Effect of fish oil on ventricular tachyarrhythmia in three studies in patients with implantable cardioverter defibrillators


CRD summary
The review concluded that there was no evidence of a protective effect of omega-3 polyunsaturated fatty acids from fish oil against recurrent life-threatening ventricular arrhythmia in patients with an implantable cardioverter defibrillator. The authors’ conclusions appeared to reflect the evidence presented, but limitations in the review methodology and the small number of included trials mean their reliability is uncertain.

Authors’ objectives
To determine the effects of omega-3 polyunsaturated fatty acids from fish on the incidence of recurrent ventricular arrhythmia in implantable cardioverter defibrillator patients.

Searching
MEDLINE, EMBASE and the Cochrane Library were searched to May 2008; search terms were reported.

Study selection
Studies that evaluated the effects of fish oil (omega-3 polyunsaturated fatty acids) compared with placebo for the treatment of spontaneous ventricular arrhythmia in patients with implantable cardioverter defibrillators were eligible for inclusion.

Interventions in the included trials were fish oil capsules (1.3 or 2.6g/day as ethyl esters; 0.9g/day as triglycerides) compared with placebo. Participants in the included trials had implantable cardioverter defibrillators and prior malignant ventricular tachycardia or ventricular fibrillation. Some participants were using class I and class III anti-arrhythmic medication; between 70 to 80% had a history of coronary artery disease or ischaemic heart disease and had a mean ejection fraction of approximately 35%. Some participants also had a high fish intake diet at baseline. Participants mean age ranged from 61 to 66 years; the proportion of males ranged from 82 to 86%. Outcomes assessed included time to first confirmed spontaneous ventricular tachyarrhythmia, ventricular fibrillation, or death from any cause.

The authors did not state how papers were selected for inclusion.

Assessment of study quality
The authors did not formally assess validity, but stated that the included studies were randomised, double-blind, placebo-controlled trials (RCTs) with high quality standards.

Data extraction
Two trials were conducted by the authors, so individual patient data (IPD) were available; data were extracted from a third published trial. As clinical endpoints varied between trials, the authors defined common clinical endpoints and re-analysed IPD data before combining with other data. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for the time to first tachyarrhythmia or death on an intention-to-treat basis. As trial duration varied, authors extracted data up to one year.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
For the meta-analysis hazard ratios from all included trials were combined using a random-effects model. Subgroup outcomes were corrected for baseline characteristics of patients.
Pooled analyses were conducted separately for IPD data, using the Kaplan-Meier method to generate time to first event graphs and Cox proportional hazard models to adjust to match the adjusted baseline characteristics. Adjusted models were based on subjects with complete data.

Heterogeneity was assessed using the $X^2$ and $I^2$ tests.

**Results of the review**

Three RCTs, \((n=1,148)\) were included. The included trials were reported to have "high quality control standards". One RCT reported non-compliance rates of approximately 35%.

There were no statistically significant differences between the effects of fish oil and placebo for time to first implantable cardioverter defibrillator intervention for a confirmed ventricular tachyarrhythmia or death (three RCTs, \(n=1,148\)). Subgroup analyses also found no statistically significant differences between groups, although there was evidence of statistical heterogeneity for some of the subgroup analyses.

The pooled IPD analysis (two RCTs; \(n=746\) patients) also found no statistically significant differences between fish oil and placebo for implantable cardioverter defibrillator intervention for ventricular tachyarrhythmia or death. Subgroup analysis reported an increased risk of these outcomes for patients taking lipid-lowering medications (HR 1.48, 95% CI 1.01 to 2.18; two RCTs, \(n=333\) patients), but the remaining subgroup analyses found no statistically significant differences between groups.

**Authors’ conclusions**

The findings did not support a protective effect of omega-3 polyunsaturated fatty acids from fish oil against recurrent life-threatening ventricular arrhythmia in patients with an implantable cardioverter defibrillator. However, the data suggested that underlying diseases may determine whether patients may benefit from fish oil or not. Furthermore, fish oil supplementation might not be advisable for all patients.

**CRD commentary**

The review question was clear and inclusion criteria were specified for intervention, population and outcomes, but not for study design. Some relevant sources were searched, but no efforts were made to reduce publication or language bias. The authors of the two trials providing individual patient data were also authors of the review, so it seemed that the primary aim was to pool these two trials, with the search for additional research only a secondary question.

Only RCTs were included in the analysis. These were reported to have "high quality control standards", but no further details are reported; consequently the reliability of the results presented could not be assessed. Two analyses were conducted: one pooled the individual patient data using standard statistical methods for time to event data; the other combined summary statistics from these trials with a third published data using random-effects meta-analysis. Both analyses appeared appropriate. There were differences between the trials in terms of dosage of fish oil and patient characteristics, but the authors reported adjusting for these.

The authors’ conclusions appeared to reflect the evidence presented, but limitations in the review methodology and the small number of included trials means their reliability is uncertain.

Two of the review authors were also authors of two of the included primary trials. One author was employed by Unilever, a producer of foods enriched with omega-3 fatty acids.

**Implications of the review for practice and research**

**Practice:** The authors stated that as data suggest that underlying diseases may determine whether patients may benefit from fish oil or not, fish oil supplementation might not be advisable for all patients.

**Research:** The authors did not state any implications for research.
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