

What to Tell Your Patients: A Critical Review of the *JAMA Cardiology* Meta-Analysis “Associations of Omega-3 Fatty Acid Supplement use with Cardiovascular Disease Risks”

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ABSTRACT

Authors of a meta-analysis recently published in *JAMA Cardiology* concluded that omega-3 fatty acids have no significant association with fatal or nonfatal coronary heart disease or any major vascular events. This critical review examines participant profile, intervention dosage, bioavailability of intervention, and duration of therapy for the cited trials and determines that the conclusion of the meta-analysis is tentative at best.

Keywords: DHA; EPA; omega-3 fatty acids; cardiovascular health; heart disease

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INTRODUCTION

Authors of a recent meta-analysis published in *JAMA Cardiology* concluded that omega-3 fatty acids have no significant association with fatal or nonfatal coronary heart disease or any major vascular events.¹ A meta-analysis is only as meaningful as the trials from which it aggregates data. Factors such as participant profile, intervention dose, bio-availability of intervention, and duration of therapy potentially affect treatment efficacy. The present critical review examines each of these factors in the context of the *JAMA Cardiology* article to help clinicians understand the article’s limitations in order to better answer patients’ questions on the topic.

The article reviewed here is entitled “Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: meta-analysis of 10 trials involving 77,917 individuals.” It was published in *JAMA Cardiology* in early 2018. It is recommended that readers obtain the original article for access to tables and figures referenced here. In addition, please watch AV’s video critique (ichnfm.org/jama2018n3) on which this article is based.

PARTICIPANT PROFILE

The mean ages of participants in each of the cited studies ranged from 59 to 74 years old (*see* the table “Characteristics of Included Trials” in the original article). Some of the studies included patients who already had metabolic syndrome and cardiovascular disease. This means the study populations were older and included people who likely had a very different risk profile from patients who begin polyunsaturated fatty acid (PUFA) supplementation early in a disease process. At least one observational study that followed patients who were hospitalized for acute myocardial infarction showed that early use of ω -3 PUFAs was associated with a reduction in 1-year all-cause mortality and recurrent infarction.² It’s important, therefore, to understand the profile of participants enrolled in studies, because it affects the generalizations that can be made about an intervention. Furthermore, if a study population is largely unhealthy, it may raise

questions about whether intervention dosing is at therapeutic levels.

INTERVENTION DOSING

The authors of the meta-analysis state, “All eligible trials required use of supplements, but no minimum daily dose of EPA or DHA was specified.” The studies included used widely different doses of the intervention, ranging from 226 mg/d eicosapentaenoic acid (EPA) plus 150 mg/d docosahexaenoic acid (DHA) to 1150 mg/d EPA plus 800 mg/d DHA. In addition, one study used only EPA (1800 mg/d) and no DHA (*see* “DHA and EPA” section below for more commentary on this). The variability in dosage alone should have been seen as a limitation in the meta-analysis. Another trial³ (not included in the meta-analysis) showed that a *minimum* of 1 g/d of ω -3 PUFAs is required in patients after infarction for cardioprotective benefit. In fact, the American Heart Association issued a science advisory in 2017⁴ which concluded that ω -3 PUFA supplementation is potentially useful for patients with prevalent coronary heart disease, but that supplement doses of even approximately 1000 mg/d are “generally too low.” Using this recommendation as a guideline, 7 of 10 studies cited in this meta-analysis used subtherapeutic dosing.

Another concern regarding dosing in the studies included in this meta-analysis is that the studies did not follow the recommendations put forward in the Omega-3 Index (O3I). The O3I is a validated biomarker of ω -3 fatty acid tissue levels. It is calculated as the proportion of EPA and DHA in red blood cell membranes and is inversely associated with the risk of coronary heart disease and coronary mortality.⁵ An O3I greater than or equal to 8% has been recommended on the basis of its association with reduced risk of all-cause mortality, cardiac death, and sudden death in post-myocardial infarction patients. A randomized controlled trial that looked at the dose-response relationship of ω -3 PUFA supplementation found that no participant assigned to a dose less than or equal to 600 mg/d attained an O3I of 8%. Participants taking 900 mg/d achieved a

median O3I of 7.6%, whereas the 1800 mg/d group achieved a median O3I of 9.9%.⁶ On the basis of these findings, the authors concluded that an average *healthy* adult with a low O3I (4.3%) would require *at least* 1 g/d of both EPA and DHA for 5 months to attain a level of 8%. Only 3 of the 10 studies cited in the meta-analysis used appropriate dosing to potentially achieve 8% on the O3I, but none of these three used at least 1 g/d of both EPA and DHA, and one study used no DHA at all. Remember also that many participants in the cited studies were not healthy; therefore, arguably even higher doses would have been needed to reach therapeutic levels.

