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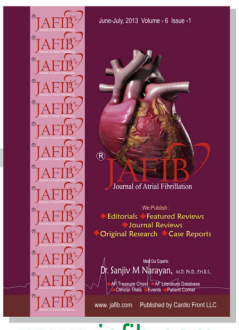

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Do Omega-3 Fatty Acids Decrease the Incidence of Atrial Fibrillation?

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Abstract

Although atrial fibrillation is a very common medical problem in general population and has a high incidence in the setting of open heart surgery, there are very few therapies to prevent occurrence or recurrence of atrial fibrillation. N-3 polyunsaturated fatty acids have been shown to change basic physiologic properties of the atrial tissue to make it less susceptible to atrial fibrillation. In this review, we first describe basic physiological mechanisms thought to be responsible for these changes and then discuss observational and interventional studies evaluating the use n-3 polyunsaturated fatty acids for primary and secondary prevention of atrial fibrillation in the general population, in subjects undergoing open heart surgery, and in special subgroups of patients.

Introduction

Burden of Atrial Fibrillation

Atrial fibrillation (AF) is a very common medical problem with estimated prevalence in the general population of 0.4-1.0%.[1] AF prevalence increases with advancing age.[2] It is associated with increased morbidity and mortality.[3,4] Major risk factors for AF in addition to age include hypertension, structural heart disease, diabetes mellitus, and thyroid disease.[3] AF is associated with 2-7 times higher incidence of ischemic stroke[5,6] and a higher incidence of mortality[7] as compared with subjects in normal sinus rhythm. Direct cost estimates of AF ranged from $2000 to $14,200 per patient-year in the USA and from €450 to €3000 in Europe in 2011.[8]

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Current Approach for Treatment and Prevention of AF

Current management of AF mainly focuses on preventing recurrence of AF and its complications, and includes prevention of stroke, rate control and rhythm control treatments, the latter consisting of antiarrhythmic medications and catheter or surgical ablations.

The idea of primary prevention of AF has been recently introduced. As we understand more about underlying pathophysiologic mechanisms and risk factors associated with AF, modifying these risks to prevent the occurrence (or recurrence) of AF is becoming possible. Upstream therapy refers to use of non-antiarrhythmic medications to decrease the incidence of AF. Currently such medications include angiotensin-converting enzymes inhibitors, angiotensin receptor blockers, statins, and omega-3 (n-3) polyunsaturated fatty acids (n-3 PUFAs). Several studies have focused on mechanisms by which each of these medications interferes with AF as well as effectiveness of each of the above medication for prevention of AF. In this review we will focus on omega-3 (n-3) polyunsaturated fatty acids (n-3 PUFAs).

Omega-3 (n-3) Polyunsaturated Fatty Acids (n-3 PUFAs)

