ARIC Manuscript Proposal #2152

PC Reviewed: 6/11/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Vitamin D and venous thromboembolism

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

2. Writing Group:
Writing group members: Aaron Folsom, Saonli Basu, Wayne Rosamond, Susan Heckbert, Mary Cushman, Pam Lutsey

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

First author: Aaron R. Folsom
Address: Division of Epidemiology and Community Health
University of Minnesota
Phone: 612-626-8862
Fax: 612-624-0315
E-mail: folso001@umn.edu

3. Timeline: Start summer 2013

4. Rationale:

An area that needs clarification is whether a low levels of serum vitamin D [25(OH)D] may predispose to VTE as it appears to do for atherothrombotic diseases. Lindqvist et al suggested this possibility by showing in a cohort of Swedish women that sunbathers had a 30% reduced VTE risk and VTE risk was 50% higher in winter than summer.[1] Vitamin D levels are clinically deficient in 38% of black women, 18% of black men, 5% of white women, and 1% of white men, and they are optimal in only 2%, 4%, 29%, and 26%, respectively.[2] Grant speculated that a link between low vitamin D and VTE might explain the African American excess of VTE.[3] Vitamin D receptor -/- mice, who display Vitamin D deficiency, have increased thrombogenic activity.[4] A large prospective study from Copenhagen recently reported an inverse association of vitamin D with VTE.[5] However, the Tromso study recently found no association of vitamin D with VTE, but was underpowered for low vitamin D levels.[6] Furthermore, administration of 1,25-di(OH)D3 (the physiologically active vitamin D hormone) reduced VTE occurrence in chronic kidney disease[7] and cancer patients.[8]

In February 2012, using ancillary R01 funding, the ARIC chemistry laboratory (University of Minnesota) began measuring a number of analytes in stored serum on the

entire ARIC cohort examined in Visit 2 (1990-92). Thus, Visit 2 measurements on approximately 14,000 of the 15,792 original ARIC participants will be available for vitamin D (25OH-Vitamin D, 3-epi-25OHD3).

5. Main Hypothesis/Study Questions:

Vitamin D is inversely associated with VTE incidence and partly explains the African American excess of VTE.

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).

Design: cohort

Endpoint: VTE incidence

Exposure: visit 2 vitamin D. Since serum vitamin D levels vary greatly by sun exposure, which is seasonal, we will account for seasonal variation by computing the residuals from a linear regression model with vitamin D as the dependent variable and month of blood draw as the independent variable. By definition, these residuals will be uncorrelated with month of blood draw. The grand mean will be added to the vitamin D residuals obtained from this model. This new variable "vitamin D adjusted for month of blood draw" will be used as the main exposure variable for all analyses.

Exclusions: VTE prior to visit 2, anticoagulant use, missing Vit D. For analyses using thrombophilia SNPs, we will also exclude on no DNA use or missing data.

Main covariates: visit 2 age, race, sex, HRT, BMI, diabetes, eGFR.

Analysis: The prospective cohort analysis for vitamin D will involve 14,000 ARIC participants followed from 1990-92 through 2011 and approximately 622 VTE events. Expected variances are 1-38% for low vitamin D (race-dependent) but these markers will also be analyzed as continuous variables. Analyses will be performed using proportional hazards modeling as in previous LITE publications. Most relevant confounding variables have been measured, and special care will be taken to deal with participants taking vitamin D supplements.

At alpha = 0.05, in ARIC alone we should have 80% power to detect HRs of 3.06, 2.23, 1.67, 1.45, 1.32, and 1.26 for prevalences of 1%, 2%, 5%, 10%, 20%, and 38%, respectively. Thus, we can reasonably detect moderate associations for low vitamin D.

Whether vitamin D explains the African American excess of VTE will be tested in a mediation model.

A supplemental analysis will look at Vit D associations with VTE in relation to people with thrombophilia SNPs or not.

REFERENCES

1. Lindqvist PG, Epstein E, Olsson H. Does an active sun exposure habit lower the risk of venous thrombotic events? A D-lightful hypothesis. *J Thromb Haemost* 2009;7:605-10.

2. Ginde AA, Liu MC, Camargo CA Jr. Demographic differences and trends of vitamin D insufficiency in the US population, 1988-2004. *Arch Intern Med* 2009;169(6):626-632.

3. Grant WB. Higher rates of venous thromboembolism for Black-Americans are likely due to lower serum 25-hydroxyvitamin D levels [Letter]. *Am J Hematol* 2010;85:907; author reply 908.

4. Wu-Wong JR. Are vitamin D receptor activators useful for the treatment of thrombosis? *Curr Opin Investig Drugs* 2009;10:919-27.

5. Brondum-Jacobsen P, Benn M. Tybjaerg-Hansen A, Nordestgaard BG. 25-Hydroxyvitmain D concentrations and risk of venous thromboembolism in the general population with 18,791 participants. *J Thromb Haemost* 2013;11(3):423-31.
6. Brodin EE, Lerstad G, Grimnes G, Braekkan SK, Vik A, Brox J, Svartberg J, Jorde R, Hansen J-B. Serum levels of vitamin D are not associated with future risk of venous thromboembolism. The Tromsø Study. *Thromb Haemost* 2013;109(5):885-90.
7. Moscarelli L, Zanazzi M, Bertoni E, Caroti L, Rosso G, Farsetti S, Annunziata F, Paudice N, Salvadori M. Renin angiotensin system blockade and activated vitamin D as a means of preventing deep vein thrombosis in renal transplant recipients. *Clin Nephrol* 2011;75:440-50.

8. Beer TM, Venner PM, Ryan CW, Petrylak DP, Chatta G, Dean Ruether J, Chi KN, Curd JG, DeLoughery TG. High dose calcitriol may reduce thrombosis in cancer patients. *Br J Haematol* 2006;135:392-4.

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

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)?

None

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 (* 2006.16 and 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.