



Should Physicians Continue to Recommend Fish Oil for Patients with Atrial Fibrillation?

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Abstract

Many physicians recommend the use of fish oil or omega-3 polyunsaturated fatty acids (n-3 PUFA) in atrial fibrillation (AF) patients. N-3 PUFA have demonstrated anti-fibrillatory properties in several animal studies, however, data regarding their efficacy in preventing AF in humans have been mixed. This article critically reviews studies that have investigated the use of n-3 PUFA for the secondary prevention of paroxysmal and persistent AF and the primary prevention of post-operative AF. We conclude that n-3 PUFA should no longer be recommended for use in any of these AF subtypes until more data are available.

Introduction

Atrial fibrillation (AF) is highly prevalent. It is responsible for significant morbidity and mortality, primarily because it increases the risk of stroke and congestive heart failure.¹ Current therapies are not always effective, and many anti-arrhythmic drugs have toxic side effects. As such, there is an unmet need to find a safe and effective anti-fibrillatory drug. Fish oil, which contains variable ratios of the long chain omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) depending on the source, has demonstrated anti-fibrillatory properties in several animal studies.²⁻⁶ However, human studies have shown mixed results and a recent meta-analysis of randomised controlled trials demonstrated no significant effect of fish oils in the prevention of AF.⁷ Most studies have indicated that omega-3 polyunsaturated fatty acids (n-3 PUFA) have an excellent drug safety profile, however, some studies in pigs suggest that they may facilitate the initiation of AF by shortening the effective refractory period

and action potential duration,^{8,9} or even promote ventricular arrhythmias during episodes of myocardial ischaemia.¹⁰ There is also evidence that n-3 PUFA may be pro-arrhythmic in humans. A randomised controlled trial (RCT) of patients with implantable cardioverter defibrillators found an increase in the number of ventricular tachycardia and fibrillation episodes in patients taking fish oil supplements.¹¹ This was statistically significant in patients who had ventricular tachycardia as their qualifying arrhythmia for study entry. Another RCT in men with angina found that those who were advised to increase their intake of n-3 PUFA through diet or supplements had a significantly higher incidence of cardiac and sudden cardiac death than those who were not; especially in the sub-population taking n-3 PUFA capsules.¹² By critically reviewing some of the major literature, this article will explore the question of whether fish oil should be recommended for use in AF. Since atrial fibrillation is a heterogeneous disease, studies for paroxysmal, persistent and post-operative AF will be presented separately.

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Table 1

Studies investigating the use of fish oil in patients with paroxysmal atrial fibrillation

Publication	Study Design	N	Intervention	Duration of Intervention	Results of Intervention	P value
Biscione 2005 ¹³	Prospective Observational Study	38	1g/d n-3 PUFA (all patients)	4 months	- Number of AF episodes reduced by 59% - AF burden reduced by 67%	P = 0.037 P = 0.029
Tatarskii 2007 ¹⁴	Prospective Observational Study	90	n-3 PUFA (dose unknown)	Unknown.	- Number of AF episodes reduced. - Decreased time to AF termination.	Unknown
Kowey 2010 ¹⁵	DB RCT	527	7 d loading dose of 8g/d n-3 PUFA followed by 4g/d (1.86g EPA + 1.5 g DHA)	6 months	- No significant difference in the number of recurrences of symptomatic paroxysmal or persistent AF between groups.	P= NS
Kumar 2011 ¹⁶	Unblinded RCT	36	6g/d n-3 PUFA(0.3g EPA + 1.5g DHA)	Mean = 40 d before EP study. Range = 30-66 d	- Longer pulmonary vein and left atrial effective refractory periods. - Lower incidence of AF initiated from the pulmonary veins (46% reduction)	P=0.0015 P=0.02

DB= double blind; RCT = randomised controlled trial; d= day; n-3 PUFA = ω -3 polyunsaturated fatty acids; NS = non-significant EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; EP = electrophysiology.

Studies Investigating the Use of Fish Oil in Paroxysmal AF

To our knowledge, there have been four adequate studies specifically on the use of fish oil in patients with paroxysmal AF (defined as arrhythmia that spontaneously terminates)¹³⁻¹⁶ (Table 1). Two small prospective observational studies demonstrated a beneficial effect of fish oil in the secondary prevention of paroxysmal AF.^{13, 14} One small RCT demonstrated that n-3 PUFA prolonged atrial and pulmonary vein effective refractory periods and significantly reduced the number of AF episodes able to be induced from the pulmonary veins.¹⁶ However, the largest multicentre, double-blind RCT conducted to date showed no benefit of n-3 PUFA in the secondary prevention of paroxysmal AF.¹⁵

Studies Investigating the Use of Fish Oil in Persistent AF

In this context, persistent AF is defined as atrial fibrillation that requires cardioversion for termination. To our knowledge, there are nine adequate studies in the literature involving patients with persistent AF^{15, 17-24} (Table 2). Three studies claimed a statistically significant effect of n-3 PUFA in

maintaining sinus rhythm post cardioversion,^{19, 21, 24} and one paper showed that n-3 PUFA significantly reduced the incidence of transient mechanical dysfunction of the atria, "atrial stunning", after electrical cardioversion.²² The remaining studies showed no benefit of n-3 PUFA therapy.

Studies Investigating the Use of Fish Oil in Post-Operative AF

We found eight satisfactory studies investigating the use of n-3 PUFA in the prevention of post-operative AF (POAF)²⁵⁻³² (Table 3). Five of these eight studies claimed a statistically significant decrease in the incidence of POAF with the use of fish oil supplements.^{25-27, 30, 32}

Why are the Results of These Studies Inconsistent?

Heterogeneity in Study Design

The most significant reason for disparity in the literature is the many methodological differences in studies conducted to date. There are very few double-blind randomised placebo-controlled tri-

Table 2 | Studies investigating the use of fish oil in patients with persistent atrial fibrillation

Publication	Study Design	N	Intervention	Duration of Intervention	Results of Intervention	P value
Kanorskii 2007 ¹⁷	RCT	187	1g/d n-3 PUFA with sotalolol 160 mg/d vs. sotalolol alone.	12 months	No significant difference in the number of patients remaining in sinus rhythm or the number of cardioversions required between groups.	NS
Margos 2007 ¹⁸	RCT	40	n-3 PUFA vs. no treatment. (dose unknown)	6 months	<ul style="list-style-type: none"> • No significant difference in the number of AF recurrences or time to recurrence of persistent AF. • At 1 month, n-3 PUFA group had significantly fewer runs of paroxysmal AF and premature atrial beats. 	NS P= <0.01
Patel 2009 ¹⁹	Nested case control study	258	n-3 PUFA (minimum of 655mg /d) vs. no treatment.	1 month prior to pulmonary vein isolation until discharge.	<ul style="list-style-type: none"> • n-3 PUFA group had a 17% absolute risk reduction (38.6% RRR) in the incidence of early AF recurrence (within 8 weeks). • n-3 PUFA group had an 8.5% absolute risk reduction (29.3% RRR) for procedural failure (AF recurrence > 8 weeks) • n-3 PUFA group had significantly lower CRP levels pre and post procedure. 	P=<0.0001 P=<0.003 P=0.04 P=0.0001
Kowey 2010 ¹⁵	DB RCT	118	7 d loading dose of 8g /d n-3 PUFA, followed by 4g/d. (1.86g EPA + 1.5 g DHA) vs. Placebo	6 months	No significant difference in the number of recurrences of symptomatic persistent AF between groups.	P= NS
Bianconi 2011 ²⁰	DB RCT	204	3g /d n-3 PUFA until ECV (mean 21 d) ~1.38g EPA + 1.17g DHA), then 2g /d vs. no treatment	6 months	<ul style="list-style-type: none"> • No significant difference in the number of AF recurrences between groups • No significant difference in the time to AF recurrence. 	P= NS P= NS
Nodari 2011 ²¹	DB RCT	199	2g/d n-3 PUFA vs. placebo (≈ 0.87g EPA + 1.7g DHA)	Started 4 weeks prior to ECV and continued for 1 year.	Significantly more patients in the n-3 PUFA group maintained sinus rhythm during follow up.	P=0.0001
Kumar 2011 ²²	RCT single blind	49	6g/d n-3 PUFA (1.08g EPA + 0.72g DHA) vs. no treatment	Started > 30 d before ECV (mean = 70 d)	n-3 PUFA group had a significantly lower level of atrial mechanical stunning, including in a multivariate analysis†	P= 0.001 †P=0.02
Ozaydin 2011 ²³	RCT	47	2g/d n-3 PUFA (0.36g EPA + 0.24g DHA) + amiodarone vs. amiodarone.	Amiodarone + n-3PUFA was started after ECV for 1 year/ until discharge	<ul style="list-style-type: none"> • No difference in the number of AF recurrences between groups. • CRP levels were similar in both groups at baseline, day 15 post ECV and at AF recurrence. 	P = NS P= NS
Kumar 2012 ²⁴	RCT OL	178	6g/d n-3 PUFA (1.02g EPA + 0.72g DHA) vs. placebo	Started > 30 d prior to ECV (mean 56 d) and continued until AF recurrence or for a year (mean 242d).	<ul style="list-style-type: none"> • n-3 PUFA group had significantly fewer AF recurrences at 90 days and at 1 year. • n-3 PUFA group had significantly longer mean time to AF recurrence (190 days vs. 77 days) 	P= <0.001 P= <0.001

OL = open label; DB= double blind; RCT = randomised controlled trial; n-3 PUFA = ω-3 polyunsaturated fatty acids d=day; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; ECV = electrical cardioversion; RRR= relative risk reduction; CRP = C Reactive Protein; NS= non-significant.

Table 3

Studies investigating the use of fish oil in post-operative AF

Publication	Study Design	N	Intervention	Duration of Intervention	Results of Intervention	P value
Calo 2005 ²⁵	RCT OL	160	~2g/d n-3 PUFA vs. usual care (0.87g EPA + 1.73g DHA)	≥ 5 d prior to surgery until discharge. Mean length of stay: 7.3 d (PUFA), 8.2d (control)	n-3 PUFA group had an 18.1% absolute risk reduction and a 54.4% relative risk reduction for developing post-operative AF compared to control arm.	P= 0.013
Heidt 2009 ²⁶	DB RCT	102	Intravenous infusion of n-3 PUFA (100mg/Kg/d) vs. soya oil	From admission until transfer to a normal ward.	n-3 PUFA group had a 13.3% absolute risk reduction and a 42.3% relative risk reduction for developing post-operative AF.	P=<0.05
Mariscalo 2010 ²⁷	Prospective Cohort Study	530	16% of cohort received 1g/d n-3 PUFA (~0.36g EPA + 0.62g DHA)	Median 5 d (range 1-26d), omitted on day of surgery.	<ul style="list-style-type: none"> n-3 PUFA group had a 16.3% absolute risk reduction and a 49% relative risk reduction for developing "early AF" occurring in the surgical department compared to those without n-3 PUFA. n-3 PUFA did not influence the incidence of "late AF" in the rehabilitation programme. n-3 PUFA group had significantly lower post-operative CRP 	<p>P=0.006</p> <p>P=NS</p> <p>P=0.025</p>
Saravanan 2010 ²⁸	DB RCT	103	2g/d n-3 PUFA "~0.96g EPA + 0.80g DHA" vs. placebo	Median 16d, (range 12-21 d), started at least 5 d before surgery.	<ul style="list-style-type: none"> n-3 PUFA had no significant impact on AF incidence, hospital/ICU/HDU length of stay or AF burden There was no significant difference in serum CRP levels between groups either within 24hrs post-op or 3d post-operatively. 	<p>P=NS</p> <p>P=NS</p>
Heidarsdottir 2010 ²⁹	DB RCT	168	2.24 g/d n-3 PUFA (1.24g EPA + 1.0 g DHA) vs. placebo.	5-7 d before surgery until discharge – max 2 weeks post operatively.	<ul style="list-style-type: none"> No significant difference in the incidence of POAF between groups. No significant difference in peak post-operative CRP between groups. 	<p>P=NS</p> <p>P=NS</p>
Skuladottir 2011 ³⁰	Nested case controlled study from Heidarsdottir 2010 study population.	125	Plasma levels of n-3 PUFA and n-6 PUFA were measured immediately before surgery and 3 d post-operatively.	N/A	<ul style="list-style-type: none"> The incidence of AF decreased significantly with increasing levels of AA, both pre-op and post-op. The incidence of AF increased significantly with increasing levels of DHA, both pre-operatively and post-operatively. 	<p>P=0.008</p> <p>P=0.003</p> <p>P=0.003</p> <p>P=0.008</p>
Farquharson 2011 ³¹	DB RCT	194	4.6g/d n-3PUFA (~2.7g EPA + DHA ~ 1.9g) vs. placebo	3 weeks prior to surgery until discharge (max 6 days)	No significant difference in the incidence of POAF between groups. Length of stay in the ICU was significantly shorter in the PUFA group.	<p>P= NS</p> <p>P=0.005</p>
Sorice 2011 ³²	DB RCT	201	2g/d n-3 PUFA	≥ 5 d prior to surgery until discharge	<ul style="list-style-type: none"> n-3 PUFA group had a significantly reduced incidence of AF, but only in those patients with "on pump" bypass surgery. n-3 PUFA group did not have a longer length of hospital stay 	<p>P=0.013</p> <p>P=NS</p>

OL = open label; DB= double blind; RCT = randomised controlled trial; n-3 PUFA = ω-3 polyunsaturated fatty acids d=day; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; ECV = electrical cardioversion; RRR= relative risk reduction; CRP = C Reactive Protein; NS= non-significant.

als (DB-RCT), the gold standard for assessing the efficacy of a pharmacological intervention. There has been only one DB-RCT conducted in patients with paroxysmal AF,¹⁵ two in patients with persistent AF,^{15, 21} and five in POAF.^{26,28,29,31,32} However, even when considering DB-RCTs alone, their results are still mixed. Liu et al.⁷ and Armaganijan et al.,³³ conducted meta-analyses of the available RCTs investigating n-3 PUFA in the prevention of all AF subtypes, and post-operative AF respectively. Neither meta-analysis found sufficient evidence to support the use of n-3 PUFA supplements, but they were significantly limited by the many differences in trial design, the most significant of which will be discussed in the following sections of this review.

Population Size

Many published studies have small sample sizes and are therefore likely to be statistically underpowered. The largest DB-RCT conducted to date by Kowey et al.¹⁵ (n= 645), was powered to detect a 32% relative risk reduction (RRR) in symptomatic AF recurrence with the use of n-3 PUFA. This trial showed no significant difference in AF recurrence for either paroxysmal or persistent AF or for these groups combined. For post-operative AF, the largest DB-RCTs to date involve about 200 patients^{31, 32} powered to detect a RRR of roughly 53%; however, they yielded inconsistent results. In their meta-analysis, Liu et al highlight that underpowered studies are a significant problem in the current literature, particularly in studies investigating POAF.⁷ Most studies of POAF in their analysis were powered to detect unrealistic treatment effects (RRR 35-55%). They argue that with a baseline AF occurrence of 30-40% in the post-operative setting, studies would need to have 1000-1500 participants in order to detect a relative risk reduction of 25%, a figure which was not reached even with pooled data.

Population Heterogeneity

Age

There are many differences in the patient populations of current studies that could account for conflicting results. Though there was no significant difference in population age among the

studies included in this review; age could influence the efficacy of fish oil. A recent prospective cohort study,³⁴ which includes a considerably older patient population than that of other studies (mean = 74 years), found that higher plasma levels of n-3 PUFA were inversely associated with the incidence of new-onset AF. It is also possible that in younger patients, in whom AF may be vagally mediated, the ability of n-3 PUFA to increase parasympathetic tone might even render them pro-arrhythmic in this population.³⁵

Comorbidities and Atrial Remodelling

Comorbidities are a potential confounder in the current literature. N-3 PUFA may not be directly anti-arrhythmic, but could secondarily prevent AF by inhibiting structural or electrical atrial remodeling, therefore lessening the ability of atrial tissue to initiate and sustain further AF episodes.³⁶⁻³⁸ An example of one such co-morbidity that may result in atrial remodelling is congestive heart failure.³⁹ Rupp and colleagues recently proposed that patients with heart failure are under-represented in the current fish oil literature,⁴⁰ possibly accounting for the many non-significant results. In addition to the potential for atrial remodelling in heart failure patients, Rupp et al also argue that these patients are deficient in n-3 PUFA, as shown by their study in which patients with left ventricular (LV) dilatation had lower serum docosahexaenoic acid (DHA) levels.⁴¹ Therefore, studies without a high proportion of heart failure patients would be unlikely to show a demonstrable benefit of n-3 PUFA supplementation, as their patients were not deficient at baseline. In support of n-3 PUFA preventing AF recurrence by improving congestive heart failure, Rupp and colleagues cite a study by Nodari et al.⁴² This study found that 12 months of n-3 PUFA supplementation improved left ventricular function in patients with dilated non-ischaemic cardiomyopathy. However, one disparity between these studies is that the Rupp et al paper found a DHA deficit mainly in patients with very advanced LV dilatation, whereas the Nodari paper used patients with a relatively mild New York Heart Association (NYHA) functional class (mean = 1.86), excluding NYHA class IV patients. It is important to note that the very large GISSI Heart Failure trial (n=6975), which included patients with NYHA class II-IV heart failure, only demonstrated

