Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 61, No. 21, 2013
ISSN 0735-1097/$36.00

CORRESPONDENCE

Research Correspondence

# Fish Oil and Post-Operative Atrial Fibrillation

## A Meta-Analysis of Randomized Controlled Trials

**To the Editor:** Post-operative atrial fibrillation (PoAF) is among the most common complications of cardiac surgery and substantially increases morbidity and healthcare costs. Despite decades of surgical, anesthetic, and medical advances, rates of PoAF remain largely unchanged. Experiments and animal models suggest that perioperative fish oil (omega-3 fatty acids) may reduce PoAF (1). We recently reported in a large, multinational randomized trial that perioperative fish oil did not reduce PoAF (2). Yet several other trials have evaluated this question, with mixed results. Most of these trials were small, and some were open label (i.e., neither double blind nor placebo controlled).

To compile all peer-reviewed evidence and evaluate reasons for potential heterogeneity, we conducted a meta-analysis, following Preferred Reporting Items for Systemic Reviews and Meta-Analyses guidelines, of randomized trials of fish oil for preventing PoAF. We searched MEDLINE from earliest available indexing through October 2012, without language restrictions. Search terms were ("fatty acids, omega-3"[MeSH] or "eicosapentaenoic acid"[MeSH/tiab] or "docosahexaenoic acids"[MeSH/tiab] or "fish oils"[MeSH] or "omega-3"[tiab] or "n-3"[tiab] or "long chain n-3"[tiab] or "fish oil"[tiab]) and ("atrial fibrillation"[MeSH/tiab]) and ("clinical trial"[MeSH/tiab] or "cardiac surgical procedures-"[MeSH/tiab]). Additional studies were identified by hand searching citation lists and directly contacting experts. Studies were included if they were randomized trials of oral or intravenous fish oil administration that evaluated PoAF after cardiac surgery; trials with additional concomitant interventions, observational studies, and duplicate publications were excluded. Inclusion and exclusion decisions and data extraction were performed in duplicate by 2 investigators. Findings were pooled using inverse-variance–weighted meta-analysis (3). Fixed-effects models were pre-specified on the basis of large differences in sample sizes and results across studies, for which random-effects models could dramatically overweight small, imprecise studies. Pre-specified potential sources of heterogeneity included placebo control (yes or no) and type of surgery (valve surgery, yes or no).

Of 83 identified abstracts, 8 full-text articles were retrieved for review. Eight randomized trials met the inclusion criteria, including 2,687 subjects and 859 PoAF events (Fig. 1). Heterogeneity was evident ($I^2$ = 52%, $Q$ = 14.5, p for heterogeneity = 0.04), principally owing to extreme results in 2 small, open-label (no placebo) studies. The presence or absence of placebo control significantly modified the effect of fish oil on PoAF (p for interaction = 0.028): benefits were seen in open-label, but not placebo-controlled, trials. Also, a preponderance of small trials with risk estimates below the pooled estimate suggested potential publication bias toward small positive trials. Little heterogeneity was evident among placebo-controlled trials ($I^2$ = 16%, $Q$ = 5.9, p for heterogeneity = 0.31), which both individually and together demonstrated no significant effect (pooled odds ratio [OR]: 0.92; 95% confidence interval [CI]: 0.78 to 1.10). In sensitivity analyses, we removed each trial individually from the pooled meta-analysis. Finding were similar; for example, removing the large OPERA (Omega-3 Fatty Acids for Prevention of Post-Operative Atrial Fibrillation) trial, the pooled OR in the remaining placebo-controlled trials was 0.86 (95% CI: 0.65 to 1.15; $I^2$ = 28%, $Q$ = 5.6). We note that only 2 open-label trials were identified, so generalizability of these findings to other research questions should not be assumed. Yet the variation in findings of small and especially open-label studies highlights the importance of large, adequately powered, placebo-controlled trials as well as appropriately performed meta-analyses such as the present study.

In the large OPERA trial, subgroup analyses suggested a potential benefit of fish oil treatment in patients undergoing valve surgery (p for interaction = 0.06) (2). We pooled these results with those from 4 other placebo-controlled trials that provided data stratified by type of cardiac surgery. In sum, data were available on 856 patients who underwent valve surgery and experienced 336 PoAF events and 1,249 patients not undergoing valve surgery who experienced 358 PoAF events. Pooling all data, the effects of fish oil on PoAF did not significantly differ according to valve surgery (p for interaction = 0.94): the OR was 0.91 (95% CI: 0.76 to 1.09) in patients undergoing valve surgery and 1.00 (95% CI: 0.78 to 1.28) in patients not undergoing valve surgery. Dosing and duration of fish oil treatment were generally similar among trials, limiting the ability to explore heterogeneity by these factors.

