Omega-3 Fatty Acids for Prevention of Post-Operative Atrial Fibrillation

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Disclosures

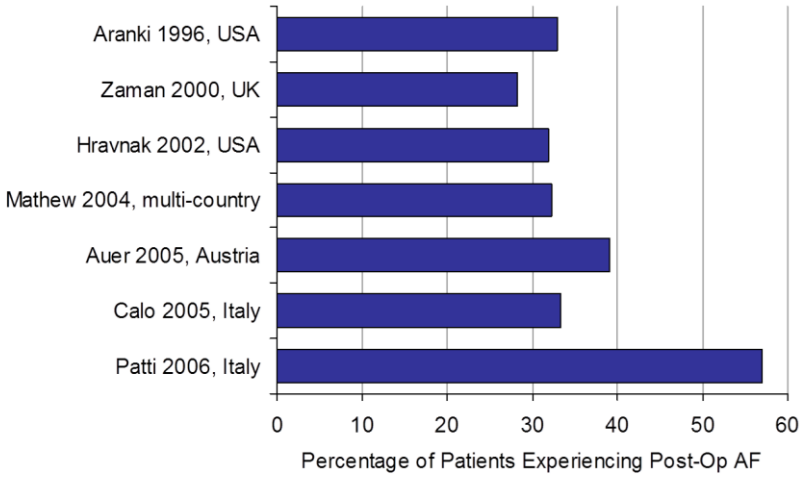
- Investigator-initiated, not-for-profit trial sponsored by the OPERA Investigators, who had full responsibility for study planning and conduct, curation of the study database, and data collection, analysis, and publication.

- Financial support was provided by the National Heart, Lung, and Blood Institute, NIH (RC2-HL101816), GlaxoSmithKline, Sigma Tau, and Pronova BioPharma, which also provided the study drug.

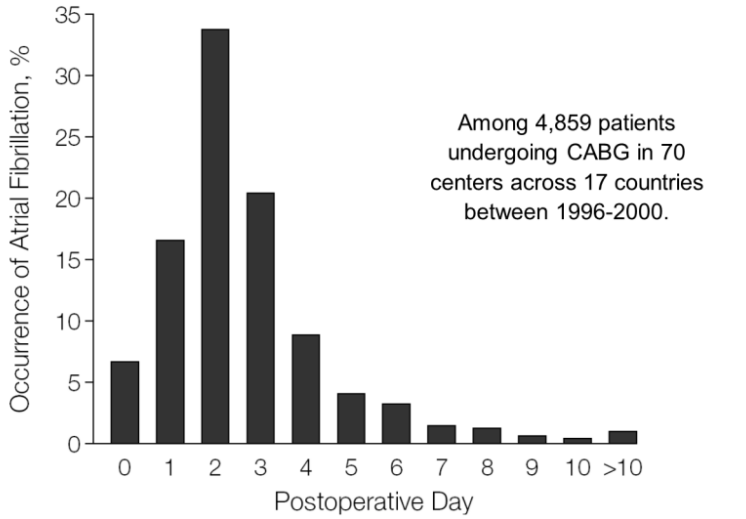
- The funding organizations had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation or approval of the manuscript.

Post-Operative Atrial Fibrillation (AF)

Post-Op AF: A Frequent Complication



Time Course of Post-Op AF



Mathew et al. JAMA 2004

- Mechanisms not well-understood.
- Similar rates of this complication over decades of surgery.
- Few effective preventive treatments.
- Increases morbidity, resource utilization, long-term mortality.

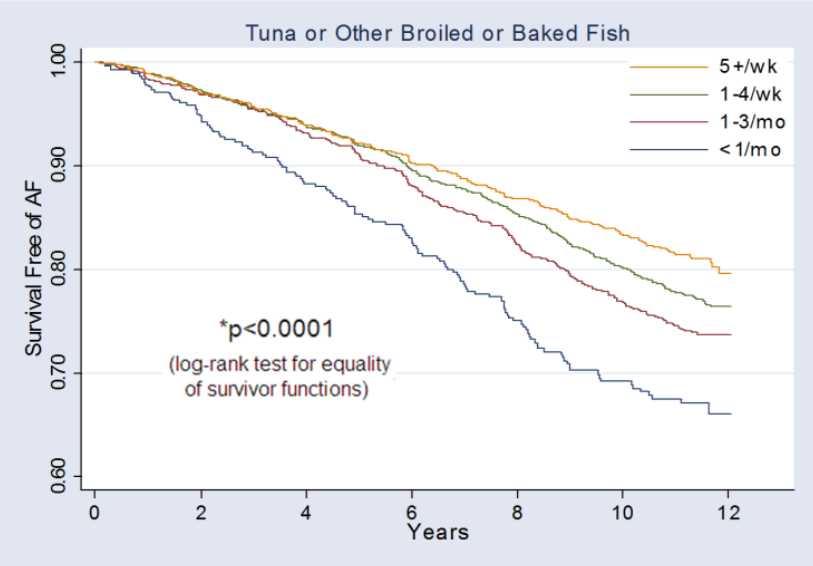
Pathways of AF risk that might be improved by n-3 polyunsaturated fatty acids (n-3 PUFA)

- Autonomic dysregulation
- Renin-angiotension-aldosterone activation
- Endothelial dysfunction
- Oxidative stress (myocardial, systemic)
- Inflammation
- Ischemic stunning/injury
- Structural remodeling
- Diastolic dysfunction
- Fluid overload
- Metabolic dysfunction
- Extracellular matrix turnover and fibrosis
- Altered connexin biology
- Altered ion channel function

Hogue et al. Chest 2005
Kaireviciute et al. Curr Pharm Des 2009

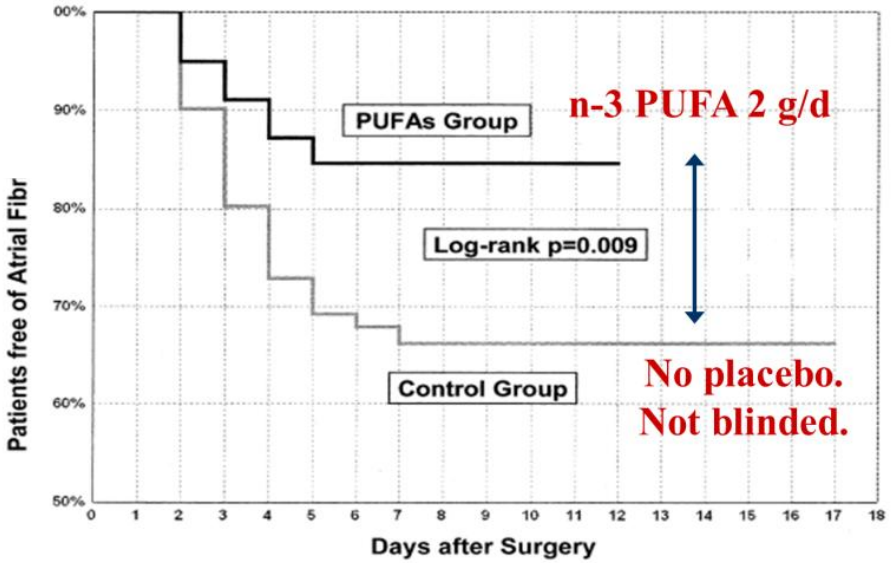
Might n-3 PUFA reduce AF ?

