Atrial fibrillation (AF) is the most common complication associated with coronary artery bypass graft surgery (CABG) (1). In addition, postoperative AF imparts an increased risk for other major complications after cardiac surgery, while also prolonging hospital length of stay, and increasing costs (1). Owing to such relevant clinical and economic implications, several studies have been undertaken in order to define effective pharmacological and nonpharmacological interventions for the prevention of this troublesome arrhythmia (2–4).

Recent experimental and clinical studies have shown that n-3 polyunsaturated fatty acids (PUFAs) may be effective in preventing cardiac arrhythmias and sudden death (5–25). In particular, PUFAs have shown significant antiarrhythmic effects on the atrial muscle in rat experimental models (24). Furthermore, the human consumption of fish inducing high plasma PUFA concentration has been associated with a lower incidence of AF in a 12-year follow-up study (25).

The aim of this study was to assess the efficacy and safety of preoperative and postoperative treatment with n-3 PUFAs in preventing the occurrence of AF after CABG.

**METHODS**

**Patients.** The study cohort consisted of 160 patients (136 men and 24 women; mean age, 65.6 ± 8.5 years) undergoing CABG. These patients were recruited from consecutive subjects referred to our institution from February 2003 to August 2004 for elective cardiac surgery. To be included in the study, patients needed to be older than 18 years of age, in normal sinus rhythm, and in stable hemodynamic conditions before surgery. Patients were excluded in the following cases: need for concomitant valvular surgery; prior history of any kind of supraventricular arrhythmias; current use of antiarrhythmic medications other than beta-receptor antagonists, calcium-channel antagonists, or digitalis. All enrolled patients provided written informed consent to take part in the investigation.

**Study design.** The study was planned as an open-label, prospective, randomized, controlled trial with parallel groups. The main goal of the study was to assess the effects of PUFAs in the prevention of the occurrence of AF after coronary surgery. The study protocol was approved by the ethics committee of our institution. Also, as currently used at our institution for investigator-initiated research that is not supported by any industrial grant, the ethics committee also served as the data safety committee.

Eligible patients were assigned to one of the two study groups. The main goal of the study was to assess the effects of PUFAs in the prevention of the occurrence of AF after coronary surgery. The study protocol was approved by the ethics committee of our institution. Also, as currently used at our institution for investigator-initiated research that is not supported by any industrial grant, the ethics committee also served as the data safety committee.

Eligible patients were assigned to one of the two study
arms according to a computer-generated randomization list: 1) control group (usual care); and 2) usual care plus PUFAs. Therapy with PUFAs, at the dosage of two capsules/day, was started immediately after randomization and continued for at least five days before surgery.

In the absence of evidence for preferred doses of treatments, we decided on the daily doses of n-3 PUFAs as two gelatin capsules containing 850 to 882 mg eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) as ethyl esters in the average ratio of EPA/DHA 1:2 (8,9). This pharmaceutical product is commercially available in Italy (Società Prodotti Antibiotici, Milan, Italy) and has already been used in other trials (8,9).

The administration of PUFAs in the immediate postoperative period (24 to 36 h) was done, if needed, through a nasogastric tube. Treatment with PUFAs continued until hospital discharge. Compliance was monitored by pill count and was 98%.

The study was not funded by any pharmaceutical company (except for the provision of PUFAs without costs).

Midline sternotomy procedures with standard surgical techniques for cardiopulmonary bypass in CABG were used. Nineteen patients underwent “off-pump” CABG. Myocardial protection was afforded with cold potassium cardioplegia.

After surgery patients were admitted to the intensive care unit and were subsequently transferred to a monitored intermediate care unit. In these two settings, continuous rhythm monitoring was performed for the first four to five postoperative days. The electrocardiographic data were stored for 24 h and reviewed on a daily basis by the cardiac surgery team. The printouts of all abnormal rhythms were also reviewed for any episodes of arrhythmia by the attending cardiologist. All printouts were included in clinical records.

After discharge from the monitored intermediate care unit to the cardiovascular ward, patients had an electrocardiogram daily until hospital discharge. Additionally, an electrocardiogram was also recorded in case of symptoms or when an arrhythmia was suspected on clinical grounds; AF episodes were always treated under the direction of the attending cardiologist.

After discharge all patients were asked to report to the outpatient department of our institution in case of any relevant symptom. Additionally, all patients had a follow-up visit four weeks after discharge, including physical examination and a 12-lead electrocardiogram.

**Study end points.** The primary end point of the study was the development of postoperative AF as detected by electrocardiography during the hospitalization period. Postoperative AF was defined as any electrocardiographically confirmed episode of AF for >5 min in duration or requiring intervention for angina or hemodynamic compromise. After an episode of AF or at hospital discharge, formal study participation ended, and the patient was withdrawn from any further analysis.

The secondary end point was the hospital length of stay after surgery. All end points were independently adjudicated after discharge by two cardiologists, blinded to treatment assignment, on the basis of clinical records and electrocardiographic tracings.

**Statistical analysis.** The primary analysis of all outcomes was by intention-to-treat. The occurrence of postoperative AF in the two treatment groups was tested with the odds ratio (OR) of the two-binomial proportion analysis.

The cumulative risk of occurrence of AF within each group was estimated by means of the Kaplan-Meier method. The survival curves of the two different treatment groups were then formally compared by use of the log-rank test.

Mean (± SD) were calculated for continuous variables, and frequencies were measured for categorical variables. Differences between groups were analyzed by an unpaired Student t test for continuous variables, while, in case of categorical variables, group differences were examined by chi-square or Fisher exact tests as appropriate. In particular, the Fisher exact tests was applied in case of an expected frequency of <5. A value of p < 0.05 was considered significant.

Sample size calculation was based on an expected 35% occurrence of postoperative AF in the control group and on an expected 20% occurrence of AF in the PUFA arm. Consequently, with a significance level of 0.05 and a test power of 0.80, the resulting sample size was 138 patients in each treatment group.

A stepwise logistic regression analysis was performed to select the predictors of AF after surgery. The model was built using variables that demonstrated a p value ≤0.10 in univariate analysis. The significance within the model was evaluated with the Wald statistical test. All tests were two-tailed and performed by SPSS 11.5 statistic software (Chicago, Illinois). According to the study protocol, an interim analysis of safety and efficacy was planned every six months during the study.

**RESULTS**

Enrollment was started in February 2003, and the third formal interim analysis was performed on August 30, 2004. By that time, 160 patients had been enrolled, and complete data were available for all patients. The interim
analysis showed a significant effect in favor of the PUFA group compared with controls (p = 0.013). Consequently, in accordance with the ethics committee of our institution, a decision was made to terminate enrollment. The study results were then reported as of September 12, 2004.

Of the 160 patients enrolled in the study, 81 were assigned by randomization to the control group and 79 to the PUFA group. The two groups were similar with regard to all clinical and surgical characteristics, as shown in Table 1.

The overall incidence of AF in the whole study sample was 24.4% (39 of 160 patients). Postoperative AF occurred in 15.2% (12 of 79) of the patients in the PUFA group compared with 33.3% (27 of 81) of those in the control group (OR 0.35; 95% confidence interval [CI] 0.16 to 0.76; p = 0.013). The consequent number of patients needed to treat was 5.51 (95% CI 3.43 to 20.40).

The Kaplan-Meier actuarial estimates of occurrence of postoperative AF in the study group are shown in Figure 1. Atrial fibrillation occurred a mean of 3.2 ± 1.1 days after surgery in patients assigned to PUFAs and 3.4 ± 1.3 days after surgery in controls (p = 0.645); AF was diagnosed during continuous electrocardiographic monitoring in the intensive or intermediate care units in 11 of 12 (91.6%) patients in the PUFA group and in 25 of 27 (92.5%) patients in the control group (p = 0.919 by chi-square). The remaining cases of AF (one in the PUFA group and two in the control group) were detected by electrocardiography after the occurrence of symptoms. The mean duration of AF was of 15.5 ± 15.8 h in patients assigned to PUFA and 23.9 ± 15.3 h in controls (p = 0.125). Symptoms attributable to AF were reported by 10 of 12 patients (83.3%) in the PUFA group and by 24 of 27 (88.8%) controls (p = 0.634 by chi-square); AF was initially treated by amiodarone in 9 of 12 patients assigned to PUFA and in 22 of 27 controls (p = 0.643 by chi-square). Spontaneous conversion to sinus rhythm without any intervention occurred in two patients receiving PUFAs and in three controls (p = 0.631 by Fisher exact test). Electrical cardioversion was performed on one patient in the PUFA group and in two controls (p = 0.920 by Fisher exact test).

