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Update on omega-3 fatty acids and CV protection

The observation that populations with high intakes of omega-3 (n-3) polyunsaturated fatty acids (such as the Eskimos) have low rates of heart disease has increased interest in the possible benefit of fish oils. This *Heartbeat* will review the benefits, guidelines for use, and protective effect of n-3 fatty acid intake on cardiovascular (CV) health based on a recent Mayo Clinic update.[1] After briefly summarizing current scientific evidence supporting the benefits of n-3 fatty acids to CV health, we will highlight indications and recommended guidelines for administration and dosing.

The American Heart Association (AHA) has endorsed the use of n-3 fatty acids for secondary prevention of CV events in people with documented coronary artery disease (CAD).[2] The recommendation calls for approximately 1 g/d of a mixture of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). The AHA statement identifies oily fish as the ideal source, but fish oil (in capsules or liquid form) is also an acceptable option.

In this review, the term *n-3 fatty acids* refers only to DHA and EPA because the evidence for a CV benefit from the plant-derived omega-3 fatty acids (flaxseed and flaxseed oil, canola oil, soybean oil, and nuts)—alpha-linolenic acid—is much weaker than it is for DHA and EPA.[3] Current recommendations are that both DHA and EPA, either from fish or from supplements, be consumed in approximately equal amounts.

This is the first time that the AHA has recommended a nutritional supplement for prevention of CAD. The recommendation is supported by a large and growing body of evidence supporting the CV benefits and triglyceride-lowering effects of n-3 fatty acids.

The most compelling evidence for the CV benefit provided by n-3 fatty acids comes from three large controlled trials of 32,000 participants randomized to receive n-3 fatty acid supplements containing DHA and EPA or to act as controls.[4] These trials showed reductions in CV events of 19% to 45%. Two major randomized clinical trials on secondary CV disease prevention, GISSI and the Japan EPA Lipid Intervention Study (JELIS), have since demonstrated significant reduced mortality rates and CV events associated with doses of 850 mg and 1.8 g/day of DHA and EPA—in addition to optimal medical treatment with standard drug therapy (eg statins, aspirin, β-blockers and angiotensin-converting enzyme inhibitors).

In the GISSI trial, 4-month treatment reduced sudden cardiac death (SCD) in post MI patients by 45% and reduced death from any cause by 28%.[5] Reduction in SCD with fish oil is more likely to be seen in populations with higher prevalence of SCD. JELIS included patients without documented CAD who showed a non-significant 18% reduction in CV events vs a significant 19% reduction in those with underlying CAD.[6] Interestingly these results are seen on people who normally eat large amounts of fish.

This data supports the suggestion that we should increase intake of n-3 fatty acids (DHA and EPA), whether from dietary sources or fish oil supplements, especially in those with or at risk for CAD. The target DHA and EPA consumption levels are about 1 g/d for those with known CAD and at least 500 mg/d for primary prevention (those without disease). Patients with hypertriglyceridemia benefit from treatment with 3 to 4 g/d of DHA and EPA, a dosage that lowers triglyceride levels by 20% to 50%. Although 2 meals of oily fish per week can provide 400 to 500 mg/d of DHA and EPA, secondary prevention patients and those with hypertriglyceridemia must use fish oil supplements if they are to reach 1 g/d and 3 to 4 g/d of DHA and EPA, respectively.

The FDA has approved an n-3 fatty acid ethyl ester formulation, at a dosage of 4.0 g/d (Lovaza), for the treatment of very high triglyceride levels. In patients with severely elevated triglyceride levels (> 500 mg/dL), 3 to 4 g/day typically lowers triglyceride levels by 45%. When added to baseline statin therapy in patients with triglyceride levels of 200 to 499 mg/dL, this dosage lowers triglyceride levels by an additional 23% to 29%. The most commonly observed adverse effects are nausea, gastrointestinal upset, and a "fishy burp." Steps to reduce burping and improve adherence include taking the omega-3 fatty acid at bedtime or with meals and keeping the fish oil capsules in the freezer. Fatty acid supplements can be taken at any time, in full or divided doses, without raising concerns about interactions with any medications.

Mechanisms of Action

N-3 fatty acids seem to confer CV benefits largely through DHA and EPA enrichment of membrane phospholipids which can increase arrhythmic thresholds, reduce blood pressure, improve arterial and endothelial function, reduce platelet aggregation, decrease triglycerides and favorably affect autonomic tone (Table 1).

Table 1. Possible n-3 fatty acid benefits (*low dose)

Anti-arrhythmic effects*	**Decreased BP**
Modulation of autonomic function*	**Anti-inflammatory**
Decreased platelet Aggregation	**Plaque stabilization**
Vasodilatation	**Decreased TG**

Evidence suggests that lowering systolic blood pressure by as little as 2 mm Hg can yield reductions of 4% in mortality due to CAD.[7]

"Combination therapy with n-3 fatty acids and a statin is a safe and effective way to improve lipid levels and cardiovascular prognosis beyond the benefits provided by statin therapy alone," the reviewers write. "Blood DHA and EPA levels could one day be used to identify patients with deficient levels and to individualize therapeutic recommendations."

Over-the counter Formulations

- 1 capsule of over-the-counter (OTC) fish oil is equivalent to 300 mg of EPA and DHA.
- 1 tablespoon of standard liquid fish oil taken twice weekly provides the same amount of omega-3 fatty acids as 6 oz of salmon twice weekly (500 mg/day of EPA and DHA).

Conclusions/Recommendations

- A combination of EPA and DHA n-3 fatty acids is beneficial for primary and secondary CAD protection and risk reduction for SCD, arrhythmias, and treatment of hypertriglyceridemia. Omega-3 fatty acids can be used safely in conjunction with appropriate statin treatment and therapeutic lifestyle changes in anyone with known CAD or

high-risk for CAD to improve CV prognosis.

- The recommended dosages for primary CAD protection is 1 to 2 capsules of OTC EPA with DHA daily equivalent to 2 meals of oily fish per week or 1 tablespoon of standard liquid fish oil taken twice weekly—approximately 500mg, which can raise red blood cell DHA and EPA levels by at least 50%. Even half this intake has been suggested as a cardio-protective target in the general population.
- For secondary prevention patients and those with hypertriglyceridemia, supplements are recommended—3 to 4 capsules of OTC EPA with DHA or 1 gm of Lovaza for patients with known CAD. This recommendation is based on GISSI.
- Hypertriglyceridemia treatment requires 10 to 14 capsules of OTC EPA with DHA or 4 gm of Lovaza daily.

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