REVIEW

Fish Oil and Prevention of Atrial Fibrillation: An Appraisal of the Evidence

Mahmoud Houmsse*, Ayman Bazerbashi², Kamal Haykal², Marwan Mohammad³

1. Department of Cardiovascular Medicine, The Ohio State University, Columbus, Ohio, USA
2. School of Biology, The Ohio State University, Columbus, Ohio, USA
3. Department of Internal Medicine, Mount Carmel Health System, Columbus, Ohio, USA

*Corresponding author: M. Houmsse Email: mahmoud.houmsse@osumc.edu
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Abstract
Atrial fibrillation (AF) is the most common cardiac arrhythmia. In the absence of optimal rhythm control therapy, due to lack of satisfaction of currently available membrane-acting antiarrhythmics and limited availability of ablative therapy, upstream therapies to prevent atrial fibrillation are emerging as a new pharmacologic strategy. Long chain n-3 (omega-3) polyunsaturated fatty acids (PUFAs) from fish have been suggested to account for these benefits. Multiple observational, clinical, and experimental studies have shown that regular fish consumption has a favorable effect on preventing AF. Experimental studies have shown a potential antiarrhythmic, antifibrotic and anti-inflammatory effect of PUFAs on atrial tissues. This effect on the atrial substrate will lower atrial tissue vulnerability for development of atrial fibrillation. Recent prospective studies regarding the preventive benefit of PUFAs on post open-heart surgery AF showed mixed results. The purpose of this treatise is to review available studies of PUFA effects on AF and outline benefits of the PUFAs as an upstream therapy to prevent AF.

Key Word: atrial fibrillation, fish oil, antiarrhythmic, n-3 polyunsaturated fatty acids.

Introduction
AF is the most common cardiac arrhythmia afflicting more than 2.2 million Americans (1). Its prevalence increased with advanced age and improvements in survival outcomes of cardiovascular disease patients (2). It has a significant impact on overall morbidity and mortality (3,4). AF results in fatigue, reduced exercise tolerance, and increased risk and severity of stroke (1). It is associated with ischemic stroke and impaired functional capacity. Current therapies focus on thrombo-embolic prevention, heart rate control, or restoration of sinus rhythm. Unfortunately, the current antiarrhythmic therapy is suboptimal in terms of both efficacy and safety. Ablative therapy as an alternative to
antiarrhythmic drugs is available for a small number of patients. Besides newer class III antiarrhythmics, such as dronedarone (5), attention has been directed to upstream therapy focusing on underlying anatomical substrates. An increasing body of evidence, including experimental findings, observational studies, and clinical trials, indicates that consumption of fish or fish oil reduces the incidence of fatal ventricular arrhythmias manifested as coronary death or sudden death (6). It is of growing interest whether fish or fish oil consumption might influence AF. Thus, prevention of AF should be the ultimate goal.

N-3 (Omega-3) Polyunsaturated Fatty Acids
The two main classes of polyunsaturated fatty acids, n-3 (omega-3) and n-6 (omega-6), are obtained through dietary intake (7). Marine oil and fish are the primary sources of n-3 PUFAs, specifically eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). However, n-6 PUFAs are primarily obtained from vegetable oil sources (parent compound, linoleic acid). In a cross-sectional study, the relationship between seafood consumption and long-chain (n-3) PUFA biomarkers were variable for the type of fish consumed. Higher consumption of non-fried fish (tuna, salmon, sardines, other broiled, steamed, baked or raw fish–trout, sole, halibut, poke, and grouper) was associated with greater levels of plasma EPA and DHA. These plasma levels of EPA and DHA will reach a plateau with approximately a twice weekly dietary intake. In contrast, no associations were found with non-fried shellfish (shrimp, lobster, crab, oysters, mussels) or fried fish (fried fish or fish sandwich, fried shrimp, calamari) (8–9), indicating that fried fish is not a good source of long-chain (n-3) PUFA (Table 1).

Antiarhythmic Effects of N-3 Fatty Acids
1. Inhibition of Sodium, Calcium, and Potassium Channels
Leaf, et al (7), found that EPA and DHA prevent arrhythmias by affecting the excitability of cultured neonatal rat cardiomyocytes, inhibiting fast, voltage-dependent sodium and L-type calcium currents. However, in the presence of n-3 PUFAs, a voltage-dependent shift to more hyperpolarized potentials occurs, primarily as a result of inhibition of a fast, voltage-dependent sodium current. This prevents the sodium channel from contributing to the generation of an action potential in partially depolarized cardiomyocytes (16).

The electrophysiological basis of PUFAs antiarrhythmic effects may be due to a slight hyperpolarization of the resting membrane potential, an increase of the current necessary to elicit an action potential, and an increase of the phase 4 refractory period (17-19). These effects were found to be related to an inhibition of the sodium current INa (20), the calcium current ICaL (21). It is also possibly related to the potassium currents IK (17). DHA has been shown to directly inhibit the delayed rectifier potassium channel, which is responsible for the depolarization phase of ventricular and atrial cardiac potentials. These effects account for an increased electrical stability that may result in a significant protection against fibrillation, which has been actually demonstrated in vitro.

