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Overview of the VITAL Trial

Results from The Vitamin D and Omega-3 Trial (VITAL) were published in the Nov. 10th issue of the New England Journal of Medicine (NEJM)[1,2]. Neither vitamin D nor omega-3 supplementation lowered the incidence of major cardiovascular events (a composite of heart attack, stroke or death from CVD causes) or invasive cancer of any type, the primary endpoints evaluated in the trial.

However a number of secondary findings could be seen as encouraging. For vitamin D vs. placebo, a lower mortality from cancer with vitamin D (17% reduction in risk) was observed. While omega-3 supplements didn't lower all major cardio events as a group, a lower incidence (28% reduction in risk) was seen for heart attack when analyzed separately. In addition, analyses found a reduced incidence of death from heart attack (50% reduction in risk) and total coronary heart disease (17% reduction in risk) with fish oil vs. placebo.

All of these secondary findings must be interpreted with caution, but raise the question of whether supplementation could be of some benefit in preventing coronary heart disease or cancer death.

It's worth noting that subgroup analyses showed a lower incidence of the primary cardiovascular endpoint with fish oil supplementation vs. placebo for those with low fish consumption. Dietary fish intake at the beginning of the study modified the fish oil intervention's effect on major cardiovascular events (significant reduction in risk of 19%) in participants consuming less than 1½ fish servings weekly. But no reductions were observed in those with higher intake. These apparent findings could be taken into account when designing future trials, particularly because poor fish intake was common in VITAL and is common in the US.

VITAL is a randomized, double-blind, placebo-controlled trial (with a two-by-two factorial design) assessing the effects of vitamin D (2,000 IU daily) and fish oil (1,000 mg daily, 460 mg EPA/380 mg DHA as ethyl esters, Lovaza) on the primary prevention of cardiovascular disease (CVD) and cancer in 25,871 men (50 and older) and women (55 and older).

The participants, with no history of cancer (except non-melanoma skin cancer) or CVD at the study's start, were assigned to take one of four regimens: both vitamin D and fish oil, vitamin D and placebo, fish oil and placebo, or two placebos daily. Participants were followed for about 5.3 years.

The strengths of the trial include the large number of people enrolled, and that the findings are likely applicable to many in the population since African Americans, men and women, and those with normal as well as low blood levels of vitamin D were included. Importantly, no adverse effects were seen for vitamin D or omega-3 supplementation in VITAL, including no excess bleeding or high blood levels of calcium.

As emphasized in an accompanying editorial[3], the positive secondary results should rightfully be interpreted cautiously because there was no statistical correction for the multiple comparisons conducted (partly due to the number of secondary end points evaluated). Additionally, for fish oil, the secondary effects observed in VITAL (e.g. less heart attacks or fatal heart attacks) have not been consistently seen in all large, well-controlled marine omega-3 trials.

For vitamin D and cancer, however, experimental studies consistently demonstrate the anti-cancer potential of vitamin D, and a recent meta-analysis reported a significant benefit with vitamin D and cancer mortality[4]. Further, in one VITAL analysis, the rate of death from cancer was 25% lower with vitamin D vs. placebo when the first two years of the five-year study were excluded. Although this was not a "pre-planned" analysis, the apparent lower rate of cancer death with vitamin D is in line with the meta-analysis findings.

Another study published in the same issue of NEJM, the 'REDUCE-IT' trial, is also worth mentioning[5]. That study, which ran for nearly 5 years, tested 4 grams daily of omega-3 (Vascepa prescription product, about 96% EPA) vs. placebo in over 8,000 patients with established CVD or who had diabetes and at least one other CVD risk factor. All participants had persistently high levels of triglycerides despite being treated with a statin. The fish oil showed a significantly lower risk of ischemic events, including cardiovascular death, compared to placebo.

***References**:*

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4. Vaughn-Shaw PG et al. The impact of vitamin D pathway genetic variation and circulating 25-hydroxy-vitamin D on cancer outcome: Systematic review and meta-analysis. Br J Cancer. 116:1092-110, 2017.
5. Bhatt DL et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. NEJM. Published online Nov. 10, 2018.