a minor decrease in all-cause mortality in patients taking n-3 PUFA supplements (6% RRR), with no statistically significant reduction in heart failure hospitalisations.⁴³ Considering these studies as a whole, it is possible that n-3 PUFA confers a benefit in LV function only in the earlier and not more advanced stages of congestive heart failure.⁴⁰ It is difficult to determine whether the proportion of heart failure patients in studies has influenced the results of the current literature. On the one hand, there is not a great difference in mean left ventricular ejection fraction (LVEF) among the populations of published studies (53.5-64.5%). On the other hand, two well-designed DB-RCTs investigating persistent AF by Bianconi et al²⁰ and Nodari et al²¹ arrived at opposite conclusions. There was very little difference between their study populations, perhaps the most significant being that the Nodari paper contained many more heart failure patients (55.3% vs. 25.7%). However, the Bianconi paper contained significantly more patients with "lone AF" than the Nodari paper (31% vs. 9.5%), a form of AF unlikely to be the result of atrial remodelling. Only a DB-RCT addressing the anti-fibrillatory effects of n3-PUFA specifically in heart failure patients can answer this important question. Likewise, future studies will need to be careful to adequately describe and account for other comorbidities such as hypertension, ischemic and valvular heart disease, all of which are potential substrates for AF and lead to atrial remodelling.

Concomitant Drug Use

There is evidence to show that drugs such as ACE inhibitors (ACEi), angiotensin receptor blockers (ARBs), calcium channel blockers, β -blockers and statins can inhibit atrial remodelling.³⁹ It is often mentioned in the literature that differences in the use of anti-remodelling drugs between studies could explain their conflicting results. Many studies have not adequately described background therapy, or they have had imbalances in treatment between groups that could magnify or reduce differences. Kowey and colleagues found no difference in the incidence of paroxysmal AF between their patient subpopulations who were or were not taking ACEi/ARBs and who had a similar use of other confounding therapies, arguing that the impact of anti-remodelling agents is likely to be small.¹⁵ There is an argument that differences in antiar-

rhythmic drug use between study populations could account for conflicting results, either because they mask the potential benefits of n-3 PUFA, or because they are required for a synergistic action with n-3 PUFA supplements. However, the study by Ozaydin et al,²³ which compared patients treated with n-3 PUFA and amiodarone versus amiodarone alone, showed no significant difference in the number of recurrences of persistent AF. Although this is a small study, the results suggest that the impact of concomitant anti-arrhythmic drug use is also minimal. The most recent publication by Kumar and colleagues demonstrated a significant benefit of long term n-3 PUFA supplementation in the prevention of persistent AF recurrence after electrical cardioversion.²⁴ A subgroup analysis demonstrated that n-3 PUFA supplementation reduced the chance of AF recurrence with or without the concurrent use of sotalol or amiodarone (patients in this study at randomisation commenced treatment with amiodarone or sotalol if they had persistent AF for > 3 months). However, in this study, patients who had been in persistent AF for < 3 months at randomisation were placed on other drugs which also have anti-arrhythmic properties: beta blockers, rate-limiting calcium channel blockers or digoxin. This makes it more difficult to determine how much of an effect concomitant drug use had on the prevention of AF in this study population. Larger studies will be required to answer this important question.

AF Subtype and Duration

AF itself can cause structural and electrical remodelling of the atrium. "AF begets AF",³⁹ therefore differences in the time between the initial diagnosis of AF and study entry could account for differences in study results. This is a variable not commonly presented in the literature. AF is a heterogeneous disease, with different pathophysiological mechanisms likely to be underlying the various subtypes. It is therefore possible that n-3 PUFA supplements may confer a greater benefit for secondary prevention of persistent rather than paroxysmal AF due to a potentially greater degree of atrial remodelling in the former. Indeed, the latest study by Kumar and colleagues which demonstrated a benefit of n-3 PUFA supplementation in the prevention of persistent AF found that the n-3 PUFA group had a

significantly longer duration of AF prior to cardioversion than the controls.²⁴ However, there are no studies which directly demonstrate a clear advantage of n-3 PUFA use in AF of longer duration, and although there is evidence to suggest that fish oils prevent structural remodelling,⁴⁴ there is no evidence to suggest that they can reverse that process.³⁵ There are clearly more studies supporting an anti-fibrillatory effect of n-3 PUFA in the post-operative AF setting. The traumatic nature of cardiothoracic surgery and resultant inflammation provides a substrate for the initiation of AF, which might be inhibited by anti-inflammatory effects of n-3 PUFA. The evidence implicating inflammation as the substrate for POAF is substantial. For example, a study by Halonen et al demonstrated that intravenous administration of hydrocortisone after cardiothoracic surgery reduced the incidence of POAF.⁴⁵ There are also considerable data supporting the anti-inflammatory effects of n-3 PUFA.⁴⁶ However, in the studies included in this review, there are inconsistencies in results that make it difficult to prove this hypothesis. For POAF, the study conducted by Mariscalco et al²⁷ showed that post-operative levels of C-reactive protein (CRP) were significantly lower in patients treated with n-3 PUFA, yet the studies by Saravanan et al²⁸ and Heidarsdottir et al²⁹ did not. Likewise of the trials for persistent AF, the study by Patel et al¹⁹ demonstrated lower CRP levels in n-3 PUFA treated patients, but the study by Ozaydin et al²³ did not. These differences could yet again be attributed to differences and limitations in study design among papers.

