ARIC Manuscript Proposal #3262

PC Reviewed: 11/13/18  Status: _____  Priority: _____
SC Reviewed: __________  Status: _____  Priority: _____

1.a. Full Title: Carotid and popliteal artery characteristics and subsequent risk of three major atherosclerotic diseases: the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters):
Carotid/popliteal & ASCVD risk

2. Writing Group:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _Y.L._ [please confirm with your initials electronically or in writing]

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3. Timeline: The analyses will use existing ARIC data, and manuscript preparation will be performed in the following 12 months.
4. **Rationale:**

Atherosclerosis is a pathological condition resulting in plaque build-up within the artery walls. Atherosclerosis usually progresses over time, leading to arterial stenosis or occlusion, and can cause coronary heart disease (CHD), stroke, and peripheral artery disease (PAD) in some individuals. Despite overall declines in incidence during the past several decades, atherosclerotic cardiovascular disease is still the leading cause of morbidity and mortality in the US and many other countries. Although CHD, stroke, and PAD are categorized as atherosclerotic diseases, their pathophysiological processes are not identical. For example, lipids are particularly strongly associated with CHD, and hypertension is an especially potent risk factor for stroke. For PAD, diabetes and smoking are particularly strong risk factors.

The evaluation of subclinical vascular characteristics (e.g., intima-media thickness [IMT]) and their associations with subsequent risk of these three major atherosclerotic diseases is limited. Specifically, many studies have characterized the associations of carotid IMT and plaque with risk of CHD and stroke, generally reporting that carotid IMT was associated with stroke more than CHD, whereas carotid plaque was more strongly associated with CHD than stroke. Although a few studies included PAD as in composite cardiovascular outcomes, none compared carotid artery characteristics and their associations with CHD, stroke, and PAD in a single study sample.

In addition, although atherosclerosis is a systemic process, atherosclerosis in different vascular beds may associate with the risk of CHD, stroke, and PAD differently. However, to our knowledge, only one cross-sectional study compared carotid and popliteal IMT for prevalent CHD, stroke, and PAD and did not necessarily find evidently different results for carotid and popliteal artery characteristics, although their wall thickness tended to be greater in prevalent cases than their counterparts. However, cross-sectional studies can be influenced by survival bias. Also, this study defined prevalent cases based on self-reported medical history or symptoms indicative of CHD, stroke, and PAD. Moreover, in addition to wall thickness, some other vascular characteristics (e.g., lumen diameter) may further promote our understanding of the pathophysiology and manifestation of clinical atherosclerotic diseases.

To address these gaps in the literature, we will investigate multiple vascular characteristics (IMT, lumen size, and plaque) of carotid and popliteal arteries and their associations with subsequent risk of CHD, stroke, and PAD over ~30 years in the single study population, the Atherosclerosis Risk in Communities (ARIC) cohort study. Of note, recently, the involvement of microvascular disease has attracted attention in the development of critical limb ischemia (CLI), a severe manifestation of PAD. We will examine CLI in this study as well.

5. **Main Hypothesis/Study Questions:**

1. Characteristics of carotid artery and popliteal artery will be associated with all of CHD, stroke, and PAD, but the magnitude of associations will vary across three types.
2. Carotid artery characteristics will be more strongly associated with stroke followed by CHD and PAD.
3. Popliteal artery characteristics will be more strongly associated with PAD followed by CHD and stroke.
4. Since microvascular disease is considered to play an important role in the development of CLI, CLI will show the weakest association particularly with carotid artery characteristics among these atherosclerotic phenotypes.

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).

Study design:

Prospective cohort study

Inclusion criteria:

All black and white ARIC study participants free of prevalent CHD, stroke, and PAD at visit 1 with data on any vascular measurements.

Exclusion criteria:

- Participants who identified themselves as non-white/non-black.
- Participants with prevalent CHD, stroke, PAD or heart failure.
- Participants with missing data on all of vascular measurements, covariates of interest, and outcomes.

Exposure:

IMT, lumen size, and plaque were assessed using high resolution B-mode ultrasound transducer (Biosound 2000 II SA). A common scanning protocol was used over four field centers, with central reading of ultrasound studies according to a standardized protocol. Carotid artery was measured bilaterally at three sites: 1) the common carotid artery (1 cm proximal to the dilatation of the carotid bulb); 2) the carotid bifurcation (1 cm proximal to the flow divider); 3) and the internal carotid artery (1 cm distal to the flow divider). Popliteal artery was measured at single site (horizontal crease behind the knee) for one leg randomly determined.

At each site, up to 11 measurements at 1 mm increment were attempted. IMT was measured from the blood-intimal to the medial-adventitial interface along the far wall (farthest from the skin surface), and specified as mean or maximum value across all measurements for each site. Mean IMT missing at any of 6 carotid sites were imputed by multivariate linear models, conditioning on carotid site, age, body mass index, arterial depth, race, and sex. Lumen size was defined as the mean distance between pairs of medial-adventitial interfaces minus twice the maximum far wall IMT. Plaque was recorded only for carotid artery by ultrasound readers.
as “presence” if 2 of the following 3 criteria were met:\(^6\) 1) IMT >1.5 mm; 2) protrusion into the lumen, or loss of alignment with adjacent arterial wall boundary; 3) brighter echoes than adjacent boundaries.

We will include mean IMT, maximum IMT, lumen size, and plaque at common carotid artery, carotid bifurcation, internal carotid artery, and popliteal artery, whenever capable, into analyses. Since carotid artery was measured bilaterally, we will take the average of mean IMT, maximum IMT, and lumen size at both right and left sides, and define presence plaque as either right or left side.

**Outcome:**

Incident CHD:\(^18\) a definite or probable myocardial infarction, or fatal CHD.

Incident stroke:\(^19\) definite or probable ischemic and hemorrhagic stroke cases, defined as sudden or rapid onset of neurological symptoms that lasted for 24 hours or led to death in the absence of another cause.

Incident PAD:\(^20-22\) the first hospital admission with PAD diagnosis or leg revascularization according to the following ICD codes: 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); leg artery revascularization (38.18, 39.25, 39.29, 39.50). Of PAD cases, those with 440.22, 440.23, and 440.24 as well as any cases with the coexisting code of leg amputation (84.1x), lower extremity ulcer (707.1x), and gangrene (785.4) were considered as CLI.

Each participant was followed from baseline through September 30, 2015, for incident CHD, stroke, and PAD.

**Covariates:**

- Demographics: age, race, gender
- Physical information: height, body mass index, blood pressure
- Lab examination: total cholesterol, high-density lipoprotein cholesterol, estimated glomerular filtration rate, menopause status for female;
- Lifestyle: education level, smoking status and drinking status
- Comorbidities: diabetes, hypertension, and other cardiovascular diseases
- Medication: antihypertensive medication, cholesterol-lowering medication, and hormone therapy
Statistical analysis:

Baseline characteristics will be compared as numbers (proportions) for categorical variables, means (standard deviation, SD) for continuous variables, across 4 groups of free of vascular events, incident CHD, incident stroke, and incident PAD as well as according to vascular characteristics (e.g., quartiles of carotid and popliteal IMT or the presence/absence of plaque).

We will conduct primary analysis using complete cases for each measurement. Poisson regression models will be used to assess age-, gender-, and race-adjusted incidence rates of CHD, stroke, and PAD over the full spectrum of each vascular measurement (except plaque), with spline knots at quartile cut-offs. We will then group each continuous vascular measurement as quartiles. Three progressively adjusted Cox proportional hazard models will be used to quantify the associations of vascular measurements with outcomes, with the 1st quartile for carotid IMT, 2nd quartile for Popliteal IMT, 4th quartile for lumen size, and absence for plaque, as the reference groups: 1) model 1: crude model; 2) model 2: + age, gender, and race; 3) model 3: + education level, smoking and drinking status, height, body mass index, systolic blood pressure, total and high-density lipoprotein cholesterol, estimated glomerular filtration rate, menopause status for female, prevalent of diabetes, and medication on antihypertension, cholesterol-lowering, and hormone therapy. To contrast the magnitude of associations across CHD vs. stroke vs. PAD, or PAD without CLI vs. CLI, We will evaluate the difference in effect size using seemingly unrelated estimation.

Moreover, we will assess potential heterogeneity by age (<55 vs. ≥55), gender, race, smoking status, the presence/absence of diabetes, hypertension (defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or taking any anti-hypertensive medication), and kidney function (estimated glomerular filtration rate <60 vs. ≥60 mL/min/1.73m²). Their potential multiplicative interactions will be evaluated using likelihood ratio test.

We will also conduct several sensitivity analyses in this study. 1) Instead of using the average carotid measurement, we will repeat analyses using higher value of mean IMT, maximum IMT, and lower value of lumen size at right or left side; or using carotid measurement at the same side for popliteal measurement. 2) Since missing measurements for popliteal artery may not be completely at random, we will apply the stabilized inverse probability-weighting method to address potential selection bias. To estimate probability of missing popliteal measurement at baseline, we will include all potential confounders, ABI at baseline, as well as carotid measurement into models. Alternative is to repeat analyses for complete cases with all vascular measurements.

All analyses will be performed with Stata version 14.0, and a p-value <0.05 will be considered statistically significant.

Limitations:
Evidence showed that it is more common to have artery stenosis in one leg rather than both in an unselected population. Popliteal measurements assessed in the single leg may not necessarily capture atherosclerotic condition and thus may attenuate their true associations with vascular events. In addition, approximately 1/3 and 1/2 of ARIC participants missed popliteal IMT and lumen size at visit 1 due to equipment failure, difficulty in scanning among obese participants and other reasons. Even for those with available readings, the association might be biased by measurement error due to poor quality of ultrasound image.

7.a. Will the data be used for non-CVD analysis in this manuscript? _____ Yes    ___ 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

    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)? Almost all ARIC proposal including popliteal artery measures were proposed more than 10 years ago. One exception is #2516 “Subclinical atherosclerosis and incident end-stage renal disease: The Atherosclerosis Risk in Communities (ARIC) Study.”, but this proposal focused on end-stage renal disease as an outcome but not atherosclerotic cardiovascular 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
    ___ A. primarily the result of an ancillary study (list number* _________)
**B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s))* __2014.05__ __________ __________)

*ancillary studies are listed by number at [http://www.cscc.unc.edu/aric/forms/](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/](http://publicaccess.nih.gov/) are posted in [http://www.cscc.unc.edu/aric/index.php](http://www.cscc.unc.edu/aric/index.php), under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit_process_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes ____ No.

References:


