Omega-3 Fatty Acids and Cardiovascular Disease: Current State of the Evidence

Focus of This Summary

This is a summary of a systematic review that evaluated the recent evidence regarding the effects of omega-3 fatty acids (FAs), primarily from marine oil supplements, on clinical and selected intermediate cardiovascular (CV) outcomes (i.e., blood pressure, lipid concentrations) and the association of omega-3 FA dietary intake and biomarkers with CV outcomes. The systematic review included 147 articles published between 2000 and June 2015. Studies that analyzed levels of fish (or other food) consumption without exact quantification of omega-3 FA intake were excluded from this review. The full report, listing all studies, is available at *www.effectivehealthcare.ahrq.gov/omega-3/*. This summary is provided to assist in informed clinical decisionmaking. However, reviews of evidence should not be construed to represent clinical recommendations or guidelines.

Background

The first observation of a link between fish consumption and cardiovascular (CV) health was made in the late 1970s in a Greenland Eskimo population. This population exhibited a comparatively low rate of CV mortality and consumed a greater than average amount of fish. Since this original observation, there have been hundreds of studies conducted to evaluate the effect of omega-3 fatty acids (FAs) on cardiovascular disease (CVD), its risk factors, and its biomarkers.

The omega-3 FAs include eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), and alpha-linolenic acid (ALA). These are essential long-chain and very-long-chain polyunsaturated fatty acids that have many physiological effects, including inflammation regulation. EPA, DHA, and DPA are found in fish and other seafood (called dietary marine oils), as well as in supplements prepared from these foods (referred to here as marine oil supplements). ALA is found in walnuts, leafy green vegetables, and oils such as canola, soy, and flaxseed.

An original systematic review of omega-3 FAs was prepared by the Agency for Healthcare and Research Quality in 2004.[1,2] Based on the observational studies available at that time, several expert panels suggested that regular consumption of fish and seafood is associated with lower risk of coronary heart disease (CHD) and cardiac death. The recommendations were based on assumptions of benefits from EPA and DHA and their content in fish and seafood.

The current systematic review aimed to update the evidence in light of the more recent literature published on the topic and included both randomized controlled trials (RCTs) and observational studies. Studies that analyzed levels of fish (or other food) consumption without exact quantification of omega-3 FA intake were excluded.

Conclusions

Observational studies suggest possible benefits of dietary intake of marine oils (such as through consumption of fish) for CV death and total stroke (mainly ischemic stroke).

In contrast, there is high strength of evidence (SOE) from RCTs that marine oil supplements do not affect the risk of major adverse cardiac events (MACE), all-cause death, sudden cardiac death, revascularization, or high blood pressure (BP). Marine oil supplements also have no effect on the risk of atrial fibrillation (moderate SOE). Importantly, RCTs focused primarily on marine oil supplements, not on food sources.

Marine oil supplements affect several intermediate outcomes. First, they significantly lower triglycerides (TGs)—possibly having greater effects in higher doses and in people with higher baseline TGs. Second, they cause small increases in both high-density lipoprotein cholesterol (HDL-c) and low-density lipoprotein cholesterol (LDL-c). Finally, marine oil supplements produce small changes in the ratio of total cholesterol to HDL-c (high SOE).

Applicability of the Findings of This Review

- The RCTs of marine oil supplements that focused on clinical CVD outcomes were mostly conducted in populations at increased risk for CVD (e.g., with diabetes, cardiometabolic syndrome, hypertension, dyslipidemia, or nondialysis-dependent chronic kidney disease) or with established CVD (e.g., a history of myocardial infarction, angina, stroke, or arrhythmia).
- The RCTs of marine oil supplements that focused on intermediate CVD outcomes (e.g., BP, lipid concentrations) were conducted in three populations of interest—generally healthy, at increased risk for CVD, and with established CVD.
- Most observational studies examined associations between dietary intake of marine oils and biomarkers of various omega-3 FAs individually and in combination with regard to long-term CVD events and were conducted in generally healthy populations.

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Overview of Clinical Research Evidence on Dietary Marine Oils and Combined Marine Oil Supplements

- Some evidence based on observational studies indicated that dietary intake of marine oils (including from fish) may be associated with lower risk of CVD death and total stroke (mainly ischemic stroke) in healthy populations (●○○).
- In RCTs, marine oil supplements had no effect on the risk of MACE, death from all causes, sudden cardiac death, and coronary revascularization (●●●) and no effect on atrial fibrillation (●●○) in populations with established CVD or at increased risk for CVD (*see Table 1*).
- In RCTs, consumption of marine oil supplements was associated with a statistically significant decrease in the concentration of TGs and a small but statistically significant increase in the concentrations of HDL-c and LDL-c (●●●) in healthy populations and in those with established CVD or at increased risk for CVD (*see Table 1*).
- Consumption of marine oil supplements also decreased the ratio of total cholesterol to HDL-c in all three population subgroups—generally healthy, at increased risk for CVD, and with established CVD (●●●).

Strength of Evidence Scale[†]

High:	●●●	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate:	●●○	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low:	●○○	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
Insufficient:	○○○	Evidence either is unavailable or does not permit a conclusion.

[†] The overall evidence grade was assessed based on the ratings for the following domains: study limitations, directness, consistency, precision, and reporting bias. Other domains that were considered, as appropriate, included dose-response association, plausible confounding, and strength of association (i.e., magnitude of effect). For additional details on the methodology used to assess strength of evidence, please refer to: Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions—Agency for Healthcare Research and Quality and the Effective Health-Care Program. J Clin Epidemiol. 2010 May;63(5):513-23. PMID: 19595577.

Table 1: Summary of Key Findings—Dietary and Supplemented Marine Oil Omega-3 Fatty Acids: Effects on and Associations With Cardiovascular and Intermediate Outcomes

Note: *Most RCTs involved evaluations of supplements. Obs-intake represents observational studies of total dietary intake, and Obs-bio represents observational studies of fatty acid biomarkers.*

Omega-3 FA [*source*]	Outcome	Key Findings	Net Change or RCT Hazard Ratio (95% CI)	Number and Type of Studies	Strength of Evidence
Marine oil (EPA + DHA ± DPA)[a] [***mainly supplements or supplemented food***]	Major adverse cardiac events	No effect in RCTs No association in Obs-intake Unclear association in Obs-bio	0.96 (0.91, 1.02)	10 RCTs 3 Obs-intake 2 Obs-bio	●●●
	All-cause death	No effect in RCTs No association in Obs-intake	0.97 (0.92, 1.03)	17 RCTs 3 Obs-intake	●●●
	Sudden cardiac death	No effect in RCTs No association in Obs-intake	1.04 (0.92, 1.17)	9 RCTs 1 Obs-intake	●●●
	Coronary revascularization	No effect in RCTs No association in Obs-intake	NA	6 RCTs 1 Obs-intake	●●●
	Atrial fibrillation	No effect in RCTs Inconsistent findings in Obs-intake	NA	3 RCTs 3 Obs-intake	●●○
	BP (SBP, DBP)	No effect	SBP: 0.1 mmHg (−0.2, 0.4) DBP: −0.2 mmHg (−0.4, 0.5)	29 RCTs	●●●
	Triglycerides	Decrease	−24 mg/dL (−31, −18)	41 RCTs	●●●
	HDL-c	Increase	0.9 mg/dL (0.2, 1.6)	34 RCTs	●●●
	LDL-c	Increase	2.0 mg/dL (0.4, 3.6)	39 RCTs	●●●
	Total cholesterol:HDL-c ratio	Decrease	−0.2 (−0.3, −0.1)	11 RCTs	●●●

bio = biomarker; BP = blood pressure; CI = confidence interval; DBP = diastolic blood pressure; DHA = docosahexaenoic acid; DPA = docosapentaenoic acid; EPA = eicosapentaenoic acid; HDL-c = high-density lipoprotein cholesterol; intake = total dietary intake; LDL-c = low-density lipoprotein cholesterol; FA = fatty acid; NA = not available; Obs = observational study; RCT = randomized controlled trial; SBP = systolic blood pressure

[a] Studies that reported combined EPA and DHA were analyzed together with studies that reported combined EPA, DHA, and DPA.

Overview of Clinical Research Evidence on Individual Omega-3 Fatty Acid Supplements

- **DHA:** DHA supplements had no effect on BP or LDL-c (●●○). Evidence is low or insufficient to permit conclusions about the effects of or associations between DHA and any clinical outcome for CVD (*see Table 2*).
- **EPA or DPA:** Evidence was low or insufficient to permit conclusions about the benefit of EPA or DPA, individually, on any clinical or intermediate outcome for CVD.
- **ALA:** ALA supplements had no effect on BP or on concentrations of LDL-c, HDL-c, or TGs (●●○). Evidence was low or insufficient to permit conclusions about the effects of or associations between ALA and any clinical outcome for CVD (*see Table 2*).

