1.a. **Full Title:** Association of Atrial Fibrillation (AF) with incident Peripheral Artery Disease (PAD) and Critical Limb Ischemia (CLI): The Atherosclerosis Risk in Communities (ARIC) Study

b. **Abbreviated Title (Length 26 characters):** AF and PAD/CLI

2. **Writing Group:**
   Writing group members: Wobo Bekwelem, Lucia Kwak, Alvaro Alonso, Lin Yee Chen, Gerardo Heiss, Kunihiro Matsushita

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

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3. **Timeline:** Statistical Analysis: 2-3 month Manuscript preparation: 2-3 months
4. **Rationale:**
Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and its prevalence is increasing over time. AF is associated with an increased risk of stroke, heart failure, and death. AF has been shown to be more prevalent in patients with peripheral artery disease (PAD) compared to the general population. Data from the international REACH registry has demonstrated the high co-prevalence of PAD and AF, and the additive risk of these two clinical syndromes. In the REACH registry, there was an 11.5% prevalence of AF among PAD patients compared to an estimated prevalence of 2.3% and 5.9% in the general population aged ≥40 years and ≥65 years, respectively. PAD has been shown to be associated with incident clinical AF regardless of age, sex, race/ethnicity, and cardiovascular risk factors among postmenopausal women and the general population.

Although the association of PAD with AF is well established, few studies have evaluated the association of AF with incident PAD and critical limb ischemia (CLI). Chia-Jung and colleagues evaluated the relationship between prevalent AF and incident PAD in Taiwan, and found that there was a 1.3-fold increased risk of PAD among AF patients. While it is known that systemic embolic events in AF can lead to limb ischemia, no prior studies have evaluated the link between prevalent AF and risk of CLI.

Therefore, we will quantified the associations of AF with PAD and CLI using data from the ARIC Study. Leveraging longitudinal data of ARIC, we will assess AF as a time-fixed exposure and a time-varying exposure.

5. **Main Hypothesis/Study Questions:**
Aim 1: Evaluate the association of AF (as time-fixed exposure at visit 4) with incident PAD and CLI.

Aim 2: Evaluate the longitudinal association of AF (as time-varying exposure from visits 1 through the end of follow-up) with incident PAD and CLI.

Aim 1 will inform whether and to what extent individuals with AF at a given time point have higher risk compared to those without, whereas Aim 2 will quantify the association of AF, as a clinical trait, to the risk of PAD and CLI.

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 population**
Visit 1 through 2015 or any available updated data

**Inclusion criterion:**
White or black participants with variables of interest summarized below

Exclusion criteria:
Non-whites, non-blacks
Missing variables of interest

**Exposure variables**
Time-fixed AF: To have enough AF cases, we will set visit 4 as baseline and participants with AF will be defined as AF identified at any ARIC visit ECG or hospitalizations with AF.

Time-varying AF: Any episode of AF detected from visit 1 through the end of follow-up will be treated as time-varying AF.

**Outcomes**
PAD-related hospitalizations will be identified 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); 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).

**Covariates**
Age, sex, race, educational level, smoking status (current, former, never), pack-years of smoking, body mass index, systolic blood pressure, diabetes, coronary heart disease, heart failure, stroke, use of antihypertensive medications, use of statins/lipid lowering medications, total cholesterol, and HDL.

**Statistical analysis**

Aim 1
Using cox proportional hazards models, we will assess the association between time-fixed prevalent AF at visit 4 and incident PAD and CLI.
Model 1: Adjusted for age, sex, and race/field center
Model 2: Model 1 + other variables at visit 4 listed in the section of “Covariates” above

Aim 2:
Using cox proportional hazards models, we will assess the association between time-varying prevalent AF from visit 1 through the end of follow-up and incident PAD and CLI
Model 1: Adjusted for age, sex, and race/field center
Model 2: Model 1 + other variables listed in the section of “Covariates” above
In this analysis we will do our best to treat as many variables as possible as time-varying covariates using data from visits and (semi-)annual phone interview.

**Supplemental analyses**

1. We will perform subgroup analysis by age, gender, race, smoking status, and a history of diabetes and other cardiovascular disease.
2. We will analyze AF based on ARIC visit ECG and AF based on hospitalization separately.

7.a. Will the data be used for non-CVD analysis in this manuscript? __ Yes ___X__ No

7.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.cscc.unc.edu/ARIC/search.php](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)?

#2505 (Association of Peripheral Artery Disease with Arrhythmia and Atrial Fibrillation Burden: The Atherosclerosis Risk in Communities (ARIC) Study) is most relevant but this proposal evaluated the association of PAD with incident AF which is opposite from the current proposal. Also, key investigators of #2505 are included in the current proposal. The authors of the proposals above will be included as co-authors in the current proposal.

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* 2013.14 and 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/](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 ____X__ No.

References:


