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ORIGINAL ARTICLE

Fish Oil and Perioperative Bleeding

Insights From the OPERA Randomized Trial

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BACKGROUND: Fish oil is among the most common natural supplements for treatment of hypertriglyceridemia or prevention of cardiovascular disease. However, concerns about theoretical bleeding risk have led to recommendations that patients should stop taking fish oil before surgery or delay in elective procedures for patients taking fish oil by some health care professionals.

METHODS AND RESULTS: We tested the effect of fish oil supplementation on perioperative bleeding in a multinational, placebo-controlled trial involving 1516 patients who were randomized to perioperative fish oil (eicosapentaenoic acid+docosahexaenoic acid; 8–10 g for 2–5 days preoperatively, and then 2 g/d postoperatively) or placebo. Primary outcome was major perioperative bleeding as defined by the Bleeding Academic Research Consortium. Secondary outcomes include perioperative bleeding per thrombolysis in myocardial infarction and International Society on Thrombosis and Hemostasis definitions, chest tube output, and total units of blood transfused. Participants' mean (SD) age was 63 (13) years, and planned surgery included coronary artery bypass graft (52%) and valve surgery (50%). The primary outcome occurred in 92 patients (6.1%). Compared with placebo, risk of Bleeding Academic Research Consortium bleeding was not higher in the fish oil group: odds ratio, 0.81; 95% CI, 0.53–1.24; absolute risk difference, 1.1% lower (95% CI, −3.0% to 1.8%). Similar findings were seen for secondary bleeding definitions. The total units of blood transfused were significantly lower in the fish oil group compared with placebo (mean, 1.61 versus 1.92; $P<0.001$). Evaluating achieved plasma phospholipid omega-3 polyunsaturated fatty acids levels with supplementation (on the morning of surgery), higher levels were associated with lower risk of Bleeding Academic Research Consortium bleeding, with substantially lower risk in the third (odds ratio, 0.30 [95% CI, 0.11–0.78]) and fourth (0.36 [95% CI, 0.15–0.87]) quartiles, compared with the lowest quartile.

CONCLUSIONS: Fish oil supplementation did not increase perioperative bleeding and reduced the number of blood transfusions. Higher achieved n-3-PUFA levels were associated with lower risk of bleeding. These novel findings support the need for reconsideration of current recommendations to stop fish oil or delay procedures before cardiac surgery.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT00970489.

Key Words: chest tubes ■ fish oils ■ hemorrhage ■ risk ■ thoracic surgery

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WHAT IS KNOWN

- Fish oil is among the most commonly used natural supplements with associated cardiovascular benefits.
- Elective surgeries/procedures for patients taking fish oil tend to be delayed because of concern for theoretical bleeding risk associated with the potential antiplatelet effect of fish oil.
- Limited clinical evidence exists to change this practice.

WHAT THE STUDY ADDS

- Our study provides the most robust evidence to date that fish oil supplementation does not lead to increase perioperative bleeding. Hence, surgeries/procedures should not be delayed for patients taking fish oil.
- A relatively novel finding that fish oil supplementation may reduce the number of blood transfusion after surgery merits further evaluation in future randomized controlled trials.

Fish oil provides a concentrated source of the long-chain omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These fatty acid have a wide array of biologic activities related to cardiovascular health, including lowered blood pressure and triglycerides, and improved endothelial vasodilator function.[1,2] Accordingly, individuals having or at risk for cardiovascular disease frequently use fish oil supplements, with about 8% of such people taking either prescription or supplement fish oil.[3,4] Yet, concerns persist about the possible bleeding risks of fish oil consumption, particularly during major surgical procedures. EPA and DHA may compete with arachidonic acid for incorporation into the platelet membrane or cyclooxygenase-mediated pathways,[5] leading to reduced production of arachidonic acid-derived prothrombotic metabolites, such as thromboxane A2, and increased production of antithrombotic EPA metabolites that could reduce platelet activation and aggregation. Concerns over the potential risk of bleeding associated with this anti-platelet effect have led to recommendations that patients stop taking fish oil supplements before surgery and for delay in elective surgical procedures for patients taking fish oil by some health care professionals.[6–11] Yet, little or no objective clinical evidence supports this practice. The risk of increased bleeding with fish oil consumption remains largely theoretical because prior clinical trials have not reported significantly increased risk of bleeding with fish oil supplementation.[12–16] However, few of these prior trials enrolled patients undergoing surgery, existing studies in surgical patients have been generally small (up to several hundred patients), and few prior studies prospectively collected information on bleeding during and after surgery in a standardized fashion. Thus, rigorous evaluation of the effect of fish oil supplements on bleeding risk during and after surgery is needed. Understanding the presence and magnitude of such possible risks has considerable importance for clinical practice and for guidelines on fish oil use before surgery for those taking fish oil, including 19 million American adults.[3]

