ARIC Manuscript Proposal #2510

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

1.a. Full Title:

Carotid Intima-Media Thickness and Risk of Sudden Cardiac Death: the Atherosclerosis Risk In Communities (ARIC) Study and Cardiovascular Health Study (CHS)

b. Abbreviated Title (Length 26 characters):

Subclinical atherosclerosis and SCD

2. Writing Group:

Writing group members:
Takeki Suzuki, MD, MPH, PhD; Wanmei Wang, MS; Kenneth R. Butler, PhD; Selcuk Adabag, MD, MS; Michael E. Griswold, PhD; Vijay Nambi, MD; 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]**

First author: **Takeki Suzuki, MD, MPH, PhD**
Address: Division of Cardiology / Department of Medicine
University of Mississippi Medical Center
2500 N. State Street
Jackson, MS 39216

Phