ARIC Manuscript Proposal #2720

PC Reviewed: 3/8/16	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Longitudinal Association of Peripheral Artery Disease (PAD) with Atrial Fibrillation (AF): The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 10 characters): PAD and AF

2. Writing Group:

Writing group members: Wobo Bekwelem, Faye Lopez, Sunil K. Agarwal, Kunihiro Matsushita, Josef Coresh, Alvaro Alonso, Lin Y Chen.

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: 1 month
Manuscript preparation: 2 months

4. Rationale:

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and its prevalence is increasing over time.[1] AF is associated with an increased risk of stroke,[2] heart failure,[3] and death.[4, 5] AF has been shown to be more prevalent in patients with peripheral artery disease (PAD) compared to the general population[6-8]. 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[7,8]. 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[8,9]. PAD has been shown to be associated with incident clinical AF regardless of age, sex, race/ethnicity, and cardiovascular risk factors among postmenopausal women[10] and the general population[11,12].

Although the association of PAD with AF is well established, it is unknown what effect the severity of PAD (as measured by the ankle-brachial index [ABI]) has on AF incidence. Specifically, if borderline ABI (0.91-0.99) has a similar association as ABI <0.9 on AF incidence.

PAD guidelines define a normal ABI range of 1.00 to 1.40, and abnormal values are defined as ≤0.90. ABI values of 0.91 to 0.99 are considered "borderline" and values >1.40 indicate noncompressible arteries (13). Individuals with noncompressible arteries may represent a higher risk/different group of PAD. This noncompressibility is related to the presence of medial arterial calcification which is more common in the elderly and diabetics, compared to just atherosclerosis in the general PAD (ABI ≤0.9) population (14).

Prior studies that have evaluated this relationship have defined PAD as ABI <1.0 or >1.4 (15,16). In a recent report by O'Neal and colleagues using data from the MESA study (16), the associations between AF and high (>1.4) and low (<1.0) ABI values were examined separately. They were found to be in the same direction as the main result for PAD (defined as both ABI <1.0 and ABI >1.4 grouped together). The adjusted HR for ABI <1.0, was 1.5, 95% CI 1.1 to 2.0; ABI >1.4, adjusted HR 1.8, 95% CI 0.65 to 4.8). The authors stated that the result for ABI values >1.4 was not significant due to the small number of participants in this group (n=40) and consequently a small number of AF cases (n=4). We anticipate that the higher number of participants and incident AF cases in ARIC will provide greater power to evaluate an association with ABI >1.4. Also, examining the borderline ABI group separately will provide insights into the effect of early stages of PAD on AF incidence.

5. Main Hypothesis/Study Questions:

Aim 1: Evaluate the longitudinal association of PAD (ABI ≤0.9 or >1.40) measured at visit 1 with AF incidence.

Hypothesis 1: PAD is independently associated with incident AF.

ABI is categorized as follows:

≤0.90	Abnormal
0.91 to 0.99	Borderline
1.0 to 1.40	Normal
>1.40	Non-compressible

Aim 2: Evaluate the longitudinal association of borderline PAD (ABI 0.91-0.99) measured at visit 1 with AF incidence.

Hypothesis 2: Compared with the normal group, borderline PAD is independently associated with incident AF.

Aim 3: Evaluate the longitudinal association between ABI ≤0.9 and ABI >1.4, separately with AF incidence.

Hypothesis 3: ABI ≤0.9 and ABI >1.4 are both associated with AF incidence.

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 (1987-89) through 2012

Inclusion criterion:
Participants attending visit 1

Exclusion criteria:
Missing ABI
Non-whites, non-blacks
Prevalent AF
Unreadable ECG
Missing covariates

Exposure variables
ABI measured at visit 1 in 4 categories (≤0.9, 0.91-0.99, 1.0-1.4, >1.40), and as guideline recommended categories as follows:

≤0.90	Abnormal
0.91 to 0.99	Borderline
1.0 to 1.40	Normal
>1.40	Non-compressible

Dependent variables
Incident AF

Covariates
Age, sex, educational level, smoking status (current, former, never), body mass index, systolic blood pressure, diabetes, coronary heart disease, heart failure, use of antihypertensive medications.

Statistical analysis
Aim 1
Using cox proportional regression models, we will assess the association between PAD (ABI ≤0.9 and ABI >1.40) and incident AF.
Model 1: Adjusted for age and sex
Model 2: Model 1 + educational level, smoking status, body mass index, SBP, use of antihypertensive medication, diabetes, coronary heart disease, heart failure,

Aim 2:
Using cox proportional regression models, we will assess the association between borderline PAD (ABI 0.91-0.99) and incident AF.
Model 1: Adjusted for age and sex
Model 2: Model 1 + educational level, smoking status, body mass index, SBP, use of antihypertensive medication, diabetes, coronary heart disease, heart failure,

Aim 3:
Using cox proportional regression models, we will assess the association between ABI ≤0.90 and ABI >1.4 separately with incident AF.
Model 1: Adjusted for age and sex
Model 2: Model 1 + educational level, smoking status, body mass index, SBP, use of antihypertensive medication, diabetes, coronary heart disease, heart failure,

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)?**

#1740 : AF and Dementia – Chen
#1739: AF and Cognitive Decline – Chen

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)
___ 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.

13. References

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