DHA AND EPA

Emerging evidence suggests that DHA may be a more potent modifier of cardiometabolic risk than EPA. This difference is reflected in O3I levels. One study found that the increase in O3I levels was significantly greater after supplementation with 2.7 g/d DHA than with a comparable dose of EPA.⁷ Seven of the ten studies cited in the *JAMA Cardiology* meta-analysis used doses of DHA that were less than or equal to 500 mg/d, with one of these studies using no DHA at all. The DHA content of the interventions in the included studies was likely insufficient to be associated with cardioprotection.

BIOAVAILABILITY OF INTERVENTION

Nine of the ten studies cited in this meta-analysis used synthetic or semisynthetic (ethyl ester) forms of ω -3 fatty acids instead of the more digestible triglyceride form. The 10th trial used only EPA without DHA. Evidence suggests that plasma levels of ω -3 PUFAs are more significant predictors of cardiovascular events than the amount consumed.^{8,9} The lack of efficacy observed in this meta-analysis could be explained in part by the possibility that the forms of intervention used had poor bioavailability.

DURATION OF TRIALS

Nutritional interventions generally have their effect over time via changes in structure and function. In contrast, pharmaceutical agents often work by the almost instantaneous blocking of enzymes and receptors. Obtaining meaningful dietary supplement and health relationship data, particularly for atherosclerotic cardiovascular disease outcomes, could take many years. It is possible that some trials included in the meta-analysis were too short to show an effect.

Box 1: *JAMA Cardiology* meta-analysis “Associations of Omega-3 Fatty Acid Supplement Use with Cardiovascular Disease Risks”: quick reference points to share with patients

This paper was a meta-analysis, which is the term for a statistical procedure that combines data from multiple studies to try to find similar effects. The authors of this meta-analysis concluded that there is no evidence to support using fish oil supplementation for protection with regard to cardiovascular disease risk. However, there were enough issues with the majority of the studies included in the meta-analysis to cast doubt on the authors’ conclusions:

- Many study participants already had cardiovascular disease, which is not equivalent to looking at the preventative effects of fish oil supplementation on cardiovascular disease or its ability to be protective if used soon after a heart attack.
- The dosages of fish oil supplements used in the different studies varied tremendously, with most of them too low to reasonably expect positive results.
- Most of the studies used fish oil supplements that were synthetic or semisynthetic and likely not as absorbable as natural forms.
- Some of the studies were too short in duration to expect to see a positive outcome.

CONCLUSION

Please watch AV’s video presentation, which is available at ichnfm.org/jama2018n3, for a step-by-step interpretation of the results presented in the original *JAMA Cardiology* article. **Quick reference points to share with patients** are given in Box 1.

IMPLICATIONS FOR CLINICIANS

On the basis of an examination of the participant profile, intervention dosage, bioavailability of intervention, and duration of therapy, the studies cited by the *JAMA Cardiology* meta-analysis are sufficiently flawed for the conclusion that omega-3 fatty acids have no significant association with fatal or nonfatal coronary heart disease or any major vascular events to be interpreted with caution. The authors themselves state that their 95% confidence intervals cannot exclude the possibilities of an association between ω -3 PUFA supplementation and a 7% reduction in the risk of major cardiovascular events and a 10% reduction in the risk of ischemic events. To provide better answers, future studies could recruit participants with a low O3I and treat them to within a predetermined therapeutic range. Until the results of better-designed trials are available, and given the low risks associated with ω -3 PUFA supplementation, clinicians are advised to, at the very least, continue with the recommendations of the American Heart Association⁴ and give patients with left ventricular dysfunction and a high arrhythmic risk who are in their first year after infarct a minimum of 1 g/d ω -3 PUFA supplementation.

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SUMMARY OF KEY POINTS

Participant profile: In general, the study populations were older and included people who already had cardiovascular disease. This is a very different risk profile from patients who begin PUFA supplementation early in a disease process.

Intervention dosage: Doses of ω -3 PUFAs varied widely among the trials. At least 7 of 10 studies used subtherapeutic dosing. One trial used only EPA and no DHA. Emerging evidence suggests that DHA may actually be more cardioprotective than EPA.

Bioavailability of intervention: Nine of ten studies used synthetic or semisynthetic (ethyl ester) forms of ω -3 fatty acid supplements, which are potentially less bioavailable than the natural triglyceride form.

Trial duration: Studies of nutritional interventions generally take longer than drug trials to yield meaningful data. Many trials included in the meta-analysis were likely of too short a duration to show a treatment effect.

Ongoing studies continue to reinforce that supplementation with ω -3 PUFAs carries low risk. Given this low-risk profile, along with the recommendations of the American Heart Association, clinicians are advised to supplement postinfarction patients who have left ventricular dysfunction and a high arrhythmic risk with *at least* 1 g/d ω -3 PUFAs.

COMPETING INTERESTS

The authors declare they have no competing interests.

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