ARIC Manuscript Proposal # 3159

PC Reviewed: 5/8/2018  Status: _____  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: Race and Sex-Based Disparities Associated with the Risk of Incident Peripheral Artery Disease

b. Abbreviated Title (Length 26 characters): Disparities in PAD

2. Writing Group:
   Writing group members: Caitlin Hicks, Lucia Kwak, Shoshana Ballew, Corey A. Kalbaugh, Aaron Folsom, Gerardo Heiss, Josef Coresh, James Black III, Elizabeth Selvin, Kunihiro Matsushita

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

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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 8-10 million individuals in the United States and more than 200 million individuals worldwide. The most severe form of PAD is critical limb ischemia (CLI), which is characterized by rest pain, ulcers, or gangrene. Even with surgical intervention, as many as 40% of patients with CLI will require major amputation at one year. Individuals with PAD also have twice the risk of overall mortality, cardiovascular mortality, and major coronary events over 10 years compared to those without PAD.

Both genetic and environmental factors are associated with PAD. Age, serum cholesterol, hypertension, cigarette smoking, diabetes, and coronary heart disease are all associated with an increased risk of PAD. Regarding sex-based differences, there have been mixed results. For example, a few community-based studies using low ankle-brachial index (ABI) to define PAD reported that the prevalence of PAD is similar between male and female participants. However, these studies may merely reflect a property of ABI being higher in taller individuals since blood pressure may progressively increase with greater distance from the heart, rather than representing similar disease burden. In contrast, clinical data have shown that women are hospitalized for PAD less frequently than men, but have a higher proportion of emergent admissions. However, these studies have the critical limitation of not having denominator data (i.e., population at risk), but only numerator data (i.e., PAD patients) for comparing the incidence rates of PAD between men and women. Also, these clinical studies usually cannot address whether sex differences in PAD can be explained by differences in risk factor profile, since data are only available after or immediately prior to the diagnosis of PAD. There have been few community-based studies with long-term follow-up which have rigorously examined potential sex-based differences in PAD risk.

There have also been a number of studies describing racial disparities in PAD. In a recent meta-analysis comparing PAD prevalence in different ethnic groups, blacks were found to have the highest prevalence of disease, followed by whites and south Asians, respectively. Notably, the race disparity for PAD is far greater than racial differences observed for other cardiovascular outcomes. Black and Hispanic patients have also been shown to have higher reintervention rates after vascular surgery compared to white patients, and have a higher likelihood of amputation. However, the limitations described above for sex-based differences in PAD risk would also be relevant to racial difference, since stature differs by races and clinical database studies looking only at PAD patients are not optimal to quantify racial differences in incident PAD. Also, to our knowledge, only a few studies have explored sex- and racial-differences in PAD simultaneously in a single study population. The proposed study is unique because it examines sex- and racial-difference in hospitalizations related to PAD from middle age to older age; it examines disparities associated with risk of both PAD and CLI; and it explores the extent to which sex- and sex differences in incident PAD risk can be explained by traditional risk factors, socioeconomic status, and/or access to care.

To overcome the important limitations in previous studies, we will seek to describe sex- and racial-based disparities in the incidence of clinical PAD and CLI using data from the Atherosclerosis Risk in Communities (ARIC) Study. We hypothesize that, despite similar PAD prevalence based on ABI, the incidence of clinical PAD and CLI will be higher in men than in women similar to the risks of other atherosclerotic diseases such as coronary heart disease and stroke. For race, we hypothesize that the incidence of
PAD and CLI will be higher in black participants compared to white participants. Understanding the differences in PAD risk for different races and sexes will help us understand the disparities in treatment outcomes that are currently being reported 16-18.

5. Main Hypothesis/Study Questions:

PAD and CLI incidence will be higher in men than in women, and in black participants compared to white participants.

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 variables of interest

Exclusions:
- Ethnicity other than black or white
- Blacks from Minneapolis and Washington County field centers
- Missing data on variables of interest
- Participants with a history of PAD at baseline visit of interest (determined by ankle-brachial index <0.9 and self-report of intermittent claudication or leg artery revascularization at visit 1)

Exposures:
Our primary exposures of interest will be race (white vs. black) and sex (male vs. female) as reported at visit 1. Participants will be categorized by both sex and race to create 4 subgroups for comparison (White-Female; White-Male; Black-Female; Black-Male).

Outcomes:
PAD-related hospitalizations will be identified according to the following ICD codes based on previous literature 9, 10: atherosclerosis of native arteries of the extremities, unspecified (440.20); atherosclerosis of native arteries of the extremities with intermittent claudication (440.21); atherosclerosis of native arteries of the extremities with rest pain (440.22); atherosclerosis of native arteries of the extremities with ulceration (440.23); atherosclerosis of native arteries of the extremities with gangrene (440.24); other atherosclerosis of native arteries of the extremities (440.29); atherosclerosis of bypass graft of the extremities (440.3); atherosclerosis of other specified arteries (440.8); peripheral vascular disease, unspecified (443.9); leg artery revascularization (38.18, 39.25, 39.29, 39.50). Of these, 440.22, 440.23, and 440.24 will be considered CLI. Also, we will consider any cases with the above code as CLI when the following codes coexist: leg amputation (84.1x), lower extremity ulcer (707.1x), and gangrene (785.4).

Other variables of interest and covariates:
Sociodemographics: age, education, income, and insurance
Physical information: body mass index (visit 1), systolic and diastolic blood pressure, and ankle-brachial index (ABI) obtained at visit 1
Lifestyle: smoking status/type of exposure, alcohol status, frequency of healthcare visits
Comorbidities: diabetes, dyslipidemia, hypertension, kidney function, coronary heart disease, stroke, heart failure, atrial fibrillation
Laboratory values: HDL cholesterol, total cholesterol, fasting glucose
Medications: antihypertensive, antidiabetic, lipid-lowering, and antithrombotic drugs

**Statistical analysis plan:**
Our primary analysis will focus on the association between race and sex and 1) incident hospitalized PAD and 2) incident hospitalized CLI.
We will estimate cumulative incidence of PAD and CLI across the four sex- and racial-groups (White-Female; White-Male; Black-Female; Black-Male) using the Kaplan-Meier method. Then, we will use Cox proportional hazards models to account for the covariates listed above to quantify the association of the 4 groups with incident PAD-and CLI-related hospitalizations over time. To evaluate whether sex and race have uniquely strong associations with CLI, we will compare HR for PAD without CLI vs. that for CLI using seemingly unrelated regression.
We will implement four models to account for the impact of potential mediators on the race/sex–PAD relationship. Model 1 will be a crude (unadjusted) model. Model 2 will adjust only for age. Model 3 will further adjust for traditional atherosclerotic factors including smoking status, drinking status, total cholesterol, HDL cholesterol, diabetes, blood pressure, use of anti-hypertensive medications, and prevalent heart failure, coronary heart disease, and stroke. Model 4 will additionally include socioeconomic factors such as education level, income, insurance, and frequency of visits.
In addition, we will conduct sensitivity analyses by stratifying the study sample into key clinical subgroups to assess whether the associations identified above are consistent across an array of populations. Specifically, we will analyze the interaction between race/sex and incident PAD and CLI for age, smoking status, diabetes, hypertension, and history of cardiovascular disease (heart failure, coronary disease, and stroke) using the likelihood ratio test. Finally, given the potential impact of the competing risk of death for estimating PAD and CLI risk, we will run Fine and Gray’s proportional subhazards models.

**Limitations:**
The main limitations of our study include potential race-site aliasing in ARIC, lack of consistent ABI data over study visits, and our use of ICD-9 codes to identify incident hospitalized PAD. We are attempting to limit the race-site aliasing by excluding Blacks from the Minneapolis and Washington County field centers. The lack of ABI data is not prohibitive, because the aim of our study focuses on clinically relevant PAD, which may be expressed differently than subclinical (study-based) PAD. Finally, the ICD-9 codes we use identify incident hospitalized PAD are well described, and thus their use will be consistent with other literature published on this topic.

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 ___ 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.cscu.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). Of these, #1832 would be most relevant since it includes sex and race as potential predictors for PAD risk. However, the lead investigator of #1832, Dr. Matsushita, will play an important role in the current proposal as well and thus will be responsible for any coordination.

#1832: Risk prediction model for incident PAD in the ARIC cohort  
#1915: Improvement of cardiovascular risk prediction using non-traditional risk factors in the chronic kidney disease (CKD) population  
#2479: Serum 25-hydroxyvitamin D and incident peripheral arterial disease: The Atherosclerosis Risk in Communities Study (ARIC)  
#2497: Microvascular disease measures and the risk of peripheral artery disease  
#2922: Obesity measures and the risk of peripheral artery disease

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)
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:


