

Review: Omega-3 polyunsaturated fatty acid supplements do not reduce major cardiovascular events in adults

Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. *JAMA*. 2012;308:1024-33.

Clinical impact ratings: **GM** ★★★★★★☆☆ **C** ★★★★★★☆☆

Question

Do omega-3 polyunsaturated fatty acids (PUFAs) reduce risk for major cardiovascular (CV) events in adults?

Review scope

Included studies compared omega-3 PUFAs, in diet or supplement form, with another diet or placebo in adults in primary or secondary settings of CV disease prevention; and had treatment duration ≥ 1 year. Outcomes were all-cause and cardiac mortality, sudden death, myocardial infarction (MI), and stroke.

Review methods

MEDLINE, EMBASE/Excerpta Medica, and Cochrane Central Register of Controlled Trials to August 2012, and reference lists of relevant systematic reviews were searched for randomized controlled trials (RCTs). 20 RCTs ($n = 68\ 680$, median age 68 y, median treatment duration 2 y) met inclusion criteria: 2 used omega-3-targeted dietary counseling, and 18 compared omega-3 supplements (mean omega-3 dose 1.51 g/d) with placebo (16 RCTs), standard care (1 RCT), or no treatment (1 RCT). 13 RCTs were done in secondary prevention settings, 4 in mixed primary/secondary prevention settings, and 3 in patients with implantable cardioverter defibrillators. 14 studies reported allocation concealment, 16 were double-blind, and 16 used intention-to-treat analysis.

Main results

Meta-analyses showed that omega-3 PUFA supplements did not reduce all-cause or cardiac mortality, sudden death, MI, or stroke more than control treatment (Table). In 2 RCTs comparing omega-3-targeted dietary counseling with non-fish oil diets, results were inconsistent for both all-cause mortality ($n = 3114$, relative risk [RR] 1.15, 95% CI 0.98 to 1.34 in one trial; $n = 2033$, RR 0.73, CI 0.56 to 0.93 in the other) and cardiac mortality ($n = 3114$, RR 1.27, CI 1.03 to 1.57 in one trial; $n = 2033$, RR 0.67, CI 0.51 to 0.89 in the other).

Conclusion

Omega-3 polyunsaturated fatty acid supplements do not reduce major cardiovascular events more than control treatment in adults.

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Commentary

In this most recent meta-analysis of the preventive effect of marine-derived omega-3 PUFAs (dietary fish or fish oil supplements), Rizos and colleagues examined 5 major CV outcomes in 20 trials, including the latest, large, negative primary prevention trial (ORIGIN) in persons with any glucose intolerance. Discarding 2 dietary trials (DART 1 and 2) that showed opposite results for cardiac death and mortality, Rizos and colleagues' results focused on 18 trials of fish oil supplements, 7 of which had > 1000 participants in each of the PUFA and placebo groups.

In 2002, the American Heart Association recommended that persons with coronary heart disease (CHD) eat 2 fish meals per week for secondary prevention of further CV events (1). In 1989, a nutritional study (DART 1) had shown that patients with acute MI randomly allocated to 2 fish meals per week or 3 fish oil pills per day had 29% lower all-cause death (predominantly ischemic heart disease deaths). In 1999, the GISSI-Prevenzione trial, a 3.5-year open-label, randomized trial of fish oil supplementation within 3 months after acute MI, found supplements reduced CV death by 17% and ischemic CV death by 26%. The largest trial of fish oil supplementation, JELIS, an open-label, Japanese primary and secondary prevention trial, found decreased major coronary events, driven by subanalysis in persons with CHD.

Meanwhile, preventive treatment of CHD with statins, antithrombotics, β -blockers, and angiotensin-converting enzyme inhibitors has been increasing, possibly explaining the lack of effect of fish oils in 2 recent post-MI/secondary prevention trials lasting 1 (OMEGA) and 3.4 (Alpha-OMEGA) years. Much larger trials may now be needed to show any residual preventive effect of fish oils. This will inflate the numbers needed to treat to prevent 1 additional event and the number of fish that need to be killed, worsening the ecological disaster of the rapidly decreasing world fish population—50% of which was estimated to be fully exploited in 2005 (2). Given this and other negative meta-analyses, our job should be to stop highly marketed fish oil supplementation in all of our patients and encourage long-term use of proven, more powerful, less expensive preventive medications now available to us.

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References

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Omega-3 polyunsaturated fatty acid supplements vs placebo, standard care, or no treatment (control) in adults*

Outcomes	Number of trials (n)	Weighted event rates		RRR (95% CI)	NNT
		Omega-3	Control		
All-cause mortality	17 (63 279)	9.8%	10.2%	4% (-2 to 9)	Not significant
Cardiac mortality	13 (56 407)	5.8%	6.4%	9% (2 to 15)	Not significant†
Sudden death	7 (41 751)	2.3%	2.6%	13% (-1 to 25)	Not significant
Myocardial infarction	13 (53 875)	2.9%	3.3%	11% (-4 to 24)	Not significant
				RRI (CI)	NNH
Stroke	9 (52 589)	2.9%	2.8%	5% (-7 to 18)	Not significant

*Abbreviations defined in Glossary. Weighted event rates, RRR, RRI, and CI calculated from relative risks and control event rates in article using a random-effects model.

†Not statistically significant after adjustment for multiple comparisons.