ONLINE FIRST

Fish Oil and Postoperative Atrial Fibrillation

The Omega-3 Fatty Acids for Prevention of Post-operative Atrial Fibrillation (OPERA) Randomized Trial

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Context Postoperative atrial fibrillation or flutter (AF) is one of the most common complications of cardiac surgery and significantly increases morbidity and health care utilization. A few small trials have evaluated whether long-chain n-3-polyunsaturated fatty acids (PUFAs) reduce postoperative AF, with mixed results.

Objective To determine whether perioperative n-3-PUFA supplementation reduces postoperative AF.

Design, Setting, and Patients The Omega-3 Fatty Acids for Prevention of Postoperative Atrial Fibrillation (OPERA) double-blind, placebo-controlled, randomized clinical trial. A total of 1516 patients scheduled for cardiac surgery in 28 centers in the United States, Italy, and Argentina were enrolled between August 2010 and June 2012. Inclusion criteria were broad; the main exclusions were regular use of fish oil or absence of sinus rhythm at enrollment.

Intervention Patients were randomized to receive fish oil (1-g capsules containing ≥840 mg n-3-PUFAs as ethyl esters) or placebo, with preoperative loading of 10 g over 3 to 5 days (or 8 g over 2 days) followed postoperatively by 2 g/d until hospital discharge or postoperative day 10, whichever came first.

Main Outcome Measure Occurrence of postoperative AF lasting longer than 30 seconds. Secondary end points were postoperative AF lasting longer than 1 hour, resulting in symptoms, or treated with cardioversion; postoperative AF excluding atrial flutter; time to first postoperative AF; number of AF episodes per patient; hospital utilization; and major adverse cardiovascular events, 30-day mortality, bleeding, and other adverse events.

Results At enrollment, mean age was 64 (SD, 13) years; 72.2% of patients were men, and 51.8% had planned valvular surgery. The primary end point occurred in 233 (30.7%) patients assigned to placebo and 227 (30.0%) assigned to n-3-PUFAs (odds ratio, 0.96 [95% CI, 0.77-1.20]; $P=.74$). None of the secondary end points were significantly different between the placebo and fish oil groups, including postoperative AF that was sustained, symptomatic, or treated (231 [30.5%] vs 224 [29.6%], $P=.70$) or number of postoperative AF episodes per patient (1 episode: 156 [20.6%] vs 157 [20.7%]; 2 episodes: 59 [7.8%] vs 49 [6.5%]; ≥3 episodes: 18 [2.4%] vs 21 [2.8%]) ($P=.73$). Supplementation with n-3-PUFAs was generally well tolerated, with no evidence for increased risk of bleeding or serious adverse events.

Conclusion In this large multinational trial among patients undergoing cardiac surgery, perioperative supplementation with n-3-PUFAs, compared with placebo, did not reduce the risk of postoperative AF.

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POSTOPERATIVE ATRIAL FIBRILLATION or flutter (AF) occurs in approximately 1 of 3 patients undergoing cardiac surgery, and rates of this complication remain unchanged, even with advances in surgical techniques, anesthetic procedures, and perioperative care.[1,2] Postoperative AF can cause hemodynamic instability or symptoms requiring cardioversion or escalation of supportive therapies and also can cause renal and neurologic complications. Antiarrhythmic and anticoagulant drugs are often required, both in-hospital and after discharge, and can cause adverse effects including bleeding. Postoperative AF at discharge can cause palpitations, fatigue, and decreased exercise tolerance. Patients with postoperative AF also have higher long-term mortality,[1,2] at least partly attributable to embolic stroke.[3]

Postoperative AF is also associated with greater intensive care unit stays, total hospital stays, and total hospital costs.[4-6] Even with use of β-blockers and amiodarone, approximately 1 of 4 patients still develop postoperative AF, with inconsistent improvements in mortality or resource utilization.[7] Hence, new therapies are needed to

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prevent postoperative AF and its associated morbidity and health care costs.

The accumulated evidence from observational studies and clinical trials suggests that habitual intake of fish or fish oil reduces risk of coronary death, possibly related to fewer primary ventricular arrhythmias.[8,9] Experimental evidence supports direct and indirect antiarrhythmic effects of long-chain n-3 polyunsaturated fatty acids (n-3-PUFAs) in fish oil, especially in the setting of acute ischemia.[8] Yet effects of n-3-PUFAs on atrial arrhythmias such as postoperative AF remain uncertain. In experimental studies and short-term clinical trials, n-3-PUFAs favorably influence several risk factors for AF.[8,10-12] Only small trials of n-3-PUFA supplementation to prevent postoperative AF have been performed, with mixed results.[13]

We designed and implemented the Omega-3 Fatty Acids for Prevention of Post-operative Atrial Fibrillation (OPERA) trial to determine whether perioperative administration of oral n-3-PUFAs reduces postoperative AF in patients undergoing cardiac surgery.

METHODS

Study Design and Patients

The OPERA trial was an investigator-initiated, double-blind, placebo-controlled, randomized clinical trial conducted in 28 centers in the United States, Italy, and Argentina to test the primary hypothesis that perioperative n-3-PUFA supplementation reduces the occurrence of postoperative AF in 1516 patients undergoing cardiac surgery. The detailed methods have been published.[14] The design was pragmatic to maximize practical application and generalizability to real-world patients and clinical care.

Inclusion criteria were broad (eTable 1, available at http://www.jama.com), including age 18 years or older, being scheduled for cardiac surgery on the following day or later, and presence of sinus rhythm on the screening electrocardiogram (ECG). Exclusions were absence of sinus rhythm at screening, regular use of fish oil, known allergy or intolerance to fish oil or olive oil, being currently pregnant, existing or planned cardiac transplant or use of ventricular assist device, or being unable or unwilling to provide informed consent. Use of chronic or prophylactic antiarrhythmic drugs, history of prior AF, and planned AF ablation were not exclusions, given the similar or higher risk of postoperative AF in these patients and no known biologic interaction that might reduce efficacy of n-3-PUFAs in such patients.

The study was approved by the human subjects committees of all participating institutions and conducted according to international standards of Good Clinical Practice (FDA Title 21 part 312, International Conference on Harmonization guidelines). All patients provided written informed consent.

