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The Omega-3 Fatty Acids for Prevention of Post-Operative Atrial Fibrillation (OPERA) Trial – Rationale and Design

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Abstract

Post-operative atrial fibrillation/flutter (PoAF) commonly complicates cardiac surgery, occurring in 25–60% of patients. PoAF is associated with significant morbidity, higher long-term mortality, and increased healthcare costs. Novel preventive therapies are clearly needed. In experiments and short-term trials, seafood-derived long-chain omega-3 polyunsaturated fatty acids (PUFA) influence several risk factors that might reduce risk of PoAF. A few small and generally underpowered trials have evaluated effects of omega-3-PUFA supplementation on PoAF, with mixed results. The Omega-3 Fatty Acids for Prevention of Post-operative Atrial Fibrillation (OPERA) trial is an appropriately powered, investigator-initiated, randomized, double-blind, placebo-controlled, multinational trial to determine whether peri-operative oral omega-3-PUFA reduces occurrence of PoAF in 1,516 patients undergoing cardiac surgery. Additional aims include evaluation of resource utilization, biologic pathways and mechanisms, postoperative cognitive decline, and safety. Broad inclusion criteria encompass a real-world population of outpatients and inpatients scheduled for cardiac surgery. Treatment comprises a total pre-operative loading dose of 8–10 g of omega-3-PUFA or placebo divided over 2–5 days, followed by 2 g/d until hospital discharge or post-operative day 10, whichever first. Based on anticipated 30% event rate in controls, total enrollment of 1,516 patients (758 per treatment arm) will provide 90% power to detect 25% reduction in PoAF. OPERA will provide invaluable evidence to inform biologic pathways, proof-of-concept that omega-3-PUFA influence cardiac arrhythmias, and potential regulatory standards and clinical use of this simple, inexpensive, and low-risk intervention to prevent PoAF.

INTRODUCTION

Post-operative atrial fibrillation or flutter (PoAF) commonly complicates cardiac surgery, occurring in 25–60% of all patients, depending on underlying patient characteristics and methods of arrhythmia ascertainment.^{1–6} PoAF can produce hemodynamic instability or symptoms requiring cardioversion or pressor support, and is associated with greater infectious, renal, and neurological complications.³ PoAF may necessitate in-hospital and/or

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See Appendix for complete list of OPERA Investigators and institutions.

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long-term antiarrhythmic and anticoagulant drug treatment, potentially increasing risk of bleeding complications and medication side effects. Patients with persistent PoAF often suffer from decreased exercise tolerance and fatigue, may undergo recurrent cardioversion attempts, and have increased long-term mortality.^{4, 5} Excess mortality appears attributable to more frequent embolic stroke,⁶ suggesting a potentially direct causal relationship to PoAF.

PoAF also substantially increases healthcare costs and utilization. Patients with PoAF spend ~0.5 more days in intensive care units and 2–4 more days in the hospital.^{1, 7} In one analysis, ~\$6,400 excess in-hospital costs were attributable to each patient developing PoAF.⁸ Use of drugs including beta-blockers and amiodarone can partly reduce risk of PoAF, but even using such medications, 25% or more of patients develop PoAF.⁹ New therapies to prevent PoAF and its complications could have considerable health and economic benefits.

Intake of fish or fish oil appears to reduce risk of coronary death, perhaps through reduction of primary ventricular arrhythmias.¹⁰ Experimental evidence supports direct and indirect antiarrhythmic effects of long-chain omega-3 polyunsaturated fatty acids (PUFA) in fish oil, eicosapentaenoic acid (EPA/20:5n-3) and docosahexaenoic acid (DHA/22:6n-3), especially in the setting of acute ischemia. Effects on other cardiac arrhythmias, such as AF, are less well-established. In experimental studies and short-term clinical trials, omega-3-PUFA influence several risk factors that might reduce AF,¹⁰ but small trials of omega-3-PUFA supplementation and PoAF have shown mixed results.^{11–14} The Omega-3 Fatty Acids for Prevention of Post-operative Atrial Fibrillation (OPERA) trial is an investigator-initiated study to determine in an appropriately powered, randomized, double-blind, placebo-controlled, multinational clinical trial whether peri-operative administration of oral omega-3-PUFA reduces occurrence of PoAF after cardiac surgery.

RATIONALE: OMEGA-3 PUFA AND ATRIAL FIBRILLATION

Experimental Evidence (see Appendix for citations in this section)

In laboratory experiments, omega-3-PUFA modulate function of myocardial Na⁺ and L-type Ca⁺⁺ channels, decreasing myocyte excitability and cytosolic calcium fluctuations. Omega-3-PUFA also terminate induced asynchronous contractile activity of cultured atrial myocytes and, in animal studies, reduce experimentally-induced AF while normalizing atrial connexin levels. Thus, omega-3-PUFA could have direct anti-arrhythmic effects, although evidence for such effects has been mixed in trials of ambulatory patients with paroxysmal clinical arrhythmias.

Omega-3-PUFA could also reduce PoAF through other biologic pathways. In animal-feeding studies, omega-3-PUFA reduce peripheral vascular resistance and left ventricular hypertrophy, lower workload-specific myocardial oxygen consumption, improve post-ischemia-reperfusion contractile recovery, and enhance ventricular diastolic function. In human trials, omega-3-PUFA supplementation lowers resting heart rate and blood pressure, attenuates vasoconstrictive responses to angiotensin-II, improves arteriolar compliance, and improves ventricular diastolic filling. Omega-3-PUFA may also favorably affect heart rate variability and baroreceptor reflex responses, suggesting modulation of balance of sympathetic versus parasympathetic control mechanisms. Omega-3-PUFA also have anti-inflammatory effects. Normalization of perturbations in each of these pathways could reduce PoAF.

Epidemiologic Evidence

In one prospective observational study, individuals who consumed fish more frequently had higher plasma phospholipid EPA+DHA and significantly lower incidence of AF during follow-up.¹⁵ Among patients followed post-myocardial infarction, higher omega-3-PUFA

consumption was associated with 81% lower risk of AF.¹⁶ In another prospective cohort, higher plasma DHA levels were associated with lower incident AF.¹⁷ Conversely, three other observational studies did not see associations between fish or EPA+DHA consumption and AF risk.¹⁰ Overall, these studies provide some evidence, albeit mixed, that omega-3-PUFA may reduce new-onset AF among ambulatory individuals.

Trial Evidence

Four small clinical trials have evaluated whether omega-3-PUFA reduces PoAF. In an open-label (nonblinded) single-center trial (n=160), omega-3-PUFA (2 g/d initiated at least 5 days pre-operatively, continued until hospital discharge) reduced PoAF (15.2% vs. 33.3%, p=0.009) and hospital length-of-stay.¹¹ In a placebo-controlled, double-blind trial (n=102) intravenous omega-3-PUFA (100 mg/d per kg body weight initiated at hospital admission, continued until ICU discharge) significantly reduced PoAF (17.3% vs. 30.6%; p<0.05) and hospital length-of-stay.¹² Conversely, two other placebo-controlled, double-blind trials (n=108, n=260) showed no significant effects of peri-operative oral omega-3-PUFA on PoAF.^{13, 14} In ambulatory patients with preexisting AF, omega-3-PUFA had no effect on recurrent AF,¹⁸ although relevance of these results to PoAF is unclear given differing pathophysiology of post-operative vs. recurrent ambulatory arrhythmias.

The mixed findings of these generally small and underpowered trials limit strong conclusions. Experimental, epidemiologic, and preliminary clinical evidence for potential benefits, as well as excess morbidity, mortality, and costs associated with PoAF, renders imperative the rigorous evaluation of whether omega-3-PUFA reduces PoAF in an appropriately designed, adequately powered clinical trial.

Dosing

Prior studies suggest potential efficacy of modest peri-operative doses. Observational studies and randomized trials suggest that omega-3-PUFA prevent ventricular arrhythmias at low doses, e.g., 250–500 mg/d EPA+DHA.¹⁰ Similar low dietary doses were associated with lower incidence of AF among ambulatory adults.¹⁵ Supplementation alters circulating and tissue levels of EPA and DHA within days;¹⁹ and in one small trial, a 10 g loading dose over 5 days pre-operatively followed by 2 g/d postoperatively reduced PoAF.¹¹ Because omega-3-PUFA persist in tissues for several days, a loading dose also provides some buffer in patients who might not tolerate oral medications for several days post-surgery. Higher doses (e.g., 5+ g/d) could increase patient dyspepsia and potential concern among treating physicians for bleeding risk (although bleeding concerns are not supported by studies to-date; see below).

STUDY DESIGN

Aims

Our primary aim is to determine in a randomized, double-blind, placebo-controlled clinical trial whether peri-operative oral omega-3-PUFA reduces occurrence of PoAF following cardiac surgery. Secondary aims include investigation of (a) effects of omega-3-PUFA on resource utilization; (b) biologic pathways related to PoAF, and effects of omega-3-PUFA on these pathways; and (c) biologic pathways related to, and effects of omega-3-PUFA on, post-operative cognitive decline.

Population

OPERA is a multi-center, multi-country (United States, Italy, Argentina) clinical trial (ClinicalTrials.gov=NCT00970489). Overarching design principles include simplicity and generalizability to maximize application to “real-world” patients and clinical care. Inclusion

criteria are broad (Table 1) to produce a general population of outpatients and inpatients scheduled for cardiac surgery. Neither history of prior AF nor planned AF ablation procedures are exclusions, given similar or higher risk of PoAF and no known biologic interaction that would reduce efficacy of omega-3-PUFA in such patients. Use of chronic or prophylactic anti-arrhythmic drugs is also allowed, as OPERA is intended to determine whether omega-3-PUFA reduces PoAF when added to current best practice.

Consent and Randomization

All identified potential subjects will be provided sufficient information to make an informed written decision on consent for participation. The protocol and consent process have been reviewed and approved by human subjects committees of all participating institutions. The trial will be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312, International Conference on Harmonization guidelines), applicable government regulations, and institutional research policies/procedures. At enrollment, the central Data Coordinating Center will block-10 randomize patients to receive omega-3-PUFA versus matched placebo by means of computer-generated numbers, stratified by enrolling medical center and planned valve surgery (yes/no). All investigators, patients, and providers will be blinded to treatment assignment.

Intervention

Patients will receive oral omega-3-PUFA or placebo (olive oil) as coated, identical-appearing capsules (Figure 1). Based on the interval between enrollment and planned surgery, a total pre-operative loading dose of 10 g will be divided over the longest of 3–5 days (or 8 g over 2 days), including the morning of surgery. Patients enrolled one day prior to surgery will receive a slightly lower loading dose (8 g in two divided doses) to avoid daily dosing above the currently approved dose for treatment of hypertriglyceridemia (4 g/d). Flexibility in pre-operative dosing maximizes generalizability by allowing enrollment of most patients, including inpatients who are often identified only one day before cardiac surgery. OPERA excludes patients undergoing emergent surgery, i.e., on the day of presentation.

Post-operatively, each patient will receive 2 g/d until hospital discharge or post-operative day 10 (i.e., administrative censoring), whichever occurs sooner. Study drug and follow-up for PoAF will be discontinued at this timepoint, because most PoAF occurs between post-operative days 2 to 7, and because the Steering and Events Committees judged that new-onset AF beyond post-operative day 10 would be difficult to attribute directly to cardiac surgery and that new-onset AF after hospital discharge would be difficult to capture systematically. For patients unable to tolerate oral medications postoperatively, the study drug may be administered via non-PVC nasogastric/gastric tube if present for clinical indications, or otherwise as soon as the patient is tolerating oral medications, consistent with OPERA's design as a trial of both efficacy and effectiveness. Study drug administration will not be altered by protocol-defined events (e.g., PoAF) due to interest in evaluating both multiple endpoints and safety outcomes in all patients, except at discretion of the treating physician or patient due to tolerance or safety concerns. Compliance will be monitored by capsule count for outpatient loading and by hospital records for inpatients.

With the exception of study drug (omega-3-PUFA or placebo), all other treatments, including surgical and anesthetic procedures; chronic or prophylactic anti-arrhythmic medication use; and treatment of arrhythmic episodes; will be entirely at discretion of the physicians caring for the patient. Current best-practice guidelines for prevention of PoAF will be strongly recommended to all Centers;²⁰ data will be collected on use of relevant peri-operative medications/treatments.

Endpoints

The primary endpoint will be the occurrence of PoAF of at least 30 seconds duration (Table 2). A secondary endpoint will be sustained or symptomatic AF, that may be considered to be a more clinical endpoint. Additional endpoints will include hospital length-of-stay, 30-day and 1-year mortality, secondary and safety outcomes, and Ancillary Biologic Studies (see below).

Centers will be encouraged to utilize continuous cardiac monitoring for at least 5 days post-surgery and daily in-hospital 12-lead ECGs, whenever possible and according to usual practice at each Center. Clinical information and confirmatory rhythm strips/12-lead ECGs will be collected on all postoperative arrhythmias of at least 30 seconds duration, including AF, other SVT, VT, and VF. Because some patients may experience a brief initial episode of AF followed by more sustained/symptomatic AF, data on at least the first 3 episodes of AF will be collected to optimize detection of the secondary AF endpoint while still maintaining reasonable Center workload.

All AF episodes and other arrhythmia endpoints will be adjudicated by the Events Committee, comprised of cardiac electrophysiologists blinded to patient treatment assignment, using prespecified algorithms that make use of clinical information and direct review of rhythm strips/12-lead ECGs. Thirty-day mortality will be assessed by Center-based clinic or telephone follow-up, with cause-specific adjudication by the Events Committee. One-year all-cause mortality will be assessed by Center-based clinic or telephone follow-up.

Covariates

Standardized data will be collected on demographics; cardiovascular risk factors; major comorbidities; past medical/surgical history; anthropometry; outpatient and inpatient medications; baseline laboratory indices; and smoking, physical activity, and dietary habits. Details of the surgical and anesthetic procedure will be recorded. Daily follow-up information, including relevant to bleeding outcomes (Table 2), and discharge information will be recorded.

Biologic and Ancillary Studies

In addition to arrhythmic endpoints, OPERA provides a rich opportunity to investigate biologic pathways related to PoAF and other surgical complications; and effects of omega-3-PUFA on these and other risk pathways. Biospecimens will be collected and centrally stored utilizing standardized procedures and equipment (Figure 2). Multiple time points will help establish time courses of effects. Multiple tissues (blood, urine, atrium, pericardial fat) will help establish pathways of effects. Planned analytes include: fatty acid concentrations in red blood cell membranes, plasma, and atrial tissue; markers of oxidative stress and inflammation including plasma, urine, and myocardial F2-isoprostanes, urine leukotriene-E4 and 11-deoxy-thromboxane-B2, and plasma high sensitivity C-reactive protein and long pentraxin PTX3; markers of myocardial injury/stress including troponinT and N-terminal proBNP; and markers of neurologic injury including serum neuron-specific enolase. Cognitive function will be measured in US patients by trained personnel at enrollment, postoperative day 2, 30-days, and 1-year, using validated, robust cognitive batteries assessing key domains (e.g., immediate and delayed memory, visuospatial construction, language, attention).

