Omega-3 Fatty Acids in the Prevention of Atrial Fibrillation Recurrences after Cardioversion: A Meta-analysis of Randomized Controlled Trials

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Abstract

Background Previous randomized studies have reported conflicting results on the efficacy of omega-3 fatty acids in preventing atrial fibrillation (AF) recurrences after cardioversion.

Objective A systematic review and meta-analysis of the role of omega-3 fatty acids in the prevention of atrial fibrillation recurrences after cardioversion was conducted.

Methods PubMed, Cochrane Library, Elsevier, Science Online database were searched up to the end of January 2012 to identify all of the studies in human subjects that reported the effects of omega-3 fatty acids on the prevention of atrial fibrillation recurrences after cardioversion.

Results Overall, omega-3 fatty acids had no significant effect on the prevention of AF recurrences after cardioversion (OR: 0.63, 95% CI 0.35-1.13; p=0.12). The heterogeneity among the studies was significant (p=0.01, I²=66%). Subgroup analysis showed that by administering omega-3 fatty acids at least 4 weeks prior to cardioversion and continuing thereafter, the recurrence rate of AF is significantly low (OR: 0.39, 95% CI 0.25-0.61; p<0.0001).

Conclusion In the subgroup administered omega-3 fatty acids at least 4 weeks prior to cardioversion and continued thereafter, the recurrence rate of AF was significantly low. More double-blind, randomized, placebo-controlled, multicenter studies with high quality and longer follow-up periods are needed to confirm our conclusion.

Key words: omega-3 fatty acids, atrial fibrillation, cardioversion, meta-analysis

Introduction

Atrial fibrillation (AF) recurrence is common after cardioversion. Although using antiarrhythmic drug can reduce the recurrence rate, the efficacy of the drug is limited (1).

Recent studies have suggested that omega-3 fatty acids in fish oils may have antifibrillatory effects (2, 3) and can prevent AF recurrence after cardioversion (4, 5). However, these studies have reported conflicting results on their role in preventing AF recurrence after cardioversion. Therefore, we set out to estimate the role of omega-3 fatty acids on preventing AF recurrence after cardioversion through a comprehensive meta-analysis of all available randomized controlled trials (RCT).

Materials and Methods

Study search

PubMed, Cochrane Library, Elsevier, and Science Online Database were searched up to the end of January 2012 to identify all of the studies in human subjects that reported the effects of omega-3 fatty acids on the prevention of atrial fibrillation recurrences after cardioversion. The key words...
we used were “omega-3 fatty acids”, “N-3 polyunsaturated fatty acids”, “n-3 fatty acids”, “fish oil”, “atrial fibrillation” and “cardioversion”. The search had no language limitation; two reviewers then selected the identified papers. Additional publications were sought using the reference lists of the identified papers and reviews on the topic. Finally, a second search without the key word “atrial fibrillation” was done to identify additional randomized controlled trials of omega-3 fatty acids that might have data on AF recurrence after cardioversion.

Two blinded reviewers assessed the quality of included RCT by the Jadad scale (6). Relevant study data were independently abstracted, in duplicate, using a predefined form. Discrepancies during data abstraction were resolved by discussion and consensus.

**Inclusion/exclusion criteria**

Studies were enrolled if they met the following criteria: 1) randomized, controlled human trials with parallel design; 2) comparison of omega-3 fatty acid with control; 3) inclusion of patients with persistent AF referred to cardioversion; 4) provision of adequate data on AF recurrence during follow-up.

**Primary outcome**

Primary outcome for comparison was the number of patients with occurrence of AF after cardioversion during follow-up.

**Statistical methods**

Data analysis was performed with Review Manager 5.0. An x² association and x² or I² heterogeneity tests were performed. P-value for significance of association and heterogeneity tests was set, respectively, at 0.05 and 0.10. If the p value of the heterogeneity tests was >0.1 or I²<50%, we chose the fixed effect model, otherwise, we chose the random effect model. The overall treatment effects were reported using odds ratios with 95% confidence intervals (CI). The technique we used was the Mantel-Haenszel test.

**Results**

Among the clinical studies, 6 randomized, controlled, clinical trials (4, 5, 7-10) including 759 patients have been identified that met the criteria for the meta-analysis and were entered into the meta-analysis. Of the 6 included RCT, four (4, 5, 9, 10) were published as full manuscripts and two (7, 8) as an abstract. Among them, four (7-10) reported no effects on AF recurrence after cardioversion, and two (4, 5) reported a significant reduction in the recurrence rate of AF after cardioversion. The included studies showed a delayed recurrence rate at the end of the study. The characteristics of the included studies are summarized in Table 1, 2. Three (4, 8, 9) of them had a placebo control and two studies (5, 7) included patients that had not received omega-3 fatty acid as the control group. One study (10) enrolled patients who had amiodarone and omega-3 fatty acid as treatment group whereas patients who had amiodarone alone as control group. The patients of three studies (4, 5, 8) started to receive the treatment drug 4 weeks before cardioversion while the patients of one study (9) started to take the drug 1 week before cardioversion. In one study (10), omega-3 fatty acid treatment and amiodarone were started after the cardioversion. Of the studies which were RCT, only Bianconi et al. (9) implemented the dosage change in which patients received 3 g/day omega-3 fatty acids 1 week before cardioversion and 2 g/day thereafter. Other studies kept the dosage which ranged from 2 g/day to 6 g/day before and after the cardioversion. One study (7) tested the C-reactive protein (CRP) levels at baseline and one study (10) tested high sensitivity CRP (hsCRP) levels at baseline and during recurrence which were similar in the both group (p>0.05 for all). In the study of Nodari (4), 2.5% patients were withdrawn because of amiodarone toxicity, but not omega-3 fatty acid and reported no other significant side effects or bleeding. In the study of Kumar (5), 5.4% of patients discontinued fish oil because of gastrointestinal disturbance and no patient on fish oil had a serious adverse event. In the study of Bianconi (9), there was no difference between the two groups in adverse events. No drug-related complications were reported by Ozaydin et al. (10). The quality of the included 6 RCT are also shown in Table 1.

Overall, the pooled estimate showed that using of omega-3 fatty acids was not associated with a significant reduction in prevention of AF recurrence after cardioversion (OR: 0.63, 95% CI 0.35-1.13; p=0.12). The heterogeneity of the studies was significant (p=0.01, I²=67%). We continued to perform subgroup and sensitivity analyses to ascertain the reliability and stability of the results. Subgroup analysis showed that administering omega-3 fatty acids at least 4 weeks prior to cardioversion and continuing thereafter, the recurrence rate of AF is significantly low (OR: 0.39, 95% CI 0.25-0.61; p<0.0001). In the subgroup which omega-3 fatty acids are taken less than 4 weeks prior to cardioversion, the use of omega-3 fatty acids was not associated with a significant reduction in the prevention of AF recurrence after cardioversion (OR: 1.22, 95% CI 0.76-1.98; p=0.41) (Fig. 1). In the sensitivity analyses, we removed 2 studies (7, 8) which were published only in abstract form, and the results were not dramatically changed (Fig. 2).

**Discussion**

This comprehensive meta-analysis showed no significant benefit of omega-3 fatty acids for reducing AF recurrence rate after cardioversion. The heterogeneity of the studies was significant. Subgroup analysis showed that by administering omega-3 fatty acids at least 4 weeks prior to cardioversion and continuing thereafter, the recurrence rate of AF is significantly low.

Most experimental studies support the atrial antiarrhythmic
Table 1.  **Trail Design of Including RCT**

<table>
<thead>
<tr>
<th>Study</th>
<th>Health condition</th>
<th>Double blinded up period</th>
<th>How AF recurrence diagnosed</th>
<th>Dosage</th>
<th>Control</th>
<th>Duration</th>
<th>Quality scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Margos (7)</td>
<td>Persistent AF</td>
<td>No</td>
<td>6 months</td>
<td>24 h Holter at 1 month, ECG at 1, 3 and 6 months</td>
<td>PUFA</td>
<td>control</td>
<td>NA</td>
</tr>
<tr>
<td>Erdogan (8)</td>
<td>Persistent AF&gt;48h</td>
<td>Yes</td>
<td>52 weeks</td>
<td>ECG after 4 weeks, 12 weeks and 1 year or at any point of occurrence of symptoms</td>
<td>PUFA</td>
<td>Placebo</td>
<td>4 weeks before and 1 year after EC</td>
</tr>
<tr>
<td>Bianconi (9)</td>
<td>Persistent AF &gt;1 month</td>
<td>Yes</td>
<td>6 months</td>
<td>Trans-telephonic monitoring three times during first week and then twice a week until the 3 month follow-up and ECG at 48-72 h, 1 week and 1, 3 and 6 months</td>
<td>PUFA</td>
<td>Placebo</td>
<td>1 week before and 2 g/day thereafter</td>
</tr>
<tr>
<td>Nodari(4)</td>
<td>Persistent AF &gt;1 month with at least 1 relapse after cardioversion and on amiodarone and RASi</td>
<td>Yes</td>
<td>1 year</td>
<td>monitore by telemetry for at least 6 hours, weekly clinical and ECG controls for the first 3 weeks, ECG, and a 24-hour Holter monitoring were performed at 1, 3, 6, and 12 months</td>
<td>2 g/day PUFA</td>
<td>Placebo</td>
<td>4 weeks before and 1 year after EC</td>
</tr>
<tr>
<td>Kumar (5)</td>
<td>Persistent AF &gt;1 month</td>
<td>No</td>
<td>1 year</td>
<td>12-lead ECG at 2 and 6 weeks and 3 monthly intervals thereafter for 1 year.</td>
<td>6 g/d fish oil</td>
<td>control</td>
<td>4 weeks before and 1 year after EC</td>
</tr>
<tr>
<td>Ozaydin (10)</td>
<td>Persistent AF, the duration of AF&gt;48h</td>
<td>No</td>
<td>1 year</td>
<td>Patients were seen at each week in the first month, then at each month thereafter, holter at 1 and 3 months.</td>
<td>Amiodarone was given intravenously 1 g/d for the first day, followed by 800 mg/d for the first week, 600 mg/d for the second week, 400 mg/d for the third week and 200 mg/d thereafter and n-3 PUFA was 2 g/d</td>
<td>Amiodarone was given intravenously 1 g/d for the first day, followed by 800 mg/d for the first week, 600 mg/d for the second week, 400 mg/d for the third week and 200 mg/d thereafter and both were started after the cardioversion</td>
<td>2</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; ECG, electrocardiograph; PUFA, omega-3 polyunsaturated fatty acids; NA, not available; EC, electrical cardioversion; RASi, renineangiotensin system inhibitor

**Effect of omega-3 fatty acids (11-15).** This may be partly attributed to the fact that positive results of animal experiments are more likely to be published. Laurent et al. (12) found that n-3 polyunsaturated fatty acid (PUFA) supplementation can reduce AF vulnerability in a new canine pacing model of atrial cardiomyopathy and the mechanism may be related to the attenuation of collagen turnover. Cunha et al. (11) found that acute n-3 PUFA treatment prevents acute atrial electrophysiological remodeling during high rate activity, which may minimize the self-perpetuation of AF. Ninio et al. (13) reported that incorporation of dietary omega-3 fatty acids into atrial tissue reduces stretch-induced susceptibility to AF in a rabbit model.

Clinical studies that explored the atrial antiarrhythmic effect of omega-3 fatty acids have conflicting results. The study of Kumar et al. showed that omega-3 polyunsaturated fatty acid supplementation commenced >1 month prior to electrical cardioversion and continued thereafter reduces the recurrence of persistent AF (5). In patients with persistent atrial fibrillation on amiodarone and a renin-angiotensin-aldosterone system inhibitor, the addition of n-3 PUFAs 2 g/d 4 weeks previously and continued thereafter improved the probability of the maintenance of sinus rhythm after direct current cardioversion (4). The study by Heidarsdottir et al. (16) showed that there is no evidence of a beneficial effect of treatment with n-3 PUFA 5-7 days prior to surgery and post-operatively on the occurrence of post-operative atrial fibrillation in patients undergoing open heart surgery.
Amiodarone plus n-3 polyunsaturated fatty acid administration starting after the cardioversion does not reduce the recurrence rates of atrial fibrillation and inflammation versus amiodarone alone (10).

