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

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Core tip: Individual variability in response to fish oil administration, in terms of eicosapentaenoic and docosahexaenoic acids in correlation into cell membranes, is responsible for controversial results of n-3 polyunsaturated fatty acids administration in patients suffering atrial fibrillation.
inflammatory effects by antagonizing pro-inflammatory prostaglandin formation\(^8\), and exert anti-fibrotic effects\(^3\), as well as cardiac autonomic modulation\(^6\).

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 PUFA 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

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**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\(^6\) | 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\(^7\) | 3326 subjects; age: 74.1 yr; United States | Serum EPA, DHA dosage | DHA, EPA serum dosage | Annual ECG; telephonie contact 2 yr; hospitalizations | Lower AF risk for top vs lowest quartile of PUFA/ DHA levels |
| Population study\(^8\) | 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\(^9\) | 4794 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\(^10\) | 5184 subjects; age 67.4 yr; the Netherlands | 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\(^11\) | 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\(^12\) | 4526 individuals; age: 72.8 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 or 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.
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 | 160 CABG pts; age: 66.2 yr; Italy; BB: 53%; 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 | 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 | 102 CABG pts; age: 67 yr; Germany | Iv 100 mg fish oil/kg per day during ICU-stay vs soya oil placebo | No PUFA dosage | Continuous monitoring during ICU-stay. AF: > 5 min | Lower AF risk with PUFA. P < 0.05 |
| Prospective cohort | 1516 CS pts; age: 64 yr; United States-Argentina. BB: 76.9%; statins: 57.5% | 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 | No lower AF despite 40% higher plasmatic PUFA |
| Double blind-RCT | 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 | 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 | 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, before 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 | 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-arthymic 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, Rodrigo 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 [38], 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 meta-analyses 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[^24] | POAF | 8 RCTs/2687 pts | No AF reduction; at meta-regression analysis: Trend toward a benefit from PUFA for administration of EPA/DHA ratio = 1:2 |
| Benedetto et al[^25] | POAF | 431 pts | AF reduction |
| Zhang et al[^26] | POAF | 8 RCT/2687 pts | No AF reduction |
| Ali-Hassan-Sayegh et al[^26] | 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 wk 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[^32] | 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 AF diagnosis |
| Prospective[^33] | 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 | No PUFA dosage | Daily ECG monitoring and at symptoms occurrence | No lower AF burden and time to first relapse |
| Double-blind RCT[^28] | 204 pts, age: 69.9 yr; Italy. LA's 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[^29] | 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 | Not specified | No lower AF with PUFA |
| Double blind RCT[^27] | 190 pts with paroxysmal or persistent AF | N-3 PUFA (4 g/d; n = 126) or placebo (n = 64) in a 2:1 ratio | N-3 PUFA serum dosage | Not specified | No reduction of AF recurrence and inflammation markers |
| Double blind RCT[^27] | 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 (n=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.

**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/adrrenergically 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.
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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