Fish Intake and Risk of Atrial Fibrillation



Epidemiologic evidence

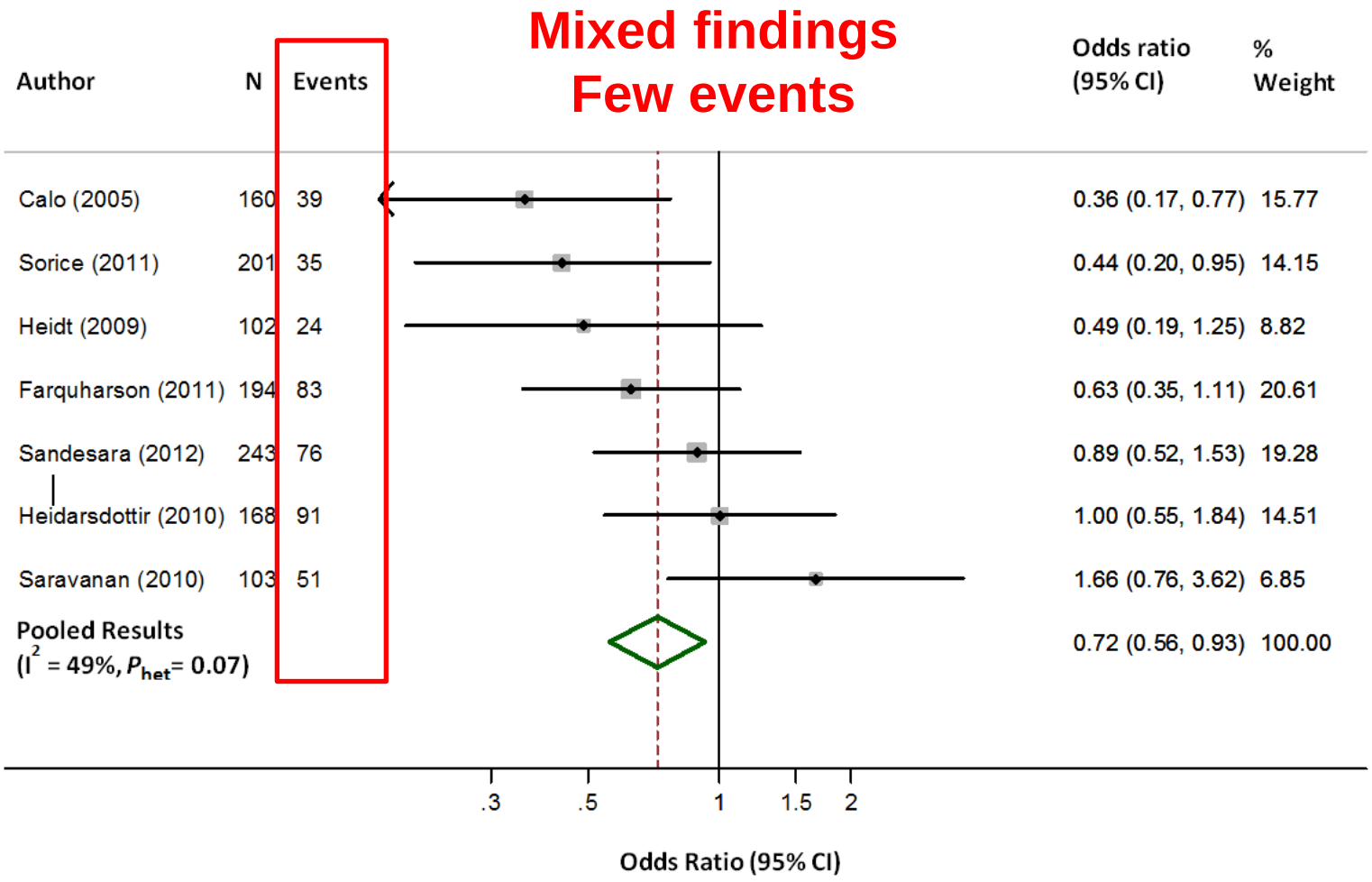
Randomized Trial Among Patients Undergoing CABG



Only 139 AF events

inical evidence

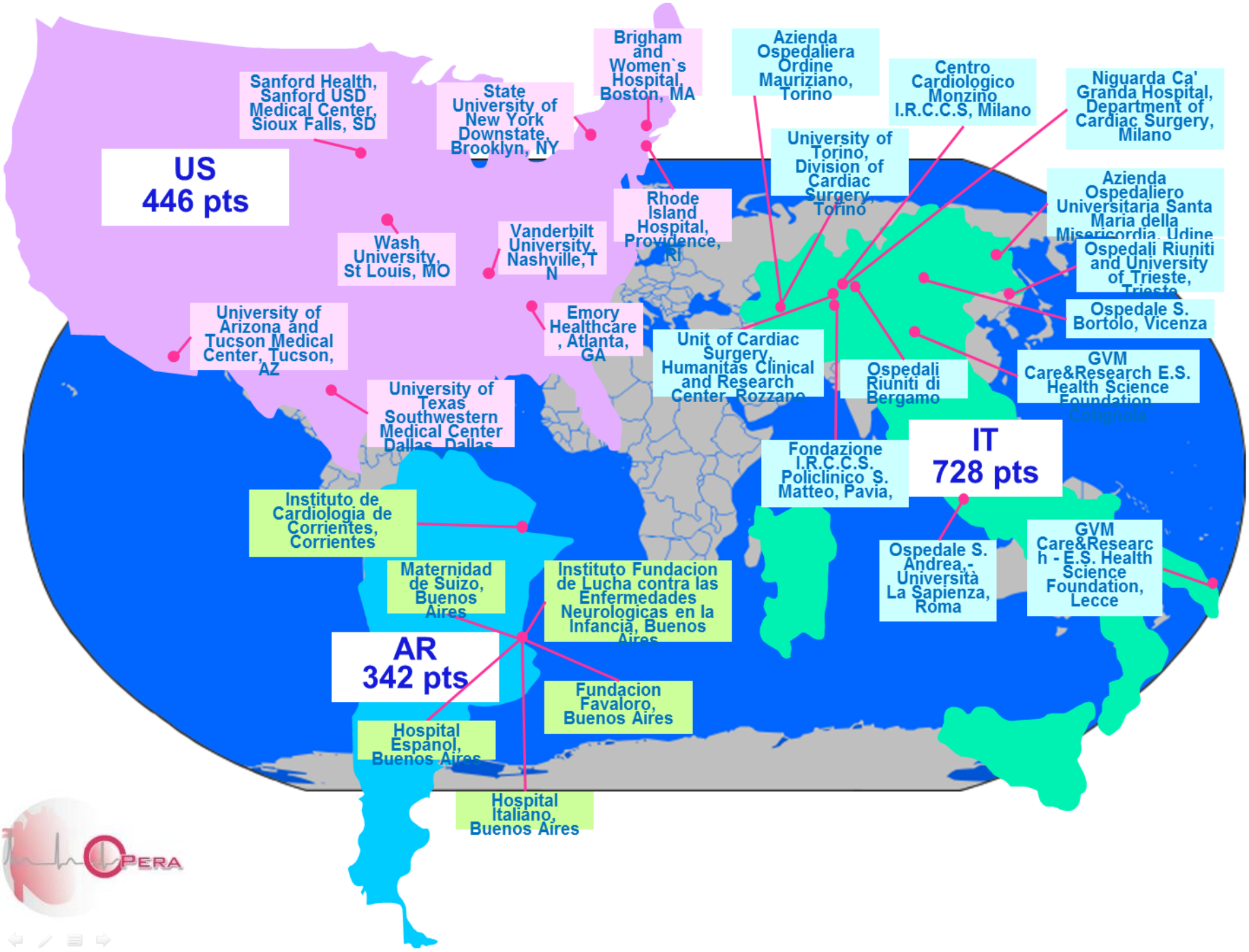
Prior RCTs of Peri-Operative n-3 PUFA to Prevent Post-Op AF



Meta-analysis by the OPERA Investigators, unpublished.

OPERA: Design

- ***Hypothesis:*** Peri-operative n-3-PUFA supplementation reduces the risk of post-op AF in cardiac surgery patients.
- ***Design:*** Multinational, randomized, double-blind, placebo-controlled clinical trial.
- ***Population:*** 1,516 patients undergoing CAS in 28 medical centers in the US, Italy, and Argentina, enrolled from Aug 2010 to Jun 2012.
- ***Primary Endpoint:*** Occurrence of any post-op AF >30 sec.
- ***Treatment:*** Fish oil capsules (1 g containing ≥840 mg n-3-PUFA as ethyl esters) or matched placebo (olive oil). Pre-operative loading dose of 10g total over 3-5 days (or 8g over 2 days) followed post-operatively by 2g/d until hospital discharge or post-op day 10, whichever first.