It is very common that recurrence occurs after cardioversion of persistent AF (1, 17). Persistent AF is associated with progressive atrial electrical, structural, and contractile remodeling, which increases the risk of AF recurrence in the days to weeks following restoration of sinus rhythm (18). Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the active components of fish oil. EPA and DHA may exert their antiarrhythmic effect due to their combination into the phospholipids of the cardiac membrane, rather than from their plasma level (9). Omega-3 administration increases the levels of EPA and DHA in the cellular membrane of myocytes (13) and can inhibit transient outward and ultra-rapid delayed rectifier K+ currents and Na+ current in human atrial myocytes (19). Furthermore, they also influence Ca²⁺ handling (20). Long term fish oil supplementation also downregulates proarrhythmic cardiac connexins (15).

**Table 2.** baseline Characteristics of Including RCT

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Group</th>
<th>No. of patients</th>
<th>Age (years)</th>
<th>Men(%)</th>
<th>BMI (Kg/m²)</th>
<th>Obesity (%)</th>
<th>Amiodarone Use (%)</th>
<th>CCB Use (%)</th>
<th>Beta-blocker Use (%)</th>
<th>RASi use (%)</th>
<th>Statin use (%)</th>
<th>Digoxin use (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>Drug</td>
<td>20</td>
<td>54</td>
<td>85</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>control</td>
<td>20</td>
<td>57</td>
<td>55</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>2007</td>
<td>Drug</td>
<td>54</td>
<td>66.5</td>
<td>70.3</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>control</td>
<td>54</td>
<td>63.5</td>
<td>74.1</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>2011</td>
<td>Drug</td>
<td>95</td>
<td>69</td>
<td>70.5</td>
<td>NA</td>
<td>NA</td>
<td>27.4</td>
<td>30.5</td>
<td>46.3</td>
<td>68.4</td>
<td>-</td>
<td>15.8</td>
</tr>
<tr>
<td></td>
<td>control</td>
<td>92</td>
<td>69</td>
<td>67.4</td>
<td>NA</td>
<td>NA</td>
<td>28.3</td>
<td>26.1</td>
<td>43.5</td>
<td>65.2</td>
<td>-</td>
<td>18.5</td>
</tr>
<tr>
<td>2011</td>
<td>Drug</td>
<td>100</td>
<td>70</td>
<td>70</td>
<td>23.8±5.2</td>
<td>14</td>
<td>100</td>
<td>7.0</td>
<td>65.0</td>
<td>100</td>
<td>53</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>control</td>
<td>99</td>
<td>69</td>
<td>63.6</td>
<td>23.6±5.3</td>
<td>14</td>
<td>100</td>
<td>7.0</td>
<td>65.0</td>
<td>100</td>
<td>44.4</td>
<td>-</td>
</tr>
<tr>
<td>2011</td>
<td>Drug</td>
<td>91</td>
<td>63</td>
<td>82.4</td>
<td>NA</td>
<td>49.3</td>
<td>33</td>
<td>**</td>
<td>45.1</td>
<td>45.6</td>
<td>36.7</td>
<td>**</td>
</tr>
<tr>
<td></td>
<td>control</td>
<td>87</td>
<td>61</td>
<td>72.4</td>
<td>NA</td>
<td>49.3</td>
<td>33</td>
<td>**</td>
<td>44.8</td>
<td>66.3</td>
<td>40.7</td>
<td>**</td>
</tr>
<tr>
<td>2011</td>
<td>Drug</td>
<td>23</td>
<td>62</td>
<td>47.8</td>
<td>28.8±5.7</td>
<td>NA</td>
<td>100</td>
<td>13</td>
<td>26.1</td>
<td>73.9</td>
<td>30.4</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>control</td>
<td>24</td>
<td>61</td>
<td>37.5</td>
<td>28±4</td>
<td>NA</td>
<td>100</td>
<td>12.5</td>
<td>25</td>
<td>45.8</td>
<td>20.8</td>
<td>-</td>
</tr>
</tbody>
</table>

BMI: body mass index, CCB: calcium-channel blockers, RASi: renin-angiotensin system inhibitor, NA: not available

** in this study, most patients took sotalol and amiodarone as antiarrhythmic drugs, and the patients were either on other beta-blockers, digoxin, or non-dihydropyridine calcium-channel antagonists which the drug group was 22% while the control group was 21.8%.

