

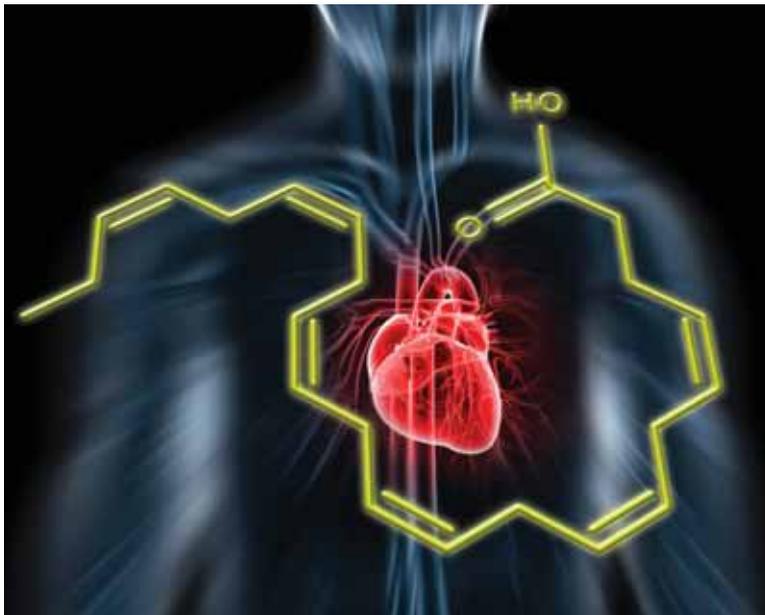
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Marine Omega-3 Fatty Acids and Cardiovascular Disease

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The public has embraced omega-3 fatty acids with enthusiasm. Sales of omega-3 supplements in the United States have risen more than 20% in recent years to make these pills the fifth best-selling dietary supplement.



Omega-3 fatty acids—EPA (eicosapentaenoic acid), DHA (docosahexaenoic acid), and ALA (alpha-linolenic acid)—are receiving increasing attention in the medical literature and popular press. EPA and DHA are found primarily in fish (and hence are often called “marine omega-3s”), whereas ALA is found in plant sources such as flaxseed, walnuts, and canola and soybean oils. To date, the scientific evidence for health benefits is

much stronger for the marine omega-3s than for ALA.

Indeed, recent observational studies strongly support the view that fish is a food that provides cardiovascular benefits.¹ In meta-analyses of large cohort studies, participants who ate fish 5 or more times per week were 21% less likely to have a nonfatal myocardial infarction (MI), 38% less likely to die of coronary heart disease (CHD), and 31% less likely to suffer a stroke than those who rarely ate fish.^{2,3}

In large, unblinded, randomized clinical trials of patients with CHD or at elevated risk for it, fish-oil supplements confer clear cardiovascular benefits. Among 11,324 MI patients who participated in the GISSI-Prevenzione trial in Italy, fish oil (EPA+DHA, 850 mg/day) lowered their risk for cardiovascular death, stroke, or recurrent MI by 20% (95% CI, 5-32) after 3.5 years.⁴ Among 18,645 patients on lipid-lowering drugs

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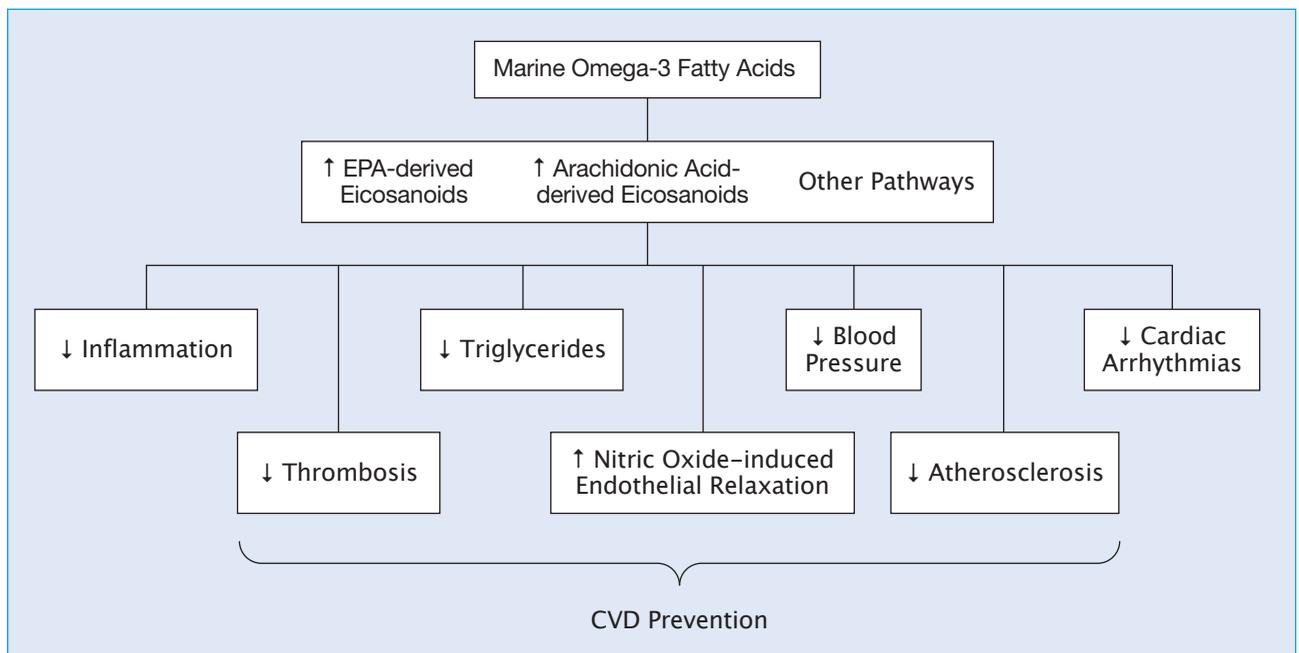


FIGURE. Mechanisms by which marine omega-3 fatty acids may lower cardiovascular risk.

(ie, statins) in the JELIS trial in Japan, fish oil (EPA, 1.8 g/day) led to a 19% reduction (95% CI, 5-31) in major coronary events after 4.6 years.⁵

With respect to ALA, some observational studies suggest a role in prevention of sudden cardiac death and possibly other cardiovascular outcomes, but results from large-scale, long-term, primary or secondary prevention trials that directly test this hypothesis are sparse.^{6,7} The recently completed double-blinded Alpha-Omega Study, in which 4,837 Dutch women and men with a history of MI were randomized to 40 months of ALA (2 g/day), EPA+DHA (400 mg/day), both, or placebo, found that ALA supplementation did not lower risk for clinical cardiovascular events, although the findings in women appeared promising.⁸ This trial also reported a null result for EPA+DHA, but the dose tested was low. Although the human body converts some ALA to EPA and then to DHA, such conversion is minimal—most studies indicate that less than 5% of ALA is converted to EPA, with even lower subsequent conversion to DHA.⁹

Cardioprotective Effects

Cardioprotective effects of the marine omega-3s include their ability to reduce the risk for atrial and ventricular arrhythmias; keep inflammation and triglycerides in check; promote nitric oxide-induced endothelial relaxation; and possibly slow atherosclerosis and lower thrombosis risk (Figure).⁹⁻¹⁴ A daily dose of 1 g of EPA+DHA appears sufficient to produce most of these benefits, although triglyceride lowering requires higher doses.¹

The anti-inflammatory effect of marine omega-3s may also help to prevent or treat rheumatoid arthritis,^{15,16} inflammatory bowel diseases,¹⁷ depression,¹⁸ and cognitive decline.^{19,20} Marine omega-3s also favorably affect the function of neuron membranes and the production of neurotransmitters, which may further account for their protective effect on the brain.

Recommendations

For heart protection, current recommendations call for adults to eat fish, particularly dark oily fish such as salmon, tuna,

herring, trout, sardines, or mackerel, at least twice per week,²¹ which is roughly equivalent to 400 to 500 mg of EPA+DHA per day. Patients with CHD should aim for a daily dose of 1 g of EPA+DHA.²¹ For some individuals, including those worried about mercury and polychlorinated biphenyls (PCBs) in fish, fish-oil supplements may be a preferable way to meet the recommendations.

Clinicians should counsel patients to read over-the-counter (OTC) supplement labels carefully. The amount of EPA+DHA in a fish-oil capsule is typically only about one-third of the fish-oil dose listed on the front of the bottle. In other words, a bottle advertising 1,000 mg of fish oil likely contains 300 mg of EPA+DHA; the fine print on the back of the bottle lists the actual amount of marine omega-3s.

To reassure patients who are concerned about possible contaminants, it is helpful to know that a *Consumer Reports* test of 16 major fish-oil brands found that none contained significant amounts of mercury, PCBs, or dioxin.²² Health care providers should caution patients against excessive consumption of EPA+DHA, as 3 g or more per day may trigger bleeding, worsen glycemia in patients with impaired glucose tolerance, and raise low-density lipoprotein cholesterol in patients with hypertriglyceridemia.¹⁰ Nevertheless, some patients with elevated triglycerides (≥ 500 mg/dL) may be appropriate candidates for the prescription fish-oil supplement Lovaza[®] (omega-3-acid ethyl esters), which delivers more concentrated doses of the marine omega-3s than that found in OTC formulations.

Conclusion

The public has embraced omega-3s with enthusiasm. Sales of omega-3 supplements in the United States have risen more than 20% in recent years to make these pills the fifth best-selling dietary supplement.²³ In addition, an increasing number of foods are omega-3 fortified; more than 1,200 such products were launched in 2006 alone.²³ (Many of these products contain ALA rather than EPA+DHA; thus,

clinicians may wish to advise patients to check food package labels because the scientific evidence to date does not support the implied advertising message that added vegetable omega-3s offer a significant cardiovascular benefit.)

Despite this popularity, there have been no large-scale randomized trials of omega-3s in the primary prevention of cardiovascular disease (CVD) and other chronic diseases in a general population that has been selected only on the basis of age and not on the basis of other vascular risk factors such as diabetes or high cholesterol. It should also be noted that the secondary prevention trials that showed benefits did not utilize a double-blind design, so that the possibility of confounding cannot be ruled out.

We and our colleagues are conducting a large double-blinded trial that is expected to provide a definitive assessment of both the benefits and risks of supplemental EPA+DHA. This trial, known as the **VITamin D and Omega-3 Trial (VITAL)** and funded by the National Institutes of Health, is testing approximately 1 g per day of marine omega-3s for the prevention of CVD, cancer, and other conditions in 20,000 initially healthy US women aged 55 and older and men aged 50 and older. (The trial is also testing supplemental vitamin D₃, which is thought to protect against many of the same conditions as the omega-3s.) For eligibility criteria, visit www.vitalstudy.org or call 1-800-388-3963.

References

1. Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health: evaluating the risks and the benefits. *JAMA*. 2006;296(15):1885-1899.
2. He K, Song Y, Daviglius ML, et al. Accumulated evidence on fish consumption and coronary heart disease mortality: a meta-analysis of cohort studies. *Circulation*. 2004;109(22):2705-2711.
3. He K, Song Y, Daviglius ML, et al. Fish consumption and incidence of stroke: a meta-analysis of cohort studies. *Stroke*. 2004;35(7):1538-1542.
4. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet*. 1999;354(9177):447-455.

5. Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet*. 2007;369(9567):1090-1098.
6. Harris WS. Alpha-linolenic acid: a gift from the land? *Circulation*. 2005;111(22):2872-2874.
7. Wang C, Harris WS, Chung M, et al. n-3 Fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. *Am J Clin Nutr*. 2006;84(1):5-17.
8. Kromhout D, Giltay EJ, Geleijnse JM, for the Alpha Omega Trial Group. n-3 fatty acids and cardiovascular events after myocardial infarction. *N Engl J Med*. 2010;363(21):2015-2026.
9. Harris WS, Miller M, Tighe AP, Davidson MH, Schaefer EJ. Omega-3 fatty acids and coronary heart disease risk: clinical and mechanistic perspectives. *Atherosclerosis*. 2008;197(1):12-24.
10. Kris-Etherton PM, Harris WS, Appel LJ, for the American Heart Association, Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation*. 2002;106(21):2747-2757.
11. Robinson JG, Stone NJ. Antiatherosclerotic and anti-thrombotic effects of omega-3 fatty acids. *Am J Cardiol*. 2006;98(4A):39i-49i.
12. Reiffel JA, McDonald A. Antiarrhythmic effects of omega-3 fatty acids. *Am J Cardiol*. 2006;98(4A):50i-60i.
13. Lee JH, O'Keefe JH, Lavie CJ, Marchioli R, Harris WS. Omega-3 fatty acids for cardioprotection. *Mayo Clin Proc*. 2008;83(3):324-332.
14. Mori TA, Beilin LJ. Omega-3 fatty acids and inflammation. *Curr Atheroscler Rep*. 2004;6(6):461-467.
15. Rosell M, Wesley AM, Rydin K, Klareskog L, Alfredsson L, for the EIRA study group. Dietary fish and fish oil and the risk of rheumatoid arthritis. *Epidemiology*. 2009;20(6):896-901.
16. Kremer JM. n-3 fatty acid supplements in rheumatoid arthritis. *Am J Clin Nutr*. 2000;71(1 Suppl):349S-351S.
17. Calder PC. Polyunsaturated fatty acids, inflammatory processes and inflammatory bowel diseases. *Mol Nutr Food Res*. 2008;52(8):885-897.
18. Freeman MP, Hibbeln JR, Wisner KL, et al. Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. *J Clin Psychiatry*. 2006;67(12):1954-1967.
19. Issa AM, Mojica WA, Morton SC, et al. The efficacy of omega-3 fatty acids on cognitive function in aging and dementia: a systematic review. *Dement Geriatr Cogn Disord*. 2006;21(2):88-96.
20. Schaefer EJ, Bongard V, Beiser AS, et al. Plasma phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer disease: the Framingham Heart Study. *Arch Neurol*. 2006;63(11):1545-1550.
21. Lichtenstein AH, Appel LJ, Brands M, et al. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. *Circulation*. 2006;114(1):82-96.
22. Consumer Reports. Omega-3 oil: fish or pills? 2003;68(7):30-32.
23. Stipp D. Fish-oil doses can be hard to swallow. *Wall Street Journal*. January 8, 2008;D1-D2.

For a **PATIENT HANDOUT** on marine omega-3 fatty acids, see page 49.

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274

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