Public Health Implications of Recent Clinical Evidence on Omega-3 Fatty Acids and Cardiovascular Disease

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Faculty

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Session #1: Making Sense of Omega-3 Headlines: Recent Evidence on Cardiovascular Outcomes and Public Health Implications *(June 6)*

Session #2: Public Health Implications of Recent Clinical Evidence on Omega-3 Fatty Acids and Cardiovascular Disease *(June 23)*

Summary of Session #1 Presentations

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Relevant Disclosures

- Seafood Nutrition Partnership - Member, Scientific Nutrition Advisory Council

Overview – Summary of:

Penny M. Kris-Etherton, PhD, RD, FAHA, FNLA, FASN, CLS - History of Omega-3 Recommendations in Cardiovascular Health and Disease

JoAnn E. Manson, MD, MPH, DrPH, FACP - How VITAL are Omega-3s for Heart Health? The VITAL Trial and Updated Meta-Analysis

Kevin C. Maki, PhD, CLS, FNLA, FTOS, FACN - Recent Clinical Evidence on EPA and DHA for CV Risk Reduction: Clinical Considerations

The FORCE Study – Exciting New Omega-3 Research

Three Updated AHA Science Advisories

- Siscovick DS et al. **Omega-3 Polyunsaturated Fatty Acid (Fish Oil) Supplementation and the Prevention of Clinical Cardiovascular Disease**: A Science Advisory From the American Heart Association. Circulation. 2017;135:e867-e884.

- Rimm EB et al. **Seafood Long-Chain n-3 Polyunsaturated Fatty Acids and Cardiovascular Disease**: A Science Advisory From the American Heart Association. Circulation. 2018;138:e35-e47.

- Skulas-Ray AC et al. **Omega-3 Fatty Acids for the Management of Hypertriglyceridemia**. A Science Advisory From the American Heart Association. Circulation. 2019;140:e673-e691.

AHA SCIENCE ADVISORY

Omega-3 Polyunsaturated Fatty Acid (Fish Oil) Supplementation and the Prevention of Clinical Cardiovascular Disease

A Science Advisory From the American Heart Association

ABSTRACT: Multiple randomized controlled trials (RCTs) have assessed the effects of supplementation with eicosapentaenoic acid plus docosahexaenoic acid (omega-3 polyunsaturated fatty acids, commonly called fish oils) on the occurrence of clinical cardiovascular diseases. Although the effects of supplementation for the primary prevention of clinical cardiovascular events in the general population have not been examined, RCTs have assessed the role of supplementation in secondary prevention among patients with diabetes mellitus and prediabetes, patients at high risk of cardiovascular disease, and those with prevalent coronary heart disease. In this scientific advisory, we take a clinical approach and focus on common indications for omega-3 polyunsaturated fatty acid supplements related to the prevention of clinical cardiovascular events. We limited the scope of our review to large RCTs of supplementation with major clinical cardiovascular disease end points; meta-analyses were considered secondarily. We discuss the features of available RCTs and provide the rationale for our recommendations. We then use existing American Heart Association criteria to assess the strength of the recommendation and the level of evidence. On the basis of our review of the cumulative evidence from RCTs designed to assess the effect of omega-3 polyunsaturated fatty acid supplementation on clinical cardiovascular events, we update prior recommendations for patients with prevalent coronary heart disease, and we offer recommendations, when data are available, for patients with other clinical indications, including patients with diabetes mellitus and prediabetes and those with high risk of cardiovascular disease, stroke, heart failure, and atrial fibrillation.

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On behalf of the American Heart Association Nutrition Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Epidemiology and Prevention; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology

Treatment is reasonable for:

- Secondary prevention of CHD and SCD among patients with prevalent CHD
- Secondary prevention of outcomes in patients with heart failure

Circulation. 2017;135:e867-e884.

Circulation

AHA SCIENCE ADVISORY

Seafood Long-Chain n-3 Polyunsaturated Fatty Acids and Cardiovascular Disease

A Science Advisory From the American Heart Association

ABSTRACT: Since the 2002 American Heart Association scientific statement "Fish Consumption, Fish Oil, Omega-3 Fatty Acids, and Cardiovascular Disease," evidence from observational and experimental studies and from randomized controlled trials continues to emerge to further substantiate the beneficial effects of seafood long-chain n-3 polyunsaturated fatty acids and cardiovascular disease. A recent American Heart Association science advisory addressed the specific effect of n-3 polyunsaturated fatty acid supplementation on clinical cardiovascular events. This American Heart Association science advisory extends that review and offers further support to include n-3 polyunsaturated fatty acids from seafood consumption. Several potential mechanisms have been investigated, including antiarrhythmic, anti-inflammatory, hematologic, and endothelial, although for most, longer-term dietary trials of seafood are warranted to substantiate the benefit of seafood as a replacement for other important sources of macronutrients. The present science advisory reviews this evidence and makes a suggestion in the context of the *2015–2020 Dietary Guidelines for Americans* and in consideration of other constituents of seafood and the impact on sustainability. We conclude that 1 to 2 seafood meals per week be included to reduce the risk of congestive heart failure, coronary heart disease, ischemic stroke, and sudden cardiac death, especially when seafood replaces the intake of less healthy foods.

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Recommendation:

- 1 to 2 seafood meals per week to reduce risk of CHF, CHD, ischemic stroke and sudden cardiac death

Circulation. 2018;138:e35–e47.

Circulation

AHA SCIENCE ADVISORY

Omega-3 Fatty Acids for the Management of Hypertriglyceridemia

A Science Advisory From the American Heart Association

ABSTRACT: Hypertriglyceridemia (triglycerides 200–499 mg/dL) is relatively common in the United States, whereas more severe triglyceride elevations (very high triglycerides, ≥500 mg/dL) are far less frequently observed. Both are becoming increasingly prevalent in the United States and elsewhere, likely driven in large part by growing rates of obesity and diabetes mellitus. In a 2002 American Heart Association scientific statement, the omega-3 fatty acids (n-3 FAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were recommended (at a dose of 2–4 g/d) for reducing triglycerides in patients with elevated triglycerides. Since 2002, prescription agents containing EPA+DHA or EPA alone have been approved by the US Food and Drug Administration for treating very high triglycerides; these agents are also widely used for hypertriglyceridemia. The purpose of this advisory is to summarize the lipid and lipoprotein effects resulting from pharmacological doses of n-3 FAs (>3 g/d total EPA+DHA) on the basis of new scientific data and availability of n-3 FA agents. In treatment of very high triglycerides with 4 g/d, EPA+DHA agents reduce triglycerides by ≥30% with concurrent increases in low-density lipoprotein cholesterol, whereas EPA-only did not raise low-density lipoprotein cholesterol in very high triglycerides. When used to treat hypertriglyceridemia, n-3 FAs with EPA+DHA or with EPA-only appear roughly comparable for triglyceride lowering and do not increase low-density lipoprotein cholesterol when used as monotherapy or in combination with a statin. In the largest trials of 4 g/d prescription n-3 FA, non–high-density lipoprotein cholesterol and apolipoprotein B were modestly decreased, indicating reductions in total atherogenic lipoproteins. The use of n-3 FA (4 g/d) for improving atherosclerotic cardiovascular disease risk in patients with hypertriglyceridemia is supported by a 25% reduction in major adverse cardiovascular events in REDUCE-IT (Reduction of Cardiovascular Events With EPA Intervention Trial), a randomized placebo-controlled trial of EPA-only in high-risk patients treated with a statin. The results of a trial of 4 g/d prescription EPA+DHA in hypertriglyceridemia are anticipated in 2020. We conclude that prescription n-3 FAs (EPA+DHA or EPA-only) at a dose of 4 g/d (>3 g/d total EPA+DHA) are an effective and safe option for reducing triglycerides as monotherapy or as an adjunct to other lipid-lowering agents.

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*This update was prepared in part by Dr Engler in her personal capacity. The opinions expressed in this article are the author's own and do not reflect the view of the National Institutes of Health, the US Department of Health and Human Services, the US Department of Defense, the US government, or the Uniformed Services University of the Health Sciences.

Key Words: AHA Scientific Statements ■ docosahexaenoic acid ■ eicosapentaenoic acid ■ fatty acids, omega-3 ■ hypertriglyceridemia ■ hypolipidemic agents ■ lipoproteins ■ triglycerides

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Main Points:

- When used to treat hypertriglyceridemia (200-499 mg/dL), n-3 FAs with EPA+DHA or with EPA-only appear roughly comparable for triglyceride lowering and do not increase LDL-C.
- In treatment of very high triglycerides (≥ 500 mg/dL) with 4 g/d, EPA+DHA agents reduce triglycerides by ≥30% with concurrent increases in LDL-C, whereas EPA-only did not raise LDL-C.