Intervention

Patients were block randomized to receive n-3-PUFAs; each 1-g capsule contained at least 840 mg of eicosapentaenoic acid (EPA) (approximately 465 mg) plus docosahexaenoic acid (DHA) (approximately 375 mg) as ethyl esters (Omacor; Pronova BioPharma, Norway) or matched placebo (olive oil) by means of computer-generated numbers, stratified by enrolling medical center and planned valve surgery (yes/no). Study drugs were prepared in identical-appearing capsules specially coated to minimize taste differences. All investigators, patients, and clinicians were blinded to treatment assignment.

Patients received a total preoperative loading dose of 10 g divided over 3 to 5 days (or 8 g divided over 2 days), including the morning of surgery.[14] For each patient, the loading dose was divided over the maximum number of days possible, based on the dates of enrollment and planned surgery. Flexibility in the loading days included in the regimen maximized generalizability by allowing enrollment of most patients undergoing cardiac surgery, including those scheduled as early as the next day. Following cardiac surgery, patients received 2 g/d until hospital discharge or postoperative day 10, whichever occurred sooner, at which time administrative censoring occurred for in-hospital follow-up.

The dosing was selected to balance potential efficacy vs patient intolerance and risk. Cohort studies suggest that n-3-PUFAs reduce risk of primary ventricular arrhythmias at low doses, eg, 250 to 500 mg/d of EPA plus DHA.[8] Similar low dietary doses have been associated with lower incident AF in ambulatory adults,[15] and, in 1 small open-label trial, a 10-g preoperative loading dose over 5 days followed by 2 g/d postoperatively reduced postoperative AF.[16] Supplementation with n-3-PUFAs alters circulating and tissue levels of EPA and DHA within days.[17] Because n-3-PUFAs persist in tissues for several days, a loading dose also provides some buffer in patients who might not tolerate oral medications for several days after surgery. Higher doses could increase patient dyspepsia as well potential concern among treating physicians for risks such as bleeding.

For patients unable to tolerate oral medications postoperatively, the study drug could be administered via polyvinyl chloride–free nasogastric or gastric tube if present for clinical indications or otherwise as soon as the patient was tolerating oral medications. Adherence was monitored by capsule count for outpatient loading and by hospital records for inpatient administration as well as by changes in plasma phospholipid n-3-PUFA levels (see "Covariates," below).

Centers were encouraged to use continuous electrocardiographic monitoring for at least 5 days post surgery. Twelve-lead ECGs were recommended daily and more frequently at the discretion of the treating physicians for symptoms or clinically suspected arrhythmia. Clinical data (eg, onset time, symptoms, treatments, duration) and confirmatory rhythm strips or 12-lead ECGs were collected for all postoperative arrhythmias of at least 30 seconds' duration, including postoperative AF

and other tachyarrhythmias (eTable 2). Data on at least the first 3 suspected episodes of postoperative AF were collected for each patient. All other treatments, including surgical and anesthetic procedures, medications including regular or prophylactic antiarrhythmic drugs, and treatment of arrhythmias remained entirely at the discretion of the physicians caring for the patient. Current best-practice guidelines for prevention of postoperative AF were strongly recommended to all centers.[18]

End Points

The primary end point was the occurrence of postoperative AF of at least 30 seconds' duration and documented by rhythm strip or 12-lead ECG (eTable 2). Secondary AF end points included postoperative AF that was sustained (>1 hour), symptomatic, or treated with pharmacological or electrical cardioversion; postoperative AF excluding atrial flutter; time to first postoperative AF; and the number of postoperative AF episodes per patient. The OPERA trial also evaluated the total number of in-hospital days in which any postoperative AF, including sustained postoperative AF, was present and the proportion of in-hospital days free of any postoperative AF. All potential episodes of postoperative AF and other tachyarrhythmias were reviewed and adjudicated by a centralized events committee of cardiac electrophysiologists. Additional end points included resource utilization, major adverse cardiovascular events, arterial thromboembolism, and 30-day mortality.

