Manuscript Proposal Template

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Title: VITAL Rhythm Study**: Atrial Fibrillation Results**

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RATIONALE (2-3 paragraphs)

Heart rhythm disorders are major causes of mortality and morbidity in United States. Atrial fibrillation (AF) is the most common heart rhythm disturbance and the prevalence is exponentially growing.[1, 2] An estimated 5.1 million people are diagnosed with AF in the United States at present, and this number is expected to rise to 7.5 million by 2020 and to 12.1 million by 2050.[3] The clinical consequences of AF are considerable and include thromboembolic stroke[4], congestive heart failure (CHF),[5] cognitive dysfunction,[6] increased mortality,[7] and a lower quality of life.[8] Current treatment options for AF are employed relatively late in the course of the disease and are associated with limited long term success and significant risks.[9,10] Even when treatment is apparently successful, AF may continue undetected and the risk of stroke may never be eliminated[11].

Therefore, substantial reductions in morbidity and mortality will require the development of low-risk, primary preventive interventions that can be applied to broad populations. Omega-3 fatty acids have been documented to influence the electrical properties of the myocardium in experimental models and influence the propensity for atrial and ventricular arrhythmias in humans[15]. Observational data regarding omega-3 fatty acid intake and atrial arrhythmias is mixed, with some studies suggesting benefit[20-22], others neutrality[23, 24], and others raising the possibility of increased risk[25, 26]. Small secondary prevention randomized trials have demonstrated reductions in AF risk[27-29], while others have not[30-33]. A recent analysis from the Reduce-IT trial, found a higher risk of hospitalization for atrial fibrillation in patients with CHD randomized to high dose EPA. However, to date, there have been no large-scale RCTs testing the benefits and risks of omega-3 fatty acids in the primary prevention of AF[35]. Although the data regarding Vitamin D supplementation with respect to AF risk is less developed, there are multiple upstream long-term mechanisms whereby vitamin D supplementation might impact atrial structural and electrical remodeling, and thus have a long-term impact on AF risk. These include activation of the renin-angiotensin system,[113-115] resulting in elevated plasma renin activity[116] and blood pressure[117,118], promoting adverse ventricular remodeling and hypertrophy[119], fibrosis[120,121], and inflammation[122]. Multiple observational studies have also demonstrated associations between vitamin D deficiency

and clinical conditions predisposing to AF, most notably including hypertension[117,118] and heart failure.[123,124] Given the association of vitamin D deficiency with multiple risk factors for AF, it is biologically plausible that vitamin D insufficiency may also elevate propensity toward AF and that supplementation might lower risk.

Despite the obvious need, dedicated AF primary prevention RCTs have not been performed, largely because they have not been viewed as feasible from a resource or economic standpoint. VITAL Rhythm will be the first.

OBJECTIVES

1. To evaluate the effects of an intervention with 1g/d of EPA/DHA vs. placebo on the incidence of atrial fibrillation among VITAL participants

2. To evaluate the effects of an intervention with Vitamin D vs. placebo on the incidence of atrial fibrillation among VITAL participants.

KEY EXPOSURE VARIABLES (at baseline from VITAL Database):

age
sex
ethnicity
BMI
height
smoking
hypertension
diabetes
alcohol intake
fish intake
statin use
randomization assignment
EPA/DHA and vitamin D levels

AF chart review database variables (Mary and Claire know the location)

Symptoms, type of AF, How AF confirmed, symptoms of AF may have proceeded randomization, and type of AF

KEY OUTCOME VARIABLES:

Atrial Fibrillation:

1. Primary endpoint: All confirmed AF events occurring during randomization (including those ascertained by self-report and CMS linkage)
2. Secondary endpoints for sensitivity analyses:
    a. Excluding AF events where symptoms were present prior to randomization.
    b. Excluding AF events ascertained by CMS linkage

3. Paroxysmal AF
4. Non-paroxysmal (persistent and chronic) AF

ANALYSIS PLAN (brief description)

Population for Analysis: VITAL population excluding prevalent AF cases at baseline defined as:

1. Self reported AF prior to randomization (n=)
2. AF events reported after randomization, but confirmed to have occurred prior to randomization during endpoint review (n=) and/or by CMS linkage (n=).

Will want to report the number of participants excluded in each category on this basis.

Statistical Analysis:

Table 1 The characteristics of the analysis population will be compared by randomized treatment assignment using 2-sample t tests for continuous variables and χ^2 statistics for categorical variables to ensure balance was achieved by the randomization. Characteristics to be examined include age, gender, race/ethnicity, BMI, height, smoking; alcohol use, physical activity, hypertension, diabetes and baseline intake of vitamin D_3, omega-3 fatty acid, and alcohol as assessed by dietary questionnaire.

Table 2 (might just be in text) (*from VITAL AF database*) The characteristic of AF cases will be reported and then compared by randomized treatment assignment using 2-sample t tests for continuous variables and χ^2 statistics for categorical variables. Characteristics to be examined include symptoms at time of AF (q21-symptoms-at_Dx, yes/no), type of AF (q26 a-c, paroxysmal, persistent, chronic permanent, how AF confirmed (q6 1 ECG, 2 medical record report), potential symptoms of AF preceded randomization (q8a, yes), LVEF (9a), atrial flutter only (q27b), and AF post cardiac surgery (q27a).

Table 3 A and B: Primary Analysis: We will compare the separate main effects of intention-to-treat with EPA/DHA and Vitamin D_3 on total AF incidence within the 2x2 factorial design. To do this, we will use Cox proportional hazards models to estimate the hazard ratio for each intervention using indicators for treatment assignment, controlling for the second intervention, age, race, and gender[168]. Time-to-event will be calculated as the interval between time of randomization and the earliest occurrence of: 1) confirmed AF event, 2) death, or 3) end of the study. The primary analysis will estimate the cause-specific hazard and the hazard ratio comparing treatment groups for each outcome of interest by censoring individuals with deaths due to other causes. To determine whether treatment effects vary over time, we will examine Schoenfeld residuals and an interaction of the intervention effects with time. Cumulative incidence curves will be derived from the Cox models as in the main trial paper.

Secondary Analyses 1). Excluding patients who may have had symptoms attributable to AF prior to randomization (q8a) will also be performed and 2). excluding those confirmed by CMS linkage since we do not have CMS linkage events for the entire follow-up period. 3). Rates of adherence in all treatment groups as defined in the main trial paper, and repeat the analyses for the primary endpoint censoring for non-adherence as was done in the main trial paper

Comment [AC1]: Eventually we decided to wait until we had them, but we kept this in since it was included in the original grant application.

Table 4 A or B (or Figure 2A or 2B) Subgroup Analyses: We will examine effect modification by prespecified subgroups: age (above and below median), sex, race (Non-Hispanic white, black,

or other), current smoker, diabetes hypertension, BMI (< 25, 25-30, 30+), height (above and below the median), weight (above and below the median), alcohol intake (<1/d, 1-2d, 2+day), and CHA_2DS_2 -VASc score (see below for derivation). We will also examine an altered CHA_2DS_2 -VASc score that does not include female sex due to recent guidelines and data that female sex does not confer an increase in risk with low scores (0-1). We can also add physical activity, but I did not see a variable in the dataset.

DHA/EPA, we will examine effect modification by randomization to Vitamin D, baseline fish intake (above or below the median), Fish Oil supplementation, and baseline levels of EPA+DHA (above or below the median) in the 16,956 patients who donated blood samples at baseline.

Vitamin D, we will examine effect modification by randomization to EPA+DHA, Baseline Vitamin D supplementation, and baseline levels of Vitamin D levels (above or below the median) in the 16,956 patients who donated blood samples at baseline.

CHA_2DS_2 - VASc score (at baseline)
Sex: Female 1, Male 0
Age: <65= 0, 65-74 =1, 75+ = 2
Self-reported Heart Failure 1
Hypertension 1
Diabetes 1
History of stroke, TIA, or thromboembolism
Vascular disease (history of MI, PAD, or prior aortic plaque)

FIGURES:

1A: Cumulative Incidence Rates of primary AF endpoint by EPA/DHA treatment Groups (as done in the main paper)

1B: Cumulative Incidence Rates of primary AF endpoint by Vitamin D treatment Groups (as done in the main paper)

Updated September 2020: Analyses added:

1. Added Prespecified Analysis: that were included in the original grant application from 11/2012 but not detailed above: "Beyond the primary analyses, we will assess the hazard ratios for a combination of vitamin D_3 and EPA/DHA versus both placebos".

2. Added Post-hoc analysis excluding atrial flutter and post-operative atrial fibrillation from the primary endpoint.

TABLES and Figures

Table 1. ***Characteristics of the participants at baseline, according to randomized groups in study population free of AF at baseline***												
Characteristics		**EPA/DHA**		**EPA/DHA Placebo**		**P value**		**VIT D**		**VIT D Placebo**		**P value**
Age (y)												
Female Sex –no (%)												
Race or ethnic group												
Non-Hispanic White												
Black												
Nonblack Hispanic												
Asian or Pacific Islander												
Native American or Alaskan native												
Other or unknown												
Body-mass index												
Height												
Smoking: Current Past Never												
Hypertension												
Diabetes												
Physical Activity												
Alcohol consumption (g or days per week)												
Fish Consumption (servings per week)												
Vitamin D supplements												
Table 2: Characteristics of AF Cases (From AF Chart Review Dataform)												

Comment [ACM2]: If this is available

	Number (%)
How AF confirmed: ECG Medical Record report	
Type of AF Paroxysmal Persistent Long standing persistent DCCV w/in 1 month	
Symptoms present at Diagnosis	
Symptoms may have preceded randomization	
AF post-cardiac surgery	
Atrial flutter only	
LVEF on echo	

Table 3A. EPA/DHA Main Results: Hazard ratios (95% confidence interval) for atrial fibrillation and AF Subtypes according to randomized groups (EPA/DHA or placebo).

End Point	**EPA/DHA Group (n=)**	**Placebo Group (n=)**	**Hazard Ratio (95% CI)**	**P-value**
Primary endpoint: All Incident AF				
Secondary endpoint: AF events excluding those with symptoms prior to randomization AF events excluding those events ascertained by CMS				
Paroxysmal AF				
Non-Paroxysmal AF				

Table 3B. Vitamin D Main Results Hazard ratios (95% confidence interval) for atrial fibrillation and AF Subtypes according to randomized groups (Vitamin D or placebo).

End Point	**Vitamin D Group**	**Placebo Group**	**Hazard Ratio**	**P-value**

		(n=)		(n=)		(95% CI)	
Primary endpoint: All Incident AF							
Secondary endpoint: AF events excluding those with symptoms prior to randomization AF events excluding those events ascertained by CMS							
Paroxysmal AF							
Non-Paroxysmal AF							

Table 4a EPA/DHA Subgroup Analyses. Hazard ratios (95% CI) of Incident AF according to subgroups					
Subgroup	No. of Participants	AF events			
		EPA/DHA	Placebo	Hazard Ratio (95% CI)	P value for Interaction
Age					
<Median of 66.7 y					
≥Median of 66.7 y					
Sex					
Male					
Female					
Race					
Non-Hispanic white					
Black					
Other					
Current Smoker					
Yes					
No					
Diabetes					
Yes					
No					
Hypertension					
Yes					
No					
Body-mass index					
<25					
25 to <30					
≥30					

Height					
<median					
≥ median					
Weight					
<median					
≥ median					
Alcohol Intake					
<1/d					
1-2d					
2+ d					
CHA_2DS_2 -VASc score					
0					
1					
2+					
CHA_2DS_2 -VASc score (-Female)					
0					
1					
2					
Baseline statin use					
Yes					
No					
Baseline Fish Intake					
<Median					
≥Median					
Baseline n-3 fatty acid levels					
<Median					
≥Median					
Randomization to Vit D					
No (placebo)					
Yes (Active agent)					

Table 4b Vitamin D Subgroup Analyses. Hazard ratios (95% CI) of Incident AF according to subgroups					
Subgroup	No. of Participants	AF events			
		EPA/DHA	Placebo	Hazard Ratio (95% CI)	P value for Interaction
Age					
<Median of 66.7 y					
≥Median of 66.7 y					
Sex					
Male					
Female					
Race					
Non-Hispanic white					
Black					
Other					
Current Smoker					
Yes					
No					
Diabetes					
Yes					
No					
Hypertension					
Yes					
No					
Body-mass index					
<25					
25 to <30					
≥30					
Height					
<median					
≥ median					
Weight					
<median					
≥ median					
Alcohol Intake					
<1/d					
1-2d					
2+ d					
CHA_2DS_2 -VASc score					
0					
1					
2+					
CHA_2DS_2 -VASc score (-Female)					
0					
1					

2					
Baseline statin use					
Yes					
No					
Baseline serum 25-hydroxyvitamin D					
<20 ng/ml					
≥20 ng/ml					
Baseline serum 25-hydroxyvitamin D					
<median					
≥ median					
Baseline vitamin D use					
Yes					
No					
Randomization to n-3 fatty acids					
No (placebo)					
Yes (Active agent)					