Effects of Vitamin D and Omega-3 on Cerebrovascular Disease

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Summary

Recently, there has been growing interest in the role that vitamin D as well as omega-3 fatty acids play in the development of cardiovascular disease events. The NIH sponsored VITamin D and OmegA-3 TriaL (VITAL) is a randomized, double blind trial testing vitamin D_3 and omega-3 fatty acid supplementation in the primary prevention of cancer and cardiovascular disease. I will leverage this trial to determine the impact of vitamin D_3 and omega-3 fatty acid supplementation on stroke outcomes.

The current research study summarized in this protocol will collect additional information on stroke outcomes which is not obtained by the parent VITAL study. To obtain this information, participants who experience a stroke will receive a questionnaire assessing functional status, functional limitations, physical disability, and social disability at 6 and 12 months after the stroke. This is the only additional information being collected as part of the current research study.

Data from this study will allow us to determine whether vitamin D_3 and omega-3 fatty acid supplementation reduces the risk for poor outcomes after a stroke event.

I. Background and Significance

Global burden of stroke.
Stroke is a leading cause of disability and death worldwide and is expected to become an even more prevalent cause of disability in the future as the population ages.[1, 2] Understanding risk factors which may prospectively influence stroke outcomes may help to reduce the morbidity burden of stroke.

Vitamin D and omega-3 fatty acids and incident stroke.
Recently, there is growing interest in the effect of vitamin D and omega-3 fatty acids on cardiovascular disease risk. A recent meta-analysis of observational studies found that individuals with the lowest serum 25-hydroxyvitamin D (25(OH)D) levels had a relative risk of 1.64 (1.27-2.10) for stroke compared to those with the highest levels.[3] In contrast, a meta-analysis of randomized trials of vitamin D supplementation did not find an effect on stroke risk (RR=1.05)[4]; however, the levels of supplementation tested in the trials were low.[5] Omega-3 fatty acid intake was associated with reduced risk of stroke among healthy individuals in a meta-analysis of observational studies.[6] No published large randomized trials of marine omega-3 fatty acids for the primary prevention of CVD in the general population exist. Randomized trials of omega-3 fatty acid supplementation among patients with cardiovascular disease (CVD)[7, 8], hypercholesterolemia[9], or dysglycemia[10] observed no effect on stroke risk.

Impact of vitamin D and omega-3 fatty acids on stroke outcomes: Gaps in knowledge.
Information on the effect of vitamin D and omega-3 fatty acid supplementation on stroke outcomes (as opposed to incident stroke) in healthy populations is limited. Studies among stroke patients observed that lower levels of 25(OH)D at hospital admission predict infarct volume[11], initial stroke severity and handicap at hospital discharge[12], as well as death and functional outcome at 90 days post-stroke.[13] However, these studies cannot test if supplementation with vitamin D in healthy populations impacts stroke severity and functional outcomes post-stroke. Several hypotheses have been formulated to explain how vitamin D may impact stroke outcomes. Vitamin D may have neuroprotective properties[14] and 25(OH)D may promote neuroplastic changes which improve recovery after stroke.[12] Additionally by preserving bone, restoring muscle strength, reducing falls, and protecting against cognitive impairment and depression, vitamin D may assist in post-stroke recovery.[15, 16] Less is known about the impact of omega-3 fatty acid supplementation on stroke outcomes. An animal study observed that a DHA-enriched diet protected against post-ischemic inflammation and injury in the brain.[17] This suggests that DHA may protect against the immune response or brain damage in ischemic stroke and may result in improved stroke outcomes.

Opportunity to determine the impact of vitamin D and omega-3 fatty acids on stroke outcomes.
The ongoing VITamin D and OmegA-3 TriaL (VITAL) (this parent study is approved by Partners IRB, Protocol #2009P001217/MGH) will examine the impact of vitamin D_3 (2,000 IU/day cholecalciferol) and omega-3 fatty acids (840 mg eicosapentaenoic acid [EPA] + docosahexaenoic acid [DHA]) on stroke incidence. Given the high morbidity burden of stroke, the impact of these supplements on stroke outcomes is of substantial scientific and public health importance. This proposal will collect additional data to determine the effect of these supplements on post-stroke outcomes. Even if they do not significantly reduce stroke incidence,

they may still reduce stroke severity and improve outcomes post-stroke. The randomized double-blind design among healthy adults will provide the highest quality data on the impact of these agents on long-term stroke outcomes.

II. Specific Aims

The primary specific aim of this study is to test whether vitamin D_3 or omega-3 fatty acid supplementation reduces the risk of poor functional outcomes as measured at hospital discharge and 6- and 12-months post-stroke (~400 strokes in VITAL).

III. Subject Selection

Participants will be selected from the VITAL study. VITAL is a NIH-funded (CA138962 with support also included from NHLBI) randomized, double-blind, placebo-controlled trial to test the effects of vitamin D_3 (cholecalciferol, 2,000 IU/d) and omega-3 fatty acid (840 mg/d of EPA/DHA [ratio of 1.3:1]) supplements in the primary prevention of CVD and cancer in a multiethnic population of 25,875 individuals.[18] The trial enrolled men aged ≥50 and women aged ≥55 without a history of cancer (except non-melanoma skin cancer), myocardial infarction, stroke, transient ischemic attack, or coronary revascularization. All subjects signed a detailed informed consent form, agreed to limit consumption of supplemental vitamin D and calcium to no more than 800 IU/d and 1200 mg/d respectively and to forgo use of fish-oil supplements during the trial. This ongoing parent study is approved by Partners IRB, Protocol #2009P001217/MGH. Additionally, VITAL received IND approval from the FDA on March 11, 2011 (IND #105558) and is registered on clinicaltrials.gov (NCT01169259).

Our specific aim examines the influence of randomized treatment assignment on risk of functional outcomes from stroke at 6 and 12-months after stroke. For this component, we will include only individuals in VITAL who experienced a stroke event.

IV. Subject Enrollment

For the VITAL participants who report a stroke event, at 6 and 12-months after their reported stroke event, we will invite them to complete an additional questionnaire asking about their current limitations in everyday activities. For non-responders, a second request will be made. Consent to participate will be implied by completing the questionnaire.

V. Study Procedures

<u>Stroke Outcomes Assessment in VITAL</u>

The parent VITAL trial collects information on stroke severity at hospital discharge as measured by the modified Rankin scale (mRS). We will send additional follow-up questionnaires at 6-months and 12-months post-stroke to assess stroke outcomes for all participants who experience a stroke. This information is not collected by the parent study and will only be collected by this study. Assessing outcomes at 6 and 12-months will allow us to determine initial stroke recovery as well as further improvements or sustained functioning. The stroke outcome questionnaires will include the same functional assessment questions as the baseline questionnaire in the parent study to allow for comparisons to baseline functional status. These questions assessed baseline

physical function and limitations in: vigorous or moderate activities; lifting or carrying groceries; climbing stairs; bending, kneeling, stooping; walking >1 mile; walking several blocks; or walking 1 block. Respondents are also asked if they received help with feeding themselves, dressing, getting in and out of bed, and taking a bath or shower.

In addition, I will ask several questions originally developed and used by the Framingham Heart Study (FHS) to assess functional limitations, physical disability, and social disability among individuals with stroke.[19, 20] Functional limitations will be assessed through the physical performance scale adapted from Nagi[21] and physical disability with the modified Katz Activities of Daily Living (ADL) Scale[22] and the Rosow-Breslau Functional Health Scale.[23] These measures have high test-retest reliability.[24-29] The adapted Nagi scale asks respondents if they experience limitations in: pulling or pushing large objects; stooping, crouching, or kneeling; reaching or extending arms above shoulder level; reaching or extending arms below shoulder level; writing or handling or fingering small objects; standing in one place for long periods; and sitting for an hour. The Rosow-Breslau Functional Health Scale asks if the respondent needs help with the following gross mobility tasks: walking 0.5 mile; walking up and down stairs to the second floor; and doing heavy work around the house. The modified Katz ADL scale asks about needing help with: bathing; dressing; eating; getting in and out of a chair; and walking 50 yards. I will also ask participants if they are completing the questionnaire themselves or if it has been completed by a proxy respondent and if they currently reside in a nursing home. I will create cumulative disability scales similar to those previously developed in stroke survivors in FHS.[19] First, I will dichotomize responses to each item as unlimited (no limitation or no help needed) versus limited (any amount of limitation or help needed). Next, each scale (Nagi, Katz, and Rosow-Breslau) will be dichotomized into unlimited (no limitation in any of the items) versus limited (limitation in at least one item). Finally, I will create a cumulative disability index with values of 0 (no limitation on any scale), 1 (limitation on Nagi scale only), 2 (limitations on Nagi and Rosow-Breslau scales), and 3 (limitations in all three scales).

Social disability will be assessed using a scale also developed in the FHS[20] which incorporates both need for assistance and unmet need for assistance. Someone with a need for assistance is not self-sufficient in performing the activity, but is able to find support to meet this need. In contrast, those with an unmet need are not able to find this support. The scale covers five social areas (housekeeping, transportation, social interaction, food preparation, and grocery shopping). Respondents are grouped into four categories (need met, no apparent problem; need met, potential problem; uncertain need met, potential problem; need unmet, current problem) for each social area using a previously published algorithm.[20] I will examine each social area individually and create summary indices for the total number of unmet needs across all areas and for the total number of unmet needs or uncertain needs met, potential problem. These indices range from 0 to 5, but to avoid problems with model convergence due to sparse data I will *a priori* categorize them as 0, 1, or ≥2.

VI. Biostatistical Analysis

We will use logistic regression to examine the effects of randomized treatment assignments in VITAL on functional limitations, physical disability, and social disability using separate models

for each outcome as defined above. Only individuals with a completed stroke outcomes questionnaire will contribute to these analyses. We will perform analyses for total stroke as well as for the ischemic strokes only. For the analysis of functional limitations and physical disability, we will also perform a sensitivity analysis in which we restricted to those individuals who did not report functional limitations at baseline in VITAL.

We will also perform a sensitivity analysis in which we will use inverse probability of treatment weights to adjust for potential differences between treatment groups since our analysis conditions on experiencing a stroke event. We will first develop a propensity score for randomized treatment assignment at the time of stroke including information on age at randomization, sex, body mass index, physical activity, statin use, alcohol consumption, history of hypertension, history of high cholesterol, race, and smoking status to predict treatment assignment. We will then use weighted logistic regression to estimate the association between randomized treatment and our outcomes. We will perform an additional sensitivity analysis in which fatal stroke events were included as the worst possible outcome category.

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