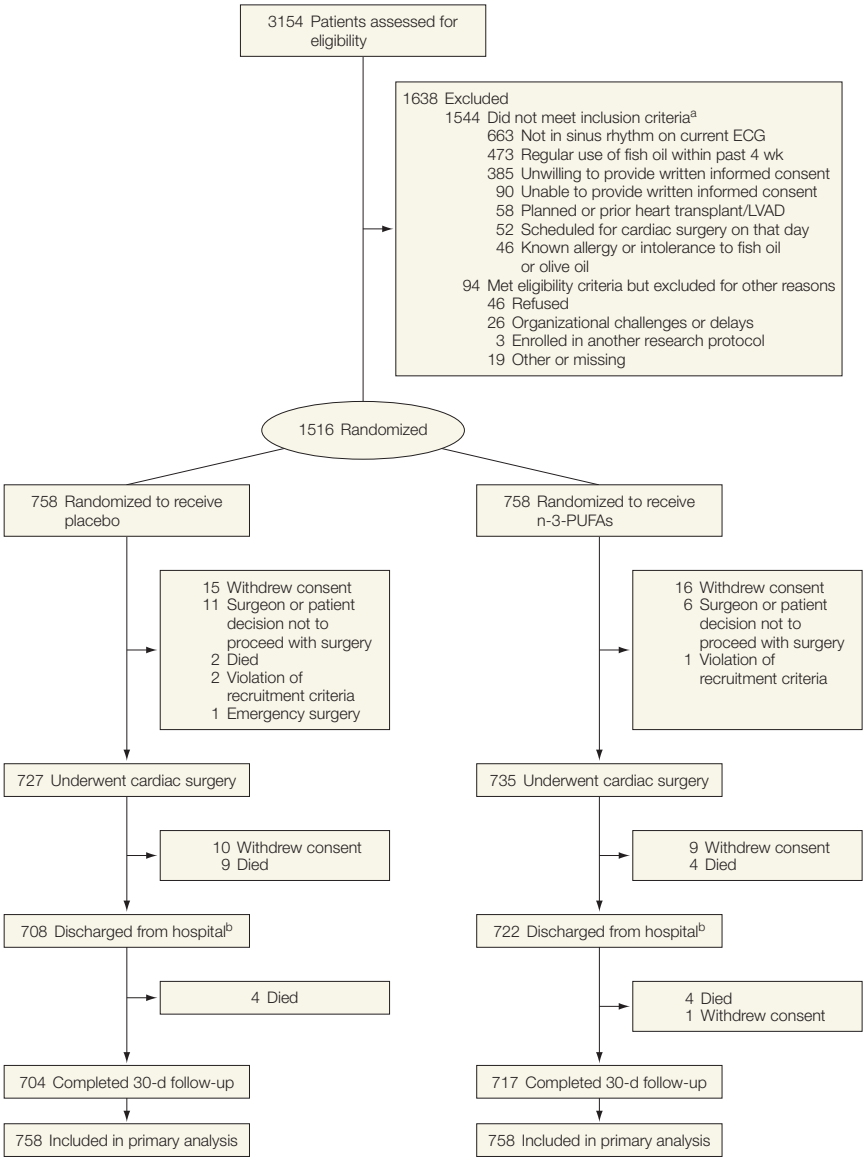
Safety Evaluation

Safety outcomes included adverse events and bleeding assessed by 24-hour chest tube output following surgery, total packed red blood cell transfusions, and composite bleeding indices (eTable 2). Potential adverse events were recorded and reported to the steering committee and the independent data and safety monitoring board (DSMB), as well as to the US Food and Drug Administration, European Medicines Agency, and Argentina National Administration of Drugs, Foods and Medical Devices. The steering committee monitored the progress of the trial, and the DSMB monitored both scientific integrity and patient safety throughout the trial and could recommend termination or other trial modifications at any time. In July 2011, the DSMB reviewed a detailed interim analysis prepared by a biostatistician not affiliated with the trial and recommended study continuation.

Covariates

Standardized data were collected on demographics, risk factors, major comorbid conditions, past medical and surgical history, anthropometry, lifestyle habits, outpatient and inpa-

Figure 1. Screening, Randomization, and Follow-up



No patients were lost to follow-up. ECG indicates electrocardiogram; LVAD, left-ventricular assist device; n-3-PUFA, omega-3 polyunsaturated fatty acid.
[a] Patients could be excluded based on more than 1 criterion; all are listed.
[b] Includes patients (102 placebo; 104 n-3-PUFA) censored at postoperative day 10 rather than discharged.

tient medications, and laboratory measures. Details of the surgical and anesthetic procedure were recorded. Daily follow-up and discharge information, including cardiac drug use and bleeding end points, was recorded. In a subset of 523 patients from centers participating in biologic studies, samples of EDTA plasma were drawn at enrollment and on the morning of cardiac surgery, stored at –70°C, and shipped on dry ice to a central repository for long-term storage at –80°C. Levels of plasma phospholipid n-3-PUFAs (EPA plus docosapentaenoic acid [DPA] plus DHA) were measured as a percentage of total fatty acids at the Fred Hutchinson Cancer Research Center (Seattle, Washington) using established methods,[19] with coefficients of variation of less than 3% for EPA, DPA, and DHA.

Table 1. Baseline Characteristics of the OPERA Participants, According to Treatment Assignment

Characteristic	No. (%) Placebo (n = 758)	No. (%) n-3-PUFAs (n = 758)	*P* Value[a]
Age, mean (SD), y	63.6 (12.4)	63.8 (12.6)	.75
Men	543 (71.6)	551 (72.7)	.65
Planned valve surgery[b]	389 (51.3)	396 (52.2)	.72
Current smoking	96 (13.0)	99 (13.5)	.78
Body mass index, mean (SD)[c]	28.4 (5.9)	28.1 (5.4)	.30
Waist circumference, mean (SD), cm	99.4 (13.5)	98.8 (14.1)	.16
Hypertension	563 (74.9)	572 (76.2)	.56
Dyslipidemia	477 (64.1)	460 (61.7)	.33
Diabetes mellitus	199 (26.3)	194 (25.7)	.78
Chronic obstructive pulmonary disease	90 (11.9)	80 (10.6)	.42
Chronic renal failure	52 (6.9)	44 (5.8)	.40
Coronary heart disease[d]	288 (38.0)	297 (39.2)	.64
Prior myocardial infarction	178 (23.6)	188 (25.0)	.55
Prior percutaneous coronary intervention	99 (13.1)	80 (10.6)	.13
Prior cardiac surgery	48 (6.3)	45 (5.9)	.75
Coronary bypass	18 (2.4)	17 (2.2)	.86
Valve surgery	27 (3.6)	23 (3.0)	.57
Other cardiac surgery	12 (1.6)	13 (1.7)	.84
Prior arrhythmias	99 (13.3)	92 (12.5)	.64
Atrial fibrillation	62 (8.4)	52 (7.1)	.35
Other supraventricular tachycardia	8 (1.1)	12 (1.6)	.40
Ventricular tachycardia or fibrillation	5 (0.7)	7 (0.9)	.51
Other	33 (4.5)	22 (3.0)	.14
Congestive heart failure	212 (28.0)	204 (27.0)	.66
NYHA class			.16
I	10 (1.3)	4 (0.5)	
II	104 (13.7)	100 (13.2)	
III	61 (8.1)	77 (10.2)	
IV	12 (1.6)	8 (1.1)	
Not available	25 (3.3)	15 (2.0)	
Ejection fraction, mean (SD), %	56.8 (11.3)	56.6 (11.4)	.67
Left atrial diameter, mean (SD), mm	42.2 (7.6)	42.1 (7.8)	.77
Prior implantable cardiodefibrillator	11 (1.5)	5 (0.7)	.13
Prior pacemaker	9 (1.2)	11 (1.5)	.54
Prior cardiac resynchronization therapy	0	1 (0.1)	.50
Prior AF ablation	6 (0.8)	6 (0.8)	>.99
EuroSCORE, median (IQR)[e]			
Logistic	3.6 (1.8-7.2)	3.7 (2.0-7.5)	.64
Additive	5.0 (3.0-7.0)	5.0 (3.0-7.0)	.68

Abbreviations: AF, atrial fibrillation; EuroSCORE, European System for Cardiac Operative Risk Evaluation; IQR, interquartile range; n-3-PUFA, omega-3 polyunsaturated fatty acid; NYHA, New York Heart Association; OPERA, Omega-3 Fatty Acids for Prevention of Post-operative Atrial Fibrillation.

[a] Differences between treatment groups were evaluated using unpaired *t* tests or Wilcoxon rank-sum tests, as appropriate, for continuous variables; and Pearson χ^2 (or Fisher exact tests for cells <10) for categorical variables.

[b] Of the 756 patients who underwent valve surgery, 522 (69.0%) underwent aortic valve surgery, 195 (28.8%) mitral valve surgery, 30 (4.0%) aortic and mitral valve surgery, and 9 (1.2%) other valve surgery; see eTable 3.

[c] Calculated as weight in kilograms divided by height in meters squared.

[d] Prior myocardial infarction, coronary revascularization, or angina.

[e] Incorporates 17 predictive factors about the patient, comorbid conditions, and the planned operation to calculate the risk of 30-day postoperative mortality.[20,21] The EuroScore can be calculated using either a logistic or additive model, with higher scores indicating higher risk. The logistic model (theoretical range, 0-100) provides a score that is directly equivalent to the predicted 30-day mortality (percent). The additive model (theoretical range, 0-39) is a simplified version that approximates the predicted 30-day mortality. Values for the 17 individual components of these scores were also well balanced between treatment groups (eTable 4).

Statistical Analysis

All analyses were prespecified prior to closing of the study database. The main analysis was by intention-to-treat, including all patients according to treatment assigned at randomization. The primary end point was evaluated using Pearson χ^2 (for 2 groups, equivalent to binomial test of proportions). Logistic regression was used to determine the odds ratio and 95% CI and for secondary multivariate analyses and tests of interaction. Survival analyses and the log-rank test were used for incident postoperative AF and major adverse cardiovascular events, arterial thromboembolism, and mortality. In all analyses, missing values were not imputed, and only observed values were used. All patients who withdrew or died were included in all analyses until their date of death or withdrawal. A sensitivity analysis considered all patients who died, withdrew, or were otherwise lost to follow-up before hospital discharge or postoperative day 10, whichever came first, as having had postoperative AF.

Planned enrollment of 1516 patients provided 90% power to detect a 25% reduction in postoperative AF with 2-tailed $\alpha = .05$, based on an estimated 30% event rate in controls and 5% dropout. The control event rate was estimated from prior studies of postoperative AF,[1,2] and the 25% reduction as a reasonable minimum clinically meaningful risk reduction that was also con-

siderably more conservative than in earlier studies.[16]

Secondary multivariable analyses were prespecified, adjusted for age, sex, country, type of cardiac surgery, use of perioperative antiarrhythmic drugs, and any baseline characteristics that were statistically different between treatment groups at $P \leq .15$. In addition to intention-to-treat analyses, we also secondarily evaluated the surgical population (the subset of patients who were enrolled without protocol violation, received at least 1 dose of study drug, and underwent cardiac surgery) and the adherent (on-treatment) population (the subset of the surgical population who took ≥80% of their loading dose [or ≥75% for patients who received study drug loading over 2 days] and also ≥80% of all assigned study capsules over the course of the study until the onset of the primary end point or the end of assigned treatment, whichever occurred first).

We hypothesized stronger efficacy of treatment in 3 prespecified subgroups: those with lower habitual consumption of oily fish (<2 vs ≥2 servings/wk), lower plasma phospholipid n-3-PUFA levels at enrollment (<4% vs ≥4%, also evaluated continuously using semiparametric restricted cubic splines), and greater number of actual study drug loading days (0 to 5 actual days, evaluated ordinally). Interaction by these subgroups was evaluated at 2-tailed $\alpha = .05$. Other subgroup analyses (eAppendix), also prespecified but considered exploratory (ie, no hypothesized direction of interaction) and based on lower statistical power to detect interaction, were evaluated at 2-tailed $\alpha = .10$. Analyses were performed using Stata version 12.1 (College Station, Texas).

RESULTS

Between August 2010 and June 2012, 1516 patients were enrolled (FIGURE 1). Formal screening logs were maintained, and 48% of all screened patients and 94% of all eligible patients were enrolled. Ineligible patients were most often excluded because they were not in sinus rhythm (40.5%), were taking fish oil (28.9%), or were unwilling to provide informed consent (23.5%). At baseline, mean age was 64 (SD, 13) years; 1094 patients (72.2%) were men, and cardiovascular risk factors were common (TABLE 1 and TABLE 2). Valve surgery was planned in 785 patients (51.8%); of the 756 who underwent valve surgery, 522 (69.0%) underwent aortic valve surgery, 195 (25.8%) mitral valve surgery, 30 (4.0%) aortic and mitral valve surgery, and 9 (1.2%) other valve surgery. The median logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation)[20,21] value was 3.7 (interquartile range [IQR], 1.9-7.4). The treatment groups had evenly matched characteristics.

Table 2. Baseline Medication Use of the OPERA Participants, According to Treatment Assignment

Medication	No. (%) Placebo (n = 758)	No. (%) n-3-PUFAs (n = 758)	*P* Value[a]
β-Blocker	433 (57.2)	444 (58.6)	.57
Statin	427 (56.3)	436 (57.5)	.64
ACE inhibitor	274 (36.2)	284 (37.5)	.59
Angiotensin II receptor blocker	103 (13.6)	114 (15.0)	.42
Calcium channel blocker	122 (16.1)	132 (17.4)	.49
Loop diuretics	168 (22.2)	190 (25.1)	.19
Aldosterone antagonists	37 (4.9)	28 (3.7)	.25
Digitalis	2 (0.3)	14 (1.9)	.004
Antiplatelets or anticoagulants	473 (62.4)	455 (60.0)	.34
Antiplatelets	407 (53.7)	389 (51.3)	.36
Aspirin	396 (52.2)	378 (49.9)	.36
Clopidogrel	53 (7.0)	62 (8.2)	.38
Ticlopidine	5 (0.7)	4 (0.5)	>.99
Other	5 (0.7)	4 (0.5)	>.99
Anticoagulants	129 (17.0)	121 (16.0)	.58
Warfarin	24 (3.2)	17 (2.2)	.27
Heparin	105 (13.9)	103 (13.6)	.88
Other	1 (0.1)	1 (0.1)	>.99
Antiarrhythmics			
Amiodarone	28 (3.7)	30 (4.0)	.78
Other[b]	12 (1.6)	14 (1.9)	.69

Abbreviations: ACE, angiotensin-converting enzyme; OPERA, Omega-3 Fatty Acids for Prevention of Post-operative Atrial Fibrillation.
[a] Differences between treatment groups were evaluated using Pearson χ^2 (or Fisher exact tests for cells <10).
[b] Including flecainide, propafenone, quinidine, disopyramide, or sotalol.

