n-3 Polyunsaturated Fatty Acids in the Prevention of Atrial Fibrillation Recurrences After Electrical Cardioversion

A Prospective, Randomized Study

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Background—n-3 polyunsaturated fatty acids (n-3 PUFAs) exert antiarrhythmic effects and reduce sudden cardiac death. However, their role in the prevention of atrial fibrillation remains controversial. We aimed to determine the effect of n-3 PUFAs in addition to amiodarone and a renin-angiotensin-aldosterone system inhibitor on the maintenance of sinus rhythm after direct current cardioversion in patients with persistent atrial fibrillation.

Methods and Results—We conducted a randomized, double-blind, placebo-controlled, parallel-arm trial in patients with persistent atrial fibrillation, with at least 1 relapse after cardioversion, and treated with amiodarone and a renin-angiotensin-aldosterone system inhibitor. Participants were assigned to placebo or n-3 PUFAs 2 g/d and then underwent direct current cardioversion 4 weeks later. The primary end point was the probability of maintenance of sinus rhythm at 1 year after cardioversion. Of 254 screened patients, 199 were found to be eligible and randomized. At the 1-year follow-up, the probability of maintenance of sinus rhythm was significantly higher in the n-3 PUFAs–treated patients compared with the placebo group (hazard ratio, 0.62 [95% confidence interval, 0.52 to 0.72] and 0.36 [95% confidence interval, 0.26 to 0.46], respectively; P=0.0001).

Conclusions—In patients with persistent atrial fibrillation on amiodarone and a renin-angiotensin-aldosterone system inhibitor, the addition of n-3 PUFAs 2 g/d improves the probability of maintenance of sinus rhythm after direct current cardioversion. Our data suggest that n-3 PUFAs may exert beneficial effects in the prevention of atrial fibrillation recurrence. Further studies are needed to confirm and expand our findings.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01198275. (Circulation. 2011;124:00-00.)

Key Words: arrhythmia ■ atrial fibrillation ■ cardioversion ■ fatty acids, omega-3 ■ recurrence

Atrial fibrillation (AF) is the most common sustained arrhythmia and is associated with considerable morbidity and mortality.1,2 Treatment of AF remains controversial. Although rhythm control and rate control strategies seem to provide comparable results,3 the restoration and maintenance of sinus rhythm remains the preferred therapy for a large number of patients.4 However, current pharmacological antiarrhythmic therapies have limited efficacy and poor safety profiles, and invasive or surgical treatments are indicated in only a minority of patients and are not free of failure and procedural risks.6,7 In patients on currently available antiarrhythmic drugs, of which amiodarone appears to be the most effective,8 the 1-year relapse rates of AF after cardioversion range from 44% to 77%.9

Editorial see p ■■■
Clinical Perspective on p ■■■

Atrial fibrillation is associated with electric and structural remodeling of the atria,10 which is mediated, at least in part, by angiotensin II, oxidative stress, and inflammation.11,12 Although the efficacy of angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARBs) in reducing the risk of AF is not conclusive, a recent meta-analysis suggests that renin-angiotensin system blockade therapy in combination with amiodarone may have more efficacy in preventing AF than amiodarone alone.13

Based on potential antiarrhythmic effects, a role of n-3 polyunsaturated fatty acids (PUFAs) in the prevention of AF has been postulated. However, the results from epidemiological14–16 and clinical17–19 studies have been conflicting, and a definitive role of n-3 PUFAs in the setting of AF has not been demonstrated. The present study was therefore designed to investigate the effects of n-3 PUFAs on the recurrence of AF after cardioversion in patients with persistent AF on amiodarone and a renin-angiotensin-aldosterone system inhibitor. We hypothesized that, compared with placebo, treatment with n-3 PUFAs would significantly increase the probability of maintenance of sinus rhythm in patients on therapy with amiodarone and an ACE-I or ARB.
Methods

Study Population
Patients with persistent AF referred to our Arrhythmia and Heart Failure Outpatient Clinic for direct current cardioversion (DCCV) were prospectively enrolled. Inclusion criteria were persistent AF lasting ≥1 month and confirmed by 24-hour ECG Holter monitoring and history of at least 1 relapse after previous successful cardioversion. Exclusion criteria included left atrial size >60 mm; severe valvulopathy; myocar- dial infarction during the previous 6 months; unstable angina; New York Heart Association class IV heart failure; hemodynamic instability; cardiac surgery during the previous 3 months; significant pulmonary, thyroid, or hepatic disease; contraindication to treatment with amiodarone, ACE-I, or ARB; chronic kidney disease (creatinine ≥2.5 mg/dL or estimated glomerular filtration rate ≤30 mL.min−1.1.73 m2); QTc ≤480 milliseconds in the absence of bundle-branch block; brady- cardia (≤50 bpm); hyperkalemia (K+ >5.5 mEq/L); pregnancy; and any disease or condition that, in the opinion of the investigators, could interfere with safety or study results. The study was approved by the Institutional Review Board of the University of Brescia. Written informed consent was obtained from each patient.

Study Design
The study had a double-blind, placebo-controlled, parallel design. Eligibility was determined at a screening visit that included medical history, physical examination, 12-lead ECG, chest x-ray, and 2-dimensional Doppler echocardiography, plus complete blood count, routine chemistry, thyroid function tests, and pregnancy test in fertile women. Eligible participants entered a run-in phase in which warfarin was adjusted to achieve an international normalized ratio of 2.0 to 3.0. Patients on long-term anticoagulation with acenocoumarol were switched to warfarin at this visit. Patients on amiodarone were continued at a maintenance dose of 200 mg/dl, whereas those who were not taking amiodarone were started at a dose of 400 mg/dl for 1 week and then continued on a maintenance dose of 200 mg/dl. Patients on ACE-I or ARBs were continued on the same agent. An ACE-I or ARB was started in those who were not on therapy. In all patients, an effort was made to achieve the highest tolerated dose. Patients in whom a new treatment was started or dosage was changed returned at 1 and 2 weeks for follow-up of international normalized ratio and/or blood pressure. All patients returned 3 weeks later for the randomization visit. At this encounter, patients underwent ECG to confirm the persistence of AF, physical examination, and blood work for routine chemistry. If no exclusion criteria were found, patients were randomized either to 1.0-g gelatin capsules containing a total of 850 to 882 mg of eicosapentaenoic acid and docosahexaenoic acid ethyl esters with an average ratio of eicosapentaenoic acid to docosahexaenoic acid of 1.2 (allowed range, 0.9 to 1.5) (OMACOR, PronovaBiopharma, Lysaker, Norway) twice daily or to 1.0-g placebo gelatin capsules (olive oil) of identical appearance twice daily. Random assignment followed a computer-generated randomization list obtained using blocks of size 4. The randomization schedule was kept in the research pharmacy area and was available only to unblinded pharmacy personnel until after the database was locked. At that time, the unblinded patient treatment information was made available to the investigators.

Direct Current Cardioversion
Outpatient DCCV was scheduled 4 weeks after randomization or after target international normalized ratio levels were documented on at least 4 consecutive weekly checks. Direct current cardioversion was performed in the morning, with the patient in the fasting state. Anesthesia was induced by the anesthesiologist with sodium thiopental 2 mg/kg, and patients were cardioverted with administration of a synchronized, biphasic current (Smart Biphasic Heart Start, Philips). The initial shock was set at 100 J if the body weight was ≤70 kg and at 150 J for higher body weights. Successful cardioversion was defined as recovery of sinus rhythm lasting at least 1 minute after the shock. If unsuccessful, a second 200-J shock, and eventually a third 200-J shock, was administered. Failure of DCCV was defined as the persistence of AF after the third attempt at cardioversion. After the procedure, patients were monitored on telemetry for at least 6 hours before discharge. Patients who did not revert to sinus rhythm or with early relapse within the observation period after DCCV were considered to have finished follow-up.

Follow-Up
Follow-up started on the day of the scheduled DCCV immediately after the procedure or at the time that a spontaneous cardioversion was documented. Patients with successful DCCV underwent weekly clinical and ECG controls for the first 3 weeks after cardioversion. Subsequently, follow-up visits with performance of clinical evaluation, ECG, and a 24-hour Holter monitoring were performed at 1, 3, 6, and 12 months after DCCV. Additional visits were scheduled in case of occurrence of symptoms. At each visit, the dose of ACE-I or ARB was adjusted if needed. The occurrence of side effects was ascertained by the examining cardiologist, and if indicated, the patient was withdrawn from the study.

Study End Point
The primary end point was the probability of maintenance of sinus rhythm at the 1-year follow-up.

Statistical Analyses
On the basis of published data, rates of relapses at 1 year in patients treated with amiodarone were estimated at 60%.8 Give an effect estimate ranging from 40% to 60% for the relapse rates in patients on an ACE-I/ARB in addition to amiodarone therapy, considering the high risk of relapses in our study population, we conservatively assumed a 50% relapse rate. We calculated that a total of 180 patients would yield 80% power to detect a clinically relevant difference of ~20% in AF recurrence with the addition of n-3 PUFA treatment with a log-rank test with a significance level of 0.05 (2 tailed). With anticipation of a 10% dropout rate, a sample of up to 1.1 times that indicated (ie, 200) was enrolled to yield 180 evaluable patients.

Data are expressed as mean±SD for continuous variables and as numbers (percent) for categorical variables. Continuous variables were compared by the 2-tailed Student t test. The Wilcoxon rank-sum test, Fisher exact test, or χ2 test was used as appropriate for categorical variables.

The end points were analyzed according to a strict intention-to-treat approach for all the randomized patients. Patients with pharmacological cardioversion and with unsuccessful DCCV were retained in the analysis as success and not success, respectively. The time to first AF recurrence was analyzed with the Kaplan-Meier method and compared with the log-rank test. Hazard ratios and confidence intervals were estimated with the Cox regression model. We analyzed the time to AF relapse using Cox proportional hazard regression to obtain the set of variables independently associated with the event. All the variables recorded at baseline associated with the time to AF relapse significantly (P<0.05) or at a borderline level (P=0.10) were included in the first Cox model; then, the variables were excluded from the final model according to a backward procedure with a threshold of P<0.05 for retention.

A value of P<0.05 was considered statistically significant. All statistical analyses were performed with SAS (version 9.13; SAS Institute Inc, Cary, NC).

Results
A total of 254 consecutive patients with persistent AF referred to our clinic for DCCV were screened between January 7, 2006, and April 30, 2007. The first patient was enrolled on January 25, 2006, and the last patient completed follow-up on May 13, 2008. Data on recruitment, eligibility, randomization, and withdrawal are detailed in Figure 1. Baseline data at the time of randomization, including demographic and anthropometric characteristics, medical history, clinical, ECG, and echocardiographic parameters and current medications, are reported in Table 1.

Amiodarone Therapy Before Direct Current Cardioversion
At the time of enrollment, 44 patients in the placebo group (44.4%) and 43 patients in the active treatment group (43%)
were already on long-term amiodarone treatment. Data on amiodarone therapy in the patients started on amiodarone at the time of enrollment are reported in Table 2.

**Pharmacological Cardioversions**

**After Randomization**

At the time of the scheduled DCCV, 6 spontaneous conversions to sinus rhythm were documented. The mean time between randomization and ECG confirmation of pharmacological cardioversion to sinus rhythm was 36\pm1 and 33\pm3 days in the placebo and n-3 PUFAs groups, respectively. Additional data on pharmacological cardioversion are reported in Table 3.

**Direct Current Cardioversion**

Direct current cardioversion was performed in 193 patients and was successful in 185 (95.9%). Failed DCCV occurred in 5 patients, and immediate AF recurrence was observed in 3 patients. Additional data on DCCV with the distribution by number of shocks in the 2 groups are reported in Table 3. The comparison of the number of shocks between groups according to an intention-to-treat analysis is reported in Table 4.

