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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

trend = NS). Furthermore, in the CTAF (Canadian Trial of Atrial Fibrillation), we observed a 6-month AF recurrence rate of ~35% with sotalol or propafenone (15). On the basis of these data, we estimated a total sample size of 332 patients, assuming a 6-month AF recurrence rate of 65% in the placebo group and 50% in the fish oil group, an accrual period of 10 months, a maximal follow-up of 16 months, a yearly loss of 10%, 90% power, and a 2-sided p value of 0.05.

A data safety monitoring committee was created to oversee safety endpoints, including bleeding. No interim efficacy analysis was performed. The committee met 3 times during the course of the trial and recommended that the trial proceed as planned.

Efficacy analyses were performed in a pre-specified manner on the modified intention-to-treat population consisting of all patients completing the loading phase and entering the follow-up period. Safety endpoints were performed on the safety population, which consisted of all participants who consumed at least 1 dose of study medication. The primary analysis consisted of an unadjusted comparison of time to first AF recurrence using the log-rank test. Kaplan-Meier estimates were displayed graphically as survival curves. Censoring occurred if the patient was lost to follow-up, died, or reached the end of the follow-up period without relapse. Secondary efficacy analyses were performed using analysis of covariance on log-transformed data. Safety endpoints, including major and minor bleeding and cardiovascular-related death or hospitalization, were compared between groups using chi-square analysis. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, North Carolina). Results are expressed as numbers and percent for categorical variables and mean ± SD for continuous variables, with the exception of hs-CRP and MPO, which are expressed as mean, minimum, and maximum. A p value <0.05 was considered statistically significant.

RESULTS

A total of 337 patients were randomized, of whom 297 (88%) completed the study (Figure 2). Subjects not completing the study were distributed equally in both groups and related primarily to withdrawal of consent (30%) and nonserious adverse events (28%). Baseline demographic, clinical, and cardiac characteristics and medication were similar between treatment groups (Table 1).

PRIMARY OUTCOME MEASURE. The overall rate of AF recurrence was high (63.6%) but did not differ between groups (Central Illustration, Table 2). Furthermore, the number of days in follow-up, percent of asymptomatic episodes, and number of AF relapses at 6 months were similar between groups. Results were consistent across all subgroups, except for a significantly higher AF recurrence for fish oil users with any ischemic heart disease (hazard ratio: 2.6; 95% confidence interval: 1.1 to 6.1); however, the absolute numbers were small, and the multiple testing suggests that this association is likely spurious (Figure 3).

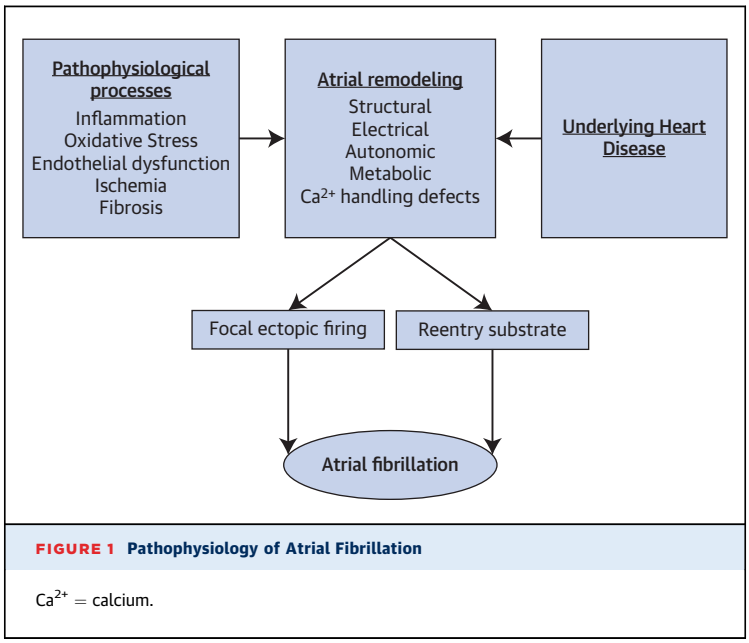


FIGURE 1 Pathophysiology of Atrial Fibrillation

Ca^{2+} = calcium.

SECONDARY OUTCOME MEASURES. MPO and hs-CRP were similar between groups at baseline and were within normal limits (Table 3). Values of both markers decreased modestly over 6 months for all patients, although no significant treatment × time interaction was noted.

TERTIARY SAFETY ENDPOINTS, ADVERSE EVENTS, AND WITHDRAWALS. Although minor bleeding occurred in 10 (7%) patients in the fish oil group and 14 (9%) in the placebo group (p = 0.5), no major bleeding occurred. One patient in the fish oil group experienced a stroke during the loading phase; the patient was withdrawn from the study, although the event was deemed unrelated to the study drug. Two patients in the placebo group experienced transient ischemic attacks. In both cases, study medication was continued, and the patients fully recovered. One death occurred in the placebo group; this was deemed unrelated to study drugs. The composite endpoint of cardiovascular-related death or hospitalization occurred in 20 patients in the fish oil group (13%) and 11 (7%) in the placebo group (p = 0.06; 95%

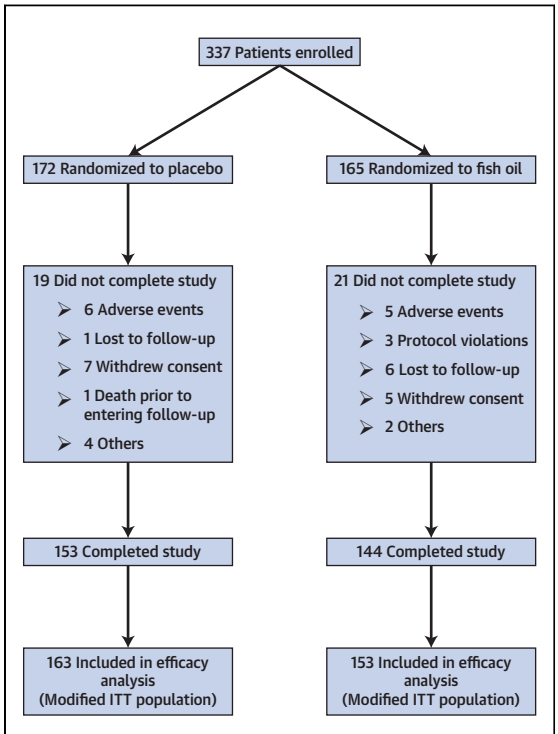


FIGURE 2 Study Flow Chart

ITT = intention-to-treat.

TABLE 1 Baseline Characteristics

	Fish Oil (n = 153)	Placebo (n = 163)
Demographic and medical variables		
Age, yrs	60 ± 12	62 ± 13
Female	48 (31)	57 (35)
BMI, kg/m^2	29 ± 5	29 ± 6
Waist circumference, cm	99 ± 12	97 ± 13
Diabetes	10 (7)	16 (10)
Hypertension	69 (45)	68 (42)
Coronary disease	22 (14)	21 (13)
Valvular disease	1 (1)	3 (2)
Class I/II heart failure	5 (3)	3 (2)
Cardiac and echocardiography parameters		
Sinus rhythm at baseline	139 (91)	150 (92)
12-lead ECG heart rate, beats/min	62 ± 13	62 ± 11
Left atrial dimension, cm	3.9 ± 0.6	4.2 ± 3.6
Left ventricular hypertrophy on echo	6/100 (6)	7/112 (6)
Left ventricular ejection fraction, %	61 ± 7	61 ± 7
AF history		
Paroxysmal AF	103 (67)	107 (66)
Persistent AF	50 (33)	56 (34)
Time since first AF diagnosis, yrs	2.5 ± 4.4	1.9 ± 3.4
Class I or III AAD use in 12 months before enrollment	37 (24)	20 (12)
Concomitant medications		
Beta-blockers	60 (39)	62 (38)
ACEI or ARB	68 (44)	59 (36)
Oral anticoagulant	105 (69)	91 (56)

Values are mean ± SD or n (%).

AAD = antiarrhythmic drug; ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BMI = body mass index; ECG = electrocardiography.

confidence interval: −0.3 to 13.2) and was primarily related to hospitalizations for AF (10 vs. 7 patients in the fish oil and placebo groups, respectively; p = 0.4).

Study medication was generally well tolerated. Only 17 patients (10 placebo, 7 fish oil) experienced an adverse event leading to discontinuation of study medication. Of these events, 11 (6 placebo, 5 fish oil) were deemed related to study treatment, primarily gastrointestinal side effects.

OMEGA-3 INDEX. As expected, the omega-3 index was similar between groups at baseline and was significantly increased in the fish oil group relative to the placebo group during follow-up (**Figure 4**). However, the index did not differ between patients with and without AF recurrence at 6 months, irrespective of treatment group. Furthermore, the change in omega-3 index from baseline was also not associated with a higher or lower risk of AF recurrence (data not shown).

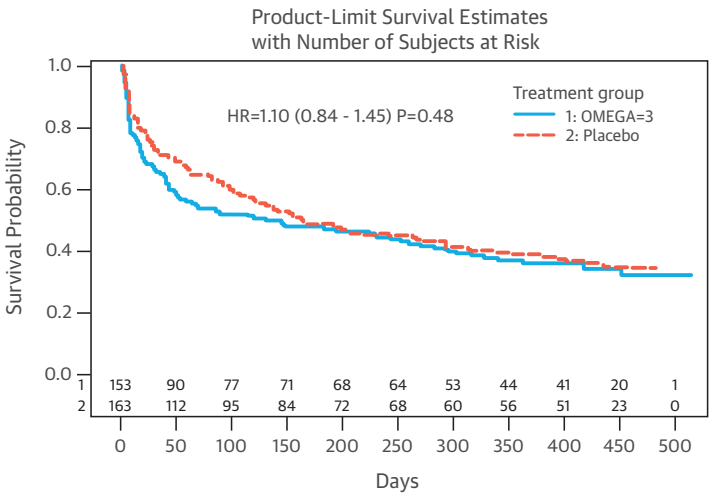
DISCUSSION

Our study demonstrates that high-dose, long-chain n-3 fatty acids do not reduce symptomatic or asymptomatic AF recurrence or the number of recurrences over a follow-up period of up to 16 months among patients with paroxysmal or persistent AF not receiving conventional AA therapy (**Central Illustration**). Importantly, fish oil at the dose used also had no impact on hs-CRP or MPO, suggesting that although both inflammation and oxidative stress may be implicated in the pathophysiology of AF, fish oil had no effect on either mechanism, which may explain its lack of efficacy.

To date, randomized trials of fish oil for the prevention of AF recurrence have provided mixed, generally negative results (8–12). The AFFORD is comparable to the 2 largest studies with respect to sample size and methodology (8,9). In the first (8), fish oil had no effect relative to placebo on the recurrence of symptomatic AF or flutter after 24 weeks. Similarly, in the FORWARD (Randomized Trial to Assess Efficacy of PUFA for the Maintenance of Sinus Rhythm in Persistent Atrial Fibrillation) (9), fish oil did not reduce episodes of symptomatic AF recurrence after 1 year compared with placebo. Importantly, all trials had ≥1 methodological

limitations including the following: 1) open-label design and lack of placebo-control group (12); 2) a potentially inadequate treatment dose (generally 1.0 to 1.7 g/dl EPA + DHA) (9–12); 3) the lack of an adequate initial loading/blanking phase (6–9) given the pharmacokinetic profile of n-3 PUFAs after ingestion (13,14); 4) the lack of consideration of asymptomatic AF episodes, which represent a significant proportion of the total AF burden (8,9,12) and are associated with a higher risk of stroke (16,17); 5) lesser capture of recurrent AF episodes due to the method of assessment used (generally 24-h Holter monitor or 12-lead electrocardiography) (8–10,12); 6) the lack of measurement of blood n-3 fatty acids as a measure of treatment adherence and efficacy (8–10,12); and 7) significant use of AADs, including amiodarone, in patients with a higher baseline risk of AF recurrence (9–12). Finally, little if any attempt was undertaken to evaluate potential underlying mechanisms (8–12).

Given the limitations of previous trials discussed in the preceding text, the AFFORD has several notable strengths. 1) The dose that we used (4 g/day) is generally considered the highest dose of fish oil free from gastrointestinal side effects; a higher dose would have made blinding not feasible in the context of a randomized, placebo-controlled trial. Again, we chose this dose because of our pilot data, showing potentially greater efficacy for the prevention of AF recurrence relative to the standard 1-g/day dose recommended for the secondary prevention of coronary heart disease. Only the study by Kowey et al. (8) used a comparable fish oil dose. 2) As noted previously, n-3 fatty acids must incorporate into cell membranes to exert their effects; steady-state plasma levels are achieved only after several weeks (13). Thus, a 3-week loading phase was incorporated into our study before AF recurrence was included in the primary outcome measures. This was not done in most previous trials (8–11). 3) We included both asymptomatic and symptomatic AF recurrence in our primary endpoints. 4) All participants were provided with a transtelephonic monitor and required to transmit rhythm strips at least weekly, enabling a more complete capture of recurrent AF episodes relative to most previous studies. 5) We assessed the omega-3 index as a measure of adherence to study medication. This further allowed us to demonstrate the lack of efficacy of fish oil for the endpoints of interest in our study. 6) Our data demonstrate that in patients at lower risk of AF recurrence high-dose fish oil lacks efficacy in the absence of class I or III AA therapy. Two-thirds of AFFORD participants had a diagnosis of paroxysmal AF, and only 9 had received amiodarone



CENTRAL ILLUSTRATION **Time to First Symptomatic or Asymptomatic Atrial Fibrillation**

AF = atrial fibrillation; HR = hazard ratio.

treatment in the year before study inclusion. Thus, they represented ideal patients for demonstrating the efficacy or lack thereof of fish oil as a sole AA agent for the prevention of AF recurrence. Finally, knowing that inflammation and oxidative stress are involved in the pathophysiology of AF, our study is the first to prospectively evaluate markers of both of these mechanisms as potential targets for n-3 fatty acids.

Omega-3 fatty acids are known to reduce systemic inflammation and oxidative stress (18,19); both mechanisms contribute to atrial remodeling and both the initiation and recurrence of AF (20,21). In our study, hs-CRP was not elevated at baseline (mean

TABLE 2 **AF Outcomes**

	Fish Oil (n = 153)	Placebo (n = 163)	p Value
AF outcomes			
Recurrence	98 (64)	103 (63)	0.5
Total follow-up time, days	266 ± 126	275 ± 132	0.8
Asymptomatic episodes, %	26	36	0.2
Relapses	4 (0, 28)	2.6 (0, 38)	0.09
Time to first AF recurrence, days*	82 ± 115	103 ± 118	0.08

Values are n (%), mean ± SD, or mean (minimum, maximum). *Only for patients with a recurrence.

AF = atrial fibrillation.

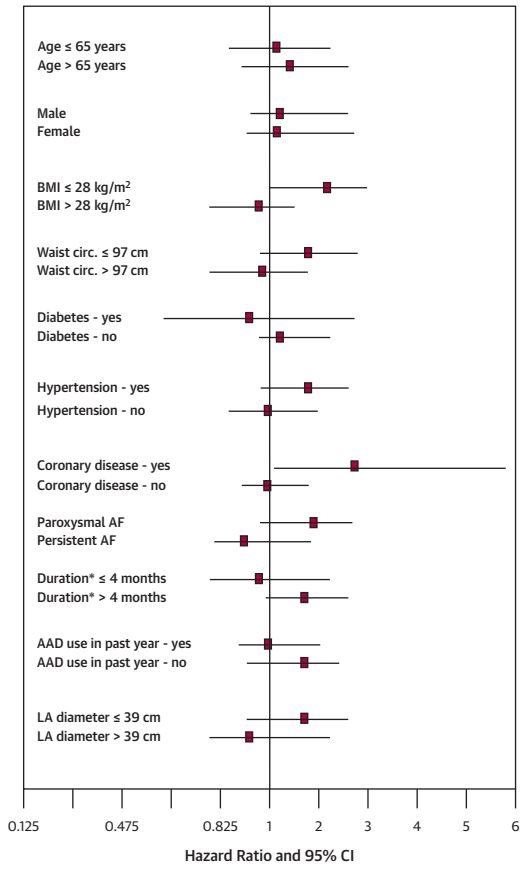


FIGURE 3 Occurrence of Primary Endpoint in Pre-Specified Subgroups

*Time since first diagnosis of AF. AAD = antiarrhythmic drugs; AF = atrial fibrillation; BMI = body mass index; CI = confidence interval; circ. = circumference; LA = left atrial.

TABLE 3 Change in Inflammatory and Oxidative Stress Markers From Baseline to 6 Months

	Baseline Mean (min, max)	% Change	p Value	p Value Interaction
hs-CRP, mg/dl				
Fish oil	2.11 (0.17, 9.62)	−11	0.04	0.9
Placebo	1.98 (0.17, 9.87)	−11	0.04	
MPO, ng/ml				
Fish oil	80 (18, 305)	−5	0.05	0.3
Placebo	79 (25, 300)	−9	0.0004	

Values are mean (minimum, maximum) unless otherwise indicated.
hs-CRP = high-sensitivity C-reactive protein; MPO = myeloperoxidase.

value, ~2 mg/dl), and decreased modestly in both groups. Similarly, MPO was within normal limits at baseline and decreased slightly in both groups (Table 3). Our findings raise 2 potential hypotheses. First, given the low values of both CRP and MPO in our sample, these mechanisms may not have been implicated in AF recurrence in AFFORD. Second, fish oil at the given dose may have been insufficient to further reduce these markers in this low-risk population.

Although previous studies showed an inverse relationship between n-3 fatty acid blood content and risk of de novo AF (6,7), ours is the first study to prospectively address the relationship between the omega-3 index and AF *recurrence*. We observed a doubling of the omega-3 index in patients in the fish oil group (~8%), whereas it remained unchanged in the placebo group (Figure 4). Previously, an omega-3 index ≥8% was noted to be associated with optimal cardioprotection and a 90% reduction in the risk of sudden cardiac death (22). Although we achieved this level in the AFFORD, fish oil did not provide protection against recurrent atrial arrhythmias. The omega-3 index was similar between those with and without an AF recurrence, and the change in omega-3 index at follow-up was also not associated with a higher or lower risk of AF recurrence, irrespective of treatment group (data not shown).

STUDY LIMITATIONS. Potential limitations of the current study include the formulation of n-3 PUFA supplements used. Fish oil capsules contained EPA and DHA in a 2:1 ratio, whereas certain data suggest that DHA may have greater AA properties than EPA (6,21,23,24). However, this ratio was protective against sudden arrhythmic death in the GISSI-Prevenzione study (25). Second, participants were not fitted with implantable loop recorders that, although costly and invasive, would have, in theory, provided the optimal means for detection of AF recurrence. As a more cost-effective alternative, patients had transtelephonic monitors, allowing them to transmit rhythm strips at will. Again, previous trials of fish oil for the prevention of AF recurrence generally used 12-lead electrocardiography or 24-h Holter monitors to detect recurrent episodes. Third, we did not assess the potential impact of fish oil in combination with either AADs or following AF ablation. However, as noted previously and in contrast to previously mentioned studies (9–12), the specific purpose of the AFFORD was to evaluate the efficacy of fish oil as the sole AA agent in a group of low-risk patients. Additionally, data on the efficacy of fish oil after AF ablation are very limited, with 1 small, nested case-control study suggesting some benefit (26). Fourth, although we observed a trend toward a higher

risk of cardiovascular death or hospitalization in the fish oil group, we believe this association to be spurious due to small numbers and multiple testing. Again, most of these endpoints were hospitalizations for AF recurrence. Furthermore, previous studies in AF (8–12) and large studies in coronary heart disease (25,27) have not shown fish oil to be associated with a higher risk of death, but suggest that it may even be protective (25). Finally, we made no effort to control for dietary sources of omega-3 fatty acids and no dietary counseling was provided to participants. Although certain macronutrients, including omega-6 fatty acids, refined sugars, and processed meats, are known to be pro-inflammatory (28–30) and therefore could potentially influence hs-CRP, given the randomized nature of the study and sample size, a significant diet × treatment group interaction is unlikely.

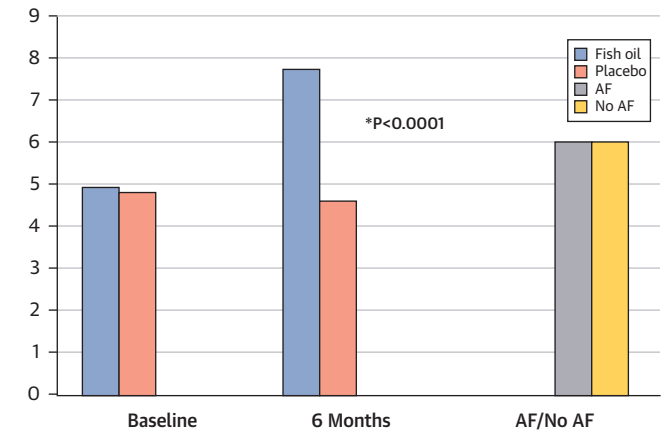


FIGURE 4 Omega-3 Index at Baseline, 6 Months, and According to the Presence or Absence of AF Recurrence.

AF = atrial fibrillation.

CONCLUSIONS

Among low-risk patients with paroxysmal or persistent AF not receiving conventional AA therapy, fish oil used at a higher dose than in most previous studies does not reduce symptomatic or asymptomatic AF recurrence. Furthermore, fish oil at the dose used did not lower systemic markers of inflammation and oxidative stress. The lack of a beneficial effect of fish oil on AF recurrence in the AFFORD may be at least partially due to its lack of effect on these pathophysiological processes, which have been implicated in AF development and progression. We believe that our results provide conclusive evidence that fish oil has no role in the rhythm-control management of patients with paroxysmal or persistent AF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Although fish oils exhibit certain anti-inflammatory and antioxidant properties, these substances do not reduce inflammation or oxidative stress in low-risk patients with atrial fibrillation or prevent arrhythmia recurrence.

TRANSLATIONAL OUTLOOK: Whether interventions such as the Mediterranean diet reduce the risk of recurrent atrial fibrillation after cardioversion or ablation requires further investigation in prospective studies.

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KEY WORDS arrhythmia, fibrillation, inflammation, omega-3 fatty acids, oxidative stress

APPENDIX For a list of investigators that participated in the trial, please see the online version of this article.