Table 2: Summary of Key Findings—Individual Omega-3 Fatty Acid Supplements: Effects on and Associations With Intermediate Outcomes

Note: *Most RCTs involved evaluations of supplements. Obs-bio represents observational studies of fatty acid biomarkers.*

Omega-3 FA [*source*]	Outcome	Key Findings	Net Change or RCT Hazard Ratio (95% CI)	Number and Type of Studies	Strength of Evidence
Purified DHA [*supplements*]	BP (SBP, DBP)	No effect	NA	3 RCTs	●●○
	LDL-c	No effect	NA	3 RCTs	●●○
ALA [*supplements*]	BP (SBP, DBP)	No effect in RCTs No association in Obs-bio	NA	5 RCTs 1 Obs-bio	●●○
	LDL-c	No effect	NA	5 RCTs	●●○
	HDL-c	No effect	NA	5 RCTs	●●○
	Triglycerides	No effect	NA	5 RCTs	●●○

ALA = alpha-linolenic acid; bio = biomarker; BP = blood pressure; CI = confidence interval; DBP = diastolic blood pressure; DHA = docosahexaenoic acid; HDL-c = high-density lipoprotein cholesterol; LDL-c = low-density lipoprotein cholesterol; FA = fatty acid; NA = not available; Obs = observational study; RCT = randomized controlled trial; SBP = systolic blood pressure

Gaps in Knowledge and Limitations of the Evidence Base

- Numerous differences exist between RCTs and observational studies, making comparisons across the two study designs difficult. For example, the doses of marine oil supplements (EPA + DHA) in RCTs were often much higher than the highest dietary intake of marine oils reported for observational studies. Additionally, few RCTs of omega-3 FA supplements attempted to control for background dietary fish or omega-3 FA intake. The response to supplementation may be modified by the background intake.
- Studies assessed in this review used heterogeneous definitions for most CVD outcomes (e.g., MACE, CVD death, CHD death, CHD), which prohibited direct comparisons across studies in several instances.
- Few studies compared the dose, formulation, or source of omega-3 FAs, which are all factors that may influence their effectiveness.
- Long-term RCTs of marine oil supplements would need to be done to determine whether they can influence CV outcomes.
- Evidence on the effects of or associations with omega-3 FAs based on population, demographic features, or cointerventions (e.g., patients also taking cholestrol-lowering statins, aspirin, or diabetes medications) was insufficient.

What To Discuss With Consumers

- Dietary intake of marine oils (including from fish) appears to be associated with lower risk of CVD death and stroke in healthy populations.
- Consumption of marine oil supplements has no effect on health outcomes such as all-cause death, sudden cardiac death, MACE, coronary revascularization, or atrial fibrillation in patients with established CVD or at increased risk for CVD.
- Consumption of marine oil supplements lowers TG concentrations, raises HDL-c concentrations, and improves lipoprotein ratios (i.e., total cholesterol:HDL-c ratio) but also raises LDL-c concentrations.
- Consumers considering a marine oil supplement are advised to check the labels for information on quality and purity. The U.S. Pharmacopeial Convention (USP) seal verifies a supplement's quality.

Companion Resource for Patients

Omega-3 Fatty Acids and Cardiovascular Disease: A Review of the Research for Adults is a free companion to this clinician research summary. It can help individuals and their caregivers talk with their health care professionals about the potential benefits of omega-3 FAs for cardiovascular health.

Ordering Information

For electronic copies of this clinician research summary, the companion patient resource, and the full systematic review, visit *www.effectivehealthcare.ahrq.gov/omega-3/*. To order free print copies of the patient resource, call the AHRQ Publications Clearinghouse at 800-358-9295.

Source

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References

1. Balk E, Chung M, Lichtenstein A, et al. Effects of omega-3 fatty acids on cardiovascular risk factors and intermediate markers of cardiovascular disease. Evid Rep Technol Assess (Summ). 2004 Mar;(93):1-6. PMID: 15133887.
2. Wang C, Chung M, Lichtenstein A, et al. Effects of omega-3 fatty acids on cardiovascular disease. Evid Rep Technol Assess (Summ). 2004 Mar;(94):1-8. PMID: 15133888.

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