Fish oils in the care of coronary heart disease patients: a meta-analysis of randomized controlled trials

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CRD summary
This review assessed the effects of fish oil supplements in patients with coronary heart disease. The authors concluded that omega-3 fatty acids can reduce the risk of death from any cause, but further research is required in patients taking statins. This was generally a well-conducted review and its conclusions are likely to be reliable.

Authors' objectives
To assess the effects of supplemental intake of omega-3 fatty acids on cardiovascular events in patients with coronary heart disease (CHD).

Searching
MEDLINE and EMBASE were searched from inception to June 2003. Additional studies were sought from abstracts of the American College of Cardiology and American Heart Association meetings (1990 to 2002). The references from retrieved articles were also screened. The search terms were reported but it was not stated whether any language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs), where individual patients were randomised, were eligible for inclusion. The duration of follow-up ranged from 4 to 42 months in the included studies.

Specific interventions included in the review
Studies of dietary or pharmaceutical fish oil supplements were eligible for inclusion. The included studies mostly assessed eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), providing a total dose of omega-3 fatty acids ranging from 1.5 to 6 g/day. One study assessed an increase in fatty fish consumption (or fish oil capsules for patients unable to comply with the dietary regime); another assessed purified fish oils and ethyl esters of fatty acids extracted from fish oil. The control treatments were either: no treatment; olive oil, with or without vitamin E; mustard oil and alumina hydroxide; non-marine fatty acids; or dietary advice to reduce fat intake and increase fibre intake.

Participants included in the review
Studies of patients with CHD were eligible for inclusion. Most of the included studies were in patients following percutaneous transluminal coronary angioplasty; two studies included patients with a recent myocardial infarction (MI) and one included patients in the acute phase of MI. The mean patient age was 59 years and the gender ratio was 5:1. In most of the studies patients were taking one or more concomitant medications including aspirin, calcium-channel blockers, beta-blockers and angiotensin-converting enzyme inhibitors.

Outcomes assessed in the review
Studies reporting one of the following outcomes were eligible for inclusion: all-cause mortality, fatal MI, nonfatal MI, nonfatal stroke and unstable angina.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Study validity was assessed using the following six criteria described by the Cochrane Collaboration: patient selection;
randomisation procedure; blinding procedure; description of the treatment and control interventions; proportion lost to follow-up; and use of intention-to-treat analysis. These were scored A if the principle was respected and applied, B if there was insufficient description, or C if the principle was not applied.

The authors did not state how many reviewers performed the validity assessment.

**Data extraction**

Two reviewers independently extracted the data, with any discrepancies resolved by consensus. The numbers of patients experiencing each outcome were extracted for the intervention and control groups, and the relative risk (RR) and corresponding 95% confidence interval (CI) were calculated. The relative risk reduction and the number-needed-to-treat were also calculated. Authors were contacted for additional information on outcomes not reported in the original publications.

**Methods of synthesis**

*How were the studies combined?*

The studies were pooled in a weighted analysis using the inverse variance of the log RR as the weight. A fixed-effect model was used in the absence of statistically significant heterogeneity. Publication bias was assessed using Rosenthal's 'file drawer' method, which estimated the number of studies with no treatment effect that would need to be added to the analysis to make a non significant result.

*How were differences between studies investigated?*

Heterogeneity was assessed using a chi-squared test. Sensitivity analyses were conducted by withdrawing trials from the analysis in decreasing order of statistical weight. Further sensitivity analyses were conducted by successively withdrawing trials in decreasing order of RR, and also by withdrawing one trial whose treatment differed from the other trials.

**Results of the review**

*Ten RCTs (n=14,727) were included.*

Five trials were considered to be of good quality as they satisfied all six quality criteria; four were rated poor because they either had an open design or did not mention intention-to-treat analysis; one trial was considered to be of moderate quality because the description of the double-blinding procedure was not sufficient. Seven studies reported no losses to follow-up; other studies reported losses from 0.1 to 13%.

*All-cause mortality.*

There was a statistically significant reduction of 16% in the risk of death for patients taking fish oils compared with placebo (6 studies; RR 0.84, 95% CI: 0.76, 0.94). There was no evidence of heterogeneity between these studies (P=0.68).

*Fatal MI.*

There was a statistically significant reduction of 24% in the risk of death due to MI for patients taking fish oils compared with placebo (4 studies; RR 0.76, 95% CI: 0.66, 0.89). There was no evidence of heterogeneity between these studies (P=0.59).

*Other outcomes.*

There were no statistically significant differences between the fish oil and placebo groups for any of the other outcomes: nonfatal MI (7 studies; RR 1.03, 95% CI: 0.87, 1.19, corresponding to a 3% increase in risk for fish oils), nonfatal stroke (3 studies; RR 1.36, 95% CI: 0.87, 2.29, corresponding to a 36% increase in risk for fish oils), and angina pectoris (7 studies; RR 1.03, 95% CI: 0.85, 1.20, corresponding to a 3% increase in risk for fish oils). There was no evidence of heterogeneity between the studies for any of these outcomes (P=0.35, P=0.39 and P=0.4 respectively).
Other analyses.

The sensitivity analyses showed that the two largest trials were having the most impact upon the results for all-cause mortality and fatal MI; deleting both these trials from the analysis meant the results were no longer statistically significant. Deleting other trials did not affect the results for these or any other outcomes. The test for publication bias showed that 11 or more trials showing no treatment effect would have to be added to produce a non-significant result for fatal MI and all-cause mortality.

Authors’ conclusions
The review findings suggested that daily supplementation with omega-3 fatty acids significantly reduced the incidence of all-cause mortality by 16% and fatal MI by 24% in patients with CHD. No significant benefit in the prevention of other cardiovascular events could be found. Further research is required to establish what fish oil supplementation adds to the beneficial cardiovascular effects of statins.

CRD commentary
This review had a clear research question and clearly defined inclusion criteria. The authors searched two appropriate databases and made some effort to locate unpublished studies by searching the abstracts of two major meetings. However, they did not state whether any language restrictions applied, and they could have extended the search for grey literature by searching clinical trials databases and other meeting or conference abstracts. The data extraction was performed in duplicate, which reduces the chance of reviewer errors and bias, although the authors did not state if the study screening and validity assessment processes were also performed in duplicate. Publication bias was assessed using a recognized method, although this method does have limitations. Study quality was assessed using appropriate criteria and the authors also considered the effect of quality upon the meta-analysis results in their discussion. The methods of analysis and explorations of heterogeneity were appropriate. This was a generally well-conducted review and its conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further research needs to be undertaken into what fish oil supplementation adds to the beneficial effects of statins, before fish oil can be recommended for systematic use in patients with CHD.

Bibliographic details

PubMedID 15482380


Indexing Status
Subject indexing assigned by NLM

MeSH
Coronary Disease /diet therapy /mortality; Dietary Supplements; Fatty Acids, Omega-3 /administration & dosage; Female; Humans; Male; Middle Aged; Randomized Controlled Trials as Topic; Treatment Outcome

AccessionNumber 12004006978
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.