**Primary End Point**

At the 1-year follow-up, the estimated probability of maintaining sinus rhythm was significantly higher in patients treated with n-3 PUFAs than in those on placebo (hazard ratio, 0.62 [95% confidence interval, 0.52 to 0.72] versus 0.36 [95% confidence interval, 0.26 to 0.46]; \(P=0.0001\), log-rank test; Figure 2). In addition, after exclusion of the patients with failed DCCV per protocol analysis, the estimated probability of remaining in sinus rhythm was still significantly higher in the n-3 PUFA group than in the placebo group (64% versus 40%, respectively; \(P=0.0004\)).

**Events During Follow-Up**

In the n-3 PUFA and placebo groups, 37 and 56 patients, respectively, experienced recurrence. The mean time between DCCV and documented first recurrence of AF was 139\pm113 days in the placebo group and 168\pm116 days in the patients treated with n-3 PUFAs. As detailed in Table 5, in both study arms, the majority of these events were asymptomatic. However, the time of detection was more frequently an unscheduled visit. In the majority of the cases, this was due to a request for an unscheduled visit by various healthcare providers such as the anticoagulation monitoring service or a general practitioner after incidental detection of an irregular heart rhythm.

**Correlates of Maintenance of Sinus Rhythm**

In a Cox proportional hazards model adjusted for potentially confounding factors selected at univariate analysis, the use of n-3 PUFAs was the only variable associated with the maintenance of sinus rhythm after cardioversion. In the same model, the main correlates of AF recurrence were the duration of AF before randomization, left atrial dimension, and ejection fraction (Table 6).

**Tolerability of n-3 Polyunsaturated Fatty Acids and Adverse Events**

Therapy with n-3 PUFAs was well tolerated. Five patients were withdrawn because of amiodarone toxicity related to asymptomatic (1 patient) or symptomatic (3 patients) abnormal thyroid function tests and to mildly abnormal respiratory function tests (1 patient). Of these adverse events, 3 occurred in the placebo group and 2 in the active treatment group. No other significant side effects or bleeding was reported.

**Discussion**

The main finding of our study is that treatment with n-3 PUFAs in addition to amiodarone and ACE-Is or ARBs is...
more effective in maintaining sinus rhythm after DCCV than therapy with amiodarone and ACE-Is or ARBs alone.

The first evidence that omega-3 may reduce the risk of AF was reported by Mozafarian and colleagues,14 who observed in a large prospective, population-based cohort study that consumption of tuna and other broiled or baked fish is associated with lower incidence of AF among elderly adults. This observation has been confirmed and expanded by Virtanen and colleagues,20 who reported that higher serum concentration of n-3 PUFAs may be associated with a reduced risk of AF in middle-aged men and that this effect may be attributable mainly to docosahexaenoic acid.

To the best of our knowledge, our study is the first investigation showing that long-term treatment with n-3 PUFAs may exert beneficial effects in the prevention of recurrences in patients with persistent AF and a history of at least 1 relapse after previous successful cardioversion. Our results are at odds with those of a recently published randomized, multicenter trial in which n-3 PUFAs did not reduce the recurrence of symptomatic paroxysmal or persistent AF in patients without evidence of substantial structural heart disease.19 Several methodological factors may partly explain these discordant findings. First, our study enrolled patients with persistent AF independently of the presence of structural cardiac disorder was among the key exclusion criteria, and only a minority (≈18%) of patients had a

Table 1. Baseline Characteristics of Study Patients

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=99)</th>
<th>n-3 PUFAs (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>69±9</td>
<td>70±6</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>63 (63.6)</td>
<td>70 (70.0)</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>76.5±10.1</td>
<td>77.0±12.8</td>
</tr>
<tr>
<td>BMI, mean (SD), kg/m²</td>
<td>23.6±5.3</td>
<td>23.8±5.2</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mm Hg</td>
<td>136±16</td>
<td>134±20</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean (SD), mm Hg</td>
<td>82±9</td>
<td>82±10</td>
</tr>
<tr>
<td>Heart rate, mean (SD), bpm</td>
<td>85±19</td>
<td>86±15</td>
</tr>
</tbody>
</table>

