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EDITORIAL COMMENT

n-3 Polyunsaturated Fatty Acids for Atrial Fibrillation Recurrence

Is the Horse Already Out of the Barn?*

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It is estimated that 2.3 million Americans experience atrial fibrillation (AF), and on the basis of documented increases in AF prevalence and incidence in U.S. population-based studies, this number may increase to anywhere from 5.6 million (1) to as much as 15.9 million by 2050 (2). Recent estimates suggest that over 10% of the population will develop AF by age 75 years (2). Once AF develops, pharmacological and invasive treatments aimed at eliminating AF and maintaining sinus rhythm have significant risks, limited long-term success rates, and have not been documented to reduce adverse outcomes associated with AF (3,4). Therefore, there is a pressing need for novel, safer therapies to not only treat established AF, but also to prevent incident AF and AF-related morbidity and mortality.

Pharmacological therapy for AF has traditionally centered on cardiac ion channel blockers, which directly alter cellular electrophysiology to suppress AF, but have little impact on the development of the atrial substrate involved in the initiation and maintenance of AF (5). In addition, these drugs are limited by incomplete effectiveness and the risk of life-threatening proarrhythmic complications. As a result, there has been significant interest in evaluating "upstream" therapies (6) that might alter the atrial substrate without inducing proarrhythmia. Long-chain n-3 polyunsaturated fatty acids (PUFAs) not only have multiple direct and indirect effects on cardiac electrophysiology (7,8), but they also have autonomic, antifibrotic, anti-inflammatory, and antioxidant properties that have the potential to alter atrial structural and electrical properties involved in the initiation and maintenance of AF (5,9). On this basis, along with observational evidence suggesting a possible link between blood levels of long-chain n-3 PUFAs and the development of incident AF (10,11), randomized trials have been conducted to test the efficacy of these nutritional supplements as therapeutic agents in AF.

To date, randomized trials of n-3 PUFAs with AF as the primary endpoint have either examined recurrent AF events in patients with established AF or short-term AF development in patients undergoing cardiac surgery. Trials have involved heterogeneous patient populations, diverse designs, different n-3 PUFA dosages and formulations, and relatively small sample sizes. Some of the smaller trials demonstrated significant reductions in AF recurrence after cardioversion and postcardiac surgery (12–14), which have not been confirmed in recent larger trials (15–17). When the results of these diverse trials are combined in a meta-analysis, pooled risk estimates are null for AF recurrence in established AF patients (relative risk: 0.95; 95% confidence interval: 0.79 to 1.13) and for postoperative AF (relative risk: 0.86; 95% confidence interval: 0.71 to 1.04), with marked statistical heterogeneity observed between trials, particularly for recurrent AF (17).

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In this issue of the *Journal*, Nigam et al. (18) report the results of another secondary prevention trial, the AFFORD (Multi-center Study to Evaluate the Effect of N-3 Fatty Acids [OMEGA-3] on Arrhythmia Recurrence in Atrial Fibrillation), a double-blind, randomized, placebo-controlled trial of fish oil (4 g/day, docosahexaenoic acid [DHA]: eicosapentaenoic acid [EPA] 1:2) versus safflower oil placebo in 337 patients

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with symptomatic paroxysmal or persistent AF. The primary endpoint of AFFORD was time to first asymptomatic or symptomatic AF recurrence lasting >30 s over a follow-up period of up to 16 months. Patients taking antiarrhythmic drugs were excluded, and weekly transtelephonic transmissions were used to screen for asymptomatic AF. The trial documented a high AF recurrence rate in this study group (63%), with a shorter time to first AF recurrence in the fish oil group, which did not reach statistical significance ($p = 0.08$). There were no significant differences between the randomized treatment arms in the secondary endpoints of inflammatory (high-sensitivity C-reactive protein) or oxidative stress (myeloperoxidase) markers measured at baseline and after treatment at 6 months. n-3 PUFA levels in this population were fairly high at baseline, but increased significantly to the levels where benefits for incident AF have been suggested by observational studies (10,11). However, in contrast to these population-based studies, no relationship between n-3 PUFA levels and recurrent AF was observed in the secondary prevention population enrolled in AFFORD.

Despite the relatively small sample size, there are several important strengths of AFFORD that address concerns raised regarding design aspects of previous clinical trials, which could have led to false-negative results. First, AFFORD used a 3-week loading run-in phase before accruing endpoints, which should have allowed substantial, albeit not full, incorporation of n-3 PUFAs into myocardial membranes (19). In the largest secondary prevention trial to date involving 663 patients (15), nearly half of the AF events occurred during the first 28 days of treatment before the time when n-3 PUFA levels reach a steady state in the atrium (19). The AFFORD also excluded patients taking antiarrhythmic drugs and was the first to use transtelephonic monitoring to document asymptomatic AF events, which resulted in a higher and more complete AF ascertainment than previous trials. The clinical significance of brief AF events detected by monitoring is unknown, but recent data in pacemaker patients suggest that episodes lasting only 6 min are associated with an increased stroke risk (20). Previous trials also had relatively short-term follow-up of 6 months to 1 year, which may not have been adequate for n-3 PUFAs to have a major impact on the process of atrial remodeling (9). The AFFORD followed some patients for as long as 16 months; however, the majority of events in the AFFORD still occurred in the first 3 months of the study, with few patients followed beyond 1 year. Finally, in contrast to studies of postoperative AF (21), the AFFORD did not find major increases in selected markers of inflammatory or oxidative stress, and these markers were not affected by n-3 PUFA supplementation.

Is the AFFORD the "final nail in the coffin" on the use of n-3 PUFAs for AF or is "the horse already out of the barn" in these patients with established AF? Clearly, these data, in combination with data from previous randomized trials, do not support the practice of using n-3 PUFAs as a substitute for antiarrhythmic drugs to prevent recurrent AF events. However, given the potential pleiotropic actions of n-3 PUFAs, it is quite plausible that these agents might be more effective at preventing, rather than reversing, the development of the atrial substrate associated with AF and/or that longer term therapy may be required to have a significant impact on atrial remodeling in patients with established AF. Therefore, important benefits for AF risk could be missed in these short-term secondary prevention trials, which might only be detected in longer term and/or primary prevention trials.

Also, the mechanistic complexities of n-3 PUFAs (8) and of the substrates that underlie AF (5) need to be considered. n-3 PUFAs have multiple actions that may both promote and prevent AF in different clinical scenarios, and their actions may vary with the baseline dietary intake of n-3 PUFAs. Observational studies examining the association between dietary intake of long-chain n-3 PUFAs and incident AF have been mixed, with some studies suggesting benefit, others neutrality, and others raising the possibility of risk (8). Given the significant proportion of the population already taking fish oil supplements (22), a better understanding of the long-term effects of these supplements on AF in large populations is needed. The VITAL (VITamin D and OmegA-3 TriaL) Rhythm Substudy is currently examining the impact of randomized treatment with 1 g/day of n-3 PUFAs on incident AF events in 25,875 men and women without cardiovascular disease over 5 years of follow-up. It is hoped that studies such as this, with planned long-term treatment and follow-up for AF events, will provide much-needed data beyond those available from observational studies to determine the summation of benefits and risks of these agents on AF incidence and recurrence in the general population. At present, n-3 PUFA supplements cannot be recommended on the basis of the available data as therapeutic agents to prevent recurrent or incident AF.

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