Polyunsaturated fatty acids for prevention of atrial fibrillation: a ‘fishy’ story

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This editorial refers to ‘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’ by L. Bianconi et al., on page 174

Several reports from population-based surveys and large randomized clinical trials have shown a remarkable 45–68% reduction in the rates of sudden cardiac death (presumably arrhythmic) with high dietary fish consumption or omega-3 polyunsaturated fatty acid (PUFA) supplements and have prompted interest in employing PUFAs as antiarrhythmic drugs.1,2 Three randomized clinical trials in patients at particularly high risk of sudden arrhythmic death, i.e. patients with internal cardioverter-defibrillators (ICDs) for secondary prevention, have followed, but surprisingly only one of these studies has shown any protective effect of PUFAs and one other even hinted at their proarrhythmic potential in some subgroups.3 Nevertheless, the quest into the antiarrhythmic effects of PUFAs has continued in patient populations with atrial fibrillation (AF).

Potential mechanisms and experimental evidence

There appears to be a good rationale behind this. Universal constituents of biological membranes, PUFAs—mainly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)—regulate membrane fluidity, modulate the activity of multiple membrane proteins, and counteract the arrhythmogenic effects of atrial stretch.4 Other potential antiarrhythmic mechanisms include anti-inflammatory and antioxidant actions, mitigation of endothelial dysfunction, and regulation of profibrotic activity of mitogen-activated protein kinases and matrix metalloproteinases.5 In addition, PUFAs may reduce the adverse impact of underlying heart disease, e.g. by vasodilatation, blood pressure reduction, and improved contractile function of the myocardium. However, most relevant antiarrhythmic action of PUFAs in AF probably results from their direct electrophysiological effects on several ion channels, such as $I_{Na}$, $I_{Kur}$, $I_{Kad}$, $I_{to}$, and $I_{Ca,L}$ currents, and the Na$^{+}$/Ca$^{2+}$ exchanger.6,7

The effects of PUFAs on structural atrial remodelling and inducibility of AF have been well demonstrated in various animal models of AF, including atrial pacing, simultaneous atrioventricular pacing, vagal stimulation, cardiac surgery and sterile pericarditis, and congestive heart failure induced by ventricular tachypacing or intracoronary infusion of doxorubicin.4 In these models, treatment with PUFAs prevented significant shortening of the atrial effective refractory period associated with AF, reduced inducibility of AF and sustainability of induced AF, and attenuated structural changes in the atrial myocardium.

Lack of efficacy in primary prevention

The positive results from the animal experiments have not been reproduced in the clinical arena. The antiarrhythmic potential of PUFAs was first tested for primary prevention of post-operative AF after coronary artery bypass grafting with or without valve surgery. The results of the early, open-label study in 160 patients were encouraging, demonstrating a 65% reduction in new-onset AF with pre-treatment with PUFAs compared with no treatment,8 but three subsequent studies with a more rigorous design (double blind, placebo controlled) showed no antiarrhythmic effect of PUFA supplements (Figure 1).9–11 Consequently, in several epidemiological analyses, high dietary fish consumption had no benefit on the prevention of AF in the general population,4 and some even reported a strong trend towards more AF among individuals eating more than five fish meals per week.12

Secondary prevention studies

The results of secondary prevention trials in AF have become known fairly recently, and several reports have not yet been

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published in full. Bianconi et al.\textsuperscript{13} reported the results of a double-blind, placebo-controlled study of PUFA supplements in 204 patients with persistent AF of more than 1 month. The study population was representative of a typical patient with AF in whom a rhythm control strategy is usually pursued: the mean age was 69 years, 70% were men, and 63% had the first episode of AF. Hypertension was a prevalent diagnosis (72%), mean ejection fraction was 58%, mean left atrial size was 4.5 cm, and only one-quarter had moderate heart failure. Patients were randomized to therapy with PUFAs 3 g/day started at least 1 week before planned electrical cardioversion and continued at 2 g/day for 6 months after cardioversion, or placebo. Trans-telephonic ECG transmission was employed for rhythm monitoring. Despite excellent compliance with treatment and suitably increased EPA and DHA levels in the treated group, the results were disappointing: PUFAs did not facilitate spontaneous conversion to sinus rhythm or electrical cardioversion, nor did they reduce the recurrence rate at 6 months compared with placebo (58.9 vs. 51.1%; \( p = 0.28 \)). The mean time to first recurrence of AF was 83 days in the PUFA-treated group and 106 days in the placebo group. Combining PUFAs with antiarrhythmic drugs (approximately two-thirds of patients) also made no difference to outcome. There was no excess in adverse events in the PUFA group.

How does the study by Bianconi et al. fit with existing evidence in secondary prevention of AF with PUFAs (see Table 1)? The results of this study are consistent with the report by Erdogan et al.\textsuperscript{14} in 108 patients who did not receive any antiarrhythmic drug therapy, but were pre-treated with PUFAs for a minimum of 4 weeks before cardioversion. In this study, therapy with PUFAs had no effect on recurrence of AF.

Of interest, when the results of the study by Bianconi et al. were first presented at the American College of Cardiology Sessions in Atlanta in March 2010, the preliminary data from another Italian group were also reported. Nodari et al.\textsuperscript{15} investigated the effects of PUFA supplements at 1 g/day in 199 patients with persistent AF of more than 1 month who had failed previous electrical or pharmacological cardioversion and were treated with amiodarone. This is in contrast to the patient population studied by Bianconi et al., the majority of whom presented with their first episode of AF (only 21% had a previous attempt at cardioversion) and just one-third of patients were taking amiodarone. There was no age difference between the two study populations, but no further data are available from the preliminary report. The results, however, were reverse: significantly fewer patients who received PUFAs had a recurrence of AF at 1 month after cardioversion compared with placebo (6 vs. 12.1%) and at a median follow-up of 8 months (40 vs. 63%).

In an earlier, small study in 40 patients with paroxysmal AF and pacemakers, treatment with PUFAs at 1 g/day for 4 months resulted in a 59% reduction in AF episodes and a 67% reduction in AF burden compared with no treatment.\textsuperscript{16} After discontinuation of therapy for a further 4 months, the number of AF episodes and AF burden reverted to baseline levels. However, in a double-blind, placebo-controlled P-OM3 (efficacy and safety of Prescription of OMega-3 fatty ethyl esters for prevention of recurrent symptomatic atrial fibrillation) study, reported at the American Heart Association Sessions in November 2010, therapy with PUFAs at 4 g/day failed to prevent recurrence of AF in 663 patients (542 with paroxysmal AF, 121 with persistent AF) during 6-month follow-up.\textsuperscript{17} There was no difference in the primary endpoint of time to first symptomatic recurrence of paroxysmal AF or atrial flutter (52 vs. 48%; \( p = 0.26 \)) or in the secondary endpoint of time to first symptomatic recurrence of persistent AF or flutter (50 vs. 33%; \( p = 0.09 \)) compared with placebo.
Table I Randomized clinical trials of polyunsaturated fatty acids for secondary prevention of atrial fibrillation

<table>
<thead>
<tr>
<th>Study</th>
<th>Bianconi et al.</th>
<th>Nodari et al.</th>
<th>Kowey et al.</th>
<th>Kowey et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>204</td>
<td>199</td>
<td>542</td>
<td>121</td>
</tr>
<tr>
<td>Clinical setting</td>
<td>Post-cardioversion</td>
<td>Post-cardioversion</td>
<td>Paroxysmal AF</td>
<td>Persistent AF</td>
</tr>
<tr>
<td>Dose</td>
<td>Oral, 8 g/day loading dose for 7 days</td>
<td>Oral, maintenance dose 4 g/day</td>
<td>Oral, maintenance dose 4 g/day</td>
<td></td>
</tr>
<tr>
<td>Follow-up</td>
<td>6 months</td>
<td>1 year</td>
<td>6 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Percentage of patients with recurrence of AF</td>
<td>Time to first recurrence of AF and the number of early (1 month) and late AF recurrences</td>
<td>Time to first symptomatic recurrence of AF or atrial flutter</td>
<td>Time to first symptomatic recurrence of AF or atrial flutter</td>
</tr>
<tr>
<td>Age (years)</td>
<td>69.2 ± 7.9</td>
<td>69.7 ± 6.5 (PUFA)</td>
<td>60.5 ± 12.8</td>
<td>58.2 ± 13.6</td>
</tr>
<tr>
<td>Men (%)</td>
<td>70</td>
<td>Not stated</td>
<td>56</td>
<td>73</td>
</tr>
<tr>
<td>Previous cardioversion</td>
<td>21.4%</td>
<td>At least one in all patients</td>
<td>No</td>
<td>At least one in all patients</td>
</tr>
<tr>
<td>RAS inhibitors (%)</td>
<td>66.8</td>
<td>Not stated</td>
<td>39</td>
<td>41</td>
</tr>
<tr>
<td>Statins (%)</td>
<td>Not stated</td>
<td>Not stated</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>Beta-blockers, %</td>
<td>44.9</td>
<td>Not stated</td>
<td>68</td>
<td>66</td>
</tr>
<tr>
<td>Antiarrhythmic drugs (%)</td>
<td>63.6 (27.8% amiodarone)</td>
<td>100 (all amiodarone)</td>
<td>13</td>
<td>17</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; PUFAs, polyunsaturated fatty acids; RAS, renin–angiotensin system.

Why the results are controversial?