Following randomization and study drug loading, 96.4% of patients underwent cardiac surgery. Details of the surgical procedure and postoperative medications are reported in eTable 3. Postoperative medications were similar by treatment group and included β-blockers in 76.9% of patients overall and amiodarone in 36.9% after cardiac surgery.

The primary end point occurred in 233 patients (30.7%) in the placebo group and 227 (30.0%) in the n-3-PUFA group ($P = .74$). None of the secondary postoperative AF end points or other arrhythmias were significantly different by treatment group (TABLE 3 and FIGURE 2). In-hospital major adverse cardiovascular events occurred in 20 patients (2.6%) in the placebo group and in 13 (1.7%) in the n-3-PUFA group ($P = .18$). At 30 days, 15 patients (2.0%) in the placebo group and 8 (1.1%) in the n-3-PUFA group had died ($P = .14$). Incidence of the secondary end points of arterial thromboembolism and arterial thromboembolism or death was significantly lower in the n-3-PUFA group ($P = .047$ and $P = .01$, respectively). The total number of days in the intensive care unit or coronary care unit, of te-

lemetry monitoring, or of total hospital stay did not differ significantly between groups.

Most postoperative AF events occurred between postoperative days 1 to 4, peaking on day 2 (eFigure). Among all 661 episodes, 353 lasted less than 1 day (median duration, 3.3 hours [IQR, 1.2-7.7 hours]), and 308 lasted 1 day or longer (median duration, 1.0 day [IQR, 1.0-3.0 days]). There were no significant differences in duration by treatment (Wilcoxon rank-sum $P=.25$). Thirty-two patients in the placebo group and 30 in the n-3-PUFA group were discharged with persistent postoperative AF.

In sensitivity analyses defining all patients who died or withdrew consent as having had postoperative AF, 266 patients (35.1%) in the placebo group and 250 (33.0%) in the n-3-PUFA group developed postoperative AF ($P=.39$). Findings were similar in multivariable analyses adjusted for age, sex, country, type of cardiac surgery, use of perioperative antiarrhythmic drugs, and baseline characteristics differing between groups (eAppendix).

Table 3. Primary and Secondary Study Outcomes in OPERA, According to Treatment Assignment.

Outcome	No. (%) Placebo (n = 758)	No. (%) n-3-PUFAs (n = 758)	OR or HR (95% CI)[a]	*P* Value[b]
Any first postoperative AF, primary end point[c]	233 (30.7)	227 (30.0)	0.96 (0.77-1.20)	.74
Postoperative AF, secondary end points				
Sustained, symptomatic, or treated postoperative AF[d]	231 (30.5)	224 (29.6)	0.96 (0.77-1.19)	.70
Postoperative AF excluding flutter[e]	220 (29.0)	217 (28.6)	0.98 (0.79-1.23)	.87
No. of postoperative AF episodes				
1	156 (20.6)	157 (20.7)	NA	.73
2	59 (7.8)	49 (6.5)		
≥3	18 (2.4)	21 (2.8)		
Total in-hospital days with any postoperative AF, mean (SD)[f]	2.75 (2.1)	2.84 (2.1)	NA	.58
Proportion of in-hospital days free of any postoperative AF, %	89.0	88.7	NA	.88
Other arrhythmias				
Other supraventricular tachycardia	6 (0.8)	11 (1.5)	1.85 (0.68-5.02)	.33
Ventricular tachycardia or fibrillation	9 (1.2)	5 (0.7)	0.55 (0.18-1.66)	.42
Other end points				
MACEs, in-hospital[g]	20 (2.6)	13 (1.7)	0.62 (0.31-1.25)	.18
Myocardial infarction	10 (1.3)	10 (1.3)	0.99 (0.41-2.39)	>.99
Stroke	8 (1.1)	4 (0.5)	0.45 (0.13-1.51)	.18
Cardiovascular death	3 (0.4)	0 (0.0)	NA	.08
Arterial thromboembolism, 30-d	13 (1.7)	5 (0.7)	0.37 (0.13-1.03)	.047
Arterial thromboembolism or death, 30-d	27 (3.6)	13 (1.7)	0.44 (0.24-0.86)	.01
Total mortality, 30-d	15 (2.0)	8 (1.1)	0.53 (0.23-1.26)	.14
Cardiac arrhythmic	0 (0.0)	1 (0.1)	NC[h]	.32
Cardiac nonarrhythmic	2 (0.3)	0 (0.0)	NC[h]	.16
Vascular	3 (0.4)	0 (0.0)	NC[h]	.08
Noncardiovascular	10 (1.3)	7 (0.9)	0.70 (0.27-1.84)	.47
Resource utilization, median (IQR), d				
Total ICU/CCU stay	2 (1-3)	2 (1-3)	NA	.38
Total telemetry monitoring	6 (5-7)	6 (5-7)	NA	.39
Total hospital stay	7 (5-8)	7 (5-9)	NA	.48

Abbreviations: AF, atrial fibrillation; HR, hazard ratio; ICU/CCU, intensive care unit/coronary care unit; IQR, interquartile range; MACEs, major adverse cardiac events (myocardial infarction, stroke, or cardiovascular death); NA, not applicable; NC, not calculable; n-3-PUFA, omega-3 polyunsaturated fatty acid; OPERA, Omega-3 Fatty Acids for Prevention of Post-operative Atrial Fibrillation; OR, odds ratio.

[a] All analyses were based on intention-to-treat. Values are ORs estimated using logistic regression for postoperative AF and other arrhythmias and HRs estimated using Cox proportional hazards for other end points such as MACEs.

[b] Determined using Pearson χ^2 (or Fisher exact tests for cells <10) for the primary postoperative AF end point, the first 2 secondary postoperative AF end points, and other tachyarrhythmias; Poisson regression for the total number of postoperative AF events per patient and the total number of in-hospital days with 1 or more episodes of postoperative AF; the Wilcoxon rank-sum test for the proportion of in-hospital days free of any postoperative AF and days of resource utilization; and the log-rank test for MACEs, arterial thromboembolism, and mortality end points.