US
446 pts
Sanford Health, Sanford USD Medical Center, Sioux Falls, SD
State University of New York Downstate, Brooklyn, NY
Brigham and Women`s Hospital, Boston, MA
Azienda Ospedaliera Ordine Mauriziano, Torino
Centro Cardiologico Monzino I.R.C.C.S, Milano
Niguarda Ca' Granda Hospital, Department of Cardiac Surgery, Milano
University of Torino, Division of Cardiac Surgery, Torino
Azienda Ospedaliero Universitaria Santa Maria della Misericordia, Udine
Rhode Island Hospital, Providence, RI
Wash University, St Louis, MO
Vanderbilt University, Nashville, TN
Ospedali Riuniti and University of Trieste, Trieste
Ospedale S. Bortolo, Vicenza
University of Arizona and Tucson Medical Center, Tucson, AZ
Emory Healthcare, Atlanta, GA
Unit of Cardiac Surgery, Humanitas Clinical and Research Center, Rozzano
Ospedali Riuniti di Bergamo
GVM Care&Research E.S. Health Science Foundation
University of Texas Southwestern Medical Center Dallas, Dallas
Fondazione I.R.C.C.S. Policlinico S. Matteo, Pavia,
IT
728 pts
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Maternidad de Suizo, Buenos Aires
Instituto Fundacion de Lucha contra las Enfermedades Neurologicas en la Infancia, Buenos Aires
Ospedale S. Andrea,- Università La Sapienza, Roma
GVM Care&Research - E.S. Health Science Foundation, Lecce
AR
342 pts
Fundacion Favaloro, Buenos Aires
Hospital Espanol, Buenos Aires
Hospital Italiano, Buenos Aires

Recruitment criteria

Inclusion Criteria

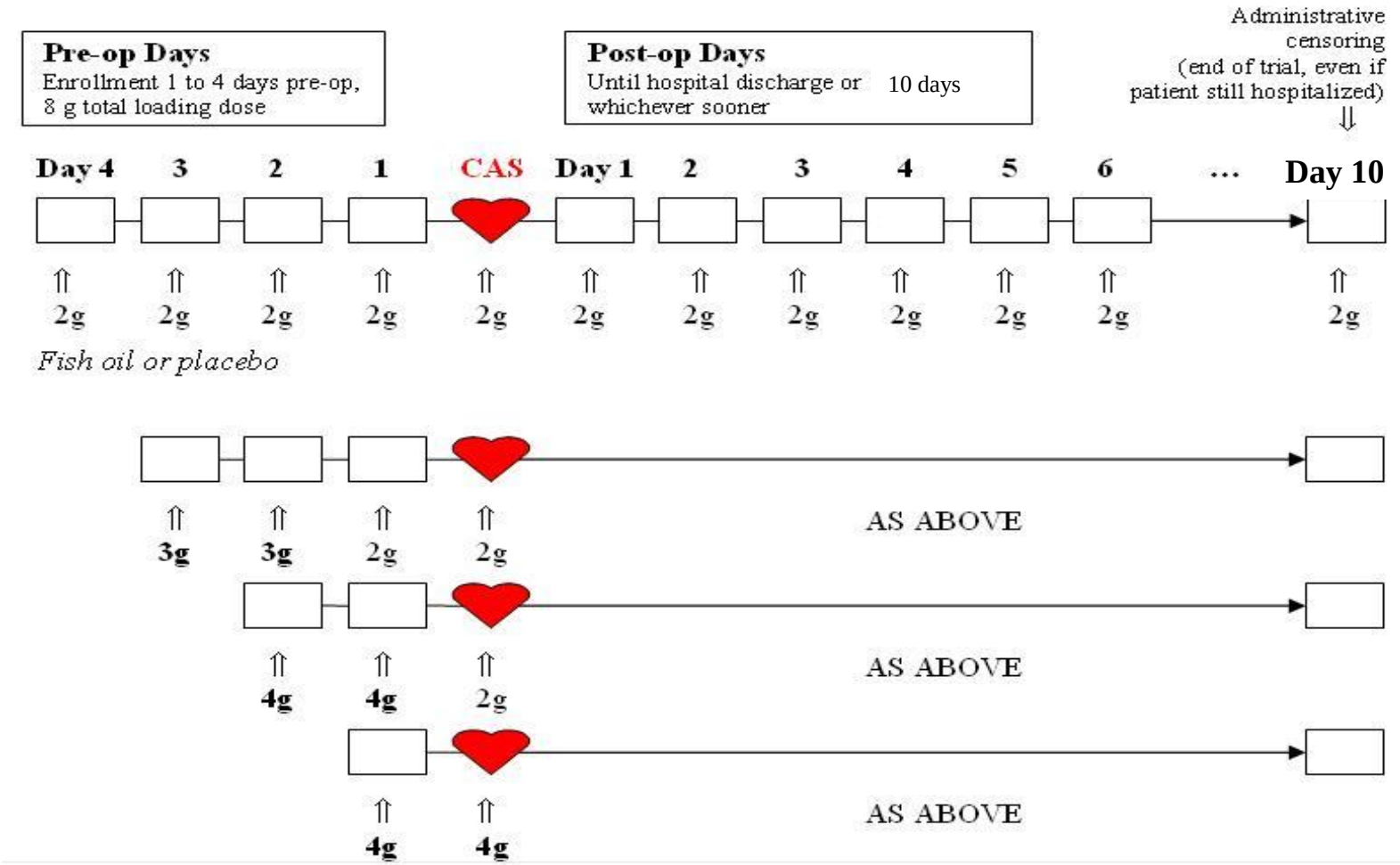
- **Age 18 y or older.**
- **Scheduled for cardiac surgery on the following day or later.**
- **Sinus rhythm on ECG at screening visit.**

Exclusion Criteria

- **Not in sinus rhythm on screening ECG (e.g., in atrial fibrillation, 100% paced).**
- **Regular use (3 or more days per week) of fish oil during the past 4 weeks.**
- **Known allergy or intolerance to fish oil or olive oil.**
- **Currently pregnant.**
- **Existing or planned cardiac transplant or left ventricular assist device.**
- **Unable or unwilling to provide informed written consent.**

**Patients with prior AF or prior or planned AF ablation could be enrolled, as such patients are at increased risk of post-op AF.*

Treatment



- All other treatments were at the discretion of the treating physicians.
- Current best-practice guidelines for prevention of post-op AF were strongly recommended to all Centers.

Primary Endpoint

- The occurrence of documented post-op atrial fibrillation or flutter (AF) of >30 sec duration and documented by rhythm strip or 12-lead ECG.
- Encouraged: Continuous telemonitoring for at least 5 days post-surgery, daily 12-lead ECGs.
- Clinical data and confirmatory rhythm strips or 12-lead ECGs were collected on all post-op arrhythmias of >30 sec duration, including post-op AF and other tachyarrhythmias. Data on at least the first 3 suspected episodes of post-op AF were collected in each patient.
- All potential episodes of post-op AF and other tachyarrhythmias were reviewed and adjudicated by a centralized Events Committee of cardiac electrophysiologists.

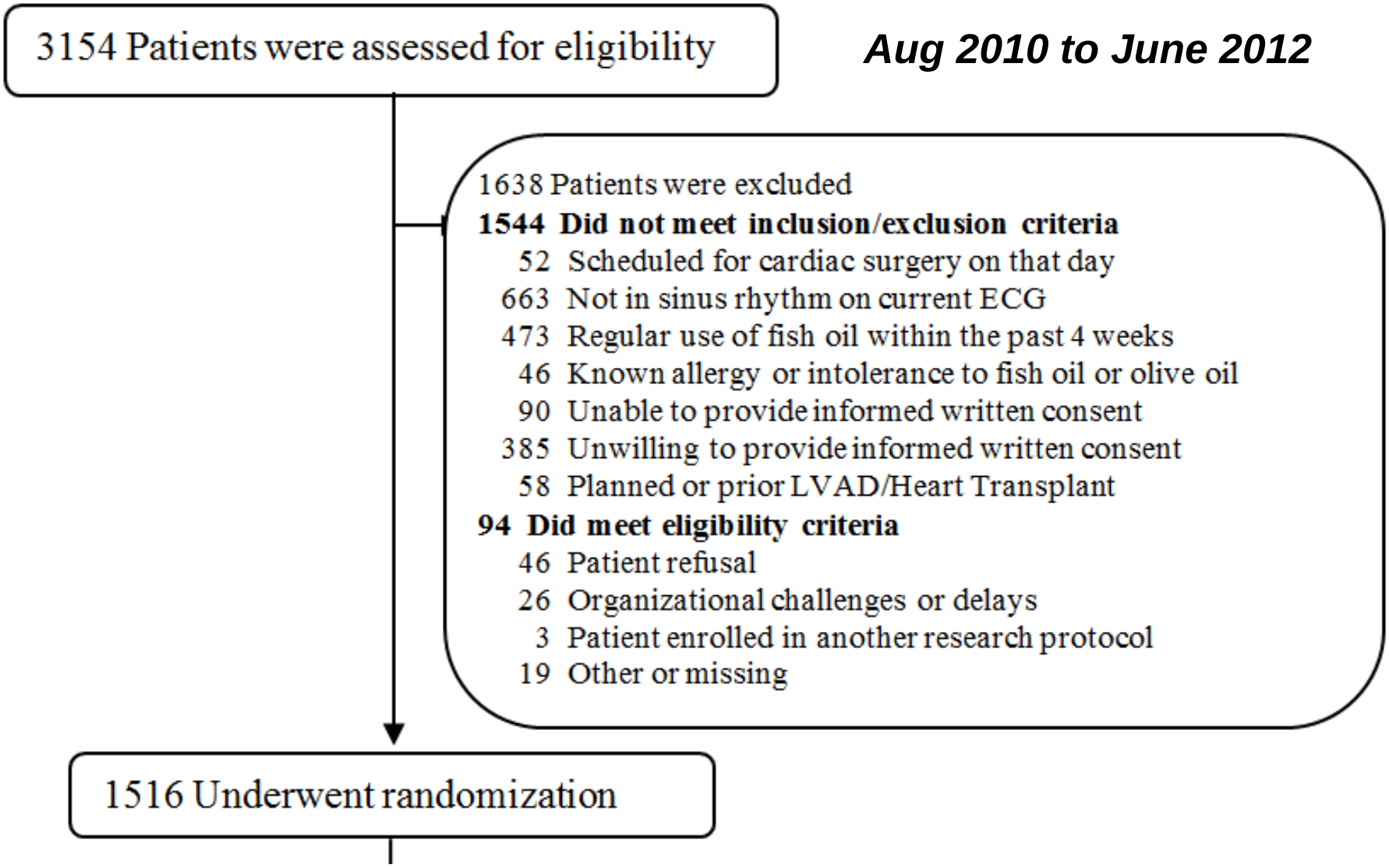
Secondary and Other Endpoints

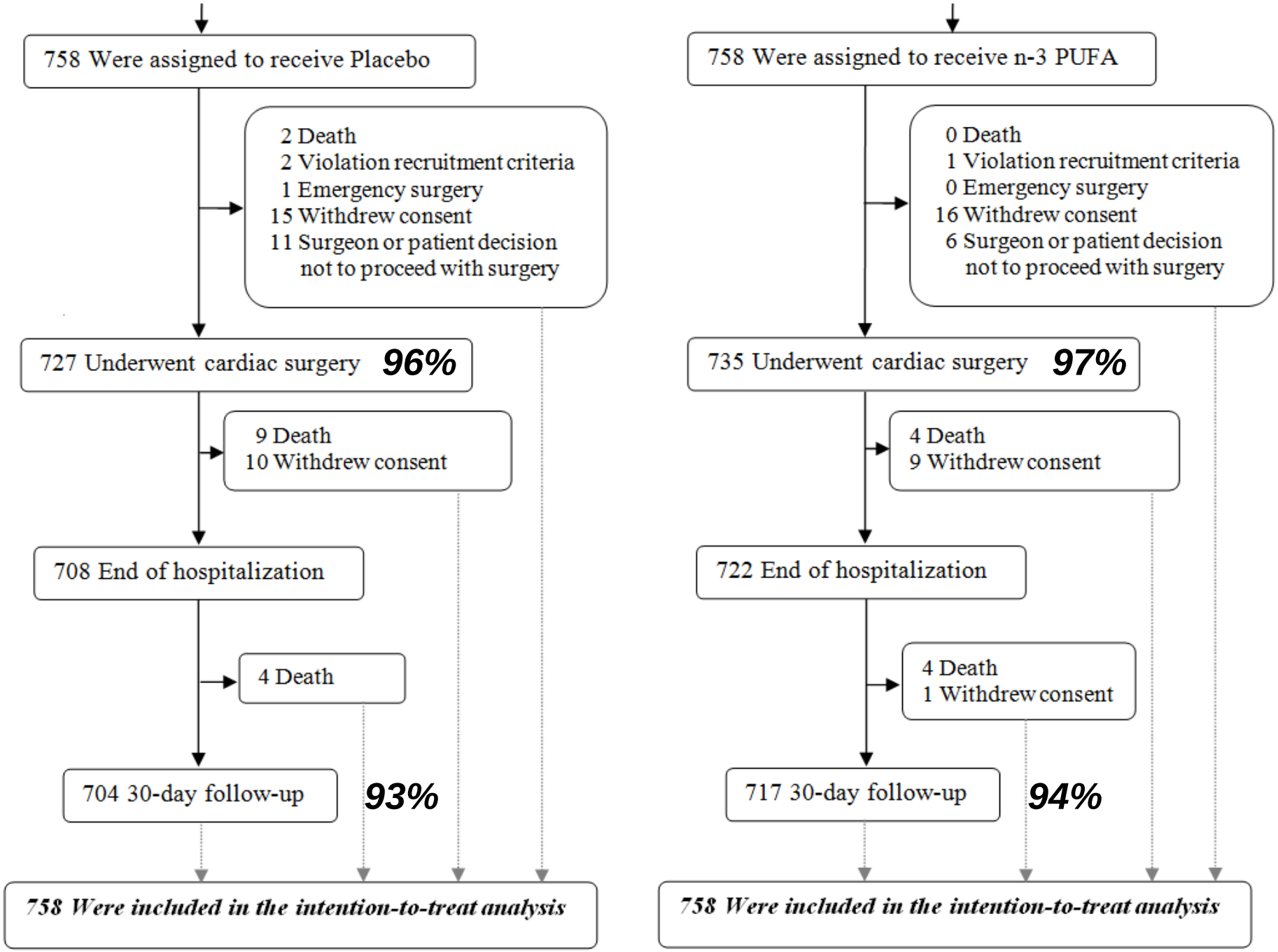
- Post-op AF that was sustained (>1 hr), symptomatic, or treated with cardioversion (electrical or drug).
- Incident post-op AF.
- Other supraventricular and ventricular tachyarrhythmias.
- In-hospital MACE, 30-day mortality, 1-year mortality.
- Arterial thromboembolism.
- Resource utilization (days in the ICU, of telemetry monitoring, and total hospital stay).
- Significant adverse events.
- Bleeding, including 24-hr chest tube output, blood transfusions, and ISTH and TIMI bleeding indices.

Statistical Analysis

- All analyses were based on intention-to-treat (ITT).
- Primary endpoint: Proportion of patients in each treatment group with post-op AF, tested using Pearson chi-square.
- Log-rank test / survival analyses for incident post-op AF and MACE, arterial thromboembolism, and mortality.
- Several sensitivity analyses, e.g. considering patients who died, withdrew, or were lost to follow-up as having had post-op AF; assessing only adherent (on-treatment) patients.
- Prespecified subgroup analyses.
- Planned enrollment of 1,516 patients provided 90% power to detect 25% reduction in post-op AF (two-tailed alpha=0.05), based on 30% event rate in controls and 5% drop-out.