Statistical Analysis

The primary analysis will be intention-to-treat, including all enrolled subjects in the analysis. The primary outcome will be the cumulative occurrence (risk) of PoAF, with

between-group differences evaluated using the binomial test of proportions, two-tailed $\alpha=0.05$. Between-group AF incidence will be compared using Kaplan-Meier survival analyses, with significance evaluated by log-rank test. Potential baseline differences between treatment groups will be evaluated using unpaired Students t-tests (continuous variables) or chi-square or Fisher exact tests (categorical variables), as appropriate. Differences in utilization (e.g., length-of-stay) will be evaluated using unpaired Students t-tests, following transformation to approximate normality if necessary. Secondary analyses will be performed comparing groups on-treatment (taking active treatment or placebo $\geq 80\%$ of intended days); using multivariable logistic regression to adjust for potential confounding characteristics not accounted for by randomization (any between-group baseline differences at $\alpha < 0.10$); and to assess effects of treatment on number of AF episodes (up to 3).

Subgroup analyses will be performed according to (1) age (\geq vs. < 70 years); (2) sex; (3) surgery (with vs. without cardiac valve repair/replacement); (4) study drug loading period (4–5 vs. 2–3 days); (5) habitual oily fish consumption (\geq vs. < 2 servings/week); (6) enrollment erythrocyte omega-3-PUFA levels (\geq vs. $<$ median); and (7) receiving vs. not receiving peri-operative (a) beta-blockers, (b) statins, (c) amiodarone, or (d) ACE-inhibitors/ARBs. The first patient was enrolled in August 2010, and we expect enrollment to conclude in Spring 2012 and primary results to be reported by Fall 2012.

Power Calculations

Although PoAF has been reported in 33–60% of surgery patients, modern rates might be lower due to improved surgical procedures or use of prophylactic medications. OPERA has the critical strength of adequate power to detect clinically-relevant effects even with modest event rates. Based on 30% event rate in controls and two-sided $\alpha=0.05$, a total of 1,516 patients (758 per treatment arm) provides 90% power to detect 25% reduction (our primary power calculation) and 80% power to detect 22% reduction in PoAF. With 35% or 25% event rate in controls, OPERA will have 90% power to detect 22.5% or 28% reduction, respectively, and 80% power to detect 20% or 24% reduction, respectively. All power calculations include anticipated 5% drop-out, a realistic value given brief treatment and in-hospital primary outcomes.

Safety Evaluation

Multiple safety outcomes will be evaluated based on prespecified definitions and procedures (Table 2). The Events Committee will adjudicate arrhythmic events and 30-day cause-specific mortality. Occurrence of major adverse cardiovascular events, bleeding, and other adverse events (AE) will be assessed. Safety assessment will be based mainly on frequency and extent of the different AE in each treatment arm. We will evaluate potential interaction with Class I or III antiarrhythmic drugs in stratified analyses. Other safety data (e.g., laboratory/ECG, vital signs, other testing) will be considered post-hoc as appropriate.

AE will be summarized for each treatment group as number and percentage having any AE, an AE in each body system, and each individual AE; and by extent of bleeding as described above. Study drug can be temporarily or permanently suspended at any time upon discretion of the treating physicians. The study period during which AE must be reported is normally defined as the period from initiation of any study procedures (enrollment) to end of study drug treatment. We will also collect information on serious AE identified up to 2 weeks following study drug discontinuation. Every serious AE suspected by local investigators to be related to study medications will be reported to the Data Coordinating Center within 24 hours of learning of its occurrence. All potential AE will be recorded and reported to the Steering Committee and an independent Data Safety and Monitoring Board (DSMB).

The DSMB will monitor both scientific integrity and patient safety throughout the trial. Duties related to scientific integrity include review and approval of scientific rationale and research protocol; evaluation of trial progress, including periodic assessments of data quality and timeliness, recruitment, accrual and retention, participant risk versus benefit, and performance of trial sites; consideration of external factors such as scientific or therapeutic developments that may impact safety, ethics or integrity of the trial; and making of recommendations and assistance in resolution of problems reported by the Investigators. Duties related to patient safety include review and approval of research protocol, informed consent documents, and plans for data and safety monitoring; monitoring of types and rates of AE; development of plans for, and assessment of results of, interim analyses and stopping rules, in advance of data analysis; protection of confidentiality of study data and monitoring results; and making of recommendations to the Steering Committee concerning continuation, termination, or other trial modifications based on observed beneficial or adverse effects of the treatment under study.

