ARIC Manuscript Proposal #2479

PC Reviewed: 12/9/14	**Status: <u>A</u>**	**Priority: <u>2</u>**
SC Reviewed: _____	**Status:** _____	**Priority:** ____

1.a. Full Title: Serum 25-hydroxyvitamin D and incident peripheral arterial disease: The Atherosclerosis Risk in Communities Study (ARIC)

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

2. Writing Group:
Writing group members: Ian R Rapson, Pamela L Lutsey, Kunihiro Matsushita, Erin D. Michos, Alvaro Alonso, Alan Hirsch.

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

First author: Ian R Rapson
Address: 1300 South 2nd St, Suite 300, Minneapolis, MN 55126
        Phone: (612) 669-4797   Fax:
        E-mail: Rapson@umn.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: Pamela L Lutsey
Address: 1300 South 2nd St, Suite 300, Minneapolis, MN 55126
        Phone: (612) 624-5812   Fax: (612) 624-031
        E-mail: Lutsey@umn.edu

3. Timeline: Data analyses will begin immediately. Goal completion by Jan 2015.

4. Rationale:

Vitamin D is the name for a group of secosteroids that are converted by the kidney to bio-active vitamin D (calcitriol). Vitamin D is acquired though exposure to sunlight or UVB (vitamin D3) or through ingestion (vitamin D2 and D3). Vitamins D2 and D3 are converted by the liver to serum 25-hydroxyvitamin D (25(OH)D). 25(OH)D is a precursor for bioactive vitamin D, and has been traditionally viewed as the best biomarker for assessing vitamin D status. The Institute of Medicine defines sufficient levels of 25(OH)D as ≥20 ng/mL, although this level is not based on recommendations for cardiovascular health.[1] In the United States approximately 25% of individuals are deficient in vitamin D, though this varies by race/ethnicity, with blacks having a higher prevalence of vitamin D deficiency than whites.[2]

Low levels of serum vitamin D are associated with a worse cardiovascular risk profile, including a greater propensity for diabetes mellitus, high blood pressure, low HDL, and inflammation.[3,4,5,6,7] Other research has associated low vitamin D with increased risk of CVD events.[9,10] For instance, a recent meta-analysis of prospective studies and clinical trials in healthy individuals found 35% greater risk of CVD death in participants in lowest tertile of vitamin D level compared to the highest tertile.[11]

Atherosclerotic lower extremity peripheral arterial disease (PAD) is defined by the presence of at least one high grade (>70%) stenosis in the arteries that supply the legs, usually present in the infrarenal aorta or more distal arteries. PAD prevalence in the US among those 40 and older is approximately 12.3%, which equates to more than 6.8 million individuals.[12]

There has been limited research into the association between 25(OH)D and PAD. Two previous cross-sectional analyses have used data from NHANES. In the first, Melamed et al reported that participants in the lowest quartile (<17.8 ng/mL) of vitamin D had a prevalence of PAD 1.80 (95% CI 1.19 – 2.74) times higher than participants in the highest quartile (≥29.2 ng/mL) after multivariate adjustment.[13] Also using NHANES data, Reis *et al.* specifically evaluated the interrelation between race and 25(OH)D on PAD prevalence. The study showed 67% higher odds of prevalent PAD in blacks compared to whites after adjustment for known cardiovascular risk factors (95% CI 1.11, 2.51). Additional adjustment for 25(OH)D reduced the odds ratio to 1.33 (0.84, 2.10), suggesting that 25(OH)D may explain racial disparities in PAD prevalence. Also, in a race stratified analysis, there was an interaction, with higher quartiles of 25(OH)D associated with lower prevalence of PAD in whites, but not in blacks.[14]

The only existing prospective study of 25(OH)D and PAD incidence used electronic medical records of 41,504 patients in the Intermountain Healthcare system who had vitamin D measured for clinical indications (e.g. osteoporosis risk). The study found a hazard ratio of 1.42 (1.04, 1.94) for patients with low vitamin D (≤15ng/ml) compared to those with normal levels (>30).[8]

Existing research on vitamin D and PAD is limited in that it has been cross-sectional (NHANES) or prospective using a clinical sample (Intermountain Health System). Results from the Intermountain Health System may be biased and not generalizable as a) only patients with a clinically indicated vitamin D test (most often for suspected osteoporosis) were included in the study, and b) incident PAD information was not universally assessed, but rather, obtained from electronic medical records. Also, it is possible that patients with low vitamin D levels may have been more likely than the control group to seek follow-up care.

As a prospective cohort the ARIC study is well positioned to fill a number of gaps in existing research. Results from the cohort would be generalizable, and can address racial differences. In addition to measurements of 25(OH)D, ARIC has information on related biomarkers such as eGFR, serum calcium, serum fibroblast growth factor 23, serum parathyroid hormone, serum phosphorus, and vitamin D binding protein SNPs rs7041 and rs4588. The information on vitamin D binding protein SNPs will allow for a more

detailed analysis of the genetic basis for racial differences in the effect of 25(OH)D on PAD incidence.

5.   Main Hypothesis/Study Questions:

We hypothesize that low 25(OH)D is associated with greater risk of incident PAD, and that this association is stronger among whites than blacks.

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).

Analysis Design

This will be a prospective analysis. 25(OH)D was measured at visit 2, thus visit 2 will be baseline for the present analysis. PAD will be a dichotomous variable based on measurement of ankle brachial index (ABI) taken at visits 1, 3, 4 and 5, and on information from incident PAD hospitalization through 2011.

Inclusion / Exclusion Criteria

We will exclude from this analysis participants with:

- Prevalent PAD (defined by an ABI of <0.9 at visit 1) at baseline, incident PAD between exams 1 and 3, and those with no ABI information at baseline.
- An ABI at baseline of greater than 1.4 (indicative of arterial stiffness that interferes with ABI as a diagnostic tool for PAD).
- Missing 25(OH)D levels.
- Those who are neither African American nor white, and African Americans from the MN and MD centers.

Variables

Exposure: Serum 25(OH)D adjusted for season, as in previous ARIC papers.[15]

Outcome: Incident peripheral artery disease, defined as an ABI of less than 0.9 at ARIC visits 3 or 4, or a hospital discharge code for peripheral artery disease during follow-up.

Potential effect modifiers: Race, sex, and vitamin D binding protein known SNPs rs7041 and rs4588.

Demographic and behavioral covariates: Age, ARIC field center, education, physical activity, smoking status.

Additional covariates: BMI, HDL cholesterol, LDL cholesterol, cholesterol medication, diabetes mellitus, eGFR, hs-CRP, hypertension medication, serum calcium, serum

fibroblast growth factor 23, serum parathyroid hormone, and serum phosphorus, systolic blood pressure.

Data Analysis

Baseline analysis will include descriptive statistics of all potential covariates and effect modifiers, stratified by categorical vitamin D exposure groups. Vitamin D levels will be represented categorically, according to clinical cut points for deficient vitamin D (<20 ng/mL), low vitamin D (20 to <30 ng/mL), and normal vitamin D (30+ ng/mL).

Primary analysis will use a Cox proportional hazards regression to model the relationship between 25(OH)D clinical categories and time to incident PAD (defined as the date of the visit 3 or visit 4 ARIC examination, or date of hospital discharge). Secondary analysis will use restricted cubic splines to visually depict the association between 25(OH)D and incident PAD.

In addition to an unadjusted model, we propose to model the relationship between vitamin D and PAD adjusting for several sets of covariates in nested models.

- Model 1: age, sex, race (as appropriate).
- Model 2: Model 1 + educational attainment, smoking status, physical activity, and BMI.
- Model 3: Model 2 + prevalent diabetes, hypertension medication use, systolic blood pressure, LDL cholesterol, HDL cholesterol, cholesterol medication use, and hs-CRP
- Model 4 (each covariate added separately): Model 3 + eGFR, serum calcium, serum fibroblast growth factor 23. serum parathyroid hormone, and serum phosphorus.

Significance of effect modification will be tested by using cross product terms for potential modifiers. Stratified results will be reported, as appropriate.

An important limitation of this analysis is that ABI was not measured at visit 2. We plan to use baseline values as a surrogate of ABI at visit 2. Will explicitly state this limitation in the manuscript text.

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)?

#2019 – 25-hydroxyvitamin D levels and incident stroke: twenty-year follow-up in a biethnic cohort

#2224 - 25-hydroxyvitamin D and risk of incident heart failure: The Atherosclerosis Risk in Communities Study (ARIC)

#2340 – 25-hydroxyvitamin D and incident diabetes: The Atherosclerosis Risk in Communities (ARIC) Study

#2377 – 25-hydroxyvitamin D levels, vitamin D binding protein gene polymorphisms, and vitamin D3 epimer with risk of incident coronary heart disease (CHD) among whites and blacks: the ARIC Study

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.

References:

1. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium; Ross AC, Taylor CL, Yaktine AL, et al., editors. Dietary Reference Intakes for Calcium and Vitamin D. Washington (DC): National Academies Press (US); 2011. Available from: http://www.ncbi.nlm.nih.gov/books/NBK56070/

2. Powe CE, Evans MK, Wenger J, et al. Vitamin D–Binding protein and vitamin D status of black Americans and white Americans. *N Engl J Med*. 2013;369(21):1991-2000. http://dx.doi.org/10.1056/NEJMoa1306357. doi: 10.1056/NEJMoa1306357.

3. Forman JP, Giovannucci E, Holmes MD, et al. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. *Hypertension*. 2007;49(5):1063-1069. doi: 10.1161/HYPERTENSIONAHA.107.087288.

4. Forman JP, Curhan GC, Taylor EN. Plasma 25-hydroxyvitamin d levels and risk of incident hypertension among young women. *Hypertension*. 2008;52:828-832

5. Krause R, Bühring M, Hopfenmüller W, Holick MF, Sharma AM. Ultraviolet b and blood pressure. *Lancet*. 1998;352:709-710

6. Mattila C, Knekt P, Männistö S, et al. Serum 25-hydroxyvitamin D concentration and subsequent risk of type 2 diabetes. *Diabetes Care*. 2007;30(10):2569-2570. doi: 10.2337/dc07-0292.

7. Shea MK, Booth SL, Massaro JM, et al. Vitamin K and vitamin D status: Associations with inflammatory markers in the framingham offspring study. *American Journal of Epidemiology*. 2008;167(3):313-320. doi: 10.1093/aje/kwm306.

8. Anderson JL, May HT, Horne BD, et al. Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population. *Am J Cardiol*. ;106(7):963-968. http://www.ajconline.org/article/S0002-9149(10)01131-8/abstract. doi: 10.1016/j.amjcard.2010.05.027.

9. Ford JA, MacLennan GS, Avenell A, et al. Cardiovascular disease and vitamin D supplementation: Trial analysis, systematic review, and meta-analysis. *The American Journal of Clinical Nutrition*. 2014. doi: 10.3945/ajcn.113.082602.

10. Wang L, Song Y, Manson JE, et al. Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: A meta-analysis of prospective studies. *Circulation: Cardiovascular Quality and Outcomes*. 2012;5(6):819-829. doi: 10.1161/CIRCOUTCOMES.112.967604.

11. Chowdhury R, Kunutsor S, Vitezova A, et al. Vitamin D and risk of cause specific death: Systematic review and meta-analysis of observational cohort and randomised intervention studies. *BMJ*. 2014;348. http://www.bmj.com/content/348/bmj.g1903.abstract.

12. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke Statistics—2014 update: A report from the american heart association. *Circulation*. 2014;129(3):e28-e292. doi: 10.1161/01.cir.0000441139.02102.80.

13. Melamed ML, Muntner P, Michos ED, et al. Serum 25-hydroxyvitamin D levels and the prevalence of peripheral arterial disease: Results from NHANES 2001 to 2004. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2008;28(6):1179-1185. doi: 10.1161/ATVBAHA.108.165886.

14. Reis JP, Michos ED, von Mühlen D, Miller ER. Differences in vitamin D status as a possible contributor to the racial disparity in peripheral arterial disease. *The American Journal of Clinical Nutrition*. 2008;88(6):1469-1477. doi: 10.3945/ajcn.2008.26447.

15. Folsom AR, Roetker NS, Rosamond WD, et al. Serum 25-hydroxyvitamin D and risk of venous thromboembolism: the Atherosclerosis Risk in Communities (ARIC) Study. Journal of Thrombosis and Haemostasis. 2014:n/a-n/a.