Two of 12 (16.6%) patients in the PUFA group had more than one episode of AF during hospitalization (two episodes and three episodes, respectively), while 5 of 27 (18.5%) patients in the control group had more than one episode of AF (three patients had two episodes and two patients had three episodes) (p = 0.889 by Fisher exact test).

Four patients (two from the PUFA group and two controls) presented to the outpatient department owing to acute symptoms (dyspnea, fatigue, chest discomfort) after discharge and before the planned follow-up visit. In all of these cases, sinus rhythm was present.

Patients had a follow-up visit in the outpatient department 28 ± 8 days after surgery, and sinus rhythm was present in each patient.

In the multivariate analysis, two variables were noted to be significant independent predictors of postoperative AF: age (OR 1.08; 95% CI 1.01 to 1.15; p = 0.022) and the use of PUFAs (OR 0.32; 95% CI 0.10 to 0.98; p = 0.013).

### Table 1. Patients’ Clinical and Surgical Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n = 81)</th>
<th>PUFAs (n = 79)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, yrs</strong></td>
<td>64.9 ± 9.1</td>
<td>66.2 ± 8.0</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Male gender</strong></td>
<td>68 (84%)</td>
<td>68 (86%)</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>Systemic hypertension</strong></td>
<td>66 (81.5%)</td>
<td>62 (78.5%)</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>26 (32.1%)</td>
<td>26 (32.9%)</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>COP disease</strong></td>
<td>13 (16%)</td>
<td>13 (16.4%)</td>
<td>0.94</td>
</tr>
<tr>
<td><strong>Chronic renal failure</strong></td>
<td>7 (8.6%)</td>
<td>8 (10.1%)</td>
<td>0.74</td>
</tr>
<tr>
<td><strong>NYHA functional class</strong></td>
<td>1.6 ± 0.8</td>
<td>1.7 ± 0.8</td>
<td>0.43</td>
</tr>
<tr>
<td><strong>Previous myocardial infarction</strong></td>
<td>43 (53.1%)</td>
<td>41 (51.9%)</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Perioperative medication</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>46 (56.8%)</td>
<td>46 (58.2%)</td>
<td>0.98</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>25 (30.9%)</td>
<td>22 (27.8%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Nitrates</td>
<td>61 (75.3%)</td>
<td>60 (74.1%)</td>
<td>0.92</td>
</tr>
<tr>
<td>Diuretics</td>
<td>26 (32.1%)</td>
<td>24 (30.4%)</td>
<td>0.81</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>48 (59.3%)</td>
<td>46 (58.2%)</td>
<td>0.89</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>15 (18.5%)</td>
<td>18 (22.8%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Statins</td>
<td>44 (54.3%)</td>
<td>47 (59.4%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Acitelsalic acid</td>
<td>44 (54.3%)</td>
<td>47 (59.4%)</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>Ejection fraction,</strong>%</td>
<td>55.3 ± 11.4</td>
<td>56.3 ± 12.1</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>Left atrial AP dimension,</strong> mm</td>
<td>39.7 ± 5.2</td>
<td>39.7 ± 5.1</td>
<td>0.90</td>
</tr>
<tr>
<td><strong>Cardiopulmonary bypass time,</strong> min</td>
<td>96.7 ± 26.3</td>
<td>101 ± 27.4</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Aorta cross-clamp time,</strong> min</td>
<td>65.9 ± 22.1</td>
<td>66.6 ± 23.1</td>
<td>0.85</td>
</tr>
<tr>
<td><strong>Sapheneous vein grafts,</strong> no./patient</td>
<td>2.3 ± 1.1</td>
<td>2.4 ± 1.2</td>
<td>0.58</td>
</tr>
<tr>
<td><strong>Internal thoracic artery grafts,</strong> no./patient</td>
<td>0.9 ± 0.5</td>
<td>1.0 ± 0.3</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Off pump CABG</strong></td>
<td>10 (12.3%)</td>
<td>9 (11.4%)</td>
<td>0.95</td>
</tr>
</tbody>
</table>

*All comparisons for categorical variables were performed by chi-square analysis.

AP = anteroposterior; ACE = angiotensin-converting enzyme; CABG = coronary artery bypass surgery; COP = chronic obstructive pulmonary; NYHA = New York Heart Association; PUFAs = polyunsaturated fatty acids.
Influence of beta-blocker therapy. The use of beta-blockers did not influence the prevalence of AF in either study group. Of 79 patients on PUFAs, 46 (56.8%) were on beta-blockers. Of these, seven (15.2%) developed AF, whereas five (15.1%) of the patients not taking beta-blockers had AF. In the control group, the prevalence of AF was 34.8% (16 of 46 patients) among the patients on beta-blockers and 31.4% (11 of 35 patients) among those not receiving beta-blockers.

In-hospital morbidity and mortality. One patient in the PUFA group developed allergic skin rash on the first day of drug administration, and PUFAs were discontinued. Non-fatal postoperative complications occurred in seven (8.6%) patients of the control group (two acute renal failure, one pneumonia, two pneumotorax, one pulmonary edema, one gastrointestinal bleeding) and in five (6.3%) patients of the PUFA group (one acute renal failure, one implantation of permanent pacemaker, one pneumotorax, one adult respiratory distress syndrome, one redo for pericardial bleeding) (p = 0.8 by Fisher exact test). There were two deaths in the control group (2.5%) and one death in the PUFA group (1.3%) (p = 1.0 by Fisher exact test).

Length of hospital stay. Patients assigned to PUFAs had a shorter length of hospital stay as compared with controls (7.3 ± 2.1 days, 95% CI for mean 6.8 to 7.7 vs. 8.2 ± 2.6 days, 95% CI for mean 7.6 to 8.7, p = 0.017). When considering the overall population, patients with AF had a longer length of hospital stay than those without AF (9.4 ± 3.0 days, 95% CI for mean 8.4 to 10.3 vs. 7.2 ± 1.9 days, 95% CI for mean 6.8 to 7.5, p = 0.0004). In the PUFA group, the mean length of stay was 9.6 ± 3.1 days (95% CI for mean 7.5 to 11.5) for patients with AF and 6.9 ± 1.6 days (95% CI for mean 6.4 to 7.2) for those without AF (p = 0.01). In the control group, patients with AF also had a longer hospital stay as compared with those without AF (9.3 ± 2.9 days, 95% CI for mean 8.1 to 10.4 vs. 7.6 ± 2.2 days, 95% CI for mean 7.0 to 8.2, p = 0.01).

DISCUSSION

Main findings. In this trial, the use of PUFAs during hospitalization in patients undergoing CABG significantly reduced the incidence of postoperative AF (18.1% absolute risk reduction, 54.4% relative risk reduction) and was associated with a shorter hospital stay. Except for a single case of allergic response, no significant adverse reactions were observed.

Previous studies. The issue of prevention of postoperative AF in cardiac surgery was addressed by a number of studies. Several agents, including digitalis, calcium antagonists, procainamide, quinidine, and propafenone did not show any beneficial effect (1,26–29). A meta-analysis, which included 42 trials conducted before 2001, compared several agents (beta-blockers, sotalol, and amiodarone) with placebo (2). Beta-blockers (27 trials, 3,840 patients) were found to reduce the incidence of AF from 33% to 19%, while sotalol (8 trials, 1,294 patients) reduced the occurrence of the arrhythmia from 37% to 17%. In four comparative trials
(900 patients), sotalol scored better than conventional beta-blockers (12% incidence of AF vs. 22%). However, all trials employing beta-blockers or sotalol excluded patients with bradycardia and obstructive lung disease. Moreover, most studies excluded patients with depressed left ventricular function or heart failure. Amiodarone was evaluated in nine trials, including 1,384 patients, and reduced the occurrence of AF from 37% to 22.5%. Also, a recent trial compared amiodarone plus metoprolol, metoprolol alone, and sotalol with placebo. Only the combination therapy and sotalol reduced the relative risk of postoperative AF, respectively, by 45% and 41%.

In this study, the incidence of AF in the placebo group was of 33%, which is similar to the mean incidence of AF reported in the literature. In our study, PUFAs determined a reduction of the relative risk of postoperative AF of 54.4%, thereby favorably comparing with the 43% reduction obtained by beta-blockers, the 54% reduction observed with sotalol, and the 39% reduction associated with amiodarone use. In addition, differently from beta-blockers and sotalol, which can be associated with cases of significant bradycardia and persistent hypotension, PUFAs showed a particularly low incidence of adverse effects, and could be used in all patients, including those with respiratory insufficiency or heart failure.