[c] The median duration of the first postoperative AF episode was 0.92 (IQR, 0.17-1.0) days in the placebo group and 1.0 (0.17-1.0) days in the n-3-PUFA group (Wilcoxon rank-sum $P=.62$).

[d] A total of 661 postoperative AF episodes occurred in 460 patients. Among these episodes, 8.9% were associated with dyspnea, chest pain, or hypotension requiring escalation of therapy; 76.7% were treated with electrical or pharmacological cardioversion (predominantly amiodarone); 87.4% lasted longer than 1 hour; and 97.9% met 1 or more of these criteria.

[e] Excluding atrial flutter and supraventricular tachycardia with some but not all characteristics consistent with AF.

[f] Among the 460 patients with postoperative AF. Among all 1516 patients, the corresponding values were 0.8 (1.7) days in the placebo group and 0.8 (1.7) days in the n-3-PUFA group ($P=.93$).

[g] See eTable 2 for detailed definitions of all events. Analyses of individual MACEs components include all subtypes of events occurring in any patient.

[h] Not reliably calculable, given few numbers of events.

Effects of n-3-PUFAs on the primary end point did not significantly differ among most prespecified subgroups (FIGURE 3). Potential interaction (prespecified $\alpha = .10$) was observed only by type of cardiac surgery ($P = .06$ for interaction), with patients undergoing valve surgery having a trend toward lower risk of postoperative AF with n-3-PUFA treatment. In post hoc analyses, risk of postoperative AF with n-3-PUFA treatment was similar whether valve surgery was aortic or mitral (eAppendix).

In the predefined surgical population (underwent surgery, received at least 1 dose of study drug), 233 of 723 patients (32.2%) in the placebo group and 225 of 728 (30.9%) in the n-3-PUFA group developed postoperative AF ($P = .60$). In the further subset of adherent patients (taking ≥80% of assigned study drug), which included 591 of 723 patients (81.7%) assigned to placebo and 596 of 728 patients (81.9%) assigned to n-3-PUFAs, 186 (31.5%) and 178 (29.9%) patients, respectively, developed postoperative AF ($P = .55$).

From the time of enrollment to the morning of cardiac surgery, plasma phospholipid n-3-PUFA concentrations increased approximately 40% in the n-3-PUFA group, from 4.65% (SD, 1.44%) to 6.40% (SD, 1.70%) of total fatty acids, whereas they remained unchanged in the placebo group (4.65% [SD, 1.43%] to 4.78% [SD, 1.43%]) ($P < .001$ for change in fatty acid levels by treatment group). Stratified by actual study drug loading days, phospholipid n-3-PUFA concentrations in the treatment group increased by 0.47% of total fatty acids at day 1, by 1.11% at day 2, by 1.91% at day 3, by 2.55% at day 4, and by 2.30% at day 5. Effects of n-3-PUFA treatment on postoperative AF, however, were not significantly different by loading days (Figure 3).

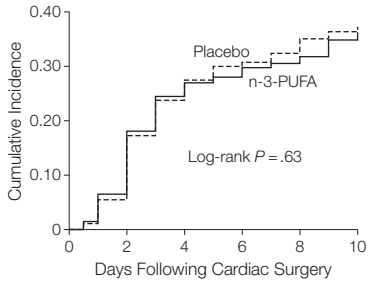
Compared with patients in the placebo group, those in the n-3-PUFA group received significantly fewer packed red blood cell transfusions, including during surgery ($P = .002$), after surgery ($P = .008$), and overall ($P < .001$) (eTable 5). Other bleeding indices did not significantly differ by treatment. Minor adverse events commonly seen with fish oil, such as gastrointestinal upset, burping, and fish oil taste, occurred more commonly in the n-3-PUFA group. Adverse events requiring discontinuation of study drug and other serious adverse events were similar between groups (eTable 6).

COMMENT

This large, multinational, double-blind, placebo-controlled randomized clinical trial found no evidence that perioperative n-3-PUFA supplementation reduced postoperative AF. Results were similar for various secondary end points, among different patient subgroups, and in various sensitivity analyses. Major strengths of OPERA include its large size and large numbers of events, which achieved anticipated statistical power. The broad inclusion criteria and multinational enrollment support the generalizability of our findings.

In controlled trials lasting weeks to months, n-3-PUFA supplementation favorably influences several physiological pathways related to AF, including blood pressure, systemic vascular resistance, heart rate, inflammation, endothelial function, left ventricular diastolic function, myocardial efficiency of oxygen use, and possibly vagal tone.[8] Our design cannot exclude potential benefits of much longer durations (eg, weeks to years) of n-3 PUFA supplementation for altering systemic physiology and risk of AF in other clinical contexts. Such prolonged durations of therapy would be impractical as a common preventive measure for most patients scheduled to undergo cardiac surgery. Based on the known benefits of n-3-PUFAs on cardiovascular risk factors and physiologic pathways, a more promising strategy may be long-term consumption to reduce the primary incidence of AF among ambulatory elderly adults with hypertension or other risk factors[15]; such an approach should be tested in appropriately designed and powered clinical trials.

Figure 2. Kaplan-Meier Incidence of Postoperative Atrial Fibrillation, According to Treatment Group