Bimonthly safety reports will be reviewed by the DSMB, and open or closed sessions held at the call of the DSMB Chair. One complete interim analysis of efficacy and safety will be prepared by a statistician not involved in the trial after enrollment of two-thirds of the patients and reviewed by the DSMB. The study can be stopped at anytime if, in the DSMB's judgment, the study participants are subjected to unnecessary risk. The DSMB can also recommend early termination because of overwhelming evidence of efficacy. Although conventional O'Brien Fleming boundaries will be examined for the interim analysis, any decision concerning early termination will be based on a comprehensive assessment of all available information, weighing both obligations to participants and to society and with clear recognition of the potential for overestimates of treatment effects (good or bad) that can arise when a trial is terminated early on the basis of limited numbers of outcomes. Contemplation of early termination for efficacy will also take into account the potential adverse effect on the multiple relevant primary, secondary, and biologic endpoints in the trial.

The modest omega-3-PUFA dose and treatment duration (maximum 2 weeks) should minimize drug-related serious AE. Smaller prior clinical trials using similar or higher doses in surgery patients did not report any treatment-related serious AE.^{11, 21, 22} In a trial among 204 patients undergoing coronary angioplasty, patients received omega-3-PUFA 6 g/d (starting ~5 days pre-angioplasty, continued for 6 months) without any significant treatment-related AE or bleeding episodes.²³ In a trial among 610 patients undergoing cardiac surgery, omega-3-PUFA 4 g/d (starting on post-operative day 2, continued for one year), together with either aspirin or warfarin, did not result in increased clinical bleeding.²⁴

CONCLUSIONS

The OPERA trial will critically assess important research questions in a carefully designed randomized, double-blind, placebo-controlled, clinical trial. The multi-country, multi-center collaboration provides a broad cross-section of "real-world" patients, with appropriate power to detect clinically-relevant effects and facilitate secondary and subgroup analyses. Prospective evaluation of utilization outcomes will inform potential projected savings of this novel approach to preventing cardiac surgery complications. Novel ancillary studies will elucidate important mechanistic pathways for PoAF and cognitive decline and potential effects of omega-3-PUFA on these pathways. The OPERA trial will provide invaluable evidence on biologic mechanisms, provide a critical test of the hypothesis that omega-3-PUFA influence cardiac arrhythmias, and inform potential regulatory standards and clinical use of this simple, inexpensive, and low-risk intervention to prevent PoAF.

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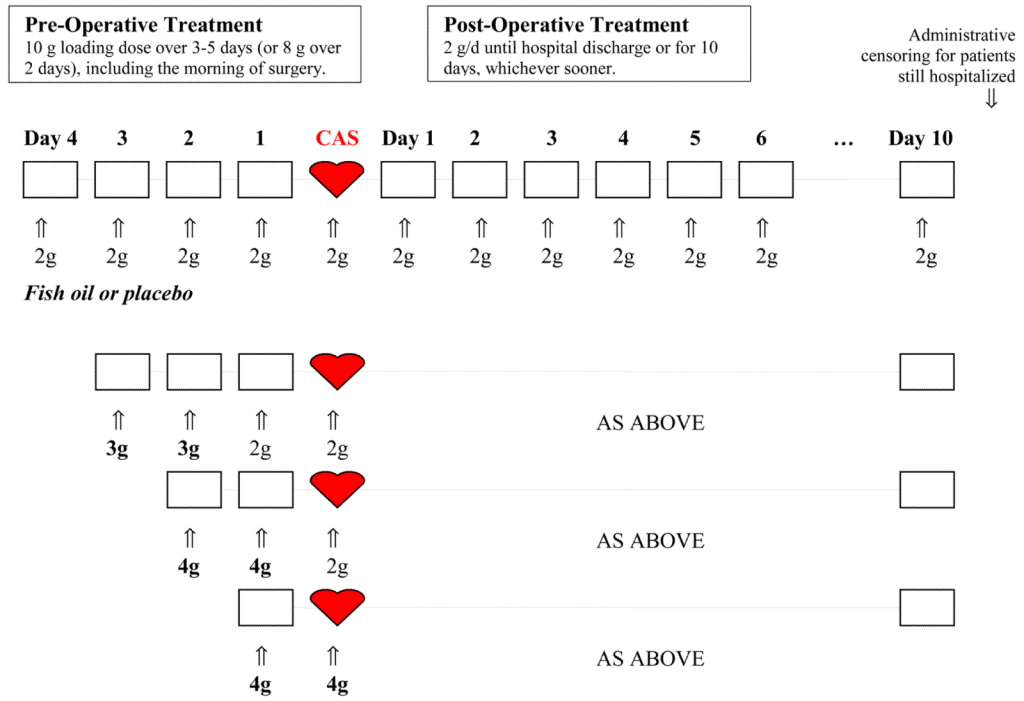


