

**ARIC Manuscript Proposal #2683**

**PC Reviewed:** 1/12/16  
**SC Reviewed:** \_\_\_\_\_

**Status:** A  
**Status:** \_\_\_\_\_

**Priority:** 2  
**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.<sup>1</sup> It is estimated that 300,000 deaths occur each year in the U.S.,<sup>2</sup> accounting for 15% of total mortality.<sup>3</sup> SCD is a leading cause of mortality in the U.S. Worldwide, 4-5 million deaths occur due to SCD each year.<sup>4</sup>

Atherosclerosis has been shown to be associated with coronary heart disease (CHD) and stroke.<sup>5</sup> The ankle-brachial index (ABI) is a simple, non-invasive measure of subclinical atherosclerosis.<sup>6</sup> The ABI offers prognostic data that are useful to predict amputation,<sup>8</sup> coronary heart disease,<sup>9</sup> burden of systemic atherosclerosis,<sup>10</sup> stroke,<sup>11</sup> cardiovascular death and all-cause mortality.<sup>12, 13</sup> 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,<sup>14</sup> ABI will be categorized as

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

## **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.<sup>7</sup>

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  $\leq 0.90$ . 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  $BMI \geq 30 \text{ kg/m}^2$ ). 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<sup>7</sup> (ABI 1.30) to evaluate robustness of the findings.

**7.a. Will the data be used for non-CVD analysis in this manuscript?**  Yes  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  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.csc.unc.edu/ARIC/search.php>**

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)?**

1. Weatherley BD, Nelson JJ, Heiss G, Chambless LE, Sharrett RA, Nieto JF, Folsom AR, Rosamond WD. The association of the ankle-brachial index with incident coronary heart disease: the Atherosclerosis Risk In Communities (ARIC) study, 1987-2001. BMC Cardiovasc Disord. 2007 ;7:3
2. Gupta DK, Skali H, Claggett B, Kasabov R, Cheng S, Shah AM, Loehr LR, Heiss G, Nambi V, Aguilar D, Wruck LM, Matsushita K, Folsom AR, Rosamond WD, Solomon SD. Heart failure risk across the spectrum of ankle-brachial index: the ARIC study (Atherosclerosis Risk In Communities). JACC Heart Fail. 2014 Oct;2(5):447-54
- 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?**  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.csc.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.csc.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 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](mailto:pingping_wu@unc.edu). I will be using CMS data in my manuscript  Yes  No.

## References

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2. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Despres J, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER, 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN,

Virani SS, Willey JZ, Woo D, Yeh RW and Turner MB. Heart Disease and Stroke Statistics-2015 Update: A Report From the American Heart Association. *Circulation*. 2014.

3. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL, Smith SC, Jr., Jacobs AK, Adams CD, Antman EM, Anderson JL, Hunt SA, Halperin JL, Nishimura R, Ornato JP, Page RL, Riegel B, American College of C, American Heart Association Task F, European Society of Cardiology Committee for Practice G, European Heart Rhythm A and Heart Rhythm S. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*. 2006;8:746-837.

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7. Weatherley BD, Nelson JJ, Heiss G, Chambless LE, Sharrett AR, Nieto FJ, Folsom AR and Rosamond WD. The association of the ankle-brachial index with incident coronary heart disease: the Atherosclerosis Risk In Communities (ARIC) study, 1987-2001. *BMC cardiovascular disorders*. 2007;7:3.

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