No. at risk

Placebo	758	684	532	354	153	74
n-3-PUFA	758	688	543	378	162	91

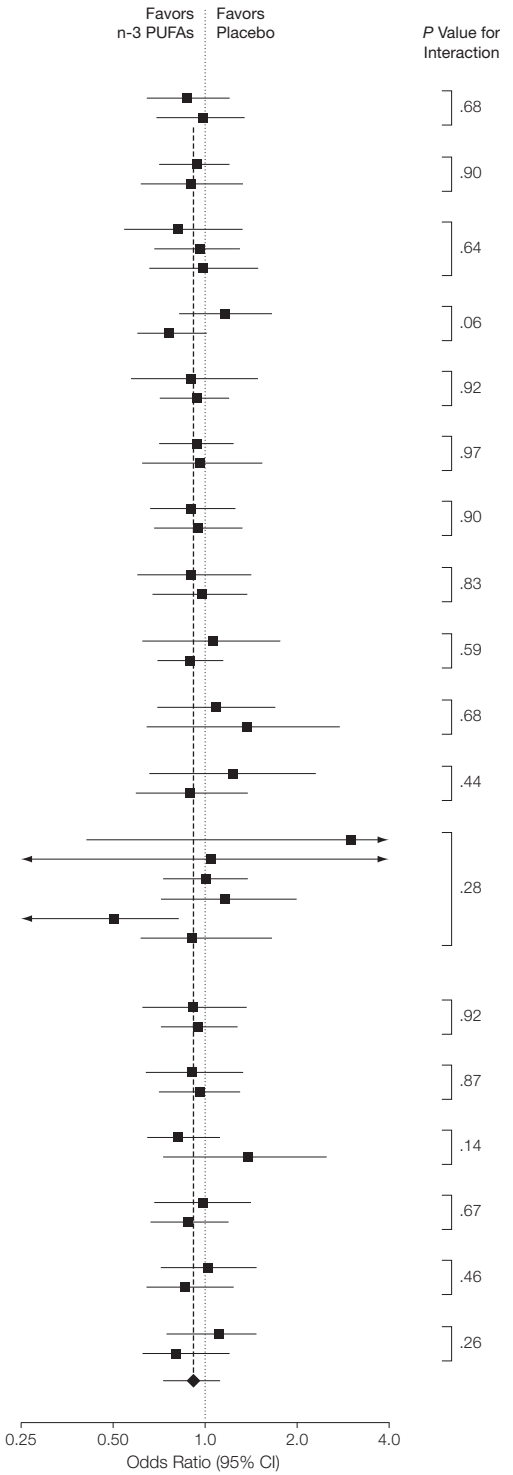
Hazard ratio, 0.96 (95% CI, 0.80-1.15). n-3-PUFA indicates omega-3 polyunsaturated fatty acid.

Subgroup analyses did not detect any difference in efficacy depending on baseline fish consumption or circulating n-3-PUFA levels. Observational studies of fish consumption and coronary heart disease death in generally healthy populations suggest that some dietary n-3-PUFAs (approximately 250 mg/d of EPA plus DHA, or about 1-2 fish servings/wk) are better than none but that greater consumption may not substantially alter risk further.[22] Our findings do not support such a dose-response relationship for postoperative AF. Findings were also similar in other subgroups, except for a suggestion of greater efficacy among patients undergoing valve surgery. Based on the multiple subgroups explored, this finding most plausibly results from chance and should be interpreted cautiously until evaluated prospectively in future studies.

Experimental studies suggest that n-3-PUFAs have antiarrhythmic actions.[23,24] Our findings provide no evidence that short-term n-3-PUFA supplementation provides clinically relevant antiarrhythmic effects in the acute setting of cardiac surgery. Further, there is no consistent evidence that n-3-PUFAs are effective antiarrhythmic agents in the context of established

Figure 3. Efficacy of Omega-3-PUFAs to Prevent Postoperative Atrial Fibrillation, According to Prespecified Baseline Characteristics

Subgroup	Events, No./Total (%) Placebo	Events, No./Total (%) n-3-PUFAs	Odds Ratio (95% CI)	*P* Value for Interaction
Age,y				
<70	114/483 (23.6)	105/477 (22.0)	0.91 (0.68-1.24)	.68
≥70	119/275 (43.3)	122/281 (43.4)	1.01 (0.72-1.41)	
Sex				
Men	169/543 (31.1)	168/551 (30.5)	0.97 (0.75-1.26)	.90
Women	64/215 (29.8)	59/207 (28.5)	0.94 (0.62-1.43)	
Country				
Argentina	52/171 (30.4)	47/171 (27.5)	0.87 (0.54-1.39)	.64
Italy	116/363 (32.0)	115/365 (31.5)	0.98 (0.72-1.34)	
United States	65/224 (29.0)	65/222 (29.3)	1.01 (0.67-1.52)	
Cardiac valve surgery				
No	84/356 (23.6)	95/351 (27.1)	1.20 (0.86-1.69)	.06
Yes	149/371 (40.2)	132/385 (34.3)	0.78 (0.58-1.05)	
Hypertension				
No	41/189 (21.7)	37/179 (20.7)	0.94 (0.57-1.55)	.92
Yes	189/563 (33.6)	188/572 (32.9)	0.97 (0.76-1.24)	
NYHA class II-IV				
No	165/556 (29.7)	162/556 (29.1)	0.97 (0.75-1.26)	.97
Yes	60/177 (33.9)	62/185 (33.5)	0.98 (0.64-1.52)	
Serum potassium, mmol/L				
<4.18	115/354 (32.5)	117/375 (31.2)	0.94 (0.69-1.29)	.90
≥4.18	110/375 (29.3)	102/355 (28.7)	0.97 (0.71-1.34)	
Left atrial diameter, mm				
<42	60/242 (24.8)	56/238 (23.5)	0.93 (0.61-1.42)	.83
≥42	108/278 (38.9)	107/277 (38.6)	0.99 (0.70-1.39)	
Ejection fraction, %				
<50	36/147 (24.5)	37/141 (26.2)	1.10 (0.65-1.87)	.59
≥50	194/601 (32.3)	187/607 (30.8)	0.93 (0.73-1.19)	
Habitual fish intake, servings/wk				
<2	56/203 (27.6)	54/178 (30.3)	1.14 (0.73-1.78)	.68
≥2	20/59 (33.9)	28/68 (41.2)	1.37 (0.66-2.81)	
Phospholipid n-3-PUFA level, %				
<4	22/97 (22.7)	28/103 (27.2)	1.27 (0.67-2.42)	.44
≥4	58/158 (36.7)	58/165 (35.2)	0.93 (0.59-1.47)	
Study drug loading d (actual)				
0	1/14 (7.1)	4/20 (20.0)	3.25 (0.32-32.7)	.28
1	3/21 (14.3)	2/13 (15.4)	1.09 (0.16-7.59)	
2	89/310 (28.7)	97/330 (29.4)	1.03 (0.74-1.46)	
3	40/144 (27.8)	45/142 (31.7)	1.21 (0.73-2.00)	
4	28/63 (44.4)	19/74 (25.7)	0.43 (0.21-0.89)	
5	72/206 (35.0)	60/179 (33.5)	0.94 (0.62-1.43)	
Perioperative medications				
β-Blockers				
No	70/232 (30.2)	65/224 (29.0)	0.95 (0.63-1.42)	.92
Yes	163/526 (31.0)	162/534 (30.3)	0.97 (0.75-1.26)	
Statins				
No	84/274 (30.7)	81/276 (29.4)	0.94 (0.65-1.35)	.87
Yes	149/484 (30.8)	146/482 (30.3)	0.98 (0.74-1.29)	
Amiodarone				
No	177/648 (27.3)	158/647 (24.4)	0.86 (0.67-1.10)	.14
Yes	31/85 (36.5)	34/75 (45.3)	1.44 (0.77-2.72)	
ACE inhibitors/ARBs				
No	94/333 (28.2)	92/322 (28.6)	1.02 (0.72-1.43)	.67
Yes	139/425 (32.7)	135/436 (31.0)	0.92 (0.69-1.23)	
On-pump time, h:min				
<1:36	92/348 (26.4)	102/373 (27.4)	1.05 (0.75-1.46)	.46
≥1:36	141/379 (37.2)	125/363 (34.4)	0.89 (0.66-1.20)	
Cross-clamp time, h:min				
<1:11	85/342 (24.9)	103/382 (27.0)	1.12 (0.80-1.56)	.26
≥1:11	148/385 (38.4)	124/354 (35.0)	0.86 (0.64-1.17)	
Overall	233/759 (30.7)	227/757 (30.0)	0.96 (0.77-1.20)	