Figure 1.
Dosing of study drug in the OPERA trial.

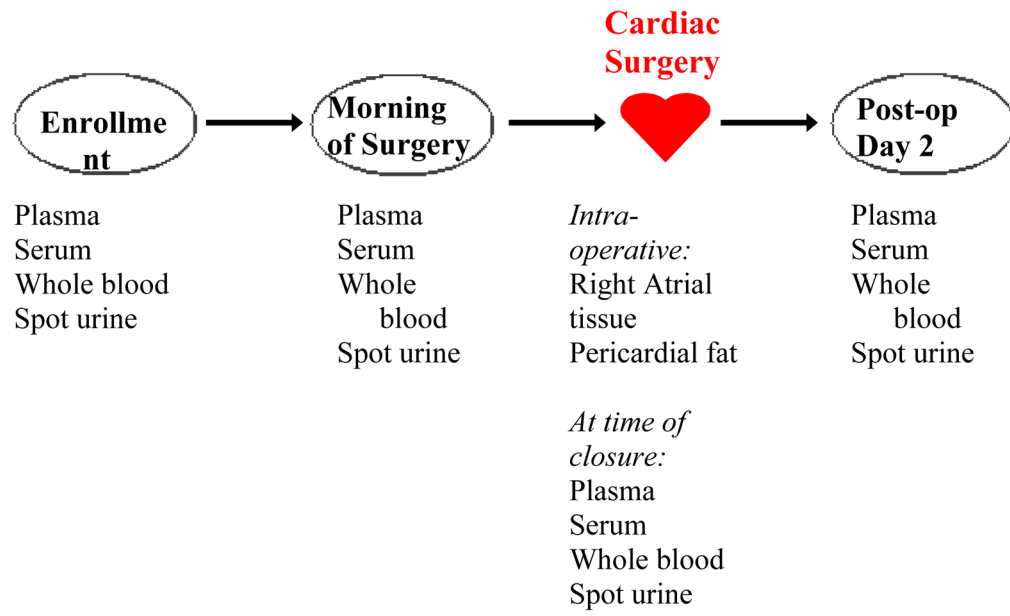


Figure 2.
Biologic specimen collection in the OPERA trial.

Table 1

OPERA Inclusion and Exclusion Criteria.

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> • Age 18 years or older. • Scheduled for cardiac surgery on the following day or later.* <ul style="list-style-type: none"> - Sinus rhythm on ECG at enrollment.[†] 	<ul style="list-style-type: none"> • 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. • Planned or existing cardiac transplant or left ventricular assist device. • Unable or unwilling to provide informed written consent.

* Cardiac surgery may include surgical coronary artery bypass, surgical valve repair or replacement, or any other open cardiac surgery that includes opening of the pericardium, including any combination of the above.

[†] Includes sinus bradycardia or tachycardia, with or without ectopic beats. History of prior AF is not an exclusion criterion.

Table 2

OPERA Endpoints.