Circulation. 2019;140:e673-e691.

How *VITAL* are Omega-3s for Heart Health?

The VITAL Trial and Updated Meta-Analysis

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Conclusions

- ***VITAL Trial***
- **Omega-3s (1 g/d) supplementation did not significantly reduce the primary endpoint of major CVD events (or total cancer).**
- **Omega-3s: ↓ Total MI by 28% (nominal p-value=0.003, adjusted p=0.015); greatest ↓ in those with low fish intake and in African Americans. PCI, fatal MI, total CHD were also ↓.**

UPDATED META-ANALYSIS

- **↓ CHD/CVD with omega-3s, with dose-response gradient. (EPA may ↓ risk more than DHA.)**

Recent Clinical Evidence on EPA and DHA for CV Risk Reduction: Clinical Considerations

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Summary/Conclusions

- RCTs using low-dose (median 840 mg/d) EPA, or EPA and DHA, have produced mixed results, but, in total, support a small benefit (5-10%) for CHD risk, particularly fatal CHD
  - Evidence generally does not support a protective effect for stroke
  - Supplementation with long-chain omega-3 fatty acids is reasonable for CV health, especially for those who do not regularly consume oily fish (e.g., see VITAL)
- RCTs have shown significant benefits for higher-dosage EPA:
  - JELIS: 1.8 g/d EPA ethyl ester; 19% reduction in primary cardiac outcome vs. placebo; no benefit for stroke in primary prevention but a 20% risk reduction for stroke recurrence
  - REDUCE-IT: 4 g/d IPE (EPA ethyl ester) in subjects with elevated TG; 25% risk reduction in the primary outcome
- IPE is recommended by the NLA and other organizations for ASCVD risk reduction in select high- and very high-risk patients
  - The FDA approved an indication for IPE for ASCVD risk reduction for statin-treated patients with TG ≥150 mg/dL (only omega-3 agent with that indication)

CIRCULATING OMEGA-3 FATTY ACID LEVELS AND TOTAL AND CAUSE-SPECIFIC MORTALITY: PROSPECTIVE EVIDENCE FROM 16 COHORTS IN THE FATTY ACIDS AND OUTCOMES RESEARCH CONSORTIUM

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Presented at the AHA Spring Epi-Lifestyle Meeting, Phoenix, AZ March 2020

TABLE 2: ASSOCIATIONS OF OMEGA-3 FATTY ACIDS WITH RISK OF TOTAL AND CAUSE-SPECIFIC MORTALITY

HR (95% CI) Fatty acid	All-cause mortality (16 cohorts)	CVD Mortality (14 cohorts)	Cancer Mortality (14 cohorts)	Other mortality (13 cohorts)
ALA	0.98 (0.94, 1.01)	1.00 (0.94, 1.06)	0.97 (0.91, 1.04)	0.99 (0.94, 1.05)
EPA	**0.92 (0.89, 0.95)*** **	**0.90 (0.84, 0.96)** **	**0.90 (0.85, 0.96)** **	**0.92 (0.87, 0.97)** **
DPA	**0.87 (0.83, 0.91)*** **	**0.89 (0.82, 0.97)** **	**0.87 (0.80, 0.95)*** **	**0.87 (0.81, 0.94)*** **
DHA	**0.89 (0.86, 0.93)*** **	**0.88 (0.81, 0.95)** **	0.93 (0.86, 1.01)	**0.91 (0.85, 0.97)** **
EPA+DHA	**0.87 (0.84, 0.91)*** **	**0.87 (0.80, 0.94)** **	**0.89 (0.82, 0.96)** **	**0.88 (0.82, 0.94)*** **

Abbreviations: ALA, alpha-linolenic acid; CI, confidence interval; CVD, cardiovascular disease; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; and HR, hazard ratio.

Hazard ratio and confidence interval (CI) were expressed per a cohort-specific range of 10th to 90th percentile of each fatty acid.

*p<0.05, **p<0.01, ***p<0.001

Speakers

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Omega-3 Fatty Acids and Cardiovascular Disease: A Continuum of Nutrition and Medicine

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The DRI Process - Considerations for Assessing Omega-3 Fatty Acids and Cardiovascular Disease in the DRI Framework of Chronic Disease Risk