Duration of n-3 PUFA Supplementation

A commonly cited reason as to why the large Kowey et al¹⁵ trial for patients with paroxysmal AF yielded non-significant results is that almost 50% of AF recurrences occurred in the first two weeks after fish oil supplementation began, therefore not allowing membrane levels of n-3 PUFA to peak. Early recurrence of AF is also a feature of the Bianconi et al²⁰ paper, which is the largest RCT conducted to date in patients with persistent AF. This argument is based on a study by Metcalf and colleagues, which showed that high dose fish oil supplementation at 6g per day, resulted in continued incorporation of n-3 PUFA into the myocyte membranes until a peak was reached at roughly 30 days.⁴⁷

When one looks at the five studies to date that have started fish oil supplementation at least 4 weeks before end point measurement,^{16,19,21,22,24} they show a statistically significant benefit of n-3 PUFA in the prevention of AF recurrence. However, two of these studies by Kumar and colleagues^{16,22} had very small sample sizes, and measured electrophysiological endpoints, which do not necessarily translate to a clinical benefit. None of the studies conducted in post-operative atrial fibrillation started fish oil supplementation 30 days prior to measuring their end points, yet a number of these studies have yielded significant results. A more recent study by Saravanan et al,²⁸ used a low dose (2g/day) of fish oil supplements for a median of 16 days and achieved successful incorporation of EPA and DHA into atrial tissue at similar levels to the Metcalf et al study. At day 30 in the Metcalf et al study, EPA and DHA amounted to roughly 12% of total fatty acids in atrial tissue. In the Saravanan study, DHA alone made up 14% of total fatty acids in a major membrane phospholipid, phosphatidyl-ethanolamine in the atrial tissue. To further refute the argument that fish oil supplementation should be carried out for a minimum of 30 days prior to measuring study endpoints, it is very unlikely that n-3 PUFA exert their antiarrhythmic effects through incorporation into myocyte membranes alone. It has been shown that plasma levels of n-3 PUFA significantly rise after a short duration of supplementation²⁹ and some studies have achieved positive results after acute administration of fish oil supplements.^{27,48}

Differences in n-3 PUFA Supplements and their Delivery to Patients

The difference in dosage of fish oil supplements used among studies is another possible reason for inconsistent results. Clearly, attaining some minimal dose and concentration is necessary but some argue that fish oil supplements are pro-arrhythmic, which could explain why studies that use high doses of n-3 PUFA (~4g/d), such as the Kowey¹⁵ and Farquharson³¹ studies produced non-significant results. However, the three studies by Kumar and colleagues^{16,22,24} and most animal studies⁴⁹ used doses of ~6g/d and yielded significant results. A study that effectively addresses the effect of dosage on the anti-arrhythmic effects of n-3 PUFA is necessary to clarify this issue.

Another area of debate is the optimal ratio of eicosapentaenoic acid (EPA) to docosahexaenoic acid (DHA) in supplements. A large cohort study in men⁵⁰ and the Kumar et al open-label RCT investigating persistent AF²⁴ both demonstrated that higher plasma levels of DHA but not EPA were associated with a statistically significant reduction in the incidence of AF. A study using isolated rabbit hearts demonstrated different electrophysiological effects of DHA and EPA and hypothesised that this was due to these fatty acids influencing potassium and sodium channels respectively.⁵¹ The studies that have been performed to date have used a varying amount of DHA within their n-3 PUFA capsules, but there is no consistent trend as to how this influences study outcome. The two largest DB-RCTs conducted to date, Kowey et al¹⁵ and Bianconi et al²⁰ for paroxysmal and persistent AF respectively, achieved a higher percentage increase in plasma EPA than in DHA at 4 weeks (Kowey: 276.10% vs. 95.6%) (Bianconi: 133.3% vs. 23.2%), and both produced non-significant results. These percentage increases are very different despite the two studies using similar doses of EPA and DHA. We clearly need more information to determine which factors influence percentage increase in n-3 PUFA levels, both in plasma and tissue. Interestingly, all studies conducted to date that used a lower dose of EPA compared to DHA produced statistically significant results in favour of n-3 PUFA use. The question of whether high levels of EPA inhibit the effects of DHA would also be interesting to address in future research. It is possible that delivering fish oil via oral supplements is not as effective as receiving n-3 PUFA through dietary intake. Differences in dietary consumption of n-3 PUFA among studies has not been reported and may be a reason for conflicting results. A study in which patients were infused intravenously²⁶ with n-3 PUFA demonstrated a decreased incidence of post-operative AF, which might indicate that the rate of delivery of fish oil supplements may also influence their efficacy.