The OPERA trial (Omega-3 Fatty Acids for Prevention of Postoperative Atrial Fibrillation) was a multinational, placebo-controlled randomized trial designed to test the effect of perioperative fish oil supplementation on postoperative atrial fibrillation in a broad, generalizable population of patients undergoing cardiac surgery.[17] This trial that included >1500 patients across 3 nations is the largest trial to date that studied randomized perioperative use of fish oil and standardized, prospective evaluation of intraoperative and postoperative bleeding outcomes. In an initial report from the OPERA trial, fish oil supplementation reduced the number of units of perioperative and postoperative blood transfusion. The present investigation more comprehensively evaluates the effect of randomized fish oil treatment on a range of standardized intraoperative and postoperative bleeding outcomes; whether other patient or surgery characteristics modified these effects; and also how circulating phospholipid omega-3 fatty acid concentrations at baseline and achieved after supplementation relate to these risks of bleeding. Although bleeding outcomes, including clinical bleeding and transfusion requirements, were prespecified safety end points of the OPERA trials, the present investigation should be considered as a secondary analysis of the trial.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Design and Patients

The design and primary results of OPERA have been described.[17,18] Briefly, 1516 patients undergoing cardiac surgery were recruited across 28 centers in the United States, Italy, and Argentina between August 2010 and June 2012 (Figure I in the Data Supplement). Inclusion criteria were broad and generalizable, including age ≥18 years, upcoming cardiac surgery (any combination of coronary artery bypass graft [CABG], valve surgery, or other cardiac surgery opening the pericardium), and sinus rhythm at enrollment. Exclusion criteria included regular use (≥3 d/wk) of fish oil within the prior 4 weeks, known allergy to fish oil or olive oil (placebo), current pregnancy, or inability to provide informed written consent. The study was approved by the institutional research boards or equivalent of all participating institutions, and all patients provided written informed consent.

Interventions

On enrollment, the central Data Coordinating Center block-randomized patients to receive 1-g capsules containing

prescription fish oil (Lovaza, GSK; 465 mg of EPA+375 mg of DHA) or matched placebo (olive oil) by means of computer-generated numbers, stratified by enrolling medical center and planned valve surgery (yes/no). All drugs were prepared in identical capsules with similar coatings to minimize taste differences. All investigators, patients, and providers were blinded to treatment assignment.

Based on the time period between enrollment and day of cardiac surgery, a total loading dose of 10 g was provided for 3 to 5 days (or 8 g for 2 days) before surgery, including 2 g on the morning of surgery. Postoperatively, a uniform dose of 2 g per day was provided starting on postoperative day 1 until discharge or postoperative day 10, whichever came first.

Fatty Acid Analysis

In a subset of 564 patients in the United States and Italy, objective biomarkers of plasma phospholipid fatty acids were measured as described previously.[19] Briefly, fasting blood samples were collected at enrollment and on the morning of cardiac surgery, EDTA anticoagulated, and stored at −70°C. Plasma phospholipid EPA, docosapentaenoic acid, and DHA were measured as percentage of total fatty acids by the Fred Hutchinson Cancer Research Institute (Seattle, WA). Phospholipids were separated by thin-layer chromatography, and fatty acid methyl esters were subsequently prepared by direct transesterification. Final analysis was performed by gas chromatography. The interassay coefficients of variation for EPA, DPA, and DHA were each <3%.

End Points

For the primary analysis, we followed the recommendations of the Bleeding Academic Research Consortium (BARC) for the standardized definition of perioperative bleeding.[20] Our main end point was the occurrence of a BARC type 4 or 5 event defined as the composite of fatal bleeding; perioperative intracranial bleeding; reoperation after closure of the sternotomy for the purpose of controlling bleeding; transfusion of 5+ packed red blood cell units or whole blood, excluding cell saver, within 48 hours; or 24-hour chest tube output >2 L. In addition, we examined other commonly used bleeding measures, including (1) TIMI major bleeding defined as fatal bleeding, any intracranial bleeding, or clinically overt bleeding with drop in hemoglobin ≥5 g/dL or hematocrit ≥15% (accounting for transfusions); (2) TIMI minor bleeding defined as nonmajor bleeding that is clinically overt with drop in hemoglobin ≥3 g/dL or hematocrit ≥10% (accounting for transfusions), not overt but with drop in hemoglobin ≥4 g/dL or hematocrit ≥12% (accounting for transfusions) or clinically overt and requiring medical or surgical intervention, prolonging hospitalization, or prompting evaluation; (3) International Society on Thrombosis and Hemostasis surgical bleeding defined as fatal bleeding, symptomatic bleeding in a critical area or organ, extrasurgical site bleeding with drop in hemoglobin ≥2 g/dL or ≥2 unit blood transfusion within 24 to 48 hours, surgical site bleeding that requires a second intervention, and surgical site bleeding that is unexpected and prolonged or causes hemodynamic instability with drop in hemoglobin ≥2 g/dL or ≥2 unit blood transfusion within 24 hours, in patients who received at least 1 dose of study drug; (4) chest tube output (mL) during the first 24 hours after cardiac surgery; and (5) total units of blood transfused. We also examined biomarkers related to bleeding, including platelet counts, international normalized ratio, PAI-1 (plasminogen activator inhibitor-1) levels, and 11-dehydrothromboxane-B2 (11-dhTXB2) levels at postoperative day 2. All bleeding outcomes were prespecified safety end points of the OPERA trials.

