ARIC Manuscript Proposal #2618

PC Reviewed: 9/8/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Kidney function, its related biomarkers, and the future risk of peripheral artery disease

b. Abbreviated Title (Length 26 characters): Kidney dysfunction and PAD

2. Writing Group:

Writing group members: Chao Yang, Lucia Kwak, Shoshana Ballew, Bernard Jaar, Aaron Folsom, Gerardo Heiss, Elizabeth Selvin, Pamela Lutsey, Josef Coresh, Kunihiro Matsushita

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

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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).

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3. Timeline: Data to be used in this proposal are available. Analyses and manuscript preparation will be performed over the next 12 months.

4. Rationale:

Peripheral artery disease (PAD) affects more than 8 million adults in the US and increases the risk of adverse health outcomes. [1] PAD is especially an important complication for those with chronic kidney disease (CKD), particularly at advanced stage. [2 3 4] Indeed, the incidence of PAD is higher than that of myocardial infarction and stroke among patients on dialysis. [5] Of note, mildly to moderately reduced kidney function has been also linked to elevated risk of PAD in several reports. [6 7 8]

Since those reports were published, new equations for estimated glomerular filtration rate (eGFR) (e.g., the CKD-EPI equations) or novel filtration markers (e.g., β2-microglobulin [B2M] and cystatin C) have demonstrated stronger associations with cardiovascular events as compared to a traditional measure of kidney function, creatinine-based eGFR using the MDRD Study equation. [9 10 11 12 13 14] However, to our knowledge, those new equations and novel filtration markers have not been exclusively tested for incident PAD risk.

Moreover, patients with kidney dysfunction are prone to have abnormal bone mineral metabolism, with altered levels of fibroblast growth factor 23 (FGF-23), parathyroid hormone (PTH), serum calcium (Ca), and serum phosphate (P).[15 16 17] Several studies suggest these biomarkers may partially explain excess cardiovascular risk among persons with kidney dysfunction [16 17 18] but have not been exclusively evaluated in the context of PAD risk. In addition, it is unknown whether the associations of kidney filtration markers and PAD risk can be explained by altered bone mineral metabolism markers.

Therefore, we plan to comprehensively study the association of kidney function and bone mineral metabolism markers with future risk of PAD using data from the Atherosclerosis Risk in Communities (ARIC) study.

5. Main Hypothesis/Study Questions:

1. Kidney function will be independently associated with future PAD risk in general population, and the association will be particularly evident when novel filtration markers are used.
2. FGF-23, PTH, Ca, and P will be associated with future PAD risk beyond kidney function.

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).

Inclusions:

-All black and white ARIC subjects with available measures of the variables of interest

Exclusions:

-Ethnicity other than black or white
-Missing data on variables of interest
-Participants with a clinical history of PAD at baseline (determined by self-report leg artery revascularization at visit 1 and any PAD-related hospitalizations prior to the visit of interest [visit 2 for primary analysis and 4 for secondary analysis])

Exposures:

-Kidney function markers:

-eGFR based on serum creatinine and/or cystatin C (visit 2, 4, and 1 [only creatinine])

-Cystatin C (visit 2 and 4)

-B2M (visit 2)

-β-trace protein (only visit 4)

-Bone mineral metabolism related markers:

-FGF23 (visit 2)

-PTH (visit 2)

-Calcium (visit 2 and 1)

-Phosphate (visit 2 and 1)

Outcomes:

Given the uniform data availability over follow-up, PAD cases will be primarily identified according to the following ICD codes based on previous literatures[19 20]: 440.20 (atherosclerosis of native arteries of the extremities, unspecified); 440.21 (atherosclerosis of native arteries of the extremities with intermittent claudication); 440.22 (atherosclerosis of native arteries of the extremities with rest pain); 440.23 (atherosclerosis of native arteries of the extremities with ulceration); 440.24 (atherosclerosis of native arteries of the extremities with gangrene); 440.29 (other atherosclerosis of native arteries of the extremities); 440.3 (atherosclerosis of bypass graft of the extremities); 440.8 (atherosclerosis of other specified arteries); 443.9 (peripheral vascular disease, unspecified); 38.18, 39.25, 39.29, 39.50 (leg artery revascularization).

Cases with 440.22, 440.23, 440.24 or those with PAD codes plus codes for amputation, ulcer, or gangrene will be considered as critical limb ischemia (CLI) and we will repeat that analysis for CLI. As a sensitivity analysis, we will also take into account self-report of a PAD diagnosis assessed at a clinic visit or during an annual telephone call.

Other variables of interest and covariates:

Socio-demographics: age, race, gender, education

Physical information: blood pressure, body mass index, presence/absence of left ventricular hypertrophy by electrocardiogram

Lifestyle: smoking status/amount and alcohol consumption

Comorbidities: diabetes, dyslipidemia, coronary heart disease, stroke, heart failure, atrial fibrillation

Medication use: use of anti-hypertensive medication and cholesterol medication

Statistical analysis plan:

The primary analysis will use Cox proportional hazards models to quantify the prospective association of kidney function markers and kidney function related markers with incident PAD. These markers will be treated as both continuous variables with splines and categorical variables (quantiles and clinical categories if any) in the models. We will adjust for the covariates listed above. To test our main hypotheses, we will assess to what extent the associations of kidney function makers are attenuated after accounting for FGF23, PTH, Ca, or P, in turn. Also, we will assess whether the

associations of FGF23, PTH, Ca, and P with PAD risk are independent of kidney function.

We will conduct a few sensitivity analyses. Firstly, we will repeat the analysis after stratifying the study sample by key demographic and clinical subgroups according to age, gender, race, smoking status and the presence/absence of diabetes, hypertension, chronic kidney disease, and history of other cardiovascular diseases at baseline. We will formally test interaction using likelihood ratio test. Secondly, we will treat incident end-stage renal disease (dialysis and kidney transplant) as a time-varying covariate. Finally, given the potential impact of the competing risk of death for estimating PAD risk, we will run Fine and Gray's proportional subhazards models.[21]

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?
____ Yes __X__ 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"?
____ 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)?
[There are several ARIC proposals with PAD as an outcome as listed below (only recent ones are listed). #1915 "Improvement of cardiovascular risk prediction using non-traditional risk factors in the chronic kidney disease (CKD) population" will be most related to this proposal and includes creatinine, B2M, and cystatin C at visit 4 as exposures and PAD as one of the cardiovascular outcomes of interest. However, it does not have a plan to investigate CLI or incorporate kidney function related markers (e.g.,

FGF23 and PTH), and key authors of that proposal are in the current proposal as well. #2184 "Parathyroid hormone and CVD" is also relevant since it looks the association of PTH with cardiovascular outcomes including PAD. However, the results from that proposal was already published (Am Heart J 2014;168:296-302) and thus the current proposal will not interfere that proposal and will deepen the analysis specifically for PAD including CLI with extended follow-up. Although #1832 "A risk prediction model for incident PAD in the ARIC cohort" includes serum creatinine in the list of exploratory potential predictors for PAD risk, that proposal focuses on visit 1 variables, and the other kidney-related predictors (cystatin C, B2M, FGF23, PTH, P, Ca) are not taken into account.

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* 2014.05, 2009.16, 2006.16)

___ 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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