Review: n-3 fatty acids do not reduce mortality, cardiovascular events, or cancer in patients at risk for cardiovascular disease

Hooper L, Thompson RL, Harrison RA, et al. **Omega 3 fatty acids for prevention and treatment of cardiovascular disease.** Cochrane Database Syst Rev. 2004;(4):CD003177.

QUESTION

In patients at risk for cardiovascular (CV) disease, do dietary or supplemental n-3 fatty acids (n-3FAs) reduce all-cause mortality and CV events?

METHODS

Data sources: MEDLINE (1998 to February 2002), EMBASE/Excerpta Medica (1998 to February 2002), National Research Register (to February 2002), Cochrane Library (to 2002, Issue 1), SIGLE, bibliographies of relevant studies, and contacting experts.

Study selection and assessment: Randomized controlled trials (RCTs) that included adults ≥ 18 years of age with any risk for CV disease, and compared dietary advice or dietary supplementation to promote n-3FA intake with a control intervention (usual diet, no advice, no supplementation, or placebo). Foods or supplements included oily fish (e.g., mackerel); fish oils; linseed, canola, perilla, purslane, mustard seed, candlenut, stillingia, and walnut as a food, oil, or spread; refined eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and α-linolenic acids, and concentrated fish oils. Study quality was assessed for allocation concealment and blinding of patients, providers, and outcome assessors.

Outcomes: All-cause mortality, composite endpoint of CV events (fatal and nonfatal myocardial infarction, angina, stroke, heart failure, peripheral vascular disease, sudden death, and nonscheduled CV interventions [coronary artery bypass surgery or angioplasty]), cancer, and adverse events.

MAIN RESULTS

48 RCTs (n = 36 913) met the selection criteria. Of 44 RCTs that evaluated dietary supplements, 36 RCTs used fish-based n-3FA capsules (0.4 to 7 g/d), and 5 RCTs used plant-based n-3FAs (α-linolenic acid). Allocation concealment was adequate in 34 RCTs, unclear in 12 RCTs, and not done in 2 RCTs. Blinding was done in patients (30 RCTs), providers (33 RCTs), and outcome assessors (44 RCTs). The n-3FA and control groups did not differ for all-cause mortality, combined CV events, or cancer (Table). More patients who received n-3FAs dropped out because of side effects (relative risk [RR] 1.62, 95% CI 1.10 to 2.40) than did those who received the control intervention. Specific side effects were bad or fishy taste or belching (RR 3.63, CI 1.97 to 6.67), nausea (RR 3.88, CI 1.42 to 10.58), and any gastrointestinal side effect (RR 1.59, CI 1.14 to 2.21).

CONCLUSION

In patients at risk for cardiovascular (CV) disease, supplemental n-3 fatty acids do not reduce all-cause mortality, combined CV events, or cancer.

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For correspondence: Ms. L. Hooper, University Dental Hospital of Manchester, Manchester, England, UK. E-mail lee.hooper@man.ac.uk. ■

n-3 fatty acids (n-3FAs) vs usual diet, no advice, no supplementation, or placebo (control) in patients at risk for cardiovascular (CV) disease at 6 to > 48 months*

Outcomes	Number of trials (n)	Weighted event rates		RRR (95% CI)	NNT
		n-3FA	Control		
All-cause mortality	44 (36 195)	5.8%	5.8%	13% (–3 to 27)	Not significant
Combined CV events	31 (35 140)	7.4%	7.4%	5% (–12 to 18)	Not significant
Cancer	10 (17 433)	2.2%	2.2%	7% (–12 to 30)	Not significant

*Abbreviations defined in Glossary; weighted event rates, RRR, NNT, and CI calculated from data in article using a random-effects model.

COMMENTARY

A previous meta-analysis (1) and a recent comprehensive systematic review (2) that examined the effect of n-3FAs on coronary heart disease (CHD) concluded that higher intakes of n-3FAs, and fish oil fatty acids in particular, lower the risk for death and CHD events. The Nutrition Committee of the American Heart Association (AHA) has recommended 1 g daily of fish oil (EPA and DHA) from supplements or fatty fish for secondary CHD prevention, and 2 servings of fatty fish per week for primary CHD prevention.

In contrast, the meta-analysis by Hooper and colleagues concluded that n-3FAs do not lower mortality or CV risk. The negative results were driven by the inclusion of a single secondary CHD prevention study (DART 2), which tested the effect of fish (2 portions/wk) or fish oil (3 g of EPA/wk) in men with angina. When the study judged to be of low quality was excluded, heterogeneity among the RCTs was eliminated and the meta-analytic results were similar to those of other studies. Even with the inclusion of DART 2, the authors found modest (albeit nonsignificant) decreases in CV events and total mortality with high intakes of n-3FAs. Of note, the authors also excluded the Lyon Diet Heart Study, which was an important secondary CHD prevention trial investigating α-linolenic acid plus other dietary changes with results that showed marked reductions in recurrent CHD events.

Despite their findings, Hooper and colleagues do not recommend reductions in n-3FAs intake, and all recent reviews conclude that fish oil fatty acids are safe for most adults. Based on the totality of the evidence, the AHA recommendations still seem reasonable.

Joel A. Simon, MD, MPH
San Francisco Veterans Affairs Medical Center
University of California, San Francisco
San Francisco, California, USA

References

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3. **Kris-Etherton PM, Harris WS, Appel LJ, et al.** Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Circulation. 2002;106: 2747-57.