Table 2. Amiodarone Therapy Before Electric Cardioversion in the De Novo Patients

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=55)</th>
<th>n-3 PUFAs (n=57)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean daily dose, mg</td>
<td>222 (0.7)</td>
<td>222 (0.9)</td>
<td>0.86</td>
</tr>
<tr>
<td>Mean cumulative dose, g</td>
<td>14.4 (0.4)</td>
<td>14.4 (0.5)</td>
<td>0.98</td>
</tr>
<tr>
<td>Time from enrollment to DCCV, mean (range), d</td>
<td>65 (61±68)</td>
<td>65 (61±70)</td>
<td>0.72</td>
</tr>
</tbody>
</table>

DCCV indicates direct current cardioversion. Data are expressed as mean (SD) when appropriate.

Table 3. Pharmacological and Direct Current Cardioversions

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=99)</th>
<th>n-3 PUFAs (n=100)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacological cardioversion, n (%)</td>
<td>2 (2)</td>
<td>4 (4)</td>
<td>0.68*</td>
</tr>
<tr>
<td>Successful direct current cardioversion, n</td>
<td>91 (97)</td>
<td>94 (96)</td>
<td></td>
</tr>
<tr>
<td>Cardioversion failure, n</td>
<td>6/97</td>
<td>2/96</td>
<td>0.257</td>
</tr>
<tr>
<td>Shock failure, n</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Immediate recurrence, n</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Shock distribution, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Shock</td>
<td>33 (33)</td>
<td>78 (78)</td>
<td></td>
</tr>
<tr>
<td>2 Shocks</td>
<td>54 (55)</td>
<td>16 (16)</td>
<td></td>
</tr>
<tr>
<td>3 Shocks</td>
<td>10 (10)</td>
<td>2 (2)</td>
<td></td>
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</tbody>
</table>

PUFAs indicates polyunsaturated fatty acids.

*Fisher exact test.
diagnosis of persistent AF. Even if the mechanisms underlying the pathogenesis of AF have not been completely elucidated, they may differ between the paroxysmal and the persistent form and may account for the differential response to therapy.21,22 Thus, it is reasonable to speculate that the beneficial effects of n-3 PUFAs may become clinically evident only in the presence of atrial remodeling.

Second, by design, n-3 PUFAs were given in addition to amiodarone, the most effective agent in preventing recurrences of AF,23 and either an ACE-I or an ARB. These latter drugs, alone24 or in combination with amiodarone,25,26 may reduce the incidence of AF and its recurrences by affecting renin-angiotensin-aldosterone system–mediated atrial remodeling.27,28 In contrast, in the Kowey et al19 study, the use of amiodarone was an exclusion criterion, and only ≈40% of patients were taking an ACE-I or an ARB. Our findings may suggest that n-3 PUFAs exert beneficial effects on AF recurrence over and above a combination of antiarrhythmic and antiremodeling therapy. However, we cannot exclude that the benefits of n-3 PUFAs on AF recurrence may become significant only in combination with membrane-active antiarrhythmic drugs, as well as with antiremodeling agents.

Third, in our study, follow-up was started immediately after DCCV, which was performed at least 4 weeks after the beginning of treatment. In contrast, patients in the Kowey et al19 trial were in sinus rhythm at the time of enrollment, and follow-up was begun at the start of study therapy. Experimental data suggest that the maximal incorporation of n-3 PUFAs in the myocardial cell membrane takes up to 28 days to occur.29 Therefore, it is possible that early recurrences, which accounted for nearly half of the events registered in the Kowey et al trial, may reflect an insufficient time for n-3 PUFAs to exert their full pharmacological effects rather than a lack of efficacy.

The findings of our investigation also differ from those of a recent study by Bianconi and colleagues,30 who reported no beneficial effects of n-3 PUFAs on the rate of recurrence after DCCV in patients with persistent AF. This discrepancy may be explained, at least in part, by pivotal differences in design between our study and that of Bianconi and colleagues. In particular, the duration of n-3 PUFAs therapy before DCCV was longer in our study (at least 4 weeks versus at least 1 week), and all of our patients were on long-term amiodarone therapy before DCCV. In contrast, antiarrhythmic drug therapy (with flecainide, propafenone, or sotalol as first choice and amiodarone as second choice) was left to the discretion of the local investigator in the Bianconi et al trial, so only ≈28% of patients were started on amiodarone after conversion to sinus rhythm. The potential relevance of these differences may be inferred by examining the event-free survival curve reported in the Bianconi et al article, which shows that the majority of recurrences occurred very early in follow-up (between 2 and 3 weeks), before the expected biological effects of n-3 PUFAs and amiodarone therapy.

Table 4. Intention-to-Treat Analysis of the Number of Shocks at Cardioversion

<table>
<thead>
<tr>
<th>Pharmacological Cardioversions</th>
<th>No. of Shocks*</th>
<th>Failed DCCV</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>2</td>
<td>33</td>
<td>5</td>
</tr>
<tr>
<td>n-3 PUFAs</td>
<td>4</td>
<td>77</td>
<td>15</td>
</tr>
</tbody>
</table>

DCCV indicates direct current cardioversion; PUFAs, polyunsaturated fatty acids.

*Shocks associated with restoration of sinus rhythm.†Wilcoxon rank sum test, n-3 PUFAs versus placebo.

Table 5. Recurrences and Time of Documentation

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=99, n (%))</th>
<th>n-3 PUFAs (n=100, n (%))</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic recurrences</td>
<td>25 (44.6)</td>
<td>15 (40.5)</td>
<td>0.96</td>
</tr>
<tr>
<td>Asymptomatic recurrences</td>
<td>31 (55.4)</td>
<td>22 (59.5)</td>
<td>0.98</td>
</tr>
<tr>
<td>Scheduled visit</td>
<td>21 (37.5)</td>
<td>14 (37.5)</td>
<td>0.86</td>
</tr>
<tr>
<td>Unscheduled visit</td>
<td>35 (62.5)</td>
<td>23 (62.2)</td>
<td>0.88</td>
</tr>
</tbody>
</table>

PUFAs indicates polyunsaturated fatty acids.

*χ² test.

Figure 2. Kaplan-Meier estimates of 1-year probability (Probal) of maintenance of sinus rhythm in the study groups. PUFAs indicates polyunsaturated fatty acids.
addition to antiarrhythmic therapy with amiodarone and renin-angiotensin-aldosterone system inhibition. Further studies are needed to confirm our findings and to determine whether treatment with n-3 PUFAs may prevent AF recurrence independently of antiarrhythmic therapy.

Sources of Funding
The study was funded by a grant from the ‘Centro per lo Studio ed il Trattamento dello Scompenso Cardiaco’ of the University of Brescia, Brescia, Italy. The work of Dr Campia was supported by National Institutes of Health grant K12 HL085790-01a1.

Disclosures
Dr Gheorghiade is a consultant for Bayer Schering Pharma AG, Debiopharm SA, Mobionic, Novartis, Otsuka Pharmaceuticals, Sigma-Tau Pharmaceuticals, Abbott, and PeriCor Therapeutics and has received travel compensation from Bayer Schering Pharma, Novartis, and Sigma-Tau Pharmaceuticals. The other authors report no conflicts.

References

Table 6. Correlates of Maintenance of Sinus Rhythm

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio</th>
<th>95% Confidence Limits</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-3 PUFA treatment</td>
<td>0.441</td>
<td>0.292–0.666</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AF duration</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3 vs 3–6 mo</td>
<td>1.479</td>
<td>0.838–2.610</td>
<td></td>
</tr>
<tr>
<td>&gt;3 vs &gt;6 mo</td>
<td>5.735</td>
<td>3.309–9.939</td>
<td></td>
</tr>
<tr>
<td>EF ≤45% vs &gt;45%</td>
<td>1.664</td>
<td>1.009–2.745</td>
<td>0.046</td>
</tr>
<tr>
<td>LA diameter</td>
<td>1.569</td>
<td>1.021–2.411</td>
<td>0.04</td>
</tr>
</tbody>
</table>

PUFAs indicates polyunsaturated fatty acids; AF, atrial fibrillation; EF, ejection fraction; and LA, left atrium.

