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ORIGINAL ARTICLE

# Omega-3 Fatty Acids for Postoperative Atrial Fibrillation: Alone or in Combination with Antioxidant Vitamins?

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**Background** The effects of omega-3 polyunsaturated fatty acids (PUFA) on the prevention of postoperative atrial fibrillation (POAF) are inconclusive in current studies. Moreover, the most appropriate composition of PUFA to play the protective role is unclear. The aim of this meta-analysis was to ascertain the protective role of PUFA on POAF and the most appropriate composition.

**Methods** Studies were identified through PubMed, CENTRAL, EMBASE, reviews and reference lists of relevant papers. The odds ratio (OR) was calculated for POAF. Statistical analyses were performed with Review Manager 5.0.

**Results** Eleven randomised controlled trials with 3137 patients were included in the analysis. The use of PUFA alone did not reduce the incidence of POAF compared with the control (OR: 0.76; 95% confidence interval [CI]: 0.57-1.03; $P$=0.08; $I^2$=52%). However, combination therapy with PUFA and vitamins C and E reduced the incidence of POAF by 68% (OR: 0.32; 95%CI: 0.17-0.60; $P$=0.0005; $I^2$=38%). Subgroup analysis indicated that the ratio of EPA/DHA 1:2 was effective in preventing POAF (OR: 0.35; 95%CI: 0.24-0.50; $P$<0.00001; $I^2$=0%), while the ratio not 1:2 failed.

**Conclusions** Combination therapy with PUFA and vitamins C and E is effective in the prevention of POAF while PUFA alone is not. The ratio of EPA/DHA may influence the incidence of POAF, and 1:2 may be most appropriate. Studies about PUFA on the prevention of POAF are still worthwhile to be conducted in the future.

**Keywords** Postoperative atrial fibrillation • Omega-3 fatty acids • Vitamins • Inflammation • Meta-analysis.

## Introduction

Atrial fibrillation is the most common arrhythmia after cardiac surgery. The incidence of postoperative atrial fibrillation (POAF) ranges from 10% to 65% [1]. The development of POAF has been shown to be associated with increased hospital costs and length of stay. In addition, patients with POAF also have higher long-term mortality and higher incidence of embolic events [1–4].

Omega-3 polyunsaturated fatty acids (PUFA) have received more and more attention in recent years. They are believed to possess antiarrhythmic effects and other pleiotropic properties, such as anti-inflammation, anti-oxidation and preventing atrial electrophysiological remodelling [5,6]. However, the

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results from current studies which assessed the protective role of PUFA on POAF are inconclusive [7,8], and even the conclusions from meta-analyses are controversial [9,10]. Moreover, studies indicate that PUFA in combination with vitamins C and E may result in a marked reduction of POAF [11,12].

Whether PUFA is effective in preventing POAF, and which one is more effective, PUFA alone or in combination with vitamins C and E, cannot be answered yet. The ratio of eicosapentaenoic acids (EPA)/docosahexaenoic acids (DHA) affects the protective role of PUFA and the most appropriate ratio is not clear as well. Therefore, we conducted the meta-analysis of available data from randomised controlled clinical trials aimed to ascertain the role of PUFA in the prevention of POAF.

# Material and methods

## Search strategy

We searched (November 2013) the PubMed, CENTRAL and EMBASE databases with the keywords and corresponding MeSH terms ''(fish oils OR omega-3 fatty acids OR omega 3 fatty acids OR n-3 PUFAs OR n-3 fatty acids OR n 3 fatty acids OR eicosapentaenoic acids OR docosahexaenoic acids) AND (cardiac surgery OR heart surgery OR coronary artery bypass surgery) AND atrial fibrillation'' without language and time limitation. The reference lists of identified articles, previous meta-analyses, and original studies identified by the hand search were also checked to find other potentially eligible studies.