Methods of Measurements for PAI-1 and 11-dhTXB2

PAI-1 antigen levels were determined using 2-site ELISA (Imulyse; Biopool AB), interassay and intra-assay CV of 0.019 and 0.024, and detection limit of 20 ng/mL.

11-dhTXB2 was measured as established by Morrow and Minton.[21] Internal standard [2H4]-11-dhTXB2 was added to acidified urine and the sample purified by C-18 solid-phase extraction and converted to the methyloxime, pentafluorobenzyl ester, trimethylsilyl ether derivative for analysis by gas chromatography/mass spectrometry. Assay interday variability was ≈10%; precision, ±7%; and accuracy, 90%.

Covariates

Standardized data were collected on other key risk factors, including patient demographics, cardiovascular risk factors, major comorbidities, medical/surgical history, anthropometry, home and perioperative medications, baseline laboratory indices, and surgical characteristics. In addition, clinical follow-up data were collected daily during the course of the trial.

Statistical Analysis

The effect of fish oil supplementation on perioperative bleeding was evaluated via intention-to-treat analysis comparing end points between the 2 randomized groups. Binary end points (eg, BARC type 4 or 5 event, TIMI major bleeding event, TIMI minor bleeding event, and International Society on Thrombosis and Hemostasis surgical bleeding) were compared using logistic regression; volume of chest tube output, as well as biomarkers of bleeding (except platelets), using linear regression (with robust variance); and total units of blood transfused and platelet counts, using Poisson regression. All analyses adjusted for stratifying variables used in the randomization process (enrolling medical center and planned valve surgery [yes/no]) to account for the potential correlation of observations within these variables.[22] We evaluated for potential interaction between treatment effect and clinically relevant variables, including age (<65 versus ≥65 years of age), sex, preoperative antithrombotic therapy (ie, antiplatelet or anticoagulant), type of surgery (ie, CABG versus valve surgery), cardiopulmonary bypass use, and surgical access (open thoracotomy versus minithoracotomy). Interactions were evaluated separately for each variable by introducing a multiplicative interaction term between the treatment effect and the variable within the same model, and statistical significance was assessed using the Wald test. Given that interaction analyses were exploratory, α-level was Bonferroni adjusted for the 6 variables (12 hypotheses) tested per end point.

In a subset of 564 subjects with blood measurements of plasma phospholipid fatty acids, the association between

omega-3 levels and occurrence of BARC type 4 or 5 bleeding event was examined based on levels at enrollment (reflecting habitual levels) and on achieved levels on the morning of cardiac surgery (reflecting habitual levels plus additional incorporation because of fish oil supplementation). The within-subject change between these 2 time points (reflecting potential interindividual variability in response to supplementation) was also calculated.[23] Each measure of omega-3 fatty acids was evaluated as indicator variable in quartiles in a multivariable logistic regression model that adjusted for potential confounding covariates, including age, sex, race, body mass index, diabetes mellitus, hypertension, dyslipidemia, smoking, alcohol, preoperative antithrombotic therapy, type of surgery, cardiopulmonary bypass use, and open versus minithoracotomy surgical access.[24–29] Test of linear trend across quartiles was assessed by entering the quartile variable as a single ordinal variable in the model. We also evaluated potential for nonlinear associations using a semiparametric multivariable-adjusted restricted cubic spline model, after excluding patients with values <1st or >99th percentile of measured phospholipid omega-3 fatty acids to minimize the influence of outliers. Finally, we evaluated independent predictors of perioperative bleeding using multivariable-adjusted logistic regression with backward stepwise selection procedure (*P* exclusion, 0.20; *P* inclusion, 0.10). Covariates above reported in the literature to associate with risk of perioperative bleeding were considered for inclusion into the model, whereas fish oil treatment assignment was retained for comparison.[24–29] All analyses were performed using STATA 14 (StataCorp, College Station, TX) with 2-tailed α of 0.05.

RESULTS

Among this large, multinational population of patients undergoing cardiac surgery, mean (SD) age was 63 (13) years, and 72% were men. CABG was planned in 52%, valve surgery in 50%, and other types of cardiac surgeries in 18% (proportions are not mutually exclusive because some patients could have >1 type of surgery). Of those enrolled and randomized, 96.4% ultimately underwent cardiac surgery. Details of surgery and perioperative medications have been published,[17] and baseline patient characteristics were comparable between the 2 treatment groups (Table 1).