*χ2 test.

The majority of patients enrolled in our study had evidence of structural heart disease. In univariate analysis, the duration of AF, left ventricular ejection fraction, and presence of atrial dilatation were significant correlates of AF recurrence. In the multivariable model, the use of n-3 PUFAs remained associated with the maintenance of sinus rhythm after adjustment for these potential confounding factors.

Potential Mechanisms of n-3 Polyunsaturated Fatty Acids in Atrial Fibrillation
Several mechanisms affecting electric and structural remodeling of the atria may underlie the effects of n-3 PUFAs in the prevention of AF. Omega-3 administration increases the concentration of eicosapentaenoic acid and docosahexaenoic acid in the cellular membrane of the myocyte,33 where they may modulate the activity of ion channels.32 Additionally, they can influence Ca2+ handling, as demonstrated in experiments conducted on rat atrial myocytes.33 Moreover, eicosapentaenoic acid and docosahexaenoic acid increase membrane fluidity, which may contribute to antiarrhythmic effects, as demonstrated by the prevention of isoproterenol-induced asynchronous contractile activity observed in atrial myocytes.34 These electrophysiological properties have been confirmed at the organ level in animal models of atrial remodeling.35–38

Study Limitations
Our patients had persistent AF with at least 1 recurrence and were treated with amiodarone and a renin-angiotensin-aldosterone system inhibitor. Therefore, the effect of n-3 PUFAs on the recurrence of AF in patients with persistent AF not on amiodarone and a renin-angiotensin-aldosterone system inhibitor cannot be inferred from our findings. In addition, because of the small number of subjects, a contribution by some of the other baseline variables to maintenance of sinus rhythm cannot be excluded.

Conclusions
In patients with persistent AF and at least 1 relapse after previous successful cardioversion, long-term treatment with n-3 PUFAs in addition to amiodarone and an ACE-I or ARB is more effective in maintaining sinus rhythm after DCCV than therapy with amiodarone and an ACE-I or ARB alone. Additionally, n-3 PUFAs appear to increase the length of time to first recurrence. Of note, n-3 PUFA treatment is not associated with relevant side effects. Our results suggest that n-3 PUFAs may exert beneficial actions on AF and may have a therapeutic role in the prevention of AF recurrence in
Atrial fibrillation (AF) is the most common sustained arrhythmia and represents a growing burden on the healthcare system. The prevalence of AF increases with age and has been estimated at 3.8% in persons 60 years of age and at 9.0% in those 80 years of age. Atrial fibrillation is associated with considerable morbidity and mortality, related mainly to increased risk of thromboembolic events and of new-onset or worsening heart failure. Treatment of AF remains controversial. Although rhythm control and rate control strategies seem to provide comparable results, restoration and maintenance of sinus rhythm would be the preferable pathophysiological approach. However, current pharmacological antiarrhythmic therapies have limited efficacy and poor safety profiles, and invasive or surgical treatments are indicated only in a minority of patients and are not free of failure and procedural risks. In this study, we tested the efficacy of n-3 polyunsaturated fatty acids in the prevention of AF recurrences in 199 patients with persistent AF on amiodarone and a renin-angiotensin inhibitor. Participants were randomized to n-3 polyunsaturated fatty acids 2 g/d or placebo followed, after at least 4 weeks, by direct current cardioversion. At 1 year, the probability of maintenance of sinus rhythm was significantly higher in the n-3 polyunsaturated fatty acids group than in the placebo group. Our results indicate that the addition of n-3 polyunsaturated fatty acids may exert beneficial effects in the prevention of AF recurrence.
n-3 Polyunsaturated Fatty Acids in the Prevention of Atrial Fibrillation Recurrences After Electrical Cardioversion: A Prospective, Randomized Study
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