There are several plausible explanations for these controversial results. The antiarrhythmic potential of PUFAs, particularly in remodelled atria, may be overrated, and the positive result in some small and/or inadequately controlled studies may reflect a random effect. The precise mechanism of the antifibrillatory effect of PUFAs has not been fully established and is considered to result from the beneficial effects on substrate formation and progression via different pathways as well as (relatively weak) direct electrophysiological effects on ion channels, the potency of which may well depend on the clinical situation and AF milieu. Animal studies reported the protective effect of PUFAs in relatively unremodelled atria, and there has been no study demonstrating reverse remodelling. Furthermore, the doses used in clinical trials were generally lower than those applied in animal experiments and could be insufficient to achieve a direct effect on ion channels, which usually becomes evident early, unlike much slower action at the substrate level. The latter requires a longer time to develop, and therefore might not be revealed in studies with short- and mid-term follow-up.

There is evidence that incorporation of PUFAs into human atrial cell membrane phospholipids continues after stable plasma concentrations have been achieved, suggesting the possibility of a delayed antiarrhythmic effect of PUFAs. The maximum PUFA content in membrane was observed at approximately 1 month of treatment with relatively high doses (6 g/day). This progressive accumulation of PUFAs may explain the early lack of efficacy in secondary prevention trials. Indeed, in both negative studies, the majority of AF recurrences occurred within the first 30–40 days of treatment.

Of interest, two studies that reported a reduction in AF recurrence used lower doses of PUFAs (1 g/day) than studies with a negative result (2–4 g/day). The possibility of the proarrhythmic effect of PUFAs, particularly in view of ICD studies, should not be easily disregarded.

The content of individual PUFAs, mainly EPA and DHA, may be more important than the total PUFA concentration because the electrophysiological effects produced by different PUFA components are not the same. Docosahexaenoic acid is thought to exert a stronger sodium current block, whereas EPA and α-linolenic acid found in vegetable oils have a greater potential to block potassium currents. In the population-based Kuopio Ischemic Heart Disease Risk Factor Study, only high serum DHA content was associated with a 38% reduction in relative risk of incident AF, whereas no such association was found for EPA and docosapentaenoic acid. Higher serum levels of DHA but not EPA were associated with decreased inducibility of AF during electrophysiological study in 50 patients who received PUFAs 2 g/day for at least 1 month. In the secondary prevention studies, DHA levels increased to a lesser extent than EPA levels: in the study by Bianconi et al., EPA levels more than doubled, whereas DHA levels only increased by 25%. Kowey et al. also reported a greater increment in EPA content (about 250% from baseline) compared with DHA concentration (a 100% increase).

Adding PUFAs to medical therapy with antiarrhythmic drugs and other agents with potential beneficial action on atrial remodelling,
such as inhibitors and the renin–angiotensin system (RAS) and statins (and beta-blockers), might dilute the protective effect of PUFAs. The use of these agents in studies by Bianconi and Kowey was relatively high, particularly as they included patients without significant structural heart disease: for example, 40–67% of patients were treated with RAS inhibitors. However, Kowey et al. found no difference in the effect of PUFAs between patients who received and who did not receive RAS inhibitors. The potential effect of dietary fish intake should also be factored in because none of the studies appeared to adequately control for dietary information. Finally, the ability of PUFAs to increase parasympathetic tone may theoretically be proarrhythmic in younger individuals with normal hearts in whom a vagal component may play a role in promoting AF. There were 58 patients (31% of the total population) with ‘lone’ AF in the study by Bianconi et al., and looking at this subgroup in detail may be interesting.

**Conclusion**

In summary, although the theoretical background and experimental evidence suggest the antiarrhythmic effect of PUFAs in AF, this has not been proven in randomized clinical trials. The dose of PUFAs that may produce the antiarrhythmic effect and the duration of treatment have not been established, and the patient populations, which may best benefit from this therapy, have not been identified. The 2010 European Society of Cardiology Guidelines have made no recommendations on the use of PUFAs for prevention of AF because of the absence of robust evidence. Several primary and secondary prevention trials are ongoing, including a large FORwARD (Fish Oil Research with ω-3 for Atrial Fibrillation Recurrence Delay) study, which is expected to enrol 1400 patients with paroxysmal or persistent AF.

**Conflict of interest:** I.S. is an advisor and speaker for sanofi aventis, Bristol Meyer Squibb, Takeda, Daiichi, Boehhringer Ingelheim, Servier, and Merck. A.J.C. is an advisor and speaker for Servier, Novartis, sanofi aventis, Astra Zeneca, Cardiome, Prism, Astellas, Xention, ARYx, Prism, Bristol Meyer Squibb, Daiichi, Merck, Medtronic, St. Jude, Biotronic, Boehhringer Ingleheim, and Boston Scientific.

**References**