**Figure 1.** Omega-3 fatty acids in the prevention of atrial fibrillation recurrences after cardioversion
The effect of omega-3 fatty acids after removing 2 studies published only in abstract form

Figure 2.

and proinflammatory cytokines implicated in AF perpetuation (21, 22). Recently, it was believed that the inflammation played a part in the pathophysiology of atrial remodeling (23). And n-3 fatty acids can attenuate inflammation in humans (24). However, in the design of the included RCT, only one study (10) tested the hsCRP levels at baseline and during recurrence.

Metcalf et al. (25) demonstrated that accumulation of EPA and DHA in the right atrium was curvilinear with time by fish oil supplementation at a dose of 6 g/d in humans, and reached a maximum at approximately 30 d of treatment. In contrast, plasma levels were more than doubled after the shorter period of administration and remained constant thereafter. Of the included RCT, only Bianconi et al. (9) designed the dosage change in which patients received 3 g/day omega-3 fatty acid 1 week before cardioversion and 2 g/day thereafter. Other studies kept the dosage which ranged from 2 g/day to 6 g/day before and after the cardioversion. In the subgroup administered omega-3 fatty acids at least 4 weeks prior to cardioversion and continued thereafter, the recurrence rate of AF was significantly low. In the subgroup in which omega-3 fatty acids were taken less than 4 weeks prior to cardioversion or operation, the use of omega-3 fatty acids was not associated with a significant reduction in the prevention of AF recurrence after cardioversion. Maybe in those studies, the dose of omega-3 fatty acid was insufficient or the duration was too short to achieve a sufficient concentration of omega-3 fatty acid in the atrial membranes, though the plasma level of omega-3 fatty acids are significantly higher in the treatment group than that of the control group (9). In the study of Saravanan (26), 108 patients undergoing coronary artery bypass graft surgery were randomly assigned to receive 2 g/d n-3 PUFA or placebo for at least 5 days before surgery (median, 16 days; range, 12 to 21 days); Omega-3 PUFA did not reduce the risk of AF after coronary artery bypass graft surgery. The reason may be the lack of time for the drug to develop an effect. From the study of Metcalf et al. (25), it suggested that initial, high-dose fish-oil supplementation would be helpful and the time course of administration before cardioversion or surgery should be sufficient for the cardioprotective effects.

Antiarrhythmic drugs can reduce the AF recurrence rate, but they are limited by their side effects. Inadequacies in current therapies for atrial fibrillation have made new drug development crucial. Omega-3 fatty acids are well tolerated (4, 5, 27) and extensive preclinical studies have been undertaken (12-15, 28, 29). In the study of Kumar et al. (5), only 5.4% of patients discontinued fish oil because of gastrointestinal disturbance and no patient on fish oil had a serious adverse event. In the study of Nodari et al. (4), only 2.5% patients were withdrawn because of amiodarone toxicity, but not omega-3 fatty acid and they reported no other significant side effects or bleeding. Because of the safety of omega-3, there are a lot of studies evaluating the efficacy of omega-3 fatty acids in preventing AF recurrence. After the meta-analysis of appropriate RCT, we suggest the later trials should administer omega-3 fatty acids at least 4 weeks prior to cardioversion or operation.

Recommendations for clinical practice

It is possible that omega-3 fatty acids given at least 4 weeks in advance can develop the antiarrhythmic effect.

Conclusion

Overall, the pooled estimate showed that the use of omega-3 fatty acids was not associated with a significant reduction in prevention of AF recurrence after cardioversion.
But the heterogeneity of the studies was significant. In the subgroup of administered omega-3 fatty acids at least 4 weeks prior to cardioversion and continued thereafter, the recurrence rate of AF was significantly low. Thus maybe it is important to give omega-3 fatty acids at least 4 weeks in advance to allow sufficient time for the drug to develop the antiarrhythmic effect.

**Limitations**

Two studies included in the meta-analysis were published in the abstract form and we could not gain the relevant information we need. The duration, the dosage, and the composition of drug differed among the included studies. And the number of RCT is limited. More double-blind, randomized, placebo-controlled, multicenter studies with high quality and longer follow-up periods are needed to affirm our conclusion.

The authors state that they have no Conflict of Interest (COI).

**Acknowledgement**

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**References**