## Study selection

Studies that met the inclusion criteria were: 1) randomised controlled trials (RCTs); 2) the study population was cardiac surgery patients; 3) reporting the use of PUFA in the prevention of POAF, regardless of the concomitant therapy; and 4) evaluating POAF as an outcome.

Exclusion criteria were: 1) irretrievable or unclear data; 2) lack of control group; 3) duplicate reports; and 4) ongoing or unpublished studies.

## Quality assessment

Quality of the included studies was evaluated according to the Jadad Scale, which evaluated the methodological quality of a clinical trial in three aspects: randomisation (0-2 points), masking (0-2 points), and dropouts and withdrawals (0-1 points) [13]. A score of 1 was given for each of the points described. A further point was obtained if the method of randomisation and/or blinding was given and appropriate; where it was inappropriate a point was deducted. Each study would get a Jadad score of between 0 and 5 (highest level of quality).

## Data extraction

Study features extracted included: study design, study population, PUFA dosage, EPA/DHA ratio, PUFA duration, POAF diagnosis criteria, methods of PUFA detection, follow-up duration, the incidence of POAF and participants' characteristics. The primary end point was the incidence of POAF during follow-up.

Study search, selection, appraisal, and abstraction were all performed by two independent reviewers. If disparities occurred, they were resolved by discussion or consensus of a third reviewer.

## Statistical analysis

Statistical analyses were performed with Review Manager 5.0 (The Cochrane Collaboration, Copenhagen, Denmark). Results of the POAF outcome were presented as odds ratio (OR) and 95% confidence interval (CI). The outcomes from individual study were combined with the fixed-effect model first, but if heterogeneity existed, then the random-effect model would be used. Heterogeneity of effects was assessed with Chi-square tests and $I^2$, and $I^2$ exceeding 50% was an indicator of significant heterogeneity between the trials [14]. Subgroup analysis was performed according to 1) studies using PUFA alone or in combination with antioxidant vitamins, 2) the ratio of EPA/DHA. Publication bias was evaluated using the funnel plot and the fail-safe number ($N_{fs}$). Any calculated $N_{fs}$ value smaller than the number of retrieved studies indicated publication bias. The $N_{fs0.05}$ was calculated as $N_{fs0.05}=(\Sigma Z/1.64)^2-k$, where k was the number of studies

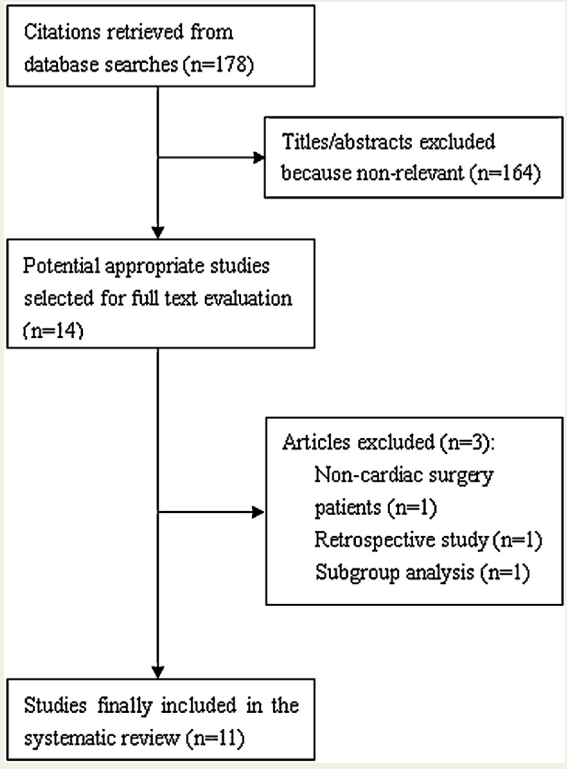


**Figure 1** Flow diagram of the trial selection process. Flow chart shows the number of citations retrieved by individual searches and the number of trials eventually included in the review.