The antiarrhythmic effect of PUFAs. Back in 1985, a study first reported that polyunsaturated alpha-linoleic acid lowered the arrhythmia threshold of the isolated rabbit heart. Several reports followed such initial findings and demonstrated that PUFAs may exert a protective effect against fatal ventricular arrhythmias in animal models after experimental coronary ligation. The electrophysiological basis of such effect has been clarified in other studies, showing at least three possible modes of action for the PUFAs on the myocyte: a slight hyperpolarization of the resting membrane potential, an increase of the current necessary to elicit an action potential, and an increase of the phase 4 refractory period. These effects were found to be related to an inhibition of the sodium current \(I_{Na}\), of the calcium current \(I_{Ca,L}\), and, possibly, of the potassium currents \(I_K\) and \(I_{to}\) (6). These effects account for an increased electrical stability that may result in a significant protection against fibrillation, which has been actually demonstrated in vitro.

Epidemiological surveys suggest that fish oil consumption may reduce the risk of fatal ventricular arrhythmias, consistently supporting an antiarrhythmic effect of PUFAs. The main hypothesis of our study was that the antiarrhythmic properties of PUFAs could also extend to the atrial myocardium, thereby protecting against the occurrence of AF. Actually, even if a previous study showed that PUFAs may reduce the asynchronous contractile activity of atrial myocytes, to date, the effects of PUFAs on supraventricular arrhythmias have not been fully investigated. In fact, our findings represent the first direct evidence that PUFA supplementation may, indeed, be effective in preventing AF. Furthermore, our findings are in keeping with a recent study in which the consumption of tuna, and other broiled or baked fish, was associated with a 30% lower incidence of AF in a 12-year follow-up. Interestingly, only the consumption of fish inducing higher concentrations of long chain n-3 fatty acids was associated with an antiarrhythmic effect, while the intake of fried fish or fish sandwiches did not induce higher plasma levels of PUFAs and did not show any protective effect against AF.

The anti-inflammatory hypothesis. A possible role of inflammation in the pathophysiology of postoperative AF has been repeatedly suggested, and the anti-inflammatory activity of PUFAs is now well-documented. There are several clinical studies reporting that PUFAs have beneficial effects in acute and chronic inflammatory diseases. Furthermore, it has been observed that EPA can act as a competitive inhibitor of arachidonic acid conversion to prostaglandin \(E_2\) and leukotriene \(B_4\), while a decreased synthesis of both of these eicosanoids has been observed after inclusion of fish oil in the diet. The inclusion of DHA in the diet may also result in decreased synthesis of leukotriene \(B_4\). As to the proinflammatory cytokines, it has been shown that dietary supplementation with encapsulated fish oil may result in a decreased monocyte synthesis of tumor necrosis factor-alpha and interleukin 1B in humans. Consequently, we can hypothesize that an anti-inflammatory action of PUFAs could play a role in the prevention of AF after cardiothoracic surgery.

Study limitations. The present study was not formally blinded; we acknowledge this as a limitation. However, this methodological limit should not have influenced the main results of the trial. In fact, two independent cardiologists, who were blinded to treatment allocation, formally adjudicated the primary end point of the study and computed the hospital length of stay on the basis of clinical records and electrocardiographic tracings after discharge. This approach somehow resembles that used in other trials, which employed a blinded end point committee.

Patients undergoing valvular surgery and patients with previous AF were excluded. Both valvular surgery and history of AF are factors that increase the risk of postoperative AF. Consequently, patients with these conditions were preliminarily excluded in order to avoid any possible confounding factor. The results of the present study are, therefore, applicable only to patients with no history of AF undergoing isolated CABG.

The patients in the PUFA group were hospitalized for significantly fewer days than those in the control group. Consequently, patients assigned to PUFA may possibly have had asymptomatic episodes of AF after discharge that were not identified. We also acknowledge this point as a potential limitation of the study.

Conclusions. n-3 Polyunsaturated fatty acid supplementations in patients undergoing isolated CABG significantly reduces the occurrence of postoperative AF, with an effect...
that is similar to that obtained with beta-blockers, sotalol, and amiodarone. In addition, PUFA supplementation is safe and can be administered to all patients undergoing CABG without the exclusion of any patient.

This is the first direct evidence of an atrial antiarrhythmic effect of PUFAs and may pave the way to other studies aimed at defining any possible atrial antifibrillatory effect of PUFAs in other clinical conditions.

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REFERENCES