

**Study:** Marine n–3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer. *N Engl J Med*; published online November 10, 2018.

**Study Design:** The Vitamin D and Omega-3 Trial (VITAL) was a randomized, double-blind, placebo-controlled trial, with a two-by-two factorial design, that assessed the benefits and risks of supplementation with vitamin D<sub>3</sub> (at a dose of 2,000 IU per day) and n–3 fatty acids (1 g per day as a fish oil capsule containing 840 mg of n–3 fatty acids, including 460 mg of eicosapentaenoic acid [EPA] and 380 mg of docosahexaenoic acid [DHA]) in the primary prevention of cardiovascular disease and cancer. The study population was men 50 years of age or older and women 55 years of age or older in the United States.

The primary endpoints were major cardiovascular events (composite of myocardial infarction, stroke, and death from cardiovascular causes) and invasive cancer of any type. Secondary cardiovascular endpoints were major cardiovascular events plus coronary revascularization (percutaneous coronary intervention [PCI] or coronary-artery bypass grafting [CABG]) and individual components of the primary endpoint. For cancer, secondary endpoints were colorectal, breast, and prostate cancers during the trial period and death from cancer.

**Results:** The study included 25,871 participants, with a mean age of 67.1 years. The median follow-up period was 5.3 years (range of 3.8 to 6.1 years). Supplementation with n–3 fatty acids did not result in a significantly lower incidence of the primary endpoints of major cardiovascular events (hazard ratio [HR] 0.92; 95% confidence interval [CI], 0.80 to 1.06) or invasive cancer (HR 1.03; 95% CI, 0.93 to 1.13) compared to placebo. Secondary analyses revealed a decreased risk in the n-3 group versus placebo of total myocardial infarction (HR 0.72; 95% CI, 0.59 to 0.90). Additionally, decreased risk of fatal myocardial infarction (HR 0.50; 95% CI, 0.26 to 0.97), PCI (HR 0.78; 95% CI, 0.63 to 0.95), and total coronary heart disease (HR, 0.83; 95% CI, 0.71 to 0.97) were observed in the n-3 group compared to placebo. In subgroup analyses, there was a possible lower incidence of the primary cardiovascular endpoint with n-3 supplementation than with placebo among participants with low fish consumption (HR 0.81; 95% CI 0.67 to 0.98). With respect to safety, no excess risks of bleeding, gastrointestinal symptoms, or other serious adverse events were observed.

**Authors' Conclusions:** “In conclusion, supplementation with n–3 fatty acids did not result in a lower incidence than placebo of the primary end points of major cardiovascular events (a composite of myocardial infarction, stroke, or death from cardiovascular causes) and invasive cancer of any type.”

**CRN's Comments:** This was a well-designed and executed clinical trial. Strengths of the trial included a cohort that was diverse with respect to race, ethnic group, and geography; a high follow-up and adherence rate; and rigorously adjudicated endpoints. Additionally, blood samples were obtained at baseline from 65.5% of study participants. Among the 15,535 participants who had blood samples at baseline that could be analyzed, the mean ( $\pm$ SD) plasma n–3 index was 2.7 $\pm$ 0.9% in each group. Among the 1,583 participants who also provided a blood sample at 1 year that could be analyzed, the mean n–3 index rose to 4.1% (increase of 54.7%) in the n–3 group and changed by less than 2% in the placebo group.

While there were no significant differences between the n-3 and placebo groups in the primary outcomes of major cardiovascular events and invasive cancer, secondary analyses of the individual components of the primary composite cardiovascular outcome suggest a lower risk of myocardial infarction with n-3 supplementation compared to placebo. Additionally, subgroup analyses showed a possible lower incidence of the primary cardiovascular endpoint in participants in the n-3 group with low fish consumption (median of less than 1.5 servings per week). These findings should be further explored in future research.

This trial was limited in that the duration of the intervention and follow-up period may not have been long enough to detect differences, particularly for cancer endpoints. The dose was moderate to low at 840 mg n-3 fatty acids (460 mg EPA/380 mg DHA) and the participants were healthy. The authors suggest that this dose was adequate based on American Heart Association (AHA) recommendations for cardio-protection in persons with a history of coronary disease, however the AHA recommendation is 1,000 mg EPA/DHA and the VITAL study provided 840 mg EPA/DHA. Further evidence that the dose may have been inadequate is that in the treatment group the mean plasma n-3 index at baseline was 2.7% and at one year 4.1%, which reflects a change from high risk (< 4.0%) to just above intermediate risk (4 – 8%). This change reflects nutrient supplementation to avoid insufficiency, not therapeutic intervention where one would expect statistically significant reductions in clinical endpoints. Higher doses have been shown to be effective for related cardiovascular endpoints (e.g., lowering triglyceride levels) in diseased populations and may confer a benefit not seen in this study.