All characteristics are at enrollment except for cardiac valve surgery (based on actual surgery performed), study drug loading days, perioperative medication use (defined as use at enrollment, on the morning after cardiac surgery, or both), on-pump time, and cross-clamp time. Only patients with complete data on the relevant stratifying variable were included in each subgroup analysis. Logistic regression was used to determine the odds ratio and 95% CI for the effect of treatment in each subgroup. The statistical significance of potential interaction was quantified using the Wald test for a multiplicative interaction term (treatment × stratifying variable). ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; n-3-PUFA, omega-3 polyunsaturated fatty acid; NYHA, New York Heart Association.

cardiac arrhythmias, such as in patients with prior ventricular arrhythmias and implantable cardiodefibrillators or with prior established chronic or paroxysmal AF.[25-31] Early clinical trials demonstrated that long-term intake of fish[32] or fish oil[33,34] reduced the risk of cardiac death in patients with recent myocardial infarction, and the overall evidence from subsequent experiments, observational studies, and clinical trials continues to point toward a reduction in cardiac death as the principal cardiovascular benefit of long-term n-3-PUFA intake.[8,9]

Prior smaller trials found mixed effects of perioperative n-3-PUFAs on postoperative AF.[16,35-40] Two studies reported a reduction in postoperative AF[16,38] but were small (<40 events each) and also open-label, ie, neither placebo-controlled nor double-blind. Five other small placebo-controlled trials found no significant effects of n-3-PUFAs on postoperative AF,[35-37,39,40] but the small numbers of events in each study (range, 24-91 events each) limited statistical power and made it difficult to draw strong conclusions about absence of effects. The OPERA trial, comprising more patients and AF events than all of these prior trials combined, provides the most definitive answer to this important research question. The variation in findings of prior small trials and especially studies without placebo control highlights the importance of conducting large, appropriately powered, placebo-controlled trials such as the present study.

Many drugs have been tested but failed to prevent postoperative AF; others, such as β-blockers and amiodarone, only partly reduce risk.[2] The effects of cardiac surgery on neurohormonal, oxidative, and inflammatory activation and atrial remodeling may simply be too great to be countered by most drugs, including n-3-PUFAs. Postoperative AF remains an intractable and enigmatic complication of surgery. Our findings and those of prior studies highlight the need for meticulous investigation of the underlying physiological, structural, and molecular underpinnings of postoperative AF to allow novel targeted preventive and therapeutic interventions.

The secondary end points of arterial thromboembolism and arterial thromboembolism or death occurred less frequently in the n-3-PUFA group. However, numbers of events were small, and these findings should be viewed with caution until confirmed in future studies. Supplementation with n-3-PUFAs was well tolerated in this large and heterogeneous population of patients undergoing cardiac surgery, and there was no evidence that n-3-PUFA supplementation was unsafe.

Although there have been theoretical concerns that n-3-PUFAs could aggravate bleeding, no increased hemorrhagic risk was seen across a variety of indices. Patients in the n-3-PUFA group required significantly fewer transfusions; this finding may be attributable to chance, but it further supports absence of increased bleeding risk. These results confirm and extend the findings of prior smaller trials that found no evidence that n-3-PUFA supplementation increased clinical bleeding following cardiac surgery,[16,35-39] surgical arterial endarterectomy,[41,42] or coronary angioplasty.[43] More than half of the patients in OPERA were taking aspirin or other anticoagulants before cardiac surgery, similar to other trials in which n-3-PUFAs were combined with aspirin or warfarin following cardiac surgery without any excess clinical bleeding.[44]

This study has limitations that should be considered. Current best-practice guidelines for preventing postoperative AF were recommended to all centers, which could have reduced the influence of any additional therapy on risk of postoperative AF. As would be reflected in clinical practice, patients were identified and assigned to receive n-3-PUFAs over varying durations ranging from 2 to 5 days prior to surgery. Shorter durations could have been less effective. Subgroup analyses, however, did not detect significantly greater risk reduction with greater numbers of days of preoperative n-3-PUFAs, providing little evidence that longer durations of loading make a difference, at least up to 5 days. The dose of n-3-PUFAs may have been too low to produce a benefit, and we did not have available data on achieved myocardial levels of n-3-PUFAs. Yet circulating n-3-PUFAs have systemic effects that could reduce risk of AF,[8] and phospholipid n-3-PUFA levels increased by an average of 40% by the time of surgery, providing novel evidence that even short-term supplementation significantly influences circulating levels. Adherence with study drug was high but not perfect. Our analysis restricted to adherent patients, however, was consistent with the main findings.

In summary, perioperative n-3-PUFA supplementation did not reduce postoperative AF in this large, adequately powered, placebo-controlled, randomized multinational trial.

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Online-Only Material: The eAppendix, eTables 1-6, and the eFigure are available at http://www.jama.com.

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