The primary end point of a BARC type 4 or 5 bleeding event occurred in 92 patients (6.1%), TIMI major bleeding in 73 patients (4.8%), TIMI minor bleeding in 113 patients (7.5%), and International Society on Thrombosis and Hemostasis surgical bleeding in 99 patients (6.5%). Risk of bleeding was not higher in the fish oil group compared with placebo for any of these outcomes (Table 2). For example, comparing fish oil to placebo, the odds ratio for BARC bleeding was 0.81 (95% CI, 0.53–1.24); absolute risk difference, 1.1% lower (95% CI, –3.0% to 1.8%). The fish oil group had significantly fewer units of blood transfused compared with placebo (mean, 1.61 versus 1.92; *P*<0.001), attributable to significantly lower requirements for blood transfusions both during (*P*=0.002) and after (*P*=0.006) surgery. No significant differences were identified in postoperative platelet counts, international normalized ratio, PAI-1, or 11-dhTXB2 levels (Table I in the Data Supplement).

In exploratory subgroup analyses, results did not differ significantly in patient subgroups by age, sex, preoperative antithrombotic therapy, or cardiopulmonary bypass use (*P* interaction, nonsignificant for each). In other subgroup analyses, the effect of fish oil on total unit of blood transfused appeared more pronounced in patients who underwent valve surgery, compared with CABG (*P* interaction, <0.001) and in patients who underwent minithoracotomy, compared with open thoracotomy (*P* interaction, 0.001; Table II in the Data Supplement).

Evaluating objective biomarkers of plasma phospholipid omega-3 fatty acids, baseline levels associated with a nonsignificant trend toward lower bleeding risk (*P* trend, 0.05; Table 3). Achieved levels of omega-3 fatty acids on the morning of cardiac surgery associated significantly with lower risk of bleeding, with 70% lower risk in the third quartile (odds ratio, 0.30 [95% CI, 0.11–0.78]) and 64% lower risk in the fourth quartile (0.36 [95% CI, 0.15–0.87]), compared with the lowest quartile (*P* trend, 0.01). Changes in plasma phospholipid omega-3 fatty acids from baseline to morning of surgery associated with a nonsignificant trend toward lower bleeding risk (*P* trend, 0.09). In restricted cubic spline analyses, there was little statistical evidence for nonlinearity in these relationships (*P* nonlinearity, ≥0.05 each), although visual inspection suggested that the lower risk of bleeding might be less pronounced (although still with little evidence for increased bleeding risk) at the highest omega-3 levels (Figure 1A through 1C).

When we evaluated independent predictors of BARC type 4 or 5 bleeding, cardiopulmonary bypass use was the strongest predictor (odds ratio, 5.65; 95% CI, 1.72–18), followed by valvular surgery (with or without concomitant CABG), preoperative antithrombotic therapy, female sex, and presence of diabetes mellitus (Figure 2).

Minor adverse events related to fish oil use, such as gastrointestinal upset, burping, and fish oil taste, occurred more commonly in the fish oil group compared with placebo. Other serious adverse events were generally similar between the 2 groups (Table III in the Data Supplement).

DISCUSSION

The OPERA trial was a multinational, placebo-controlled randomized trial that showed that fish oil supplementation does not decrease the incidence of postoperative atrial fibrillation in cardiac surgery patients. In this secondary analysis of OPERA, we showed that fish oil supplementation did not lead to increased perioperative bleeding across multiple commonly used bleeding definitions. On the contrary, patients randomized to fish oil

Table 1. Baseline Characteristics of 1516 Patients Undergoing Cardiac Surgery in the OPERA Trial, Overall and According to Treatment Assignment

	Total (n=1516)	Fish Oil (n=758)	Placebo (n=758)
Age, y; mean (SD)	64 (13)	64 (13)	64 (12)
Men, n (%)	1094 (72)	551 (73)	543 (72)
White race, n (%)	1450 (96)	724 (96)	726 (96)
Country, n (%)			
Italy	764 (50)	383 (51)	381 (50)
United States	445 (29)	221 (29)	224 (30)
Argentina	307 (20)	154 (20)	153 (20)
BMI, kg/m^2; median (IQR)	27 (6.01)	27 (5.93)	27 (6.22)
Waist circumference, cm; median (IQR)	98 (15)	97 (15)	99 (17)
Diabetes mellitus, n (%)	393 (26)	194 (26)	199 (26)
Hypertension, n (%)	1135 (76)	572 (76)	563 (75)
Current smoking, n (%)	195 (13)	99 (13)	96 (13)
Dyslipidemia, n (%)	937 (62)	460 (61)	477 (63)
Total cholesterol, mg/dL; mean (SD)	176 (42)	175 (42)	177 (42)
Congestive heart failure, n (%)	416 (27)	204 (27)	212 (28)
Chronic renal failure, n (%)	96 (6.32)	44 (5.81)	52 (6.92)
History of atrial fibrillation, n (%)	114 (7.51)	52 (6.92)	62 (8.23)
COPD, n (%)	170 (11)	80 (11)	90 (12)
Prior PCI, n (%)	179 (12)	80 (11)	99 (13)
Cardiac surgery, n (%)*			
CABG	782 (52)	378 (50)	404 (54)
Valvular‡	756 (50)	385 (51)	371 (49)
Others	274 (18)	139 (18)	135 (18)

BMI indicates body mass index; CABG, coronary artery bypass graft surgery; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; OPERA, Omega-3 Fatty Acids for Prevention of Post-Operative Atrial Fibrillation; and PCI, percutaneous coronary intervention.

*Numbers for each type of cardiac surgery are not mutually exclusive because some patients underwent multiple procedures (eg, CABG+valve surgery).

‡Valvular surgery performed includes aortic (69%), mitral (26%), combination of aortic and mitral (4.0%), and others (1.2%).

required fewer units of blood transfusions, compared with placebo. In addition, high achieved (post-supplementation) levels of plasma phospholipid omega-3 fatty acids, reflecting habitual levels plus additional incorporation because of fish oil supplementation, associated with lower risk of perioperative bleeding.

Findings were similar across multiple patient subgroups, with none showing higher bleeding risk with fish oil supplementation. This was also true for subgroups experiencing increased absolute risk of perioperative bleeding, such as for patients receiving cardiopulmonary bypass, valve surgery, and preoperative antithrombotic therapy. The broad recruitment criteria, multinational population, and consistent results across patient subgroups support generalizability of our findings. The beneficial effect of fish oil on total units of blood transfused was also apparent across subgroups. The potentially larger benefit among patients who underwent valve surgery, compared with CABG, and among those who had minithoracotomy, compared with open thoracotomy, should be considered exploratory subgroup analyses and viewed with caution.

Omega-3 polyunsaturated fatty acids in fish oil lower blood triglycerides and improve cardiovascular hemodynamics and endothelial function.[2] Numerous prospective observational studies and large randomized clinical trials have evaluated the clinical benefits of these fatty acids,[30–32] and multiple randomized trials like Reduction of Cardiovascular Events With EPA - Intervention Trial (REDUCE-IT) Outcomes Study to Assess STatin Residual Risk Reduction With EpaNova in HiGh CV Risk PatienTs With Hypertriglyceridemia (STRENGTH) are ongoing.[33,34] Although findings of more recent randomized trials have been inconsistent, meta-analyses suggest that omega-3 polyunsaturated fatty acids significantly reduce coronary heart disease mortality, including fatal myocardial infarction and sudden cardiac death, leading the American Heart Association to recommend fish oil supplementation to prevent cardiovascular disease events in patients with prevalent coronary heart disease

Table 2. Effect of Fish Oil Supplementation on Risk of Perioperative Bleeding in 1516 Patients Undergoing Cardiac Surgery in the OPERA Trial

	Fish Oil (n=758)	Placebo (n=758)	OR or RR* (95% CI)	*P* Value
BARC type 4 or 5 bleeding, n (%)	42 (5.51)	50 (6.61)	0.81 (0.53–1.24)	0.34
TIMI major bleeding, n (%)	31 (4.12)	42 (5.51)	0.71 (0.44–1.14)	0.16
TIMI minor bleeding, n (%)	54 (7.11)	59 (7.81)	0.89 (0.60–1.30)	0.55
ISTH surgical bleeding, n (%)	45 (5.92)	54 (7.10)	0.80 (0.53–1.21)	0.30
24-h chest tube output, mL; median (IQR)	388 (330)	370 (300)		0.48
Total units of blood transfused, mean (SD)	1.61 (2.62)	1.92 (3.33)	0.83 (0.77–0.90)	<0.001
Median (25th–75th percentile)	1.00 (0–2.00)	1.00 (0–3.00)		
Total units during surgery, mean (SD)	0.80 (1.51)	1.00 (1.80)	0.84 (0.76–0.94)	0.002
Median (25th–75th percentile)	0 (0–2.00)	0 (0–2.00)		
Total units after surgery, mean (SD)	0.81 (1.82)	0.92 (2.13)	0.85 (0.76–0.95)	0.006
Median (25th–75th percentile)	0 (0–1.00)	0 (0–1.00)		

BARC indicates Bleeding Academic Research Consortium; IQR, interquartile range; ISTH, International Society on Thrombosis and Hemostasis; OPERA, Omega-3 Fatty Acids for Prevention of Post-Operative Atrial Fibrillation; OR, odds ratio; RR, rate ratio; and TIMI, Thrombolysis in Myocardial Infarction.