Screening and Enrollment

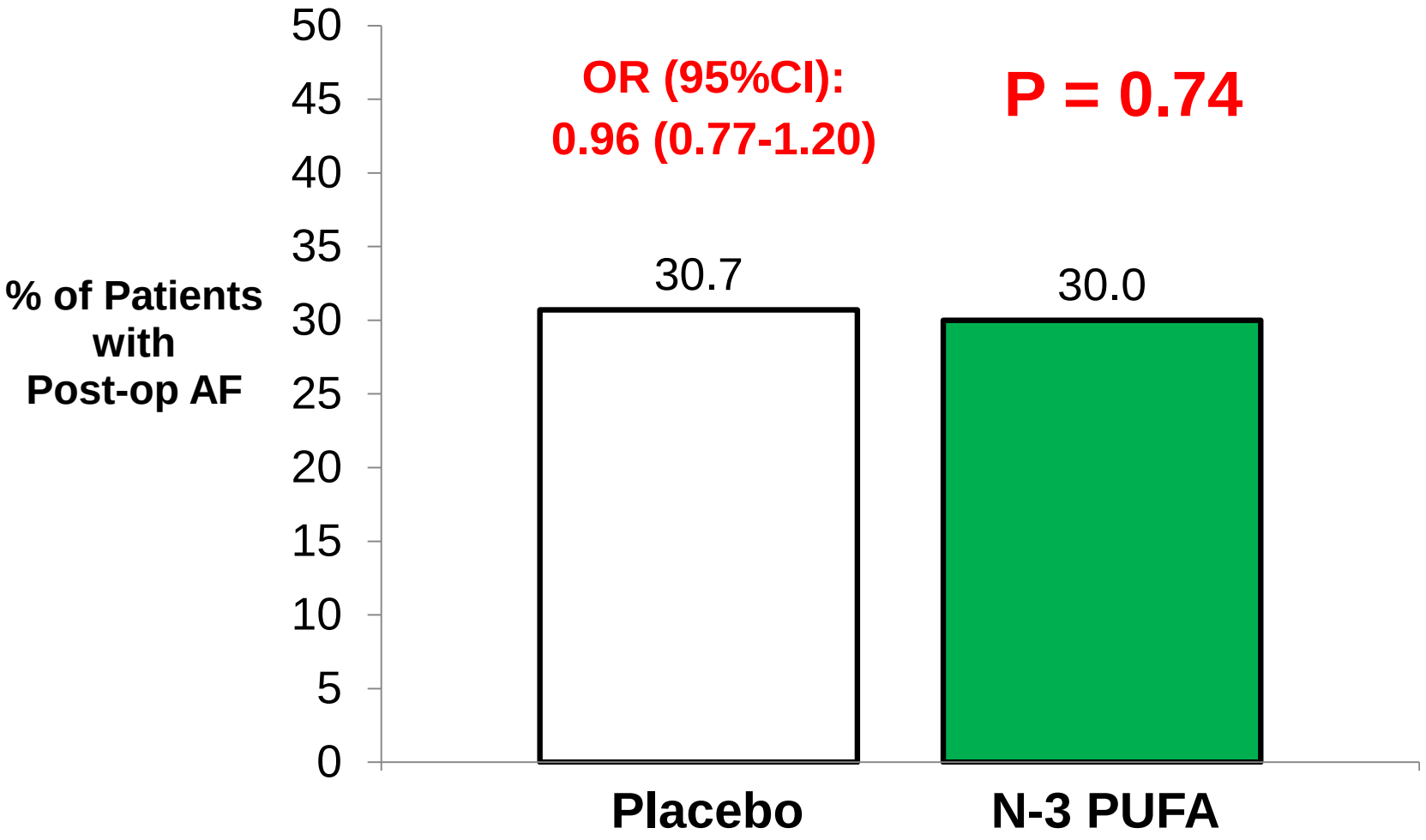



758 Were assigned to receive Placebo
2 Death
2 Violation recruitment criteria
1 Emergency surgery
15 Withdrew consent
11 Surgeon or patient decision not to proceed with surgery
727 Underwent cardiac surgery
96%
9 Death
10 Withdrew consent
708 End of hospitalization
4 Death
704 30-day follow-up
93%
758 Were included in the intention-to-treat analysis
758 Were assigned to receive n-3 PUFA
0 Death
1 Violation recruitment criteria
0 Emergency surgery
16 Withdrew consent
6 Surgeon or patient decision not to proceed with surgery
735 Underwent cardiac surgery
97%
4 Death
9 Withdrew consent
722 End of hospitalization
4 Death
1 Withdrew consent
717 30-day follow-up
94%
758 Were included in the intention-to-treat analysis

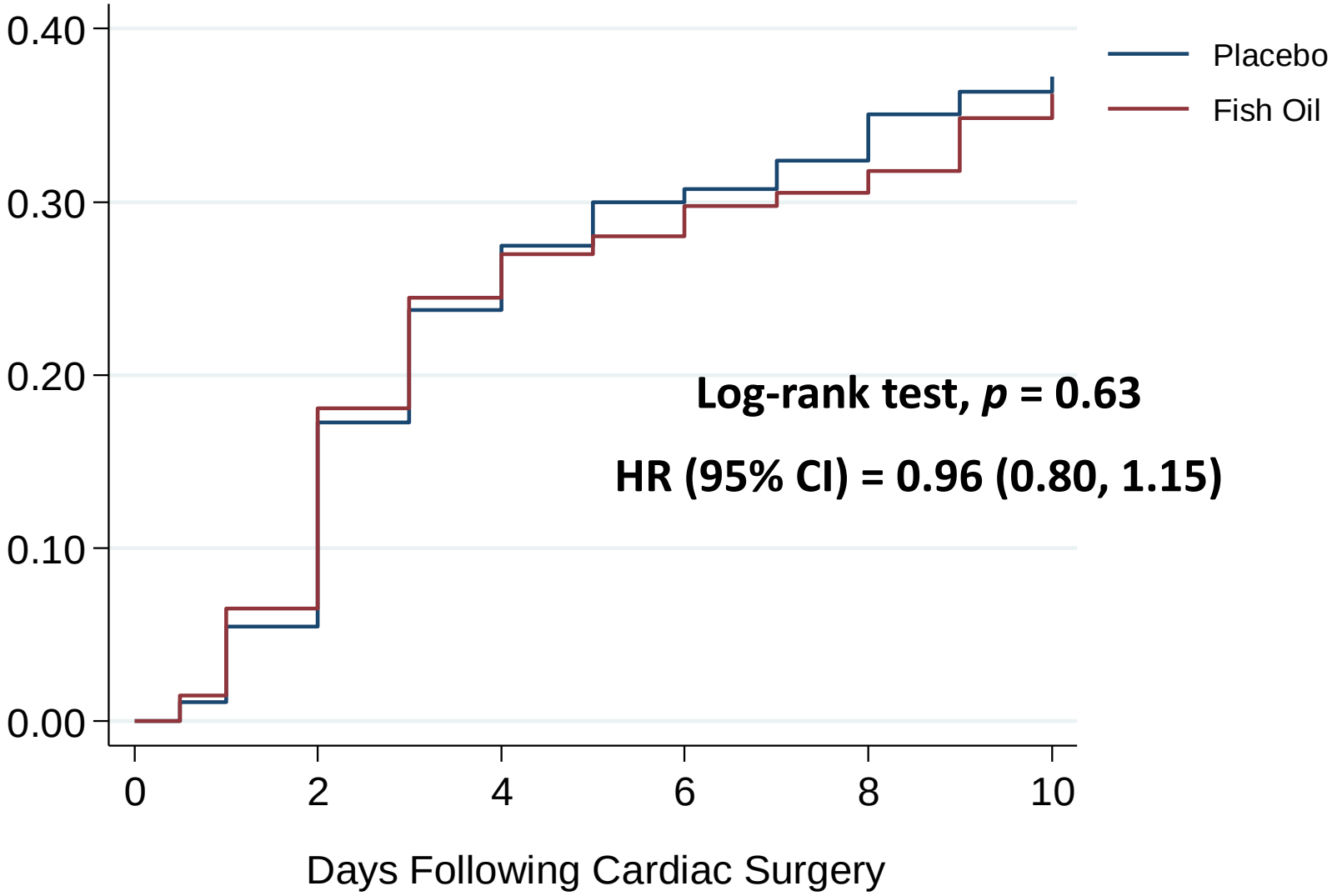
Baseline Characteristics	Placebo (N=758)	n-3 PUFA (N=758)	P value
Age, years (SD)	63.6 (12.4)	63.8 (12.6)	0.75
Male, n (%)	543 (71.6)	551 (72.7)	0.65
Euro Score, logistic, median (IQR)	3.6 (1.8, 7.2)	3.7 (2.0, 7.5)	0.64
Hypertension, n (%)	563 (74.9)	572 (76.2)	0.56
Dyslipidemia, n (%)	477 (64.1)	460 (61.7)	0.33
Diabetes mellitus, n (%)	199 (26.3)	194 (25.7)	0.78
CHD, n (%)	288 (38.0)	297 (39.2)	0.64
CHF, n (%)	212 (28.0)	204 (27.0)	0.66
Current smoking, n (%)	96 (13.0)	99 (13.5)	0.78
BMI, kg/m^2 (SD)	28.4 (5.9)	28.1 (5.4)	0.30
Prior AF	62 (8.4)	52 (7.1)	0.35
LA diameter, mm (SD)	42.2 (7.6)	42.1 (7.8)	0.77
Beta blocker	433 (57.2)	444 (58.6)	0.57
Statin	427 (56.3)	436 (57.5)	0.64
ACE-inhibitor or ARB	377 (49.8)	398 (52.5)	0.59
Antiplatelets or anticoagulants	473 (62.4)	455 (60.0)	0.34
Amiodarone	28 (3.7)	30 (4.0)	0.78

