ARIC Manuscript Proposal #2505

PC Reviewed: 3/10/15  Status: A  Priority: 2
SC Reviewed:  _________  Status: _____  Priority: _____

1.a. Full Title: Association of Peripheral Artery Disease with Arrhythmia and Atrial Fibrillation Burden: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): PAD and Arrhythmias

2. Writing Group:

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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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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Or

Name: Alvaro Alonso, MD, PhD
Address: Division of Epidemiology and Community Health
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 whether the severity of PAD (as measured by the ankle-brachial index [ABI]) correlates with AF burden (% time a person is in AF). Further, little is known about whether PAD is associated with other arrhythmias such as PACs, SVT (including atrial tachycardia), PVCs, and NSVT.

The relationship between PAD (as well as other markers of systemic atherosclerosis) and AF may be bidirectional. For example, higher carotid intima-media thickness, carotid-femoral pulse wave velocity, and lower aortic elasticity indices\(^13,14\) are associated with higher incidence of AF. The mechanisms underlying these associations may relate to increased arterial stiffness leading to left ventricular diastolic dysfunction, left atrial remodeling, and finally left atrial fibrosis which promotes AF\(^15,16\). Alternatively, systemic and coronary atherosclerosis leading to atrial ischemia and atrial fibrosis is another mechanism\(^17\). On the other hand, recurrent AF-related thromboembolic events contribute to progression of PAD. If PAD is found to be associated with other arrhythmias such as atrial tachycardia or NSVT, it would support the notion that systemic atherosclerosis leads to arrhythmia and AF, rather than the other way around. This notion, in turn, would underscore the importance of treating atherosclerotic risk factors to reduce the burden of arrhythmia, including AF.

The availability of Zio®Patch—a non-invasive, leadless, 2-week ECG recording device that is easy to use—has now made it possible to record arrhythmias and arrhythmia burden (including AF burden).\(^18\) We will leverage Zio®Patch data that were collected from 325 participants in an ARIC pilot study and ABI data at Visit 5 to investigate the relationship between PAD and arrhythmias.
5. **Main Hypothesis/Study Questions:**
Aim 1: Evaluate the cross-sectional association of PAD (ABI ≤0.9 or >1.40) measured at visit 5 with AF, PACs, SVT, PVCs, and NSVT.
Hypothesis 1: PAD is independently associated with AF, PACs, SVT, PVCs, and NSVT.

Aim 2: Evaluate the cross-sectional association of ABI measured at visit 5 with arrhythmia burden, including AF burden. ABI is categorized as follows:

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.90</td>
<td>Abnormal</td>
</tr>
<tr>
<td>0.91 to 0.99</td>
<td>Borderline</td>
</tr>
<tr>
<td>1.0 to 1.40</td>
<td>Normal</td>
</tr>
<tr>
<td>&gt;1.40</td>
<td>Non-compressible</td>
</tr>
</tbody>
</table>

Hypothesis 2: Using AF burden as an example, there will be a U-shaped relationship between ABI and AF burden with AF burden being highest for ABI ≤0.90 and >1.40 and lowest for ABI: 1.0 to 1.40.

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**

**Inclusion criterion:**
1. Participants at the Washington County and Minneapolis field center with analyzable Zio Patch ECG data of ≥48 hours

**Exclusion criteria:**
1. Participants with amputation
2. Missing ABI
3. Non-whites

**Exposure variables**

ABI measured at visit 5 in 3 categories (≤0.9, 0.91-1.40, >1.40), and as guideline recommended categories as follows:

<table>
<thead>
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**Dependent variables**

AF (present or absent, % burden)
PAC (present or absent, % burden)
SVT (present or absent, no. of episodes/day)
PVC (present or absent, % burden)
NSVT (present or absent, no. of episodes/day)
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, and left ventricular ejection fraction

Statistical analysis
Aim 1
Using logistic regression models, we will assess the association between PAD (ABI ≤0.9 and ABI >1.40) and presence of arrhythmia.
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, and left ventricular ejection fraction

Aim 2:
We will use the general linear model to assess association of % burden or no. of episodes of each arrhythmia with each ABI category:
   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, and left ventricular ejection fraction

As a sensitivity analysis, excluding those with prevalent AF at visit 4, we will examine the relation of ABI at visit 4 to AF and AF burden at visit 5. This will demonstrate a temporal association of PAD and AF burden, and support the notion that notion that systemic atherosclerosis leads to arrhythmia and AF, rather than the other way around.

As a further sensitivity analysis, we would repeat the above analyses using sampling weights. This is important given that the individuals with ZioPatch were selected among those who had brain MRI, who were a sub-sample of individuals in visit 5.

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.cscce.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