II. Improving Autonomic Function
Chronic imbalance of the autonomic nervous system, which is mainly characterized by an increase in sympathetic and/or a decrease in parasympathetic tone, will increase the risk of major cardiovascular (CV) events and dysrhythmias (22-25) including vagally-mediated AF (AF with slowed heart rate). Several randomized controlled trials show that n-3 PUFAs improve sympahto-vagal balance. DHA was associated with the risk of AF, which is consistent with previous studies of long-chain n-3 PUFAs and CV risk. For example, in rats, DHA inhibited cardiac arrhythmias (26).

In humans, DHA concentrations in blood showed a beneficial affect on heart rate variability (HRV), (27,28) and is a predictor of arrhythmic events (29,30). The preferential accumulation of DHA over EPA in myocardial cell membranes (31), together with the results from these studies, suggests that DHA may be the principal long-chain n-3 PUFA responsible for the cardioprotective effects. DHA is the primary fatty acid in cell membranes (32), which serve as a repository unite and contribute to serum/plasma levels along with dietary intake. Therefore it is possible that serum DHA might better reflect long-term fish intake patterns than the other long-chain n-3 PUFAs. In addition to the benefits to the autonomic nervous system, long-chain n-3 PUFAs can reduce heart rate in heart transplantation independently of vagal activation (33).

III. Anti-inflammatory Effect
Despite the inconsistency of the effects of n-3 PUFA on C-reactive protein (34), these agents have been shown to suppress production of pro-inflammatory cytokines such as interleukin-1B, interleukin-6, and tumor necrosis factor-alpha (35). Experimental and clinical data of AF suggest that inflammation, (36,37) increased oxidative stress (38), and the renin–angiotensin–aldosterone system (39-41) plays an important role in the development of atrial remodelling and fibrosis associated with persistent AF.
Inflammation seems to be involved during the early phase of persistent AF (electrical remodeling), while the renin–angiotensin system (RAS) may influence both the electrical and structural remodeling seen during later stages of AF development. Therefore the anti-inflammatory effect of n-3 RUFA will prevent the early phase of atrial remodeling in AF (43). During myocardial biopsy on fish oil fed dogs for 14 days, there was almost 100% increase in the atrial n-3 PUFA and a 50% reduction atrial connexin 43 (gap junction), which could be another mechanism of antiarrhythmic effect of n-3 PUFA (44).

IV: Prevention of Acute Atrial Electrophysiology Remodeling
Attuel, et al, reported an increase in vulnerability to AF as a result of the loss of normal rate-related adaptation of the atrial effective refractory period (ERP) (45). This observation has been confirmed in experimental models of AF or rapid pacing, which are characterized by shortening and loss of rate-adaptation of the atrial ERP (46). Reduction of the atrial ERP is believed to be an important early remodeling event that favors the development and perpetuation of AF whereby AF begets AF (47). N-3 PUFA treated group compared to n-6 PUVA's (48). Sarrazin, et al, have evaluated the effect of fish oil in a canine model of vagally induced AF. Adult dogs were fed fish oil for 14 days. Atrial fibrillation was induced by both extra stimulus (premature atrial complex [PAC]) and burst-pacing techniques. In the fish-oil-fed dogs, the risk of sustained AF was =70% to 80% lower for PAC-induced AF and 42% lower for burst pacing-induced AF (p < 0.05 for each comparison) (44).

N-3 Fatty Acid and Prevention of Atrial Fibrillation
In a prospective observational study among elderly subjects (mean age 72.8), usual dietary intake assessed at baseline in 1989–90 was compared with atrial fibrillation incidence and frequency of paroxysmal AF over 12 years of follow-up. Data was gleaned from hospital discharge records and annual electrocardiograms. Consumption of tuna or other broiled or baked fish (non-fried) was associated with a 28% reduced incidence of AF in persons ingesting these foods 1–4 times/wk (p < 0.005) and a 31% reduced incidence in those ingesting these foods >5 times/wk (p < 0.008) (12). In contrast, two other observational studies showed no inverse relationship between consumption of non-fried fish and incidence of AF. The Danish Diet, Cancer, and Health Study (mean age 56) found no association between dietary n-3 fatty acid consumption and a reduced risk of AF (49).
The Rotterdam Study also failed to find an association between dietary n-3 fatty acid intake from fish sources and AF (50). It has been suggested that the discrepancy between the previous three observational studies may be due to the heterogeneity of AF subtypes across cohorts (51). The use of dietary intake questionnaires to estimate dietary n-3 fatty acid content was different and much more subjective (table 2).

**Differences in ages of the study populations**
In older populations, AF is related to structural heart disease, systemic inflammation, atrial fibrosis, and impaired hemodynamics, whereas in younger populations, 20-45% of AF occurs with no associated co-morbidities or structural heart disease (51,52). Variability in the detection of AF was also noted since it is often asymptomatic (53).

Virtanen, et al, prospectively studied 2174 men to assess effects of high serum concentrations of long chain n-3 PUFAs (EPA, DHA) and docosapentaenoic acid (DPA). These serve as markers of fish or fish oil consumption, and were associated with a decreased risk of incident AF in men aged 42-60 as noted from data collected between 1984-89. The authors intended to confirm fish or fish oil intake by determination of serum levels of PUFA concentrations. They also included all ages of adult patients in the study. During 17.7 years of follow up, data revealed 240 AF events occurred. An increased concentration of long-chain n-3 PUFAs in serum may protect against AF. Serum docosahexaenoic acid (DHA) concentrations were shown to provide the greatest impact (54).

**N-3 Fatty Acids for Prevention of AF following Open Heart Surgery**
A randomized controlled trial of 160 patients assessed whether the administration of PUFAs (2 g/day) would reduce the incidence of postoperative AF after coronary artery bypass grafting (CABG) compared to placebo. The development of AF was significantly reduced in patients receiving PUFAs (15.2% versus 33.3%). This study demonstrates that PUFAs administration during hospitalization in patients undergoing CABG reduced the incidence of postoperative AF (54.4%) and was associated with a shorter length of stay (55).

Mariscalco, et al. reported the incidence of both early and late AF in 530 patients who underwent open-heart surgery and who were randomized to preoperative PUFAs over a period of four years. They defined “early AF” and “late AF” as AF documented in the surgical department or during the rehabilitation program, respectively. They found that the overall incidence of early AF in the entire study sample was 44.7% [31.0% with PUFAs versus 47.3% without PUFAs (p = .006)]. In contrast, late AF occurred in 14.7% patients and was not influenced by a preoperative PUFA regimen (11.9% vs 15.2%, p = .43). Preoperative PUFAs were independently associated with a 46% reduction in risk of early AF development. Preoperative PUFA therapy is associated with a decreased incidence of early AF after cardiac surgery but not late AF. Patients undergoing cardiac surgery may benefit from a preventive PUFA approach (56).

Another prospective, randomized, double-blinded, placebo-controlled trial failed to show a beneficial effect of treatment with n-3 PUFA on the occurrence of postoperative AF in patients undergoing open-heart surgery. The authors concluded that specific factors were associated with postoperative AF included advanced age, peak post-operative C-reactive protein level, valvular surgery, lower body mass index, and non-smoking, but n-3 PUFA concentration in plasma lipids was not associated with post-operative AF (57). In the postoperative setting, Fish oil produced relatively acute benefits which included possible effects on post ischemic recovery (58), left ventricular filling (59), vagal activity (60), or atrial electrophysiology, e.g. due to the effects on myocardial ion channels (7) or connexins (44).

For the AF seen with aging, mechanisms that produce long-term benefits may be more important, such as effects of fish oil on Blood pressure (61), Systemic vascular resistance (63,64) reactivity (65,66), Endothelial activation (66), which might mitigate long-term ventricular (and atrial) remodeling and augment myocardial compliance. Kaireviciute, et al (68), reviewed the incidence of AF following cardiac surgery. They concluded that: 1) advanced age is the best predictive clinical factor. 2) ECG and echocardiographic parameters lack a high specificity and positive prediction value, 3) in terms of preventive options, only beta blockers, rate-limiting calcium antagonists, and amiodarone have shown potent effects on the suppression of AF postoperatively (not digoxin), 4) In the prophylaxis and management of post-operative AF, the appropriate use of thrombo-prophylaxis and correction of identifiable precipitants (such as electrolyte imbalance or hypoxia) are recommended, and 5) the role of other drugs, such as n-3 PUFAs, Renin-aldosterone angiotensin system blockers (Angiotensin converting enzyme inhibitor, Angiotensin receptor blocker), and statins in preventing the incidence of post-operative AF needs further studies.
**Conclusion**

AF is a common arrhythmia, and can be very complex electrophysiological disorder. AF in most cases (except for lone atrial fibrillation) presents as a final clinical manifestation of multiple and relatively distinct pathological entities. Such entities range from adrenergic and vagal activity in athletes and younger adults to reduced myocardial compliance and ventricular dysfunction in older adults. This heterogeneity suggests that risk factors and effective treatments will likely vary depending on the specific characteristics and predominant pathology of AF in the population (e.g. comparing younger vs. older adults, spontaneous vs. postoperative AF, or primary prevention vs. restoration of sinus rhythm vs. prevention of recurrence). These issues must be carefully considered, and heterogeneity may account for the conflicting results of studies of fish or fish oil and its relationship to AF (69).

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