Surgical Details, Peri-op Meds	Placebo (N=758)	n-3 PUFA (N=758)	P value
Any valve surgery, n (%)	371 (48.9)	385 (50.8)	0.47
Aortic	253 (33.4)	269 (35.5)	
Mitral	94 (10.4)	101 (13.3)	0.67
Aortic + mitral	18 (2.4)	12 (1.6)	
Any CABG, n (%)	407 (53.7)	380 (50.1)	0.17
Cardiopulmonary bypass, n (%)	627 (82.7)	634 (83.6)	0.63
Off pump, n (%)	86 (11.4)	90 (11.9)	0.75
Mini thoracotomy, n (%)	45 (5.9)	46 (6.1)	0.91
Pump time, hours (SD)	1.7 (1.0)	1.6 (1.0)	0.47
Cross clamp time, hours (SD)	1.2 (0.7)	1.2 (0.8)	0.99
Atrial pacing, n (%)	93 (12.3)	100 (13.2)	0.59
Beta blocker	554 (73.1)	570 (75.2)	0.35
Amiodarone	268 (35.4)	271 (35.8)	0.87
ACE-inhibitor or ARB	336 (44.3)	336 (44.3)	0.97
Statin	436 (57.5)	449 (59.2)	0.50

Results: Primary Endpoint



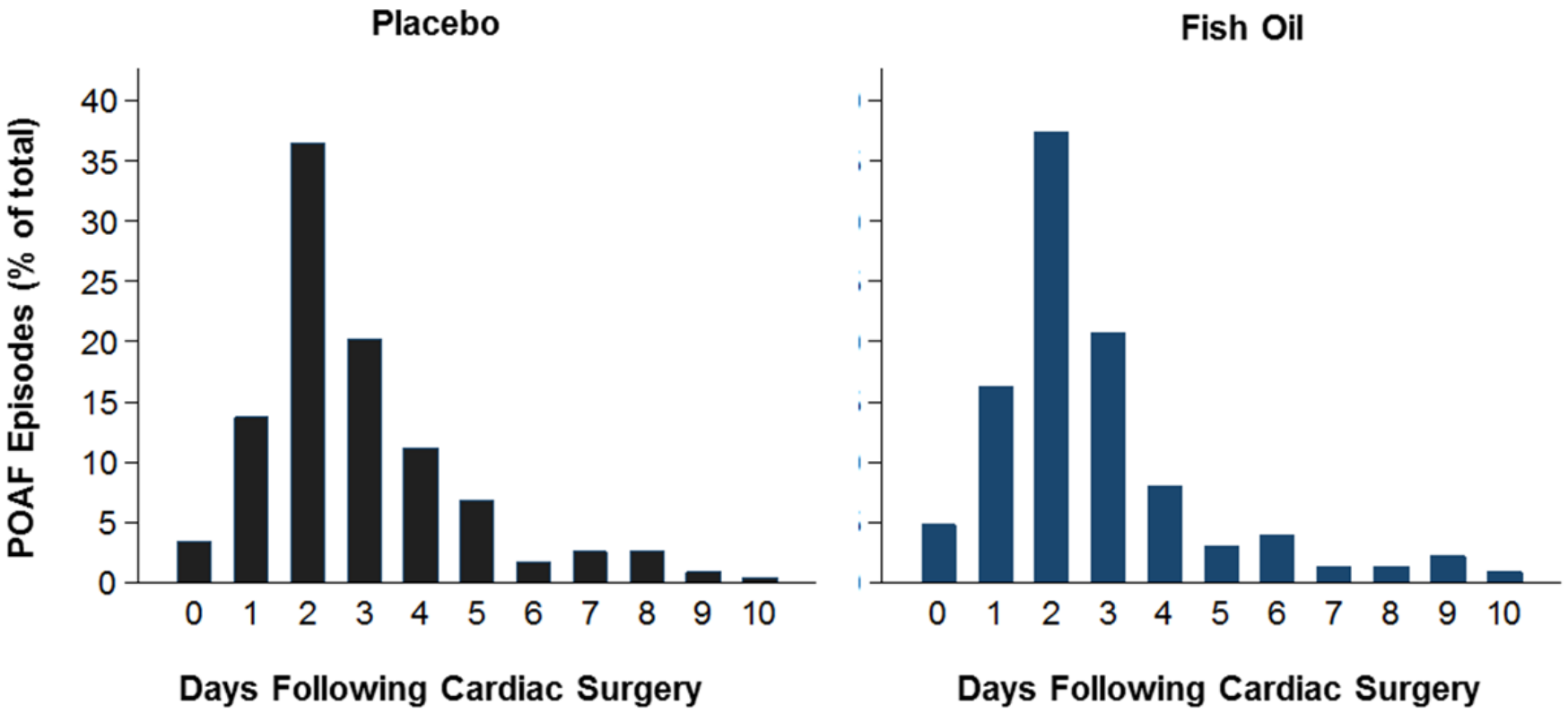
661 Post-op AF episodes documented in 460 patients



Number at risk

Placebo	758	684	532	354	153	74
Fish oil	758	688	543	378	162	91

Day of Initial Occurrence of Post-Op AF



Secondary Post-op AF Endpoints

No significant differences in any secondary post-op AF endpoints:

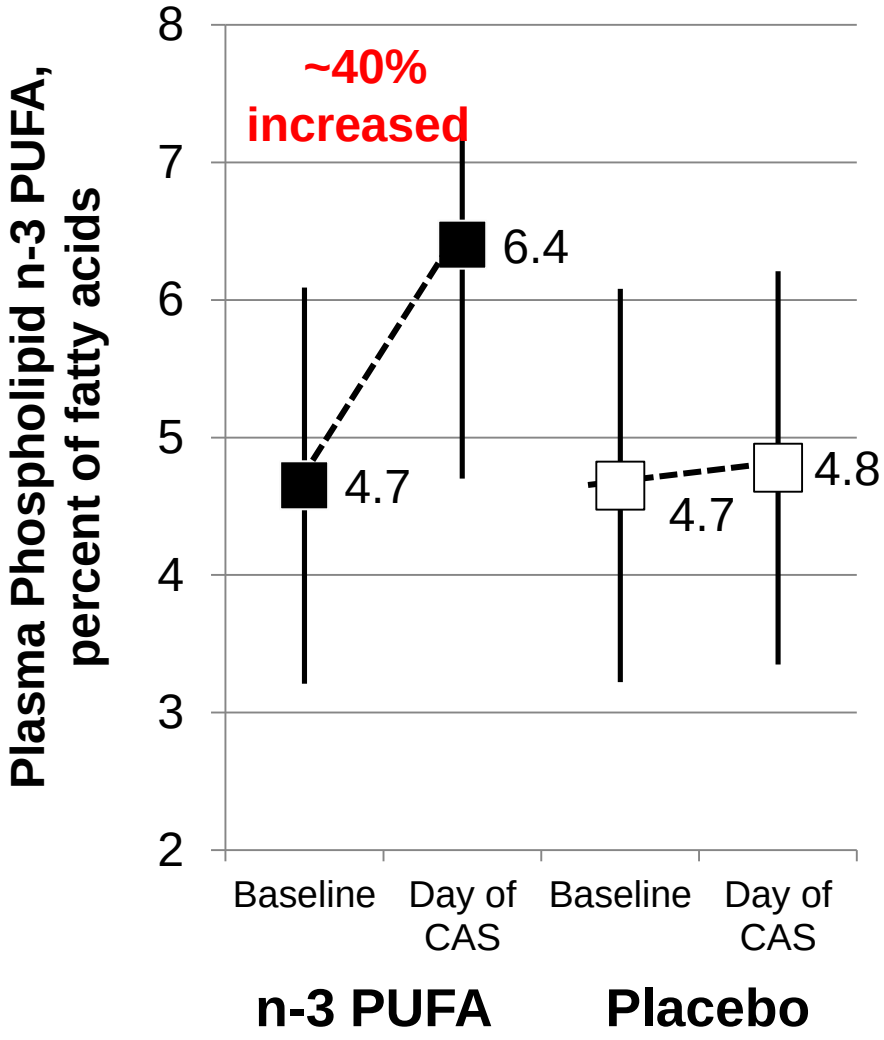
- Sustained, symptomatic, or treated post-of AF (P=0.70).
- Post-op AF excluding atrial flutter (P=0.87).
- Total number of days with any post-op AF (P=0.58).
- Proportion of days free of post-op AF (P=0.88).

