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Fish Oil for the Reduction of Atrial Fibrillation Recurrence, Inflammation, and Oxidative Stress

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ABSTRACT

BACKGROUND Recent trials of fish oil for the prevention of atrial fibrillation (AF) recurrence have provided mixed results. Notable uncertainties in the existing evidence base include the roles of high-dose fish oil, inflammation, and oxidative stress in patients with paroxysmal or persistent AF not receiving conventional antiarrhythmic (AA) therapy.

OBJECTIVES The aim of this study was to evaluate the influence of high-dose fish oil on AF recurrence, inflammation, and oxidative stress parameters.

METHODS We performed a double-blind, randomized, placebo-controlled, parallel-arm study in 337 patients with symptomatic paroxysmal or persistent AF within 6 months of enrollment. Patients were randomized to fish oil (4 g/day) or placebo and followed, on average, for 271 ± 129 days.

RESULTS The primary endpoint was time to first symptomatic or asymptomatic AF recurrence lasting >30 s. Secondary endpoints were high-sensitivity C-reactive protein (hs-CRP) and myeloperoxidase (MPO). The primary endpoint occurred in 64.1% of patients in the fish oil arm and 63.2% of patients in the placebo arm (hazard ratio: 1.10; 95% confidence interval: 0.84 to 1.45; p = 0.48). hs-CRP and MPO were within normal limits at baseline and decreased to a similar degree at 6 months (Δhs-CRP, 11% vs. −11%; ΔMPO, −5% vs. −9% for fish oil vs. placebo, respectively; p value for interaction = NS).

CONCLUSIONS High-dose fish oil does not reduce AF recurrence in patients with a history of AF not receiving conventional AA therapy. Furthermore, fish oil does not reduce inflammation or oxidative stress markers in this population, which may explain its lack of efficacy. (Multi-center Study to Evaluate the Effect of N-3 Fatty Acids [OMEGA-3] on Arrhythmia Recurrence in Atrial Fibrillation [AFFORD]; NCT01235130) (J Am Coll Cardiol 2014;64:1441–8) © 2014 by the American College of Cardiology Foundation.

Conventional rhythm-control treatment of atrial fibrillation (AF) involves the use of antiarrhythmic drugs (AADs) or AF ablation procedures. Current AADs provide modest protection against AF recurrence and are associated with non-negligible side effects (1). Although potentially more efficacious, catheter ablation is limited by its availability at experienced centers and high upfront costs (2). Alternatives to both of these treatments that are inexpensive and safe and that target specific pathophysiological processes, including inflammation and oxidative stress, are required (**Figure 1**). Long-chain

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ABBREVIATIONS AND ACRONYMS

AA = antiarrhythmic

AAD = antiarrhythmic drug

AF = atrial fibrillation

DHA = docosahexaenoic acid

EPA = eicosapentaenoic acid

hs-CRP = high-sensitivity C-reactive protein

MPO = myeloperoxidase

PUFA = polyunsaturated fatty acid

n-3 polyunsaturated fatty acids (PUFAs) possess antiarrhythmic (AA) properties and provide protection from ventricular arrhythmias and sudden death (3,4). As a consequence, their potential utility for the prevention and treatment of AF has been suggested. Both higher consumption of fresh fish and higher blood n-3 PUFA levels are associated with a lower incidence of de novo AF (5–7). However, randomized trials of fish oil for the prevention of AF recurrence have provided mixed results to date (8–12). Importantly, these trials had several methodological limitations and did not attempt to evaluate potential underlying mechanisms.

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The AFFORD (Multi-center Study to Evaluate the Effect of N-3 Fatty Acids [OMEGA-3] on Arrhythmia Recurrence in Atrial Fibrillation) was designed to assess the efficacy of high-dose n-3 PUFAs for the prevention of AF recurrence, inflammation, and oxidative stress among patients with a documented history of symptomatic, paroxysmal, or persistent AF within 6 months of enrollment.

METHODS

STUDY DESIGN. The AFFORD was a Canadian, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial that sought to test the efficacy of high-dose fish oil versus placebo on AF recurrence, inflammation, and oxidative stress among patients with a history of paroxysmal or persistent AF who had a rhythm-control strategy planned. The study was conducted at 23 sites across Canada. All centers obtained approval from an institutional review board, and all study participants provided written informed consent. Patients were recruited from March 2009 to March 2012, with follow-up ending on December 15, 2012. Please see the Online Appendix for a list of study investigators and committee members.

STUDY POPULATION. Eligible patients were those 18 years of age and older with a history of documented, symptomatic paroxysmal or persistent AF lasting ≥10 min within 6 months of enrollment, who had a rhythm-control strategy planned by the treating physician. Major exclusion criteria were AF continuously present for ≥3 months, the need for continued class I or III AA therapy, New York Heart Association functional class III-IV heart failure, left ventricular ejection fraction <40%, known secondary cause of AF (e.g., hyperthyroidism, fever, anemia, postoperative AF), and the use of n-3 PUFA supplements within 3 months of enrollment.

STUDY INTERVENTION. Subjects were randomized to 2 1-g enteric-coated capsules of fish oil twice daily (total dose 4 g/day) or matching placebo (Genuine Health, Toronto, Ontario, Canada). Each 1-g fish oil capsule contained 400 mg of eicosapentaenoic acid (EPA) and 200 mg of docosahexaenoic acid (DHA). Placebo capsules consisted of 1 g of safflower oil. Safflower oil is free of n-3 PUFAs and has no purported AA effects. Given the pharmacokinetic profile of EPA + DHA after long-term ingestion (13,14), a 3-week loading phase represented a balance between adequate incorporation of n-3 PUFAs into biological tissues permitting potential AA effects and achieving a steady state for maximal efficacy. Therefore, treatment began at enrollment, with patients first entering a 3-week loading/blanking phase and then a follow-up phase beginning on day 22. Patients not in sinus rhythm on day 21 were required to undergo cardioversion; failed cardioversion was considered an AF recurrence. Patients were followed for 6 to 16 months. Patients who had an AF recurrence before 6 months were followed until the 6-month study visit, with class I or III AA therapy permitted after the first recurrence. Patients without AF recurrence at 6 months were followed until the first AF recurrence or for 16 months.

Recurrence of AF was monitored by weekly transtelephonic monitor transmissions to detect potentially asymptomatic episodes, whereas symptomatic episodes were assessed by transtelephonic monitor strips, 12-lead electrocardiography or any implanted device. The omega-3 index, representing the erythrocyte membrane content of EPA + DHA as a percent of total membrane fatty acids, was used as a measure of adherence to study medication and performed at baseline and at AF recurrence or the 6-month visit, whichever occurred first.

STUDY ENDPOINTS. The primary endpoint was time to first asymptomatic or symptomatic AF recurrence lasting ≥30 s. Secondary endpoints, high-sensitivity C-reactive protein (hs-CRP) and myeloperoxidase (MPO) were measured at baseline and at 6-month follow-up visit. Tertiary endpoints included bleeding and cardiovascular-related death or hospitalization. An independent events committee adjudicated AF recurrences, bleeding, strokes, transient ischemic attacks, and deaths.

SAMPLE SIZE CALCULATION AND STATISTICAL ANALYSES. In our unpublished randomized pilot study in 45 patients, we observed a 3-month AF recurrence rate of 50% in the placebo group, 42% in the low-dose (1.2 g/day EPA + DHA), and 36% in the high-dose (2.4 g/day EPA + DHA) fish oil group (p for