Conclusions

There are few large, high quality randomised double blind placebo control trials investigating the anti-fibrillatory effects of n-3 PUFA for paroxysmal, persistent and post-operative atrial fibrillation, and there is considerable heterogeneity in

study design, both in RCTs and prospective observational studies. The result is a confusing literature with many variables that could confound the analyses. These include population age; comorbidities potentially associated with atrial remodeling such as congestive heart failure; concomitant drug use; duration of AF before study entry; and the n-3 PUFA dosage, ratio of EPA to DHA, duration of treatment and its method of delivery. Large DB-RCTs need to be conducted that account for and investigate the influence of these variables on the efficacy of n-3 PUFA, particularly for persistent and post-operative AF, where the available DB-RCTs show contrasting results. Trials should seek to use the methodology used by Kowey et al,¹⁵ but incorporating other, older and sicker patient populations, perhaps with longer periods of observation to observe clinical effects. These studies should employ 2-sided efficacy analyses since n-3 PUFA could be proarrhythmic under some circumstances and in specific patient populations. The American Heart Association guidelines for diet and lifestyle recommendations currently recommend the consumption of oily fish at least twice per week, with fish oil supplements as an alternative.⁵² This may be beneficial for general health and improving other cardiovascular endpoints. However, until more and better data are available, physicians should not recommend n-3 PUFA for the primary or secondary prevention of AF using either commercial supplements or prescription formulations.

Disclosures

- Dr. Peter Kowey has previously consulted for GlaxoSmithKline.
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References

1. Pratt CM, Reiffel JA, Ellenbogen KA, Naccarelli GV, Kowey PR. Efficacy and safety of prescription omega-3-acid ethyl esters for the prevention of recurrent symptomatic atrial fibrillation: a prospective study. *Am Heart J*. 2009; 158(2):163-169.e1-3.
2. Ninio DM, Murphy KJ, Howe PR, Saint DA. Dietary fish oil protects against stretch-induced vulnerability to atrial fibrillation in a rabbit model. *J Cardiovasc Electrophysiol*. 2005;16(11):1189-1194.
3. Sarrazin JF, Comeau G, Daleau P, Kingma J, Plante I, Fournier D, Molin F. Reduced incidence of vagally induced atrial fibrillation and expression levels of connexins by n-3 polyunsaturated

