therapeutic option in the management of AF. Hence, we addressed this question in the same subset of patients with a more stringent trial design and robust monitoring of primary outcome of postoperative AF. In our study, we have shown that there is no benefit with n-3 PUFA supplementation and that there may be a trend toward increased AF in the n-3 PUFA–treated group. Hence, we believe that larger clinical trials are needed to assess the risk and benefit of n-3 PUFA therapy in various forms of AF seen in clinical practice.
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