

## VITAL Study Notes (For Internal CRN Member Discussions)

### Overall

- No significant effects on the primary outcomes of invasive cancer incidence or major cardiovascular events (composite of myocardial infarction, stroke, or death from cardiovascular causes).
- There were suggested benefits based on pre-specified secondary and subgroup analysis in the omega-3 arm and the post-hoc analyses of the vitamin D arm.
  - However, appropriately and as expected the authors stated that the potential benefits shown in secondary and exploratory endpoints, as well as those regarding subgroups, should be interpreted with caution because statistical adjustments were not made to account for multiple comparisons.
- Study reaffirms safety of both vitamin D and omega-3 fatty acids.
  - Discounts previous concerns of omega-3 fatty acids and prostate cancer (Braskey, et al.)
- CRN members supplied vitamin D (Pharmavite) and omega-3 (Pronova/BASF).
- The study is a two-by-two factorial design, and therefore there is a group that took both omega-3 and vitamin D. There were no interactions observed between the vitamin D and omega-3 interventions.
- The omega-3 and vitamin D interventions in VITAL provide moderate-to-low levels of supplementation to healthy people. These levels of supplementation are typically used to fill nutrient gaps related to dietary intake; however, the VITAL trial was designed to assess therapeutic endpoints with drug-like expectations.
  - For example, this clinical trial provided 840 mg EPA/DHA to healthy individuals
  - Drug clinical trials typically provide 2,000 – 4,000 mg EPA/DHA in people with disease.
    - Statistically and clinically significant results are more likely to be found in clinical trials that use higher levels of omega-3 and vitamin D performed in diseased individuals (one relevant example being the results of the REDUCE-IT pharmaceutical clinical trial that tested 4 g icosapent ethyl in patients with established heart disease).

### Omega-3

- No significant effects on either primary outcome.
- Dose was moderate/low at 840 mg omega-3 fatty acids (460 mg EPA/380 mg DHA)
  - Authors suggest 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
  - Mean plasma omega-3 index at baseline (2.7%) and one year (4.1%) reflects a change from high risk (< 4.0%) to just over the line for intermediate risk (4 – 8%). This reflects nutrient supplementation, not therapeutic intervention.
- There is important evidence of risk reduction that should not be ignored in the pre-specified secondary analysis and subgroup analysis.
  - Secondary analyses of the individual components of the primary composite cardiovascular outcome suggest a lower risk of myocardial infarction with omega-3 supplementation compared to placebo.
    - Overall 28% reduction in heart attacks in omega-3 group.

- 77% reduction in heart attacks in African Americans
- Subgroup analyses showed a possible lower incidence of the primary cardiovascular endpoint in participants in the omega-3 group with low fish consumption (median of less than 1.5 servings per week).
  - e.g., in people who don't eat the recommended 1-2 serving/week of cold water fatty fish, one gram of omega-3 supplements were linked to 40% reduction in heart attacks. This was not seen in people who ate fish.

Despite the conclusion that 840 mg of EPA/DHA did not demonstrate statistically significant results with regard to the pre-specified primary trial endpoints, there is still evidence that ensuring adequate omega-3 in the diet is important because of the important role that omega-3 fats play in:

- Decrease risk for arrhythmias.
- Decrease risk for thrombosis.
- Maintain healthy triglycerides.
- Decrease rate of growth of the atherosclerotic plaque.
- Improve endothelial function.
- Lower blood pressure (slightly).
- Reduce inflammatory responses.

## **Vitamin D**

- No significant effects on either primary outcome.
- There is important evidence that should not be ignored that is found in the post-hoc and subgroup analysis; however, these results need to be interpreted with caution.
  - Post-hoc analyses of the rate of death from cancer suggested a possible benefit after excluding early follow-up data (i.e., excluding the first two years of follow up).
  - In subgroup analyses, normal-weight participants who received vitamin D had a lower incidence than those who received placebo.

Despite the conclusion that 2,000 IU vitamin D did not demonstrate statistically significant results with regard to the pre-specified primary trial endpoints, there is still evidence that ensuring adequate vitamin D in the diet is important for other reasons, including bone health.

## **Summary**

- Pre-planned media coverage focuses on pre-specified primary trial endpoints, and are cautious about secondary outcomes.
- Secondary endpoints reveal interesting subplots that need further exploration. Many ancillary studies are expected to be published from the VITAL data in the next few years.