World Journal of Cardiology

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DOI: 10.4330/wjc.v8.i2.114

World J Cardiol 2016 February 26; 8(2): 114-119
ISSN 1949-8462 (online)

EDITORIAL

Omega 3 and atrial fibrillation: Where are we?

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Conflict-of-interest statement: The authors declare no conflict of interest.

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Received: June 3, 2015
Peer-review started: June 3, 2015
First decision: September 26, 2015
Revised: November 24, 2015
Accepted: December 29, 2015
Article in press: January 4, 2016
Published online: February 26, 2016

Abstract

Anti-arrhythmic properties of n-3 polyunsaturated fatty acids, at least in part mediated by anti-oxidant, anti-inflammatory and anti-fibrotic power, have been widely proved. Effect of fish oil on atrial fibrillation, both in primary and in secondary prevention and after cardiac surgery, are controversial, mostly due to lack of homogeneity between studies but also due to individual variability in response to fatty acids administration. Inclusion of measurement of incorporation of fish oil into cell membranes, appears to be essential in future studies, to assess their antiarrhythmic effect.

Key words: N-3 polyunsaturated fatty acids; Atrial fibrillation; Upstream therapy; Omega-3 index; Cardiac surgery

Core tip: Individual variability in response to fish oil administration, in terms of eicosapentaenoic and docosahexaenoic acids in corporation into cell membranes, is responsible for controversial results of n-3 poly-unsaturated fatty acids administration in patients suffering atrial fibrillation.

Martino A, Pezzi L, Magnano R, Salustri E, Penco M, Calo' L. Omega 3 and atrial fibrillation: Where are we? *World J Cardiol* 2016; 8(2): 114-119 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i2/114.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i2.114

INTRODUCTION

N-3 poly-unsaturated fatty acids (PUFA) anti-arrhythmic effects have been debated for several years, since their electrophysiological properties have been recognized.

Through direct interaction with membrane bound proteins and thanks to incorporation into the phospholipid bilayer, n-3 PUFA are well known to influence ion channels and transmembrane pumps[1] to modulate signal transduction, protein trafficking and ion channels kinetic and to regulate gene expression[2]. N-3 PUFA can also exert anti-

Table 1 Clinical studies investigating the effect of n-3 poly-unsaturated fatty acids on primary prevention for atrial fibrillation

Study design	Population	PUFA administration	PUFA quantification	AF diagnosis	Results
Prospective cohort[5]	4815 individuals; age 72.8 yr; United States	Broiled/backed fish assessment. FU: 12 yr	FFQ	Annual ECG; hospital discharge diagnoses	Lower AF risk of 31% with fish intake ⩾ 5 times/wk *vs* < 1/mo. $P = 0.008$
Prospective cohort[12]	2174 subjects; mean age: 52.8 yr; Finland	Serum EPA and DHA and dosage. FU: 17.7 yr	DHA, EPA serum dosage	National computerized hospitalization registry	Lower AF risk of 38% for higher DHA levels. $P = 0.02$
Prospective cohort[6]	3326 subjects; age: 74.1 yr; United States	Serum EPA, DHA dosage	DHA, EPA serum dosage	Annual ECG; telephonic contact 2/yr; hospitalizations	Lower AF risk for top *vs* lowest quartile of PUFA/DHA levels
Population study[7]	3242 subjects affected by acute myocardial infarction; age: 54.1 yr; Italy	Previous PUFA intake *vs* not. FU: 360 d	FFQ	AF episodes during hospitalization	Lower risk of AF with fish oil
Prospective cohort[8]	47949 subjects; age: 46 yr; Denmark	Fish-oil intake assessment. FU: 5.7 yr	FFQ	Danish national hospitalization registry	Higher AF risk for top *vs* lowest quintiles of fish intake
Prospective cohort[9]	5184 subjects; age 67.4 yr; the Netherland	Fish-oil intake assessment. FU: 6.4 yr	FFQ	Two ECGs during FU; clinical data from general practitioners	No AF risk reduction in the highest tertile of fish intake
Prospective cohort[10]	44720 female; age: 63 yr; United States	Fish intake assessment. FU: 6 yr	FFQ	ECG at baseline and at the third and sixth years	No lower AF risk for higher fish intake
Prospective cohort[11]	4526 individuals; age: 62 yr; United States	Fish intake assessment. FU: 4 yr	FFQ	Two ECGs every 4 yr of FU; hospitalizations	No AF risk reduction in the top *vs* the lowest tertile of fish intake
Post-hoc analysis of a RCT (Aleksova)[13]	5835 systolic heart failure-subjects	N-3 PUFAs 1 g/d *vs* placebo; FU 3.9 yr	No PUFA dosage	ECG during FU visits	No AF risk reduction with n-3 PUFA

FU: Follow-up; FFQ: Food frequency questionnaires; AF: Atrial fibrillation; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid; RCT: Randomized controller trial; PUFA: Poly-unsaturated fatty acids.

inflammatory effects by antagonizing pro-inflammatory prostaglandin formation[2], and exert anti-fibrotic effects[3], as well as cardiac autonomic modulation[4].