Endpoint	Definition	Characteristics
Atrial Fibrillation * (primary endpoint)	Any documented atrial fibrillation (AF) or atrial flutter (AFL) of at least 30 seconds duration and documented by rhythm strip or 12-lead ECG. If only a shorter duration ECG is available, then the diagnosis of AF/AFL is based on the arrhythmia being present at onset or termination.	<ul style="list-style-type: none"> • AF - Irregular ventricular response independent of rate, with the following characteristics: <ul style="list-style-type: none"> – QRS complex unchanged from baseline or functional bundle branch block, and – absence of P waves, or – presence of fibrillatory waves in isoelectric periods of the ECG. • AFL - With variable block, 2:1, 3:1, or 4:1, but not sinus tachycardia, with the following characteristics: <ul style="list-style-type: none"> – QRS unchanged from baseline or functional bundle branch block, and – absence of sinus P waves, and – presence of flutter waves in isoelectric periods of the QRS complex of the ECG. • AF/ AFL (unable to distinguish) - Presence of RR interval irregularity will favor AF diagnosis. • SVT/ suspect AF - Paroxysmal SVT not consistent with AFL or sinus tachycardia, with characteristics of SVT (see below) except >0.02 second variation in successive cardiac cycles, but not definite AF.
Sustained or Symptomatic Atrial Fibrillation * (secondary endpoint)	AF/AFL meeting all requirements for the primary endpoint, plus being either sustained, symptomatic, or both.	<ul style="list-style-type: none"> • Sustained: Presence for at least one hour duration. • Symptomatic: <ul style="list-style-type: none"> – treated with electrical or pharmacological cardioversion, or – temporally associated with new or worsening chest pain or shortness of breath, or – treated with fluid or pressor treatment for hypotension (drop in blood pressure requiring escalation of treatment).
Other Arrhythmias *	Other supraventricular tachycardia (SVT)	<ul style="list-style-type: none"> • SVT/ suspect not AF - Paroxysmal SVT not consistent with AFL or sinus tachycardia, with the following characteristics: <ul style="list-style-type: none"> – mean ventricular rate \geq 100 beats per minute, and – QRS complex unchanged from baseline or functional bundle branch block, and – <0.02 second variation in successive cardiac cycles unless cycle length alternans is seen, and – no evidence of atrioventricular dissociation, and – absence of sinus P waves.
	Ventricular tachycardia (VT)	<ul style="list-style-type: none"> • Wide complex QRS (>120 msec), rhythm > 100/min, with AV dissociation, capture or fusion beats.
	Ventricular fibrillation (VF)	<ul style="list-style-type: none"> • Completely disorganized ventricular electrical activity.
Utilization Endpoints	Unit and hospital length-of-stays	<ul style="list-style-type: none"> • Total intensive/coronary care unit length-of-stay • Total days of telemetry monitoring • Total hospital length-of-stay

Endpoint	Definition	Characteristics
Mortality and Safety Endpoints	Mortality	<ul style="list-style-type: none"> • 30-day mortality, including cause-specific mortality: † <ul style="list-style-type: none"> – cardiac arrhythmic – cardiac nonarrhythmic – vascular – non-cardiovascular – unknown • 1-year mortality, all-cause
	Major adverse coronary events (MACE)	<ul style="list-style-type: none"> • Myocardial infarction, stroke, and cardiovascular death †
	Bleeding	<ul style="list-style-type: none"> • Chest tube output during the first 24 hours after cardiac surgery. • Total RBC transfusions from enrollment to hospital discharge or post-operative day 10 (whichever sooner). • Any bleeding requiring re-exploration or surgery. • All other episodes of minor and major bleeding. • Composite TIMI bleeding indices, including major, minor, and loss no site bleeding.
	Other adverse events and serious adverse events	<ul style="list-style-type: none"> • Coded as appropriate using the MedDRA dictionary.

* From the time of cardiac surgery until hospital discharge or post-operative day 10, whichever occurs first.

† Standardized definitions, available from the authors upon request.