Journal of the American College of Cardiology
© 2005 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 45, No. 10, 2005
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2005.02.079

N-3 Fatty Acids for the Prevention of Atrial Fibrillation After Coronary Artery Bypass Surgery

A Randomized, Controlled Trial

Leonardo Calò, MD, FESC, Leopoldo Bianconi, MD, Furio Colivicchi, MD, FESC, Filippo Lamberti, MD, Maria Luisa Loricchio, MD, Ermenegildo de Ruvo, MD, Antonella Meo, MD, Claudio Pandozi, MD, FESC, Mario Staibano, MD, Massimo Santini, MD, FESC, FACC

Rome, Italy

OBJECTIVES The aim of this study was to assess the efficacy of preoperative and postoperative treatment with n-3 polyunsaturated fatty acids (PUFAs) in preventing the occurrence of atrial fibrillation (AF) after coronary artery bypass graft surgery (CABG).

BACKGROUND Postoperative AF is a common complication of CABG. There is growing clinical evidence that PUFAs have cardiac antiarrhythmic effects.

METHODS A total of 160 patients were prospectively randomized to a control group (81 patients, 13 female, 64.9 ± 9.1 years) or PUFAs 2 g/day (79 patients, 11 female, 66.2 ± 8.0 years) for at least 5 days before elective CABG and until the day of discharge from the hospital. The primary end point was the development of AF in the postoperative period. The secondary end point was the hospital length of stay after surgery. All end points were independently adjudicated by two cardiologists blinded to treatment assignment.

RESULTS The clinical and surgical characteristics of the patients in the two groups were similar. Postoperative AF developed in 27 patients of the control group (33.3%) and in 12 patients of the PUFA group (15.2%) ($p = 0.013$). There was no significant difference in the incidence of nonfatal postoperative complications, and postoperative mortality was similar in the PUFA-treated patients (1.3%) versus controls (2.5%). After CABG, the PUFA patients were hospitalized for significantly fewer days than controls (7.3 ± 2.1 days vs. 8.2 ± 2.6 days, $p = 0.017$).

CONCLUSIONS This study first demonstrates that PUFA administration during hospitalization in patients undergoing CABG substantially reduced the incidence of postoperative AF (54.4%) and was associated with a shorter hospital stay. (J Am Coll Cardiol 2005;45:1723–8) © 2005 by the American College of Cardiology Foundation

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 PUFA in preventing the occurrence of AF after CABG.

From the Department of Cardiac Diseases, San Filippo Neri Hospital, Rome, Italy.
Manuscript received January 20, 2005; revised manuscript received February 18, 2005, accepted February 22, 2005.

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

JACC Vol. 45, No. 10, 2005
May 17, 2005:1723–8

Abbreviations and Acronyms

AF = atrial fibrillation
CABG = coronary artery bypass graft surgery
CI = confidence interval
DHA = docosahexaenoic acid
EPA = eicosapentaenoic acid
OR = odds ratio
PUFA = n-3 polyunsaturated fatty acid

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