Effect of fish oil on arrhythmias and mortality: systematic review
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CRD summary
This review investigated the effects of fish oil on mortality and arrhythmias. The authors found that fish oil supplementation was associated with a significant reduction in deaths from cardiac causes but was not beneficial for arrhythmic events or all-cause mortality. The authors' conclusions reflected the results but the reliability of these is unclear given heterogeneity between studies and unclear reporting.

Authors’ objectives
To investigate the effects of fish oil – docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) – on mortality and arrhythmias and to explore dose response and formulation effects.

Searching
Several sources including MEDLINE, EMBASE, The Cochrane Library, PubMed, CINAHL, Web of Science and ProQuest Dissertations and Theses were searched in 2006 without language restrictions (search dates varied, spanning 1966 to 2006). Search terms were reported. Heart disease and omega 3 fatty acid papers from the IBIDS database and reference lists of included studies were also examined to identify additional studies. An update search was performed in March 2007.

Study selection
Randomised controlled trials (RCTs) in which fish oil was investigated as a dietary supplement were eligible for inclusion. Trials that included pregnant women or children, or those that lasted less than three months were excluded. The following outcomes were eligible for inclusion: arrhythmic end points of appropriate implantable cardiac defibrillator intervention (confirmed by electrogram); sudden cardiac death (primary outcomes); all cause mortality and death from cardiac causes (secondary outcomes).

The included studies were conducted in a variety of patient populations (for example, implantable cardiac defibrillation, after percutaneous coronary angioplasty and acute myocardial infarction patients). The mean age of the treatment group ranged from 48.5 to 66.2 years and the control group 49.2 to 65.3 years. The doses of EPA ranged from 18.2 - 2,800mg/day and DHA 0 - 2,340mg/day. The control also varied. Follow-up ranged from 1 to 60 months.

Two reviewers independently selected studies and a third reviewer acted as mediator should discrepancies occur.

Assessment of study quality
Methodological quality was determined using a form derived from the Jadad scale (which assesses features such as randomisation, blinding and withdrawals to give a quality score out of 5). Additional quality criteria were assessed, such as concealment of treatment allocation, funding agencies and use of intention to treat (ITT) analysis.

Validity was assessed independently by two reviewers

Data extraction
The outcomes of interest were extracted to calculated odds ratios (ORs) and corresponding 95% confidence intervals (CIs) by two independent reviewers. A third reviewer mediated in the event of discrepancies.

Methods of synthesis
ORs were pooled in a random effects meta-analysis (DerSimonian and Laird method) and presented as odds ratios (ORs) and corresponding 95% confidence intervals (CIs). Statistical heterogeneity was assessed using the X² test and I² test. Overall effect was determined by the z test. A meta-regression analysis of deaths from cardiac causes was carried out using a random-effects model to investigate any dose-response effect. Relative risk of non-cardiovascular adverse
effects was evaluated. Treatment effects and adverse effects were expressed as number needed to treat (NNT) and number needed to harm (NNH). A funnel plot was used to assess publication bias.

**Results of the review**

Twelve RCTs were included in the review (n=32,779). Two large trials (n=29,979) provided the majority of participants. Five studies had a quality score of 5/5, four studies 4/5, two studies 3/5 and one study 2/5.

Supplementation with fish oil was associated with a statistically significant (20 per cent) decrease in death from cardiac causes (11 RCTs, n=32,519) OR 0.80 (95% CI: 0.69, 0.92, p=0.002). There was evidence of publication bias but no evidence of significant statistical heterogeneity.

In a subgroup of patients with coronary artery disease or after myocardial infarction fish oil supplementation was associated with a statistically significant (26 per cent) reduction in sudden cardiac death compared with control (four RCTs, n=15,528) OR 0.74 (95% CI: 0.59, 0.92, p=0.008), and a statistically significant (20 per cent) reduction in death from cardiac causes compared with control (eight RCTs, n=16,390) OR 0.80 (95% CI: 0.69, 0.93, p=0.004). No statistically significant heterogeneity was detected.

Adverse effects occurred in 10.5 per cent of patients who took fish oil compared with 6.7 per cent of control patients. Most of the effects were described as mild. The NNT to prevent one cardiac death was 189 and the NNH was 26.

Fish oil supplementation was not associated with a significant reduction in the risk of appropriate implantable cardiac defibrillator intervention or the incidence of sudden cardiac death (the primary outcomes) or all cause mortality. No dose-response relationship was found between DHA and EPA and death from cardiac causes.

**Authors’ conclusions**

Fish oil supplementation was associated with a significant reduction in deaths from cardiac causes, but is was not beneficial in terms of arrhythmic events or all-cause mortality.

**CRD commentary**

The review question was clear and there were inclusion criteria for study design, intervention, participants and outcomes. The authors searched published sources and studies reported in any language were sought, which reduced the possibility of language bias. No attempt to identify unpublished studies was reported, increasing the possibility of publication bias. Validity of the primary studies appeared to be assessed appropriately. Study selection, validity assessment and data extraction were performed independently by two reviewers, minimising the risk of reviewer bias and error. Statistical heterogeneity and publication bias were assessed and taken into consideration by the authors. Given the clinical heterogeneity of the studies in terms of participants and intervention, pooling of these studies may not have been appropriate. The results of the review were driven by two very large trials. One study with one month follow-up was included despite this being less than the specified inclusion criteria for follow-up. The authors’ conclusions reflected the results, but the reliability of these is unclear given the clinical differences between studies.

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

Practice: the authors stated that it would be reasonable to use a daily formulation of 465 mg EPA/386mg DHA (similar to that of the GISSI-Prevenzione trial).

Research: the authors did not state any implications for research.

**Funding**

Not stated

**Bibliographic details**

Original Paper URL
http://www.bmj.com/content/337/dec23_2/a2931

Indexing Status
Subject indexing assigned by CRD

MeSH
Arrhythmias, Cardiac; Cardiovascular Diseases; Dietary Supplements; Docosahexaenoic Acids; Eicosapentaenoic Acid; Fatty Acids, Omega-3; Fish Oils; Humans

AccessionNumber
12008107698

Date bibliographic record published
03/02/2009

Date abstract record published
07/04/2009

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.