- fatty acids in dogs. *J Am Coll Cardiol*. 2007; 50(15):1505-1512.
4. Laurent G, Moe G, Hu X, Holub B, Leong-Poi H, Trogadis J, Connelly K, Courtman D, Strauss BH, Dorian P. Long chain n-3 polyunsaturated fatty acids reduce atrial vulnerability in a novel canine pacing model. *Cardiovasc Res*. 2008; 77(1):89-97.
 5. Mayyas F, Sakurai S, Ram R, Rennison JH, Hwang ES, Castel L, Lovano B, Brennan ML, Bibus D, Lands B, Barnard J, Chung MK, Van Wagoner DR. Dietary omega3 fatty acids modulate the substrate for post-operative atrial fibrillation in a canine cardiac surgery model. *Cardiovasc Res*. 2011; 89(4):852-861.
 6. Zhang Z, Zhang C, Wang H, Zhao J, Liu L, Lee J, He Y, Zheng Q. N-3 Polyunsaturated Fatty Acids Prevents Atrial Fibrillation by Inhibiting Inflammation in a Canine Sterile Pericarditis Model. *Int J Cardiol*. 2011; 153(1):14-20.
 7. Liu T, Korantzopoulos P, Shehata M, Li G, Wang X, Kaul S. Prevention of atrial fibrillation with omega-3 fatty acids: a meta-analysis of randomised clinical trials. *Heart*. 2011; 97(13):
 8. Verkerk AO, van Ginneken AC, Berecki G, den Ruijter HM, Schumacher CA, Veldkamp MW, Baartscheer A, Casini S, Opthof T, Hovenier R, Fiolet JW, Zock PL, Coronel R. Incorporated sarcolemmal fish oil fatty acids shorten pig ventricular action potentials. *Cardiovasc Res*. 2006;70(3):509-520.
 9. Den Ruijter HM, Berecki G, Opthof T, Verkerk AO, Zock PL, Coronel R. Pro- and antiarrhythmic properties of a diet rich in fish oil. *Cardiovasc Res*. 2007;73(2):316-325.
 10. Coronel R, Wilms-Schopman FJ, Den Ruijter HM, Belterman CN, Schumacher CA, Opthof T, Hovenier R, Lemmens AG, Terpstra AH, Katan MB, Zock P. Dietary n-3 fatty acids promote arrhythmias during acute regional myocardial ischemia in isolated pig hearts. *Cardiovasc Res*. 2007;73(2):386-394.
 11. Raitt MH, Connor WE, Morris C, Kron J, Halperin B, Chugh SS, McClelland J, Cook J MacMurphy K, Swenson R, Connor SL, Gerhard G, Kraemer DF, Oseran D, Marchant C, Calhoun D, Shnider R, McAnulty J. Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implantable defibrillators: a randomized controlled trial. *JAMA*. 2005;293(23):2884-2891.
 12. Burr ML, Ashfield-Watt PA, Dunstan FD, Fehily AM, Breay P, Ashton T, Zotos PC, Haboubi NA, Elwood PC. Lack of benefit of dietary advice to men with angina: results of a controlled trial. *Eur J Clin Nutr* 2003;57(2):193-200.
 13. Biscione F, Totteri A, De Vita A, Lo Bianco F, Altamura G. Effect of omega-3 fatty acids on the prevention of atrial arrhythmias. *Ital Heart J Suppl*. 2005; 6(1):53-59.
 14. Tatarskii BA. Alternative approaches to treatment of paroxysmal atrial fibrillation. *Vestn Ross Akad Med Nauk* 2007; 4:3-9.
 15. Kowey PR, Reiffel JA, Ellenbogen KA, Naccarelli GV, Pratt CM. Efficacy and safety of prescription omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: a randomized controlled trial. *JAMA*. 2010; 304(21):2363-2372.
 16. Kumar S, Sutherland F, Teh AW, Heck PM, Lee G, Garg ML, Sparks PB. Effects of chronic omega-3 polyunsaturated fatty acid supplementation on human pulmonary vein and left atrial electrophysiology in paroxysmal atrial fibrillation. *Am J Cardiol*. 2011; 108(4):531-535.
 17. Kanorskii SG, Bodrikova VV, Kanorskaia I. Influence of perindopril, rosuvastatin, or omega-3 polyunsaturated fatty acids on efficacy of antirecurrence therapy with sotalol in patients with persistent atrial fibrillation. *Kardiologiia*. 2007; 47(12):39-44.
 18. Margos P, Leftheriotis D, Katsouras G, Livanis E, Kremastinos DT. Influence of n-3 fatty acids intake on secondary prevention after cardioversion of persistent atrial fibrillation to sinus rhythm. In: Abstracts of the Meeting of the European Heart Rhythm Association 24-27 June 2007, Lisbon, Portugal. *Europace*. 2007;9(Supplement 3):iii51.
 19. Patel D, Shaheen M, Venkatraman P, Armaganijan L, Sanchez JE, Horton RP, Di Biase L, Mohanty P, Canby R, Bailey SM, Burkhardt JD, Gallinghouse GJ, Zagrodzky JD, Kozeluhova M, Natale A. Omega-3 polyunsaturated Fatty Acid supplementation reduced atrial fibrillation recurrence after pulmonary vein antrum isolation. *Indian Pacing Electrophysiol J*. 2009;9(6):292-298.
 20. Bianconi L, Calo L, Mennuni M, Santini L, Morosetti P, Azzolini P, Barbato G, Biscione F, Romano P, Santini M. N-3 Polyunsaturated Fatty Acids for the Prevention of Arrhythmia Recurrence After Electrical Cardioversion of Chronic Persistent Atrial Fibrillation: a Randomized, Double-Blind, Multicentre Study. *Europace*. 2011;13(2):174-181.
 21. Nodari S, Triggiani M, Campia U, Manerba A, Milesi G, Cesana BM, Gheorghide M, Dei Cas L. N-3 Polyunsaturated Fatty Acids in the Prevention of Atrial Fibrillation Recurrences After Electrical Cardioversion: a Prospective, Randomized Study. *Circulation*. 2011;124(10):1100-1106.
 22. Kumar S, Sutherland F, Wheeler M, Heck PM, Lee G, Teh AW, Garg ML, Morgan JG, Sparks PB. Effects of chronic omega-3 polyunsaturated fatty acid supplementation on human atrial mechanical function after reversion of atrial arrhythmias to sinus rhythm: reversal of tachycardia-mediated atrial cardiomyopathy with fish oils. *Heart Rhythm*. 2011;8(5):643-649.
 23. Ozaydin M, Erdogan D, Tayyar S, Uysal BA, Dogan A, Icli A, Ozkan E, Varol E, Turker Y, Arslan A. N-3 polyunsaturated fatty acids administration does not reduce the recurrence rates of atrial fibrillation and inflammation after electrical cardioversion: a prospective randomized study. *Anadolu Kardiyol Derg*. 2011;11(4):305-309.
 24. Kumar S, Sutherland F, Morton JB, Lee G, Morgan J, Wong J, Eccleston DE, Voukelatos J, Garg ML, Sparks PB. Long-term omega-3 polyunsaturated fatty acid supplementation reduces the recurrence of persistent atrial fibrillation after electrical cardioversion. *Heart Rhythm*. 2012; 9: 483-491.
 25. Calo L, Bianconi L, Colivicchi F, Lamberti F, Loricchio ML, de Ruvo E, Meo A, Pandozi C, Staibano M, Santini M. N-3 Fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a randomized, controlled trial. *J Am Coll Cardiol*. 2005;45(10):1723-1728.
 26. Heidt MC, Vician M, Stracke SK, Stadlbauer T, Grebe MT, Boening A, Vogt PR, Erdogan A. Beneficial effects of intravenously administered N-3 fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a prospective randomized study. *Thorac Cardiovasc Surg*. 2009;57(5):276-280.
 27. Mariscalco G, Sarzi Braga S, Banach M, Borsani P, Bruno VD, Napoleone M, Vitale C, Piffaretti G, Pedretti RF, Sala A. Preoper-

- ative n-3 polyunsaturated fatty acids are associated with a decrease in the incidence of early atrial fibrillation following cardiac surgery. *Angiology*. 2010;61(7):643-650.
28. Saravanan P, Bridgewater B, West AL, O'Neill SC, Calder PC, Davidson NC. Omega-3 fatty acid supplementation does not reduce risk of atrial fibrillation after coronary artery bypass surgery: a randomized, double-blind, placebo-controlled clinical trial. *Circ Arrhythm Electrophysiol*. 2010;3(1):46-53.
29. Heidarsdottir R, Arnar DO, Skuladottir GV, Torfason B, Edwardsson V, Gottskalksson G, Palsson R, Indridason OS. Does treatment with n-3 polyunsaturated fatty acids prevent atrial fibrillation after open heart surgery? *Europace*. 2010;12(3):
30. Skuladottir GV, Heidarsdottir R, Arnar DO, Torfason B, Edwardsson V, Gottskalksson G, Palsson R, Indridason OS. Plasma n-3 and n-6 fatty acids and the incidence of atrial fibrillation following coronary artery bypass graft surgery. *Eur J Clin Invest*. 2011;41(9):995-1003.
31. Farquharson AL, Metcalf RG, Sanders P, Stuklis R, Edwards JR, Gibson RA, Cleland LG, Sullivan TR, James MJ, Young GD. Effect of dietary fish oil on atrial fibrillation after cardiac surgery. *Am J Cardiol*. 2011;108(6):851-856.
32. Sorice M, Tritto FP, Sordelli C, Gregorio R, Piazza L. N-3 polyunsaturated fatty acids reduces post-operative atrial fibrillation incidence in patients undergoing "on-pump" coronary artery bypass graft surgery. *Monaldi Arch Chest Dis*. 2011;76(2):93-98.
33. Armaganijan L, Lopes RD, Healey JS, Piccini JP, Nair GM, Morillo CA. Do omega-3 fatty acids prevent atrial fibrillation after open heart surgery? A meta-analysis of randomized controlled trials. *Clinics (Sao Paulo)*. 2011;66(11):1923-1928.
34. Wu JH, Lemaitre RN, King JB, Song X, Sacks FM, Rimm EB, Heckbert SR, Siscovick DS, Mozaffarian D. Association of Plasma Phospholipid Long-Chain Omega-3 Fatty Acids with Incident Atrial Fibrillation in Older Adults: The Cardiovascular Health Study. *Circulation*. 2012 Jan 26 online before print.
35. Camm AJ, Savelieva I. Fish oil for secondary prevention of atrial fibrillation: should we still believe in its antiarrhythmic effect? *Circulation*. 2011;124(10):1093-1096.
36. Saravanan P, Davidson NC, Schmidt EB, Calder PC. Cardiovascular effects of marine omega-3 fatty acids. *Lancet*. 2010;376(9740):540-550.
37. Duda MK, O'Shea KM, Tintinu A, Xu W, Khairallah RJ, Barrows BR, Chess DJ, Azimzadeh AM., Harris WS, Sharov VG, Sabbah HN, Stanley WC. Fish oil, but not flaxseed oil, decreases inflammation and prevents pressure overload-induced cardiac dysfunction. *Cardiovasc Res*. 2009;81(2):319-327.
38. Ramadeen A, Laurent G, dos Santos CC, Hu X, Connelly KA, Holub BJ, Mangat I, Dorian P. n-3 Polyunsaturated fatty acids alter expression of fibrotic and hypertrophic genes in a dog model of atrial cardiomyopathy. *Heart Rhythm*. 2010;7(4).
39. Kowey PR, Mohamand-Borkowski A, Burke JF. *Clinical Management of Atrial Fibrillation*. 1st Ed., New York, Professional Communications, Inc. 2011; p. 50,87.
40. Rupp H, Rupp TP, Alter P, Maisch B. Failure of omega-3 fatty acids in atrial fibrillation? No deficiency of highly unsaturated fatty acids in the absence of heart failure. *Europace*. 2011;13(9):1357; author reply 1357-8.
41. Rupp H, Rupp TP, Alter P, Maisch B. Inverse shift in serum polyunsaturated and monounsaturated fatty acids is associated with adverse dilatation of the heart. *Heart*. 2010;96(8):595-598.
42. Nodari S, Triggiani M, Campia U, Manerba A, Milesi G, Cesana BM, Gheorghide M, Dei Cas L. Effects of n-3 polyunsaturated fatty acids on left ventricular function and functional capacity in patients with dilated cardiomyopathy. *J Am Coll Cardiol*. 2011;57(7):870-879.
43. GISSI-HF Investigators, Tavazzi L, Maggioni AP, Marchioni R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;372(9645):1223-1230.
44. Rennison JH, Van Wagoner DR. Impact of dietary fatty acids on cardiac arrhythmogenesis. *Circ Arrhythm Electrophysiol*. 2009;2(4):460-469.
45. Halonen J, Halonen P, Jarvinen O, Taskinen P, Auvinen T, Tarkka M, Hippelainen M, Juvonen T, Hartikainen J, Hakala T. Corticosteroids for the prevention of atrial fibrillation after cardiac surgery: a randomized controlled trial. *JAMA*. 2007;297(14):1562-1567.
46. Mori TA, Beilin LJ. Omega-3 fatty acids and inflammation. *Curr Atheroscler Rep*. 2004;6(6):461-467.
47. Metcalf RG, James MJ, Gibson RA, Edwards JR, Stubberfield J, Stuklis R, Roberts-Thomson K, Young GD, Cleland LG. Effects of fish-oil supplementation on myocardial fatty acids in humans. *Am J Clin Nutr*. 2007;85(5):1222-1228.
48. Jahangiri A, Leifert WR, Patten GS, McMurchie EJ. Termination of asynchronous contractile activity in rat atrial myocytes by n-3 polyunsaturated fatty acids. *Mol Cell Biochem*. 2000; 206(1-2):33-41.
49. Savelieva I, Camm AJ. Polyunsaturated fatty acids for prevention of atrial fibrillation: a 'fishy' story. *Europace*. 2011;13(2):149-152.
50. Virtanen JK, Mursu J, Voutilainen S, Tuomainen TP. Serum long-chain n-3 polyunsaturated fatty acids and risk of hospital diagnosis of atrial fibrillation in men. *Circulation*. 2009;120(23):2315-2321.
51. Dhein S, Michaelis B, Mohr FW. Antiarrhythmic and electrophysiological effects of long-chain omega-3 polyunsaturated fatty acids. *Naunyn Schmiedebergs Arch Pharmacol*. 2005;371(3):202-211.
52. American Heart Association Nutrition Committee, Lichtenstein AH, Appel LJ, Brands M, Carnethon M, Daniels S, Franch HA, Franklin B, Kris-Etherton P, Harris WS, Howard B, Karanja N, Lefevre M, Rudel L, Sacks F, Van Horn L, Winston M, Wylie-Rosett J. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. *Circulation*. 2006; 114 (1): 82-96.