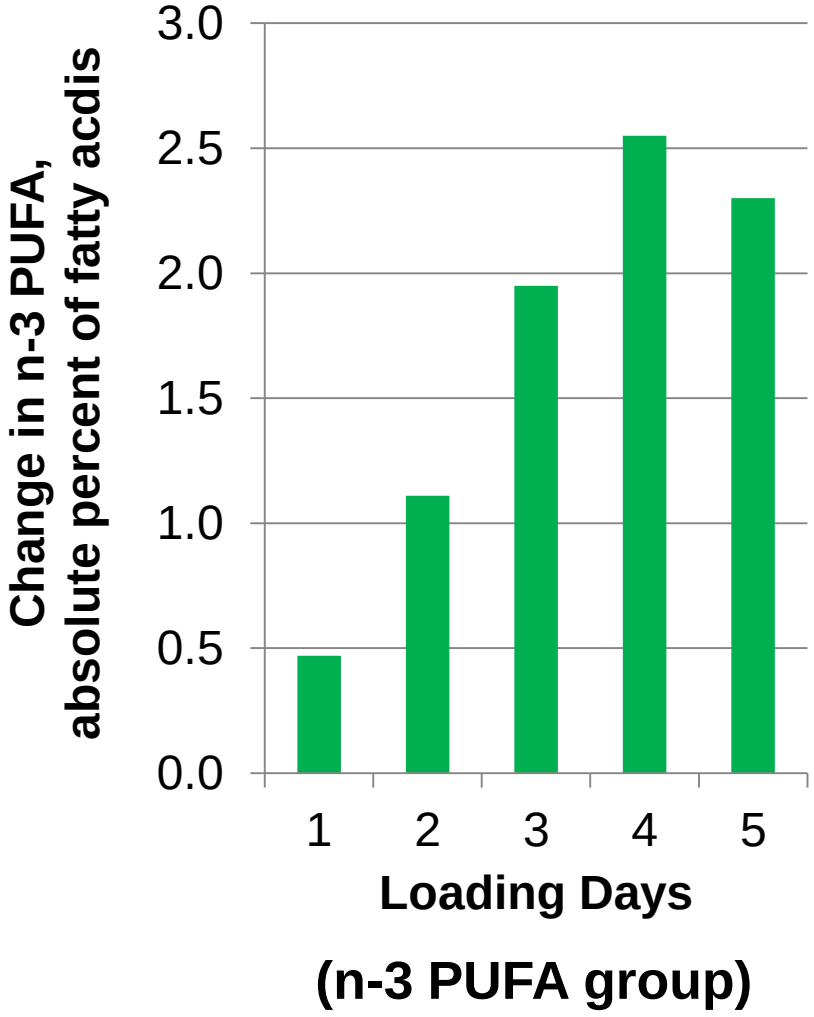
Similar results in sensitivity analyses, including in the subset of adherent patients (taking 80%+ of study drug).

Other Endpoints

	Placebo	n-3 PUFA	OR (95%CI)	P-value
Other arrhythmias, n (%)				
Other supraventricular tachycardia	6 (0.8)	11 (1.5)	1.85 (0.68, 5.02)	0.33
Ventricular tachycardia or fibrillation	9 (1.2)	5 (0.7)	0.55 (0.18, 1.66)	0.42
Other endpoints, n (%)				
MACE, in-hospital ¶	20 (2.6)	13 (1.7)	0.62 (0.31, 1.25)	0.18
Myocardial infarction	10 (1.3)	10 (1.3)	0.99 (0.41, 2.39)	1.00
Stroke	8 (1.1)	4 (0.5)	0.45 (0.13, 1.51)	0.18
Cardiovascular death	3 (0.4)	0 (0.0)	n/a	0.08
Arterial thromboembolism, 30 days	13 (1.7)	5 (0.7)	0.37 (0.13-1.03)	0.047
Arterial thromboembolism or death, 30 days	27 (3.6)	13 (1.7)	0.43 (0.22-0.84)	0.01
Total mortality, 30 days	15 (2.0)	8 (1.1)	0.53 (0.23-1.26)	0.14
- Cardiac arrhythmic	0 (0.0)	1 (0.1)	--	0.32
- Cardiac nonarrhythmic	2 (0.3)	0 (0.0)	--	0.16
- Vascular	3 (0.4)	0 (0.0)	--	0.08
- Noncardiovascular	10 (1.3)	7 (0.9)	0.70 (0.27-1.84)	0.47
Resource utilization, median (25^{th}, 75^{th} %)				
Total ICU/CCU stay, days	2 (1, 3)	2 (1, 3)	n/a	0.38
Total telemetry monitoring, days	6 (5, 7)	6 (5, 7)	n/a	0.39
Total hospital stay, days	7 (5, 8)	7 (5, 9)	n/a	0.48