In particular, the influence of n-3 PUFA on atrial fibrillation (AF) primary and secondary prevention, including post-operative AF (POAF) has also been the object of numerous clinical studies.

N-3 PUFA in primary and secondary prevention and in POAF

Primary prevention: With regard to primary prevention of AF (Table 1), two studies involving elderly subjects[5,6] and one focusing on patients affected by acute myocardial infarction[7] proved n-3 PUFA to be protective against AF, while other studies[8-12], showed no benefit. The influence of various diet habits, including fish consumption[8,9], can possibly explain different results, as well as different methodologies used for assessment of fish intake and for AF diagnosis. In particular, positive studies, generally included elderly individuals[5-7], suggesting benefit from antifibrotic properties of fish-oil. However, a post-hoc analysis of the randomized controlled trial GISSI-HF[13] showed no effect of long-term PUFA administration on AF development in heart failure patients, thus allowing no conclusions for the role of n-3 PUFA in AF primary prevention.

Post-operative AF: The effect of n-3 PUFA in the context of POAF, that is characterized by inflammation, electrolyte disturbances and hemodynamic instability secondary to cardiac surgery, have also been also widely investigated. An open label study[14] firstly observed a short-term n-3 PUFA administration-related decrease in POAF incidence after coronary artery bypass grafting. Two papers[15,16] also gained benefit from various fish-oil preparations and administration timings (Table 2). A recent randomized-controlled trial (RCT)[17] also observed reduction of POAF with n-3 PUFAs plus vitamins C and E administration in comparison to placebo, in 203 patients scheduled for cardiac surgery. Further studies however, failed to prove both prevention of AF[18,19] and decrease of inflammation[20] from higher serum levels of n-3 PUFA, eicosapentaenoic acid (EPA), or docosahexaenoic acid (DHA), and from higher n3-PUFA atrial content[21,22]. Recently, the multicenter double-blind RCT "OPERA"[23] showed no influence on POAF occurrence, from short-term n3-PUFA administration. The effect was unrelated to patients characteristics, kind of cardiac-surgery, antiarrhythmic drugs, fish intake and serum n-3 PUFA. In a substudy of this trial indeed[24], including 564 subjects receiving short-term PUFA or placebo before surgery, the risk of POAF was unrelated to fish oil concentrations at enrollment and day of surgery. Interestingly, PUFA increase, was characterized by significant inter-individual variableness (0.7%-7.5% after 5 d of supplementation). Finally, Metcalf *et al*[25], by using combined data from previous RCTs, demonstrated less incidence of POAF among subject within the fourth quintile of red blood cell

Table 2 Principal clinical studies investigating the effect of n-3 poly-unsaturated fatty acids on post-operative atrial fibrillation

Study design	Population	PUFA administration	PUFA quantification	AF diagnosis	Results
Randomized, open label[14]	160 CABG pts; age: 66.2 yr; Italy; BB approximately 57%; statins approximately 58%	N-3 PUFA 2 g/d (EPA/DHA: 1:2) ⩾ 5 d before CS, until discharge *vs* not	No PUFA dosage	Continuous 5 d monitoring + daily ECG up to discharge. AF: > 5 min/requiring therapy	Lower AF risk. $P = 0.013$
Prospective observational[15]	530 CS pts; age: 66.4 yr; Italy. BB: 53%; statins: 46%	N-3 PUFA 1 g/d (EPA/DHA: 0.9:1.5) 5 d pre-CS *vs* not	No PUFA dosage	Continuous monitoring during ICU-stay. AF: ⩾ 5 min	Lower POAF during ICU stay. $P = 0.006$
Double blind-RCT[16]	102 CABG pts; age: 67 yr; Germany	Iv 100 mg fish oil/kg per day during ICU-stay *vs* soya oil	No PUFA dosage	Continuous monitoring during ICU-stay	Lower AF risk with PUFA. $P < 0.05$
Prospective cohort[19]	125 CABG pts; age: approximately 68 yr; Iceland. BB: 77.4%; statins: 84%	N3-PUFA (EPA/DHA: 1.2:1) 2.2 g/d 7 d pre-CABG *vs* placebo	PUFA dosage basally, before, 3 d after CS	Continuous monitoring during hospital stay. AF: ⩾ 5 min	Positive DHA/POAF association (U-curve relationship)
Double blind-RCT[23]	1516 CS pts; age: 64 yr; Italy-United States-Argentina. BB: 76.9%; statins: 57.5%	N3-PUFA (EPA/DHA: 4.6:3.7) 2 g/d 5 d pre-CS up to discharge *vs* placebo	Serum PUFA dosage basally, before CS	Continuous 5 d monitoring. AF: ⩾ 30 s	No lower AF despite 40% higher plasmatic PUFA
Double blind-RCT[18]	243 CS pts; age: 62.7 yr, United States. BB: 79%; statins: 73%	N-3 PUFA 2 g/d *vs* corn oil	Basal serum PUFA dosage, before, 3 d post CS	Continuous ECG during hospital stay; FU: 1 mo. AF: Episodes requiring treatment	No lower AF; plasma PUFA increase
Double blind-RCT[20]	170 CS pts; age: 67 yr; Iceland. BB approximately 76%	N3-PUFA (EPA/DHA: 1.2:1) 2 g/d 1 wk before and 2 after CS *vs* olive oil	Serum DHA, EPA dosage basally, pre 3 d post CS	Continuous monitoring during hospital stay. AF: ⩾ 5 min	No lower AF; plasma n-3 PUFA increase
Double blind-RCT[22]	200 CS pts; age: 64 yr; Australia, BB: 43%; statins: 73%	N-3 PUFA oil (EPA/DHA: 2.7:1.9) for 3 wk *vs* placebo	Dosage of serum PUFA basally, pre-CS; atrial PUFA	Continuous 72 h monitoring. AF/flutter ⩾ 10 min/requiring treatment	No lower AF risk; increase in serum and atrial PUFA
Double blind RCT[21]	108 CABG pts; age: 64 yr; United Kingdom; BB: 88%; statins: 98%	N-3 PUFA (EPA/DHA: 1.2:1) 2 g/d for approximately 16 d *vs* olive oil	Dosage of serum PUFA basally, 3 d post CS; atrial PUFA	Continuous 5 d monitoring + daily ECG. AF: > 30 s	No lower AF risk; higher serum and atrial PUFA

CABG: Coronary artery bypass grafting; pts: Patients; BB: Beta blockers; CS: Cardiac surgery; ICU: Intensive care unit; PUFA: Poly-unsaturated fatty acids; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid; AF: Atrial fibrillation.

n-3 DHA, thus suggesting a U-shaped relation between n-3 PUFA intake and POAF. Four recent meta-analyses of the previously presented studies showed in turn, overall protective or neutral effect on POAF from n-3 PUFA[26-29] (Table 3). Of note, none of these meta-analyses has assessed n-3 PUFA treatment duration to surgery as a covariate in a meta-regression analysis (Figure 1).

Dissimilarities may be explained by various study designs and populations, AF definitions, cardiac surgery, co-administration of anti-arrhythmic or anti-inflammatory drugs, dietary PUFA intake, EPA/DHA ratios and fish oil-administration modes (*i.e.*, intravenous or through nasogastric tube) and fish-oil administration time courses. Conversely, no effects of n-3 PUFA administration on myocardial infarction and bleeding after cardiac surgery, eventually influencing POAF occurrence, have been demonstrated[27].

Interestingly, all RCTs that failed to demonstrate a beneficial effect, used a formulation containing 1.24 EPA: DHA ratio[18,20,23]. In contrast, Rodorigo *et al*[17] administered PUFA with an EPA:DHA ratio equal to 0.5.

Secondary prevention: Several studies have finally investigated the effect on n-3 PUFA on relapses of paroxysmal and persistent AF. Two studies[30,31], found fish oil administration (from 1 mo before, to 6 mo after cardioversion) helpful in AF prevention (Table 4). On the other hand, 4 further studies[32-35] failed to prove any effect.

A recent study[36] including 337 patients with symptomatic paroxysmal/persistent AF, randomized to receive fish oil (4 g/d) or placebo, showed no difference in time to first AF recurrence, as well as no significant decrease of inflammatory markers at 6 mo. Similarly, another RCT[37], proved no effect from n-3 PUFA on the time to AF relapses, as well as on concentrations of biomarkers of oxidative stress and inflammation and at follow-up. In particular, a large RCT[34] involving 586 patients with symptomatic paroxysmal or persistent AF, randomized to n-3 PUFA (1 g/d) *vs* placebo for 1 year, also proved no significant differences between the two arms, in terms of symptomatic recurrence of AF.

