ARIC Manuscript Proposal #2425

PC Reviewed: 9/9/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Serum 25-hydroxyvitamin D levels and incidence of atrial fibrillation: the ARIC study

b. Abbreviated Title (Length 26 characters): Vitamin D and AF

2. Writing Group: Alvaro Alonso, Jeffrey R. Misialek, Erin D. Michos, Lin Y. Chen, Elsayed Z. Soliman, Elizabeth Selvin, Myron Gross, John Eckfeldt, Pamela L. Lutsey

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __AA__ **[please confirm with your initials electronically or in writing]**

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3. Timeline:
Data analysis: 2-3 months
Drafting of manuscripts: 2-3 months

4. Rationale:
In epidemiologic studies, low levels of serum 25-hydroxyvitamin D have been associated with increased risk of cardiovascular disease.[1] Mechanisms through which vitamin D may reduce cardiovascular risk include modulation of inflammatory processes, inhibition

of the renin-angiotensin-aldosterone system, and enhancement of insulin sensitivity, to name a few. Through similar mechanisms, low levels of circulating vitamin D could affect the risk of developing atrial fibrillation (AF), a common cardiac arrhythmia.

Despite the biological plausibility for an effect of vitamin D on AF risk, the epidemiologic evidence thus far does not support the presence of an association. An analysis of the Framingham Heart Study found that serum concentration of 25-hydroxyvitamin D was not associated with AF risk (HR 0.99, 95%CI 0.88-1.10 for a 1-SD increment in vitamin D levels).[2] Similarly, serum concentrations of 25-hydroxyvitamin D were not associated with AF risk in the Multi-Ethnic Study of Atherosclerosis (MESA) and Cardiovascular Health Study (CHS) (HR 0.92, 95%CI 0.81-1.03 and 1.00, 95%CI 0.88-1.14 per 10 ng/mL increase, respectively).[3]

However, the published studies leave some questions unanswered. Specifically, these studies did not assess the impact of vitamin D binding protein (DBP) levels, a modifier of vitamin D bioavailability, on the associations, as well as the potential interaction with magnesium concentrations, which affect levels of parathyroid hormone (PTH)[4] and are associated with the risk of AF.[5] Similarly, no previous studies have explored the association of vitamin D_3 epimer with AF risk. Finally, they have limited sample size, which may have led to reduced statistical power to identify associations of small to moderate strength.

5. Main Hypothesis/Study Questions:

We propose to address the following aims:

1. To determine the association of serum 25-hydroxyvitamin D levels (total and epimer) with incidence of AF, in the entire cohort and by race.
2. To study the interaction between DBP genetic variants, vitamin D levels, and AF risk.
3. To explore the potential interaction between serum magnesium and serum vitamin D and AF incidence.

We hypothesize that lower levels of vitamin D will be associated with higher AF risk, but that this association will only be observed among those genetically predisposed to high DBP concentrations and thus lower predicted levels of bioavailable 25-hydroxyvitamin D. Also, we hypothesize that the inverse association of vitamin D with AF risk will be stronger among individuals with lower serum magnesium levels.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

<u>Study population</u>

We will include ARIC participants examined at visit 2 with available data on serum vitamin D concentrations. Participants will be excluded if they had prevalent AF at visit 2, had missing values in relevant covariates, had race other than white or blacks, or were non-whites in the Minneapolis and Washington County field centers.

Participants who did not consent to genetic analyses will be excluded from analysis including DBP polymorphisms.

Main independent variables

All measured in visit 2:

- Serum 25-hydroxyvitamin D (adjusted for season as described elsewhere).[6]
- 25-hydroxyvitamin D epimer
- Serum magnesium

Outcome ascertainment

The outcome of interest, AF, will be defined as previously described. Briefly, AF is defined as the presence of a study ECG with AF or atrial flutter, presence of ICD-9-CM codes 427.31 or 427.32 in a hospitalization discharge, or AF as a cause of death (ICD-9 427.3 or ICD-10 I48).

Other covariates of interest

We will consider the following variables as potential confounders:

- Age, sex, race/center, education, body mass index and height, physical activity, alcohol intake, smoking

Variables that could be considered as confounders or mediators include:

- Systolic and diastolic blood pressure, use of antihypertensive medication, diabetes, prevalent CHD, prevalent heart failure, NT-proBNP, C-reactive protein, $eGFR_{cysC\text{-}creat}$

Other covariates to be considered include molecules related to vitamin D metabolism: calcium, phosphorus, PTH, and FGF-23, and the polymorphisms rs7041 and rs4588 as proxies to levels of DBP.

Statistical analysis

The association of serum 25-hydroxyvitamin D concentrations with AF incidence will be assessed with a Cox proportional hazards model. The appropriate modeling of 25-hydroxyvitamin D will be explored using restricted cubic splines. An initial model will adjust for the variables described as confounders above, while a second model will additionally include those variables that could also be consider mediators. Supplementary models will adjust for vitamin D metabolism-related molecules.

Interactions between DBP polymorphisms and 25-hydroxyvitamin D, and between magnesium and vitamin D, will be explored through stratified analysis and including multiplicative terms in the models. We will conduct additional stratified analyses by race, sex, and eGFR.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes __X__ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and

for DNA analysis RES_DNA = "CVD Research" would be used? ____ Yes ____ No
(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript?
__X__ Yes ___ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"?
__X__ Yes ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

__X__ Yes _____ No

No overlap with existing manuscript proposals

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes ____ No

11.b. If yes, is the proposal
__X__ A. primarily the result of an ancillary study (list number* 2009.17)
___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from

http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

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3. Mathew JS, Sachs MC, Patton KK, Heckbert SR, Hoofnagle AN, Alonso A, Chonchol M, Deo R, Ix JH, Siscovick DS, Kestenbaum BR, De Boer IH. Fibroblast growth factor-23 and incident atrial fibrillation: the Multi-Ethnic Study of Atherosclerosis (MESA) and the Cardiovascular Health Study (CHS). *Circulation.* 2014;Jun 11. pii: CIRCULATIONAHA.113.005499 [Epub ahead of print].

4. Rude RK, Singer FR, Gruber HE. Skeletal and hormonal effects of magnesium deficiency. *J Am Coll Nutr.* 2009;28:131-141.

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