N-3 PUFAs extracted from fish oil mainly contain eicosapentaenoic

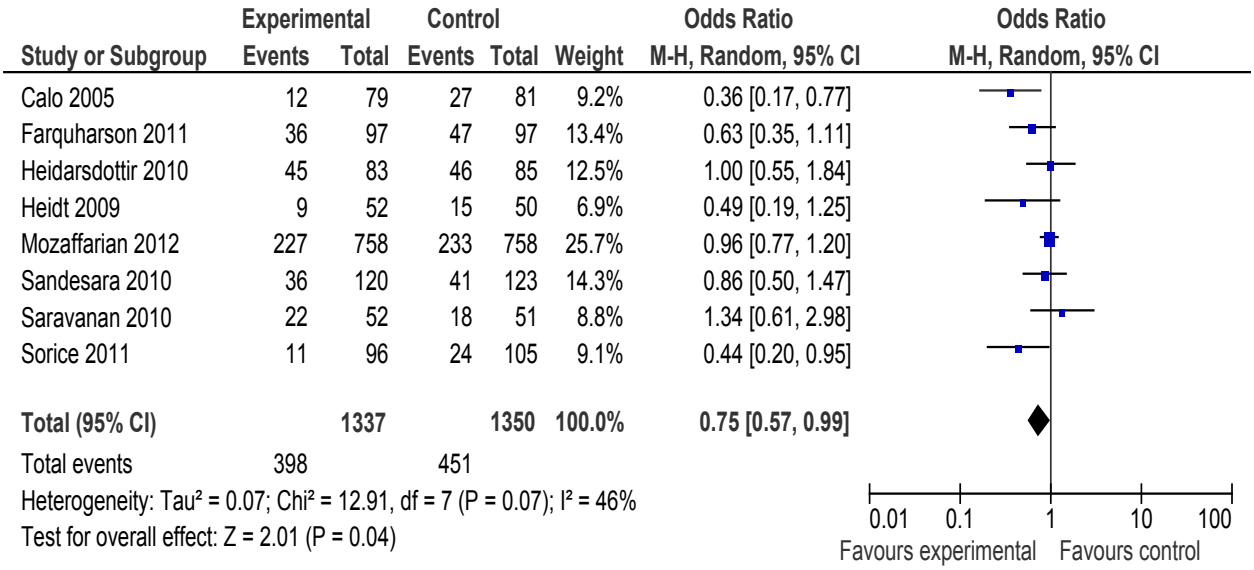

Figure 1: **Effects of n-3 polyunsaturated fatty acids vs. control on the incidence of post-operative atrial fibrillation**

acid (EPA) and docosahexaenoic acid (DHA),[9] whereas alpha-linoleic acid (ALA) is found in flax seed and other plants.[9] ALA can be converted to EPA and DHA, however, endogenous conversion is limited in humans, which makes availability (and levels) of EPA and DHA dependent upon dietary consumption.[10]

The effects of n-3 PUFAs on AF have been studied extensively in the last decade. N-3 PUFAs are known to have antiarrhythmic effects. They have been shown to augment vagal tone and have anti-inflammatory properties, which leads to decreased rate of interstitial fibrosis.[11] N-3 PUFAs do not appear to exhibit significant side effects with chronic administration and are relatively cheap and easily available for oral intake. If proven effective, N-3 PUFAs could easily be introduced into clinical practice for AF prevention either to the general population or to those with a higher risk of AF. In subsequent paragraphs, we will first review the mechanisms by which n-3 PUFAs could affect AF and experimental basic science models, supporting these mechanisms. Then we will describe physiological effects of n-3 PUFAs observed in human studies in connection with possible effects on AF. Lastly, observational and interventional studies evaluating links between n-3 PUFA and incidence of AF will be discussed.

Physiologic effects of n-3 PUFAs on AF

Multiple mechanisms have been suggested to produce anti-arrhythmic action of n-3 PUFAs on AF. Some of the mechanisms were directly or indirectly confirmed by animal models, while others were shown in human studies.

Physiologic Effects of n-3 PUFAs on AF Shown on Animal Models

N-3 PUFA produce direct electrical effect on ion channels,[12,13,14,15] and could modulate connexins.[16] In a canine model, infusion of n-3 PUFAs (both EPA and DHA) immediately before atrial pacing (AP) significantly attenuated reduction of effective refractory period (ERP) observed in control groups treated with either normal saline or n-6 PUFA prior to atrial pacing.[17] AP-induced reduction of ERP was shown to be highly predictive of inducibility of AF in canine models.[18] Dietary fish oil was shown in an animal model to improve cardiac response to ischemia and reperfusion.[19] In an isolated rabbit heart model, incorporation of n-3 PUFA into the diet for 12 weeks preceding the experiment was associated with reduction of stretched induced atrial susceptibility to AF.[20] In a canine model, pre-treatment with n-3 PUFAs was shown to have attenuated CHF-induced atrial fibrotic changes[21] and prevent AF by inhibiting inflammation.[22]

Above data provide support to the hypothesis that n-3 PUFAs may produce anti-arrhythmic effects via multiple mechanisms,[23] including effect on cardiac electrophysiology, stabilization of atrial myocyte membranes, direct vasodilatory effect with decrease in blood pressure, improvement of contractile function of the myocardium, modulation of cardiac ion channels, and anti-inflammatory effect.

In contrast to human studies, doses of the n-3 PUFAs used in animal models are much higher. For example, in the study of Mayyas et al,[24] which used adult mongrel dogs weighing 15-25 kg, the dose of the n-3 PUFA was 0.6mg/kg/day, which is at least three times higher than a typical dose of n-3 PUFA given to humans.