*The first 4 estimates are odds ratios; the remainder, rate ratios.

and reduce mortality and hospitalizations in patients with heart failure with reduced ejection fraction.[35] The US Food and Drug Administration has approved fish oil for the treatment of hypertriglyceridemia and also a qualified health claim that omega-3 fatty acids may reduce the risk of coronary heart disease.[36] It is, therefore, unsurprising that 19 million American adults take fish oil daily.[3]

Yet, questions about a potential bleeding risk with fish oil use have persisted. An initial suggestion of potential bleeding risk was seen among Eskimos consuming high levels of omega-3 fatty acids from sea mammals,[37] who had higher medically tested bleeding time compared with typical westerners, as well as high levels of EPA and DHA in platelet lipids. After these early results, several mechanistic studies of EPA and DHA and platelet function suggested diminished platelet aggregation, with a variety of proposed molecular mechanisms.[37–43] These experimentally observed effects raised concern about a potential bleeding risk with fish oil supplements,[8,11] which has led many healthcare providers and organizations to request that patients should stop taking fish oil for at least 1 week before surgery.[9,10,44,45] This standard of practice can, therefore, delay patient care, as well as increase hospital length of stay and cost. Yet, these recommendations, based

Table 3. Association Between Circulating Plasma Phospholipid Omega-3 Fatty Acid Levels and Risk of Bleeding Academic Research Consortium Type 4 or 5 Perioperative Bleeding in 564 Patients Undergoing Cardiac Surgery in the OPERA Trial

	Quartiles of Plasma Phospholipid Omega-3 Fatty Acid Levels*				*P* for Trend†
	First	Second	Third	Fourth	
Baseline concentration					
Percentage of fatty acids, mean±SE	3.25±0.03	3.99±0.02	4.79±0.03	6.61±0.11	0.05
No. of cases/no. of patients	19/142	11/140	12/141	11/141	
Odds ratio (95% CI)	1.00 (reference)	0.54 (0.23–1.31)	0.49 (0.21–1.13)	0.42 (0.17–1.02)	
Postsupplementation concentration on the morning of surgery					
Percentage of fatty acids, mean±SE	3.61±0.04	4.84±0.03	6.00±0.03	8.03±0.10	0.01
No. of cases/no. of patients	19/139	14/136	8/138	11/137	
Odds ratio (95% CI)	1.00 (reference)	0.58 (0.26–1.3)	0.30 (0.11–0.78)	0.36 (0.15–0.87)	
Change in concentration from baseline to morning of surgery					
Percentage of fatty acids, mean±SE	–0.26±0.06	0.32±0.01	1.05±0.03	2.77±0.08	0.09
No. of cases/no. of patients	14/131	19/131	7/131	11/130	
Odds ratio (95% CI)	1.00 (reference)	1.80 (0.79–4.1)	0.56 (0.21–1.5)	0.81 (0.32–2.0)	

DHA indicates docosahexaenoic acid; EPA, eicosapentaenoic acid; and OPERA, Omega-3 Fatty Acids for Prevention of Post-Operative Atrial Fibrillation.

*Omega-3=sum of EPA+docosapentaenoic acid+DHA.

†Test of linear trend across quartiles was assessed by entering the quartile variable as a single ordinal variable in a multivariable-adjusted logistic regression.

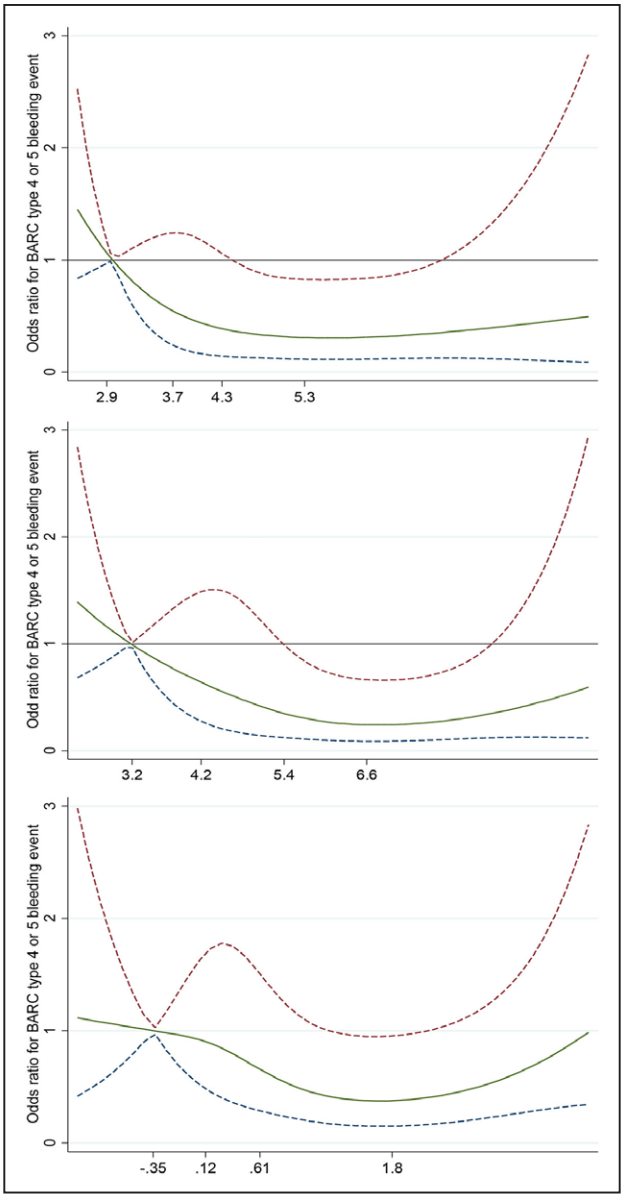

Figure 1. Multivariable-adjusted association between baseline (top), morning of surgery (middle), and change in (bottom) plasma phospholipid omega-3 fatty acids and risk of Bleeding Academic Research Consortium (BARC) type 4 or 5 perioperative bleeding in 564 patients undergoing cardiac surgery in the OPERA trial (Omega-3 Fatty Acids for Prevention of Postoperative Atrial Fibrillation).
The solid green line and the dashed lines represent odds ratio and 95% CIs, respectively, in comparison with the reference level (fifth percentile) representing the median value of the first decile. The values shown on the *x* axis correspond to the 5th, 25th, 50th, and 75th percentiles of plasma phospholipid omega-3 fatty acid levels. *P* values for nonlinearity: 0.15, 0.07, and 0.10, respectively; *P* values for linearity: 0.05, 0.01, and 0.09, respectively.

on theoretical and mechanistic concerns, have not been supported by empirical evaluations of bleeding risk in clinical practice.

Few prior studies have suggested increased clinical bleeding related to fish oil use. Clarke et al[46] reported increased incidence of epistaxis in children treated for hypercholesterolemia, but this finding could not be reproduced in a similar study involving children on dialysis, who could have even higher absolute risk of bleeding.[47,48] Yokoyama et al[49] reported a higher rate of minor bleeding (fundal, subcutaneous and epistaxis) with EPA ethyl ester and statin (1.1%) versus statin alone (0.6%) in an adult Japanese cohort with hypercholesterolemia, speculated to be because of higher baseline levels of EPA among Japanese populations.[13] Yet, other large trials of fish oil in patients with hypercholesterolemia or at higher cardiovascular risk have not reported increased bleeding risk.[12–16] Fewer trials, generally up to several hundred patients each, have evaluated bleeding risk with fish oil in patients undergoing major surgery, finding no significantly increased risk.[15,50,51] However, none of these prior reports have assessed or reported a comprehensive range of bleeding end points. Our study, involving a large, diverse patient population undergoing various high-risk cardiac surgical procedures, provides the most robust prospective evaluation to date of the effect of randomized fish oil supplementation on perioperative bleeding.

Few prior studies have evaluated fish oil in relation to blood transfusion requirements. In a randomized controlled trial of 200 cardiac surgery patients who were randomized to fish oil versus placebo, Farquharson et al[50] reported reduced rate of red blood cell transfusion in the fish oil group compared with controls. In addition, there was a nonsignificant lower rate of major bleeding (defined as total blood loss >3 L through chest tube drains) and volume of blood loss in the fish oil group compared with controls. Together with our findings, these results suggest that fish oil could reduce blood transfusion requirements in patients undergoing cardiac surgery. This claim is further supported by the finding of an inverse association between achieved (post-supplementation) levels of plasma phospholipid omega-3 fatty acids and the risk of bleeding in our study. Similar inverse association was also reported by Del Brutto et al[52] who demonstrated a lower rate of cerebral microbleed among adults who consumed large amounts of oily fish, concluding that fish oil supplementation may prevent incident cerebral microbleed among high-risk individuals. Although the exact mechanism for this beneficial effect of fish oil in patients undergoing surgery is unknown, previously described platelet-sparing effect of fish oil may potentially play a role. Acute inflammation and biochemical changes associated with components of cardiac surgery have been shown to lead to platelet activation and paradoxically increase loss of platelet function and increase bleeding risk. For example, platelets are known to be activated during cardiopulmonary bypass,[53] resulting in both quantitative and qualitative platelet defects. Hence, it is not uncommon to use platelet-sparing medications to prevent hemorrhage during cardiopulmonary bypass. Fish oil may provide platelet-sparing effects similar to these medications and reduce bleeding and transfusion needs. Our

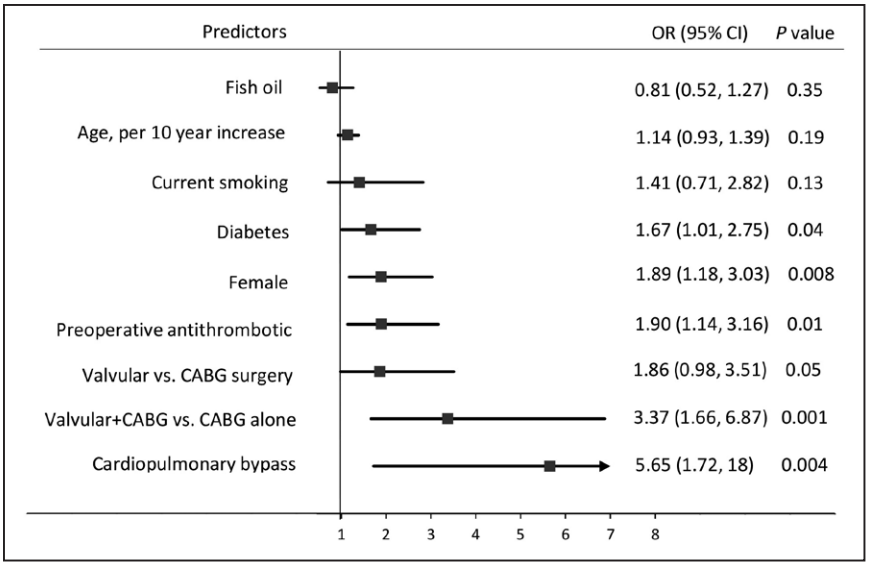

Figure 2. Variables retained in the selection model predicting a Bleeding Academic Research Consortium type 4 or 5 perioperative bleeding event in 1516 patients undergoing cardiac surgery in the OPERA trial (Omega-3 Fatty Acids for Prevention of Postoperative Atrial Fibrillation).
Randomized fish oil supplement use is retained in the model for comparison. CABG indicates coronary artery bypass graft; and OR, odds ratio.

findings, therefore, support the need for further experimental and clinical studies to test this hypothesis and evaluate relevant pathways.

Our investigation has several strengths. Notably, it is the largest study to date to provide detailed evaluations of several standardized bleeding end points in a randomized controlled analysis. In addition, the broad inclusion criteria and multinational enrollment enhance the external validity of our findings. The consistently lower trend of bleeding end points in the fish oil group, compared with control, across multiple subgroups and similar to other prior smaller trials implies a reassuring robust conclusion from our result.

Potential limitations require consideration. Although bleeding outcomes, including clinical bleeding and transfusion requirements, were prespecified safety end points of the OPERA trials, these findings should be considered as secondary analyses of the trial. Long-term effects of fish oil supplementation may differ from short-term effects. In this light, our analysis of the relationship between plasma phospholipid levels at enrollment with perioperative bleeding may best reflect habitual/long-term dietary exposure and provide relevant findings for this question. The similar observed trend for lower perioperative bleeding risk with higher omega-3 levels at both enrollment (baseline) and morning of surgery (post-supplementation) does not support any major difference between long- and short-term effects. OPERA was not specifically designed to test the effect of fish oil supplements on perioperative bleeding. For example, it is possible that the identified lower bleeding risk is a chance finding. However, bleeding outcomes were prespecified safety end points, and the lower absolute risk of bleeding across multiple bleeding end points in the fish oil group provides strong evidence of at least no increased perioperative bleeding risk with fish oil use. Lastly, this trial involved patients undergoing cardiac surgery, which may limit generalizability to other types of surgery. Yet, similar absence of bleeding risk has been reported in prior, smaller studies of patients undergoing other types of procedures.[12,54,55]

Few concerns over potential antiplatelet effect of oleic acid in olive oil (placebo in OPERA) have been alluded to,[56,57] which may raise the question of whether olive oil is a suitable control for this analysis. As found in prior systematic reviews of fish oil randomized control trials,[31,32] olive oil is a commonly used placebo. No prior studies have identified any molecular or clinical signal of bleeding risk with olive oil. In addition, the dose used in OPERA is so minor, compared with background intake, as to be unlikely to have a significant effect. Olive oil contains mainly oleic acid (≤83%)[58]—a monounsaturated fatty acid commonly found in numerous vegetable oils and animal fats. Olive oil (ie, ≈1.6 g of oleic acid) 2 g/d was provided as placebo in OPERA. In the United States, mean monounsaturated fat intake is about 30 g/d.[59] Hence, it is unlikely that adding an additional 1.6 g/d (5%) above background intake would have any meaningful effects. Furthermore, nearly half of the participants in OPERA trial were enrolled in Italy—a country where olive oil is an essential ingredient in their cuisine and where background intake would be even higher. We also found no significant difference when analysis was stratified by the 3 countries in OPERA. Thus, it seems unlikely that the use of olive oil as a placebo explains the findings.

In summary, in this large, multinational population of contemporary patients undergoing cardiac surgery, fish oil supplementation did not increase perioperative bleeding and reduced the number of perioperative blood transfusions. Higher achieved omega-3 levels were associated with lower risk of bleeding. These novel findings support the need for mechanistic studies to elucidate potential mechanisms, such as platelet-sparing effects, as well as reconsideration of current recommendations to stop fish oil or delay procedures before cardiac surgery.

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