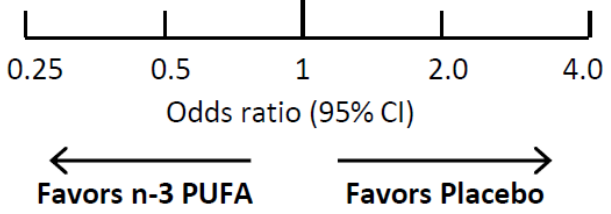
Changes in n-3 PUFA Levels



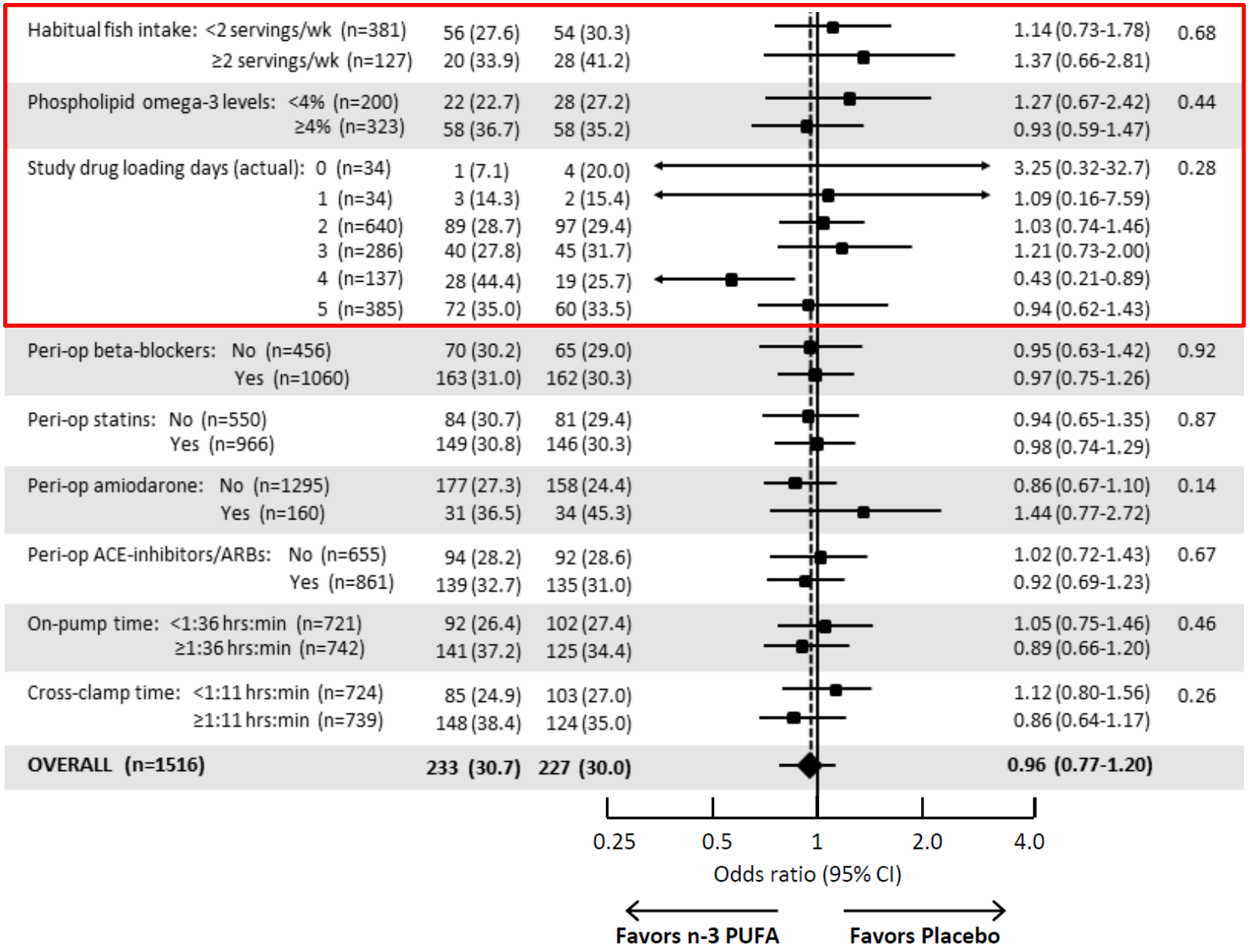


Prespecified Subgroups

Subgroup	Events (%) Placebo	Events (%) n-3 PUFA	Odds ratio (95% CI)	P for Interaction
Age: <70 years (n=960)	114 (23.6)	105 (22.0)	0.91 (0.68-1.24)	0.68
≥70 years (n=556)	119 (43.3)	122 (43.4)	1.01 (0.72-1.41)	
Sex: Male (n=1094)	169 (31.1)	168 (30.5)	0.97 (0.75-1.26)	0.90
Female (n=422)	64 (29.8)	59 (28.5)	0.94 (0.62-1.43)	
Country: Argentina (n=342)	52 (30.4)	47 (27.5)	0.87 (0.54-1.39)	0.77
Italy (n=728)	116 (32.0)	115 (31.5)	0.98 (0.72-1.34)	
USA (n=446)	65 (29.0)	65 (29.3)	1.01 (0.67-1.52)	
Cardiac valve surgery: No (n=707)	84 (23.6)	95 (27.1)	1.20 (0.86-1.69)	0.06
Yes (n=756)	149 (40.2)	132 (34.3)	0.78 (0.58-1.05)	
Hypertension: No (n=368)	41 (21.7)	37 (20.7)	0.94 (0.57-1.55)	0.92
Yes (n=1135)	189 (33.6)	188 (32.9)	0.97 (0.76-1.24)	
NYHA class 2-4: No (n=1111)	165 (29.7)	162 (29.1)	0.97 (0.75-1.26)	0.97
Yes (n=362)	60 (33.9)	62 (33.5)	0.98 (0.64-1.52)	
Serum potassium: <4.18 mmol/L (n=729)	115 (32.5)	117 (31.2)	0.94 (0.69-1.29)	0.90
≥4.18 mmol/L (n=730)	110 (29.3)	102 (28.7)	0.97 (0.71-1.34)	
Left atrial diameter: <42 mm (n=480)	60 (24.8)	56 (23.5)	0.93 (0.61-1.42)	0.83
≥42 mm (n=555)	108 (38.9)	107 (38.6)	0.99 (0.70-1.39)	
Ejection fraction: <50% (n=288)	36 (24.5)	37 (26.2)	1.10 (0.65-1.87)	0.59
≥50% (n=1208)	194 (32.3)	187 (30.8)	0.93 (0.73-1.19)	



Prespecified Subgroups



Post-op Bleeding	Placebo (N=758)	n-3 PUFA (N=758)	P value
24-hour chest tube output (ml), median (IQR)	271 (150, 450)	270 (150, 435)	0.47
Total units of blood, mean (SD)	1.9 (3.3)	1.6 (2.6)	<0.001
median (IQR)	1.0 (0, 3.0)	1.0 (0, 2.0)	
Units during surgery, mean (SD)	1.0 (1.8)	0.8 (1.5)	0.002
median (IQR)	0 (0, 2.0)	0 (0, 2.0)	
Units post-surgery, mean (SD)	0.9 (2.1)	0.8 (1.8)	0.008
median (IQR)	0 (0, 1.0)	0 (0, 1.0)	
Fatal bleeding, n (%)	3 (0.4)	0 (0)	0.08
Bleeding requiring reexploration or surgery, n (%)	25 (3.3)	20 (2.6)	0.45
ISTH surgical bleeding (%)	32 (4.2)	19 (2.5)	0.06
TIMI cardiac surg. bleeding, n (%)	50 (6.6)	39 (5.2)	0.23
TIMI major bleeding, n (%)	26 (3.4)	21 (2.8)	0.46
TIMI minor bleeding, n (%)	25 (3.3)	21 (2.8)	0.55

Adverse Events	Placebo (N=758)	n-3 PUFA (N=758)	P value
Adverse events commonly seen with fish oil	**60 (7.9)**	**86 (11.4)**	**0.02**
Gastrointestinal upset	27 (3.6)	44 (5.8)	0.04
Burping	19 (2.5)	33 (4.4)	0.05
Fish oil taste	12 (1.6)	22 (2.9)	0.08
Infection	5 (0.7)	6 (0.8)	0.76
Liver inflammation	2 (0.3)	0 (0.0)	0.50
Skin rush or allergic reaction	2 (0.3)	2 (0.3)	1.00
AE's leading to stopping of study drug	**25 / 20 (2.6)**	**19 / 19 (2.5)**	0.87
Bleeding	7 / 7 (0.9)	2 / 2 (0.3)	0.18
Cardiac	3 / 3 (0.4)	6 / 6 (0.8)	0.51
Constitutional symptoms	1 / 1 (0.1)	0 / 0 (0.0)	1.00
GI, hepatobiliary, or pancreas	2 / 2 (0.3)	8 / 8 (1.1)	0.11
Infection	1 / 1 (0.1)	1 / 1 (0.1)	1.00
Neurologic	5 / 5 (0.7)	1 / 1 (0.1)	0.22
Pulmonary	3 / 3 (0.4)	1 / 1 (0.1)	0.62
Renal or genitourinary	2 / 2 (0.3)	0 / 0 (0.0)	0.50
Vascular	1 / 1 (0.1)	0 / 0 (0.0)	1.00

Potential Limitations

- Current best-practice guidelines for preventing PoAF were recommended to all Centers, which could have reduced the impact of any additional therapy on risk of PoAF.
- Patients were identified and allocated n-3 PUFA over varying durations from 2 to 5 days prior to surgery. However, subgroup analyses did not identify different effects by days of loading.
- The dose of n-3-PUFA may have been too low to produce a benefit. However, circulating n-3-PUFA have systemic effects that could reduce AF risk, and phospholipid n-3-PUFA levels increased by ~40% by the time of surgery.
- Compliance with study drug was high but not perfect. Analyses restricted to adherent patients, however, were consistent with the main findings.

Other Ongoing Analyses

Effects of peri-operative n-3 PUFA on:

- Post-op cognitive decline.
- Systemic and myocardial oxidative stress and inflammation.
- Myocardial stress and injury.
- Myocardial structure and immunohistochemistry.

Conclusions

- In this large, multinational, placebo-controlled trial, peri-operative n-3 PUFA did not reduce PoAF.
- n-3 PUFA was well tolerated, without evidence for significant adverse events or higher bleeding.
- More promising may be long-term (years) n-3 PUFA to prevent the initial onset (not recurrence) of AF in higher risk adults: needs to be tested in RCTs.
- Post-op AF remains and enigmatic and difficult to prevent complication of cardiac surgery.

Acknowledgements

We sincerely thank each of the 1,516 patients who participated in OPERA.

We also gratefully acknowledge the efforts and collaboration of each of our co-investigators and colleagues, including on the

- Steering Committee
- Events Committee
- Biologic Studies Committee
- Data Safety and Monitoring Board
- Biomarker and Cognitive Decline Ancillary Study
- Coordinating Centers in Italy and USA
- The 28 Clinical Centers in Italy, Argentina, and USA

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