Physiological Effects of n-3 PUFAs on AF Observed in Humans Studies

Fish oil was shown to affect cardiac electrophysiology in humans. For example, a meta-analysis showed that fish oil reduces heart rate in humans,[25] either by its effects on the sinus node, or by altering autonomic function. Patients with paroxysmal AF undergoing pulmonary vein isolation who were pre-treated with fish oils for more than 30 days were found to have distinctly different electrophysiologic properties (such as increased ERP of both left atrium and pulmonary veins) and decreased inducibility of AF compared with controls.[26,27] Patients with AF and atrial flutter undergoing reversion of arrhythmia who were pre-treated with fish oil for a mean of 70 days were found to have less mechanical stunning of the left atria (evaluated by cardiac echo) following the reversion.[28] Several studies evaluated association between the levels of n-3 PUFAs and AF in different groups of patients. For example, DHA level was found to be inversely associated with AF in hemodyalisis patients.[29] These studies

provide evidence from both animal models and human studies that n-3 PUFAs change basic physiologic properties of the atrial tissue, making it less susceptible to AF. It should be noted, that contrary to animal models, most of human studies were done in connection with AF ablation. Therefore, currently there are no human studies in which a response to a mechanistical intervention (other than AF ablation) were evaluated in association with AF or other risk factors for AF (i.e., ion channels, connexins, ERP and others).

Data Obtained from Observational and Interventional Studies

Multiple studies evaluated effects of n-3 PUFAs intake on incidence of AF, among them randomized controlled trials (RCTs) evaluating AF recurrence after cardioversion,[30,31,32,33,34,35] non cardioverison-associated RCTs,[36] RCTs evaluating n-3 PUFA intake for AF prevention in association with cardiac surgery,[37,38,39,40,41,42,43,44] population-based cohort studies,[45,46,47,48,49,50] and studies examining special subgroups of subjects, such as a cohort study evaluating AF and n-3 PUFA intake in association with myocardial infarction,[51] or a nested case-control study evaluating AF and n-3 PUFA intake following AF ablation.[52]

Population-Based RCTs Evaluating n-3 PUFAs for Secondary Prevention of AF not Associated with Cardiac Surgery

Most of the RCTs evaluating n-3 PUFAs for secondary prevention of AF were done in subjects following cardoiversion.[30,31,32,33,34,35] Three of these studies were double blinded (30 34 31) . The follow-up period was either 6 months,[33,34] 52 weeks,[30] or one year.[31,32,35] The studies showed either no effect of n-3 PUFA on prevention of AF[30,33,34,35] or decrease in recurrence of AF.[31,32] A meta-analysis, which included the above studies (n=759) found no significant effect of n-3 PUFAs on the prevention of AF recurrence after cardioversion (pooled OR 0.64; 95% CI 0.35-1.13).[53] There was evidence of heterogeneity among studies (I^2=66%). In contrast, there was significant reduction of recurrent AF when restricted to subgroup of studies,[30,31,32] (n=485), in which n-3 PUFA was administered at least four weeks prior to cardioversion and continuing thereafter (OR 0.39; 95% CI 0.25-0.61).[53]

A single study was done evaluating the effects of prescription n-3 PUFA on prevention of recurrent symptomatic AF in the absence of, which was not following antecedent cardioversion.[36] This study was a multi-center double-blind, placebo-controlled trial, and it included US outpatients with paroxysmal (n=542) or persistent (n=121) AF, who received prescription n-3 PUFA or placebo, and were followed up to six months. The study found no reduction of paroxysmal (HR 1.15; 95% CI 0.90-1.46), persistent (HR 1.64; 95% CI 0.92-2.92), or overall (HR 1.22; 95% CI 0.98-1.52) AF compared with placebo.

Population-Based Cohort Studies not Associated with Cardiac Surgery

Overall, population-based cohort studies[45,46,47,48,49,50] did not show significant reduction of AF in association with n-3 PUFA intake. These studies were part of a large meta-analysis conducted by our group.[54] A sub-analysis (n = 53,689), which only included above studies (see [54] table 2 – sensitivity analysis) showed OR of 0.97 (95% CI 0.74-1.27). The two subset of subjects which showed lower risk of AF with n-3 PUFAs were participants of the Cardiovascular Health Study (CHS) consuming broiled or baked fish,[48] and participants of the Kuopio study with increased n-3 PUFA level in serum (which is a marker of fish or fish oil consumption).[50] In the Kuopio study serum DHA level concentration had the greatest effect.

RCTs Evaluating n-3 PUFA Intake for AF Prevention in Association with Cardiac Surgery

Overall, it is believed that n-3 PUFAs decrease the incidence of AF following cardiac surgery. A meta-analysis including six RCTs,[37,38,39,40,41,42] in which n-3 PUFA were taken perioperatively for primary prevention of AF (n = 833) showed significant decrease in AF in association with n-3 PUFA intake (OR 0.66, 95% CI 0.49-0.88).[55] The heterogeneity among these studies was modest (I^2 = 44%). The follow-up period was much shorter than in non-cardiac surgery-associated studies, the longest being four weeks after discharge.[37] Four of the studies[37,38,40,42] were post CABG, and the other two[39,41] were post open heart surgery.

Since the publication of the meta-analysis described above, two additional studies[43,44] became available, with large number of participants (n = 2296 for both studies combined). Therefore, we conducted a new meta-analysis, in which we combined above studies with the two most recent studies[43,44] (Fig. 1). The addition of the new studies did not significantly change the results (pooled OR 0.75, 95% CI 0.57-0.99). There was still evidence for heterogeneity across studies (I^2 = 46%).

Studies Evaluating n-3 PUFA for Prevention of AF in Special Subgroups of Subjects

A cohort study evaluating AF and n-3 PUFA intake in association with myocardial infarction in 197 subjects and 197 controls[51] showed significant lower risk of AF in a n-3 PUFA group (HR 0.19, 95% CI 0.07-0.51). This study followed consecutive post-myocardial infarction subjects for a period of one year. A nested case-control study evaluating n-3 PUFAs intake and AF following AF ablation (129 subjects and 129 controls)[52] demonstrated lower incidence of AF in the n-3 PUFA group (early recurrence 27.1% vs. 44.1% (p<0.0001); procedural failure 23.2% vs. 31.7% (p<0.003)).

Discussion

Although there is evidence based on both animal models and human studies that n-3 PUFAs change basic physiologic properties of the myocardium, making it less susceptible to AF, the relation of n-3 with AF in human studies (observational as well as interventional) remains inconsistent.

The reasons for these inconsistencies are not clear. The discrepancy between animal models and human studies could be explained by a higher dose of n-3 PUFA used in animal models compared to human studies; different duration of intake of n-3 PUFAs in human studies vs. basic animal research; and difference in study design (experiments in animal and mostly observational study design in human studies).

In the human studies, a decrease in incident AF with n-3 PUFA intake was mainly observed in subjects undergoing cardiac surgery and those with myocardial infarction. These observations suggest that subjects with coronary heart disease might be more susceptible to n-3 PUFAs than other subgroups in terms of AF prevention. It is interesting to note that n-3 PUFAs have been shown to have anti-ischemic properties in certain populations,[56] a mechanism consistent with above results of n-3 PAFAs and AF in CHD patients patients. Another important point is that a relatively small percentage of subjects in the population based studies described above had lone AF. Specifically, among the six population-based cohort studies not

associated with cardiac surgery,[45,46,47,48,49,50] three studies([45,46,49]) had the mean age of the participants more than sixty years old, and in one study,[48] the mean age was above seventy years old. Those subjects who had cardiovascular disease, hypertension or echocardiographic evidence of cardiac abnormalities precluding the diagnosis of lone AF were not excluded. Therefore, it is possible that studies described above simply did not have enough cases of lone AF.

In contrast, a Japanese cohort study[57] showed higher levels of n-3 PUFAs in subjects with lone AF than in normal subjects. Thus, it is possible that subjects with different types of AF may respond differently to n-3 PUFAs.

Conclusions:

Population-based cohort studies have not demonstrated benefits of n-3 PUFA intake as a tool to prevent AF occurring without antecedent cardiac surgery. RCTs showed benefit of n-3 PUFA for prevention of AF only in subjects undergoing cardioversion (when n-3 PUFAs were administered at least four weeks prior to cardioversion and continued thereafter) as well as in people undergoing cardiac surgery, those with myocardial infarction or patients who underwent AF ablation. It is possible that n-3 PUFAs might be more effective in preventing AF in subjects with coronary heart disease than in people free of CHD. More double-blind, randomized, placebo-controlled studies are needed to further clarify the impact of n-3 PUFA on AF risk.

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