We evaluated pooled evidence for safety, including numbers of patients with major bleeding, total mortality, and other reported serious adverse events. Fish oil was associated with less bleeding (n = 165 events, data reported in 5 trials: OR: 0.76; 95% CI: 0.60 to 0.96; $I^2$ = 34.1, $Q$ = 6.1, p for heterogeneity = 0.19), a nonsignificant trend toward lower mortality (n = 32 events, data reported in 6 trials: OR: 0.68; 95% CI: 0.32 to 1.41; $I^2$ = 0%, $Q$ = 1.98, p for heterogeneity = 0.58), and no difference in other reported serious adverse events (n = 528 events, data reported in 6 trials: OR: 1.0; 95% CI: 0.81 to 1.25; $I^2$ = 0%, $Q$ = 4.7, p for heterogeneity = 0.45) The unexpectedly lower bleeding risk could be due to chance. Conversely, this observation could plausibly relate to lower cardiopulmonary bypass–induced activation and loss of platelets and clotting factors (4); further investigation of potential mechanisms is required. At the least, the observed lower bleeding risk counters concerns that antiplatelet effects of fish oil might increase blood loss during cardiac surgery. Overall, the findings indicate that perioperative fish oil use was well tolerated and safe, suggesting little need for its discontinuation in patients who are taking fish oil before cardiac surgery.

In sum, our meta-analysis provides convincing evidence that short-term fish oil use does not appreciably reduce PoAF and indicates that heterogeneity in prior findings results from extreme results of small, open-label trials as well as potential publication bias. In addition, we found little evidence for differing efficacy according to

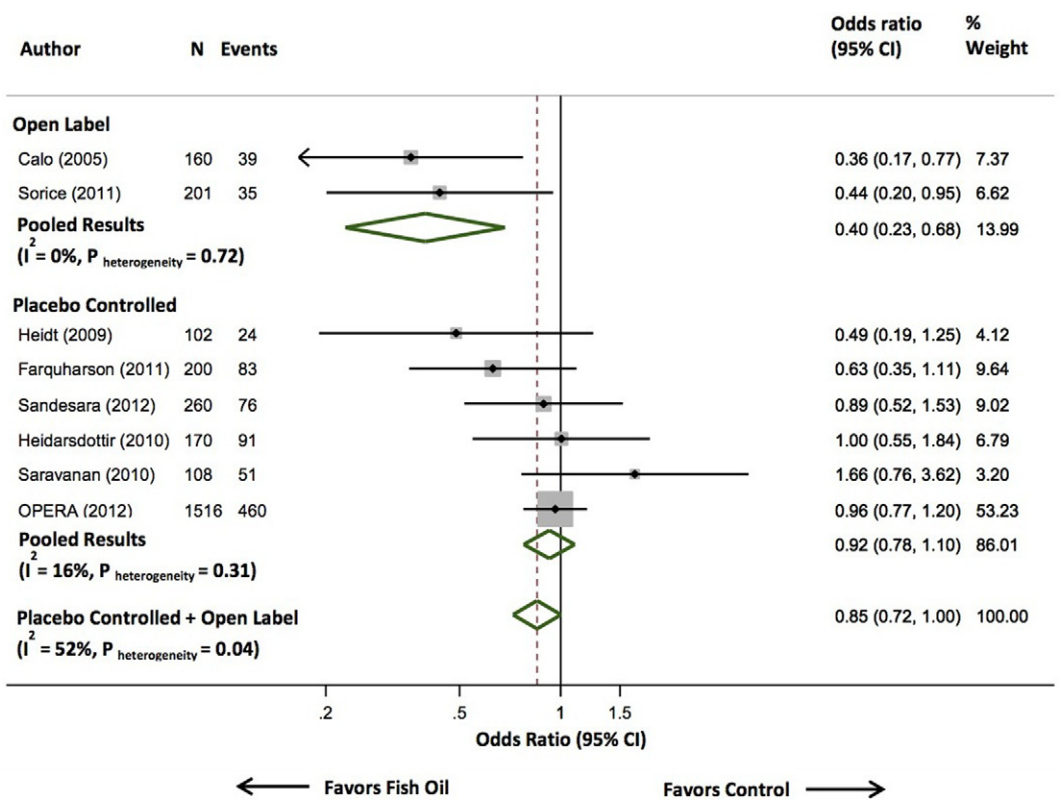


**Figure 1** **Randomized Controlled Trials of Perioperative Fish Oil Supplementation to Prevent Post-Operative Atrial Fibrillation**

