ARIC Manuscript Proposal # 3310

PC Reviewed: 12/11/18 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Ankle-brachial index and subsequent risk of infectious disease in older individuals

b. Abbreviated Title (Length 26 characters): ABI and infections

2. Writing Group:
Writing group members: Yejin Mok, Junichi Ishigami, Pamela Lutsey, Hirofumi Tanaka, Michelle Meyer, Gerardo Heiss, Kunihiro Matsushita

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _____ **[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: Analyses and manuscript preparation will be performed over the next 6 months.

4. Rationale:
Patients with cardiovascular disease (CVD) have high risk of infectious disease,[1-6] and beneficial effects of vaccination have been shown in this clinical population.[6-8] Consequently, the Advisory Committee on Immunization Practice includes CVD as one of high risk conditions for indication

of vaccination.[9] Moreover, the recent clinical practice guidelines recommend influenza and pneumococcal vaccination in patients with CVD.[10-15]

In this context, a recent study have demonstrated that infection was the most common reason for readmission in severe peripheral artery disease (PAD) patients.[16] In addition, diabetes, which is prevalent in PAD patients,[17, 18] is associated with an increased risk of several types of infections such as skin infections, osteomyelitis, sepsis, urinary tract infections, and cellulitis.[19-21] However, a comprehensive analysis on the risk of infections among persons with PAD is lacking. Such an analysis may help guide appropriate prevention strategies (e.g., vaccination) in PAD patients.

Therefore, we will evaluate the association of a representative indicator of PAD, ankle-brachial index (ABI), with risk of infection in a large community-based cohort, the Atherosclerosis Risk in Communities (ARIC) Study. In addition to overall infection, we will evaluate specific types of infections, including pneumonia, urinary tract infection, bloodstream infections, and cellulitis, separately. Also, since the concept of polyvascular disease attracts attention,[22, 23] we will contrast infection risk among coronary heart disease (CHD)/stroke+PAD, CHD/stroke alone, PAD alone vs. neither of them.

5. Main Hypothesis/Study Questions:

- Lower ABI will be associated with higher risk of infections independently of comorbidities such as diabetes, or history of cardiovascular disease.
- Infectious disease risk will be highest in CHD/stroke+PAD, followed by PAD alone, CHD/stroke alone and neither of them.

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

- We will quantify the association of ABI at visit 5 (2011-2013) with incident risk of infectious disease

Inclusions:

- All ARIC participants with data on ABI and other necessary covariates at visit 5

Exclusions:

- Race other than black and white
- Missing data on ABI and other covariates at visit 5

Exposure:

- Exposure of interest will be ABI at visit 5. Systolic blood pressure of both upper and lower extremity was simultaneously measured twice (five minutes apart) using an automated oscillometric device OMRON VP-1000 plus (Kyoto, Japan) by certified technician. The higher value of the right or left brachial systolic blood pressure was used as the denominator, and the ABI, the ratio of ankle systolic blood pressure to brachial systolic blood pressure, was calculated for right and left legs. The mean ABI of the two measurements was recorded for each leg. For this analysis, we will use the lower value of

the right and left ABI. However, the higher value will use only when the higher ABI is greater than 1.3 and the lower ABI is normal (1.0-1.3), to avoid missing potentially pathophysiological information from exceptionally high ABI indicating arterial non-compressibility.[24]

- CHD and stroke will be defined as definite of probable cases adjudicated by ARIC physician panel.

Outcomes:

- Primary outcome of interest will be hospitalization with four types of infection (cellulitis, pneumonia, urinary tract infections, and bloodstream infections) after visit 5 (2011-2013) through December 31, 2016.
- Infections will be defined based on ICD-9 codes (cellulitis [040.0, 681, 682, and 730.0-2], pneumonia [480-486]; urinary tract infections [590.1, 599.0, and 601.0], and bloodstream infections [038, 054.5, 785.52, 790.7, 995.91, and 995.92]) or corresponding ICD-10 codes.
- As secondary outcome, we will investigate outpatient infections as well. Outpatient visits for infections will be identified from CMS Medicare data (at least two visits for infections as primary exposure and at least a visit as secondary exposure)

Covariates: socio-demographic characteristics (age, race, gender, education), alcohol intake, smoking status, body mass index, history of heart failure, hypertension (systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of antihypertensive medication), diabetes (fasting blood glucose ≥126 mg/dL, non-fasting glucose ≥200 mg/dL, reported history of diabetes, or use of anti-diabetes medication), lipid parameters (Total cholesterol, HDL cholesterol and LDL cholesterol), antidyslipidemia medications, C-reactive protein, health insurance status (besides Medicare), self-rated health (annual follow-up data), physical activity and frailty at visit 5.

Statistical analysis

1. ABI will be categorized as ≤0.90, 0.91-1.00, 1.01-1.10, 1.11-1.20, 1.21-1.30, and >1.30.[24] The category of 1.11-1.20 will be used as reference according to literature and the distribution in ARIC.[25] To assess a potential association of cardiovascular disease with infections, as secondary categorization, we divided into those with and without history of cardiovascular disease, then subdivided those without history of cardiovascular disease into ABI ≤0.90, 0.91-1.00, 1.01-1.10, 1.11-1.20, 1.21-1.30, and >1.30.
2. We will summarize baseline characteristics by ABI categories.
3. We will quantify the association of ABI with overall infections using Cox proportional hazards models. Those models will adjust for covariates listed above.
4. Subsequently, we will repeat analysis for four subtypes of infections.
5. We will conduct a few sensitivity analysis
    a. To compare the contribution of ABI to infections in subgroups, we will perform subgroup analysis according to age, gender, race, smoking status, health insurance status (besides Medicare) and clinical conditions (diabetes, hypertension, and history of heart failure). In order to test potential effect modification, likelihood ratio test will be used.

b. Since we cannot capture outpatient visits for infectious disease outside of Medicare fee-for-service beneficiaries aged ≥65 years, we will restrict to ARIC participants enrolled continuously in Medicare Parts A and B through a fee-for-service after visit 5 to either of date of infectious diagnosis or censoring (death loss to follow-up and end of follow-up of CMS claims data) and repeat analysis. Also, we repeat analysis outpatient outcome for infectious disease separately.
c. To avoid a potential association of ulcer or gangrene with cellulitis, we will censor those with incident ulcer/gangrene before cellulitis.

6. We will repeat analysis with CHD/stroke+PAD, CHD/stroke alone, PAD alone vs. neither of them as an exposure.

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)?
#3056: Ankle-brachial index and short-term risk of cardiovascular events in older adults
#2871: Cardiac Markers and Risk for Hospitalization with Infection: The Atherosclerosis Risk in Communities (ARIC) Study

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ 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)* _____ _____ _____)

*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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