Efficacy of omega-3 fatty acid supplements (eicosapentaenoic acid and docosahexaenoic acid) in the secondary prevention of cardiovascular disease: a meta-analysis of randomized, double-blind, placebo-controlled trials

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CRD summary
The review concluded that there was insufficient evidence of a secondary preventive effect of omega-3 fatty acid supplements against overall cardiovascular events among patients with a history of cardiovascular disease. The authors’ conclusions reflected the evidence available and appear likely to be reliable.

Authors’ objectives
To investigate the efficacy of omega-3 fatty acid supplements eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in the secondary prevention of cardiovascular disease.

Searching
PubMed, EMBASE and The Cochrane Library were searched to April 2011 for studies in English; search terms were reported. Bibliographies of relevant papers were searched.

Study selection
Randomised controlled trials (RCTs) of omega-3 fatty acid supplements in adults (≥18 years) with a history of cardiovascular disease were eligible. Trials needed to be double-blinded and placebo-controlled. Trials had to have a treatment duration of at least one year and report outcome measures such as angina, unstable angina, cardiovascular disease or events, sudden cardiac death, cardiovascular death, all-cause mortality, congestive heart failure, transient ischaemic attack and stroke, or fatal or nonfatal myocardial infarction.

Where reported, mean age of participants was 63.4 years and 79% were male. Included patient groups were those with stable coronary heart disease, recent myocardial infarction, implanted cardioverter defibrillators, congestive heart failure and other cardiovascular diseases. Daily doses of eicosapentaenoic acid or docosahexaenoic acid ranged from 0.4g to 4.8g. Follow-up ranged from 1.0 to 4.7 years. Placebo groups received vegetable oils, mixed fatty oil and other “inert” or poorly defined substances.

Two reviewers independently selected studies for inclusion. Disagreements were resolved by discussion or by a third reviewer.

Assessment of study quality
Study quality was evaluated using the Jadad scale of randomisation, blinding and withdrawals/drop-outs. The maximum possible score was 5 points.

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

Data extraction
Event data for intention-to-treat populations were extracted in order to calculate relative risks (RR) with 95% confidence intervals (CI).

The authors did not state how many reviewers extracted data.

Methods of synthesis
Meta-analyses were performed to calculate pooled relative risks (RRs) with 95% CIs, using a random-effects model. Heterogeneity was assessed using the $I^2$ statistic ($I^2>50\%$ indicated substantial heterogeneity). Publication bias was assessed using a funnel plot and the Egger test. Subgroup analyses investigated the effect of history (type) of cardiovascular disease, geographic area (inland versus coastal), duration of treatment (less than two years versus two years or more), dosage (<1.7 versus ≥1.7g/day), use of fish oil supplementation only as treatment, type of placebo
material in the trial (oil versus non-oil), Jadad score (≤4 versus 5 points), country and concomitant medication use.

**Results of the review**
Fourteen RCTs (20,485 patients, range 59 to 6,975) were included. The mean Jadad score was 4.4 out of 5 (13 out of 14 trials scored 4 or 5).

Omega-3 fatty acid supplementation did not reduce the risk of overall cardiovascular events (RR 0.99, 95% CI, 0.89 to 1.09, I²=27%; 14 RCTs), risk of all-cause mortality (13 RCTs), sudden cardiac death (five RCTs), myocardial infarction (11 RCTs), fatal myocardial infarction (five RCTs), nonfatal myocardial infarction (seven RCTs), angina and unstable angina (seven RCTs), congestive heart failure (six RCTs) and transient ischaemic attack and stroke (seven RCTs). There was a significant reduction in cardiovascular death (RR 0.91, 95% CI 0.84 to 0.99, I²=0%; 11 RCTs), which became non-significant when a study with a significant baseline imbalance (for history of angina) was removed.

No significant preventive effect was observed in any of the subgroup analyses.

There was no evidence of publication bias. There were no significant differences between groups in occurrence of gastrointestinal problems (eight RCTs) and gastrointestinal bleeding (one RCT) adverse events.

**Authors' conclusions**
There was insufficient evidence of a secondary preventive effect of omega-3 fatty acid supplements against overall cardiovascular events among patients with a history of cardiovascular disease.

**CRD commentary**
The review addressed a clear question and was supported by appropriate inclusion criteria. Attempts to identify relevant studies were undertaken by searching electronic databases and checking references. The search did not include unpublished studies and excluded studies in languages other than English, but there was no evidence of publication bias. The authors used suitable methods to reduce risks of reviewer error and bias during study selection, but they did not report such methods for assessment of study quality and data extraction.

Sufficient study details were provided. Appropriate methods were used to pool data and assess heterogeneity. Study quality was assessed using the Jadad scale and the results were used in a sensitivity analysis. Limitations of using the Jadad scale were evident when in a sensitivity analysis the authors made a post hoc exclusion of a study with baseline imbalances (despite there being no evidence of statistical heterogeneity). No forest plot was presented; a forest plot would have enabled the reader to make a more informed opinion of how appropriate this particular analysis was.

The authors' conclusions reflected evidence available and appear 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 large trials were needed and these should have longer treatment durations.

**Funding**
Not stated.

**Bibliographic details**
Kwak SM, Myung SK, Lee YJ, Seo HG. Efficacy of omega-3 fatty acid supplements (eicosapentaenoic acid and docosahexaenoic acid) in the secondary prevention of cardiovascular disease: a meta-analysis of randomized, double-blind, placebo-controlled trials. Archives of Internal Medicine 2012; 172(9): 686-694

**PubMedID**
22493407

**DOI**
10.1001/archinternmed.2012.262
Original Paper URL

Indexing Status
Subject indexing assigned by NLM

MeSH
Cardiovascular Diseases /prevention & control; Cause of Death; Dietary Supplements; Docosahexaenoic Acids /therapeutic use; Double-Blind Method; Eicosapentaenoic Acid /therapeutic use; Fatty Acids, Omega-3 /therapeutic use; Female; Humans; Male; Randomized Controlled Trials as Topic; Secondary Prevention; Stroke /prevention & control; Treatment Outcome

AccessionNumber
12012017448

Date bibliographic record published
16/04/2012

Date abstract record published
20/04/2012

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.