ARIC Manuscript Proposal #2683

PC Reviewed: 1/12/16  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: Ankle-Brachial Index and Risk of Sudden Cardiac Death: the Atherosclerosis Risk In Communities (ARIC) Study

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

2. Writing Group:
Writing group members: Takeki Suzuki, MD, MPH, PhD; Selcuk Adabag, MD, MS; Kunihiro Matsushita, MD, PhD; Kenneth R. Butler, PhD; Michael E. Griswold, PhD; Alvaro Alonso, MD, PhD; Wayne Rosamond, PhD, MS; Nona Sotoodehnia, MD, MPH; Thomas H. Mosley, PhD; others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. TS [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:
Data to be used in this proposal are currently available. Analyses and manuscript preparation will be performed over the next 6 month
4. **Rationale:**
Sudden cardiac death (SCD) is an important public health problem.\(^1\) It is estimated that 300,000 deaths occur each year in the U.S.;\(^2\) accounting for 15% of total mortality.\(^3\) SCD is a leading cause of mortality in the U.S. Worldwide, 4-5 million deaths occur due to SCD each year.\(^4\)

Atherosclerosis has been shown to be associated with coronary heart disease (CHD) and stroke.\(^5\) The ankle-brachial index (ABI) is a simple, non-invasive measure of subclinical atherosclerosis.\(^6\)\(^7\) The ABI offers prognostic data that are useful to predict amputation,\(^8\) coronary heart disease,\(^9\) burden of systemic atherosclerosis,\(^10\) stroke,\(^11\) cardiovascular death and all-cause mortality.\(^12,13\)

Although CHD and SCD share many of the risk factors, whether subclinical atherosclerosis, measured by ABI, is associated with risk of SCD remains unknown.

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

**Aim:** To determine the relation between ABI and SCD in the general population

**Hypothesis #1:** ABI is associated with risk of SCD after adjustment by traditional cardiovascular risk factors.

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**

**Inclusions:**
All ARIC subjects with data of ABI at Visit 1

**Exclusions:**
Subjects without ABI at Visit 1 or missing covariates
Subjects with history of peripheral intervention (leg revascularization)
Non-black and non-white participants in ARIC

**Exposures measurement**

**ABI at baseline:**
ABI will be used as a continuous variable as well as a categorical variable. Based on a scientific statement from the American Heart Association,\(^14\) ABI will be categorized as

<table>
<thead>
<tr>
<th>Value</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>
Outcomes measurement

Primary Outcome: Incident SCD
SCD was adjudicated by a committee of physicians in ARIC through 2012. All events classified as fatal coronary heart disease (CHD) (definite MI, definite fatal CHD, or possible fatal CHD, in and out of hospital) were reviewed. SCD was defined as unexpected deaths that occurred within 1 hour of the onset of symptoms, when death was witnessed, and within 24 hours of last being seen alive, when it was unwitnessed. Circumstances of the event, medical comorbidities and body position of the victim were also considered when adjudicating SCD cases. After review of available data, cases were classified as definite sudden arrhythmic death, possible arrhythmic death, not sudden arrhythmic death, or unclassifiable. For the purposes of this analysis all patients with possible or definite SCD will be considered as SCD.

Secondary Outcome: Non-SCD (NSCD)
Non-SCD will be defined as all-cause mortality minus SCD.

Other variables of interest and covariates:
Sociodemographics: age, race/center, gender, education, field center
Physical information: systolic and diastolic blood pressures, body mass index (BMI), Cornell Voltage, heart rate, and corrected QT interval on electrocardiogram
Lifestyle: smoking status and alcohol consumption, physical activity
Comorbidities: prevalent CHD, prevalent heart failure (HF), hypertension, diabetes mellitus (DM), dyslipidemia
Medications: beta blockers, anti-arrhythmic drugs
Time-dependent variable: interval CHD and HF

Statistical analysis
Poisson regression models will be used to estimate incidence rates of SCD based on ABI with linear splines after adjustment for age, sex, and race. Knots will be placed at the 0.05, 0.35, 0.65, and 0.95 ABI quantiles in the overall study population, as performed in the previous ARIC study. Participants will be categorized based on baseline ABI by the commonly-used guideline-based categories (normal ABI range of 1.00 to 1.40, and abnormal ≤0.90. ABI of 0.91 to 0.99 is “borderline”, and >1.40 indicates non-compressible arteries). Kaplan-Meier curves for SCD based on baseline ABI categories will be generated.

Cox proportional hazards regression model will be used to evaluate associations of incident SCD with baseline ABI. ABI will be treated as a continuous variable (per 0.10 decrement) as well as categorical variable. We will construct a number of adjustment models including: (M1) age, sex, race, and field center; (M2) M1 + education, CHD, HF, hypertension, diabetes mellitus, Cornell
voltage, heart rate, QTc, BMI, HDL and LDL cholesterols, current drinking, and current smoking; (M3) M2 + time-varying covariates (CHD and HF).

Sub-analyses will be performed stratified by age-group, sex, race, CHD, HF, diabetes, hypertension, obesity (defined as BMI≥30 kg/m²). Stratified analysis and interaction term will be used to evaluate for possible interactions. In case we find significant association between ABI and SCD, we will repeat the analysis the secondary endpoint of (NSCD) to assess whether the association is particularly strong for SCD. We will use a different ABI cutpoint as used in the previous ARIC study (ABI 1.30) to evaluate robustness of the findings.

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)?


• MP #575: Ankle-Brachial Index and Ischemic Stroke Incidence: The ARIC Study. Tsai, A
• MP#2328: The association between ankle-brachial index and incident diabetes mellitus: The Atherosclerosis Risk in Communities (ARIC) Study. Hua, Simin
• MP#2022: Peripheral arterial disease and risk of incident heart failure in the Atherosclerosis Risk in Communities Study. Gupta, Deepak

We have included some authors above as co-authors in the current manuscript.

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* AS#2013.01 (PI: Sotoodehnia)

___ 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. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC 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 __x__ Yes ____ No.

References