Studies were pooled using inverse-variance–weighted meta-analysis with fixed effects. Although the overall pooled result was of borderline statistical significance, substantial heterogeneity was evident ($I^2$ = 52%, $Q$ = 14.5), which was largely explained by whether trials were open label (top 2 studies) or placebo-controlled (bottom 6 studies). The open-label studies suggested a benefit, but the double-blind, placebo-controlled trials confirmed no significant effect of fish oil on post-operative atrial fibrillation (odds ratio [OR]: 0.92; 95% confidence interval [CI]: 0.78 to 1.10), with little heterogeneity between studies ($I^2$ = 16%, $Q$ = 5.93). Sensitivity analyses using random-effects meta-analysis showed similar findings for the overall pooled results (OR: 0.76; 95% CI: 0.57 to 1.03; $I^2$ = 52%, $Q$ = 14.5, p for heterogeneity = 0.04), results restricted to open-label trials (OR: 0.40; 95% CI: 0.23 to 0.68; $I^2$ = 0%, $Q$ = 0.13, p for heterogeneity = 0.72), and results restricted to placebo-controlled trials (OR: 0.91; 95% CI: 0.73 to 1.13; $I^2$ = 16%, $Q$ = 5.93, p for heterogeneity = 0.31). OPERA = Omega-3 Fatty Acids for Prevention of Post-Operative Atrial Fibrillation.

type of cardiac surgery. There is also little evidence that intermediate-term (<1 year) fish oil use reduces recurrent arrhythmias in patients with established atrial fibrillation (5). Fish oil may still prove useful in other clinical contexts, such as long-term use (years) for preventing the initial onset of atrial fibrillation among ambulatory elderly adults with hypertension or other risk factors. Such primary, rather than secondary, prevention approaches must be tested in large, appropriately powered, placebo-controlled clinical trials.

***Dariush Mozaffarian, MD, DrPH†‡§‖**
**Jason H. Y. Wu, PhD§**
**Marcia C. de Oliveira Otto, PhD§**
**Chirag M. Sandesara, MD¶**
**Robert G. Metcalf, MD#**
**Roberto Latini, MD****
**Peter Libby, MD†**
**Federico Lombardi, MD††**
**Patrick T. O'Gara, MD†**
**Richard L. Page, MD‡‡**
**Maria G. Silletta, MS§§**
**Luigi Tavazzi, MD‖‖**
**Roberto Marchioli, MD§§**

*Brigham and Women's Hospital
Harvard Medical School
Department of Medicine, Division of Cardiovascular Medicine
665 Huntington Avenue, Building 2-319
Boston, Massachusetts 02115
E-mail: dmozaffa@hsph.harvard.edu

http://dx.doi.org/10.1016/j.jacc.2013.02.045

From the †Division of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; ‡Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; §Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts; ‖Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts; ¶Virginia Cardiovascular Associates, Manassas, Virginia; #Center for Heart Rhythm Disorders, University of Adelaide and Rheumatology Unit, Royal Adelaide Hospital, Adelaide, Australia; **Department of Cardiovascular Research, Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy; ††Department of Health Sciences, University of Milan, Milan, Italy; ‡‡Department of Medicine,

University of Wisconsin, School of Medicine & Public Health, Madison, Wisconsin; §§Department of Clinical Pharmacology and Epidemiology, Consorzio Mario Negri Sud, Santa Maria Imbaro, Italy; and the ‖‖GVM Hospitals of Care and Research, Villa Maria Cecilia Hospital, Cotignola, Italy

Please note: This study was funded by grant RC2-HL101816 from the National Heart, Lung, and Blood Institute, National Institutes of Health. Dr. Mozaffarian has received research grants from GlaxoSmithKline, Sigma Tau, and Pronova Biopharma for an investigator-initiated, not-for-profit, randomized clinical trial of fish oil supplements for the prevention of post-surgical complications; ad hoc travel reimbursement and/or honoraria for one-time scientific presentations on diet and cardiometabolic diseases from the International Life Sciences Institute, Bunge, SPRIM, Pollock Institute, and Nutrition Impact; and ad hoc consulting fees from Foodminds and McKinsey Health Systems Institute. Dr. Mozaffarian is a member of the scientific advisory board for Unilever North America. Dr. Mozaffarian receives royalties from UpToDate for an online chapter on fish oil. Dr. Mozaffarian is listed as a co-inventor on a provisional patent application filed by Harvard University for the use of transpalmitoleic acid to prevent and treat insulin resistance, type 2 diabetes, and related conditions. Dr. Libby is an unpaid consultant or is involved in clinical trials for AstraZeneca, GlaxoSmithKline, Merck, Novartis, Pfizer, Pronova Biopharma, and Sigma Tau; and is a member of the scientific advisory boards for Athera Biotechnologies, Carolus Therapeutics, Interleukin Genetics, and BIND Biosciences. Dr. Tavazzi is a consultant for Servier; and a member of boards for Medtronic, St. Jude Medical, Vifor Pharma, Boston Scientific Corporation, Bristol-Myers Squibb, and Cardiorentis. Dr. Marchioli has received institutional grants for trials testing omega-3 polyunsaturated fatty acids from Sigma Tau, GlaxoSmithKline, SPA, Pronova Biopharma; and honoraria for presentations from Pronova Biopharma, Ferrer, Sigma Tau, and SPA. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

## REFERENCES

1. Mozaffarian D, Wu JH. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. J Am Coll Cardiol 2011;58:2047–67.
2. Mozaffarian D, Marchioli R, Macchia A, et al. Fish oil and postoperative atrial fibrillation: the Omega-3 Fatty Acids for Prevention of Post-operative Atrial Fibrillation (OPERA) randomized trial. JAMA 2012;308:2001–11.
3. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
4. Sniecinski RM, Chandler WL. Activation of the hemostatic system during cardiopulmonary bypass. Anesth Analg 2011;113:1319–33.
5. Kowey PR, Reiffel JA, Ellenbogen KA, Naccarelli GV, Pratt CM. Efficacy and safety of prescription omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: a randomized controlled trial. JAMA 2010;304:2363–72.

## Letters to the Editor

# Improving Quality of Life and Functional Capacity in Atrial Fibrillation and Congestive Heart Failure

We read with interest the paper by Suman-Horduna et al. (1) published in the January 2013 issue of the *Journal*. The investigators analyzed important quality-of-life data from a substantial substudy (n = 749) of a landmark trial (2), comparing rate control to rhythm control for patients with paroxysmal (~30%) or persistent atrial fibrillation (AF) and congestive heart failure (CHF). Overall, each strategy was associated with similar improvements in symptoms and quality of life, but results were confounded by the high proportion of patients with paroxysmal AF (29.6%) assigned to rate control who remained in sinus rhythm (i.e., crossed over to rhythm control) and by patients assigned to rhythm control who remained in AF (22.4%) (i.e., in whom rhythm control failed).

We previously conducted a small, randomized study exclusively of patients with persistent AF and CHF (3), and encountered similar problems in maintaining sinus rhythm but with no spontaneous return to sinus rhythm in those assigned to rate control; therefore, we had a much lower rate of cross over than in the AF-CHF trial. We found significant improvements in quality of life, left ventricular function, and N-terminal pro–brain natriuretic peptide concentrations overall, which benefited those in whom sinus rhythm was restored and maintained during follow-up. The 6-min walk test distance also improved for patients in whom a rhythm control strategy was successful.

Unfortunately, despite some encouraging results, the Achilles' heel of a rhythm control strategy remains arrhythmia recurrence. Treatment directed at CHF, including angiotensin-converting enzyme inhibitors, beta-blockers, and aldosterone antagonists, helps to reduce the incidence of AF (4). However, safe and effective antiarrhythmic therapy is lacking for patients with left ventricular dysfunction. This includes amiodarone, which was associated with excess mortality in the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) study among patients with more advanced symptoms (5). Although preliminary results of catheter ablation, either of AF itself or of atrioventricular nodal ablation followed by biventricular pacing (6), are encouraging, adequately powered randomized clinical trials are needed to evaluate longer term safety and efficacy before any firm recommendations can be made. However, in the context of CHF, the evidence that it is better to be in sinus rhythm rather than AF is compelling. We just need to identify interventions that are less harmful or toxic than the problem.

***Rhidian J. Shelton, MD**
**John G. F. Cleland, MD, PhD**

*Department of Cardiology
Cumberland Infirmary
Newtown Road
Carlisle, Cumbria CA2 7HY
United Kingdom
E-mail: rhidian@gmail.com

http://dx.doi.org/10.1016/j.jacc.2013.01.083

## REFERENCES

1. Suman-Horduna I, Roy D, Frasure-Smith N, et al. Quality of life and functional capacity in patients with atrial fibrillation and congestive heart failure. J Am Coll Cardiol 2013;61:455–60.
2. Roy D, Talajic M, Nattel S, et al., for the Atrial Fibrillation and Congestive Heart Failure Investigators. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med 2008;358:2667–77.
3. Shelton RJ, Clark AL, Goode K, et al. A randomised, controlled study of rate versus rhythm control in patients with chronic atrial fibrillation and heart failure: (CAFÉ-II). Heart 2009;95:924–30.
4. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2010;364:11–21.