Contrasting outcomes between studies may be related to differences in PUFA somministration and populations characteristics. Generally, papers including subjects with more evident cardiac disease[30], more often co-administered with amiodarone[30] showed benefit. Of note, some unfavorable papers proved AF relapses to occur mostly within 3 wk, prior

Table 3 Recent metaanalises of studies of n-3 poly-unsaturated fatty acids in post-operative atrial fibrillation

Ref.	Clinical setting	NO. of studies and of patients	Results
Costanzo *et al*[26]	POAF	8 RCTs/2687 pts	AF reduction
Benedetto *et al*[27]	POAF	431 pts	No AF reduction; at meta-regression analysis: Trend toward a benefit from PUFA for administration of EPA/DHA ratio = 1:2
Zhang *et al*[28]	POAF	8 RCT/2687 pts	No AF reduction
Ali-Hassan-Sayegh *et al*[29]	POAF	23 RCTs/4278 pts	AF reduction

RCTs: Randomized controller trials; pts: Patients; PO: Post-operative; AF: Atrial fibrillation; PUFA: Poly-unsaturated fatty acids; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid.

Table 4 Clinical studies investigating the effect of n-3 poly-unsaturated fatty acids on secondary prevention for atrial fibrillation

Study design	Population	PUFA administration	PUFA quantification	AF diagnosis	Results
Double blind-RCT[30]	109 pts, age: 70 yr; Italy; heart structural abnormality: 90%; Amiodarone + ACE-i/ARBs: 100%	N-3 PUFA (EPA/DHA 1.2:1) 2 g/d, 1 mo before and 12 after ECV *vs* olive oil	No PUFA dosage	Weekly ECG for the first 3 wk after ECV and ECG + Holter ECG after 1, 3, 6, 12 mo and at symptoms occurrence	Less AF relapses with PUFA
Open-label randomized[31]	178 pts, Australia. Concomitant amiodarone, sotalol, ACE-i/ARBs	N-3 PUFA (EPA/DHA 1.3:1) 1.8 g/d for approximately 56 d before ECV and 1 year thereafter *vs* not	Serum dosage of EPA, DHA basally, before ECV	ECG at week 2 and 6 and every 3 mo. AF: ⩾ 1 wk	Less AF relapses at 90 d and 1 yr with PUFA, $P < 0.001$; higher serum EPA, DHA
Double blind-RCT[33]	663 pts; paroxysmal AF: 18%; age: 60.5 yr; United States. No heart abnormality. Amiodarone: 0%, antiarrhythmic drugs: 13%; ACE-i/ARBs: 39%	N-3 PUFA (EPA/DHA 4.6:3.7; load: 8 g/d for 1 wk) 4 g/d for 24 wk *vs* oil	Serum DHA, EPA dosage basally, after 4 and 24 wk	Biweekly transtelephonic monitoring	No lower symptomatic AF recurrence in the paroxysmal and persistent
Prospective[35]	50 pts; ⩾ 2 previous AF episodes; age: 54 yr, Japan. IC antiarrhythmic drugs: 100%	Observational period: no PUFA for 6 mo. Interventional period: EPA 1.8 g/d for 6 mo	Serum EPA, DHA dosage basally and at study end	Daily ECG monitoring and at symptoms occurrence	No lower AF burden and time to first relapse
Double blind-RCT[32]	204 pts, age: 69.3 yr; Italy. LAs 45 mm. First ECV: 59%; IC antiarrhythmic drugs: 29.5%, sotalol: 12.6%, amiodarone: 27.4%	N-3 PUFA (EPA/DHA 1.2:1) 3 g/d ⩾ 1 wk before and 2 g/d after ECV for 6 mo *vs* olive oil	N-3 PUFA serum dosage basally, 6 mo after ECV	Transtelephonic monitoring: 2/first week after ECV and 3/wk for 3 mo + clinical visits after 7 d, 1, 3, 6 mo	No difference in ECV success, AF incidence, time to first relapse. Increase of EPA and DHA
Double blind RCT[36]	337 pts; symptomatic paroxysmal or persistent AF within 6 mo of enrollment	Fish oil (4 g/d) or placebo	Followed, on average, for 271 ± 129 d	Trans-telephonic event recorder, 12-lead ECG or Holter	No lower AF with PUFA
Double blind-RCT[37]	190 pts with paroxysmal or persistent AF	N-3 PUFAs (4 g/d; n = 126) or placebo (n = 64) in a 2:1 ratio	No PUFA dosage	Not specified	No reduction of AF recurrence and inflammation markers
Double blind-RCT[34]	586 pts with symptomatic paroxysmal AF requiring ECV (n = 428), at least 2 episodes of AF in the 6 mo before (n = 55), or both (103)	N-3 PUFA (1 g/d) or placebo for 12 mo	No PUFA dosage	Not specified	No lower AF with PUFA

RCTs: Randomized controller trials; pts: Patients; PO: Post-operative; AF: Atrial fibrillation; PUFA: Poly-unsaturated fatty acids; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid; ACE-I: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blockers.

to an eventual effect from n-3 PUFA.

DISCUSSION

The effect of n-3 PUFA on AF primary and secondary prevention and after cardiac surgery, remains controversial. A major reason for this uncertainty, is to be found in differences between studies, in particular regarding study designs, patients characteristics, AF definition and types (lone, vagally/adrenergically induced, secondary to structural disease), fish oil-administration modes, formulations and time courses. Moreover, a great variability in n-3 PUFA serum concentrations between subjects, despite similar fish-oil administration, has been recently proved, likely secondary to genetic predisposition in PUFA metabolism.

Noteworthy, however, a recent RCT[38] examined the effects of high (6 g/d) or medium dose (3 g/d) fish oil supplementation, with or without multivitamin, on the inclusion of n-3 and n-6 PUFA within membranes of red blood cells after 16 wk. The authors found all treatments effective in increasing EPA composition of cell membranes

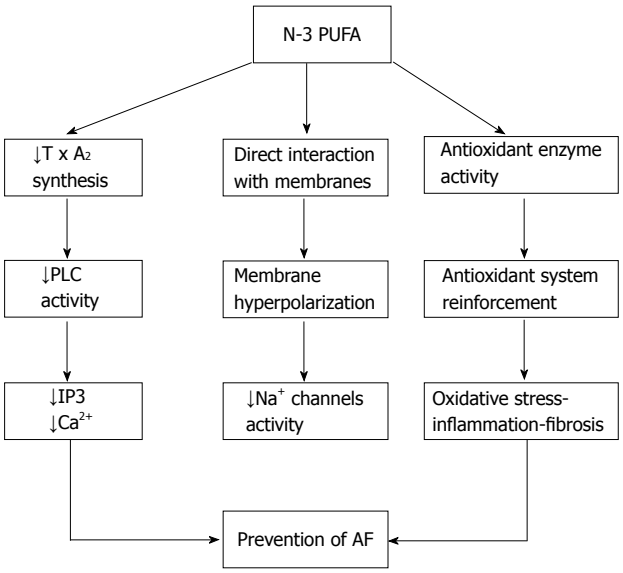

Figure 1 Antiarrhythmic effects of n-3 poly-unsaturated fatty acids. N-3 PUFA: N-3 poly-unsaturated fatty acids; TxA_2: Thromboxane A_2; PLC: Phospholipase C; IP_3: Inositol triphosphate; AF: Atrial fibrillation.

in females, but not in males, for whom the higher dose n-3 PUFA plus multivitamin combination was necessary. As a consequence, discrepancies between trials could be partially related to individual capability of n-3 PUFA incorporation, which in turn, could be influenced by sex, age, vitamin and/or drug administration. To counteract the variability in response to fish oil administration, inclusion of blood measures of n-3 PUFA status appears therefore to be essential in future studies.

The "Omega-3 Index" is the percentage of PUFA composed of EPA + DHA in red blood cell membranes[39] may represent a measurement of clinical utility to assess individual response to fish oil intake. Moreover, it may contribute to better understand the pharmacokinetics and pharmacodynamics of PUFA. Considering the results of recent studies showing an U-curve relationship between PUFA concentrations and AF[19,25], the greater protection from AF could be obtained from an individually-targeted approach for fish oil inclusion within membranes.

CONCLUSION

The complexity of the biological interactions of n-3 PUFA, their incorporation into cell membranes and the variability of clinical contexts, likely justify why PUFA administration does not automatically lead to AF reduction. RCTs focusing on clinical contexts of AF, and characterized by more accurate follow-ups and definitions of PUFA incorporation into red blood cells (or hopefully, in atrial tissue in the setting of cardiac surgery), are required. The RCT NCT00692718, will hopefully add information regarding fish oil effect on AF prevention in the context of HF and/or AMI.

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P- Reviewer: Bonanno C, Chen SJ, Ho KM, Letsas K
S- Editor: Qiu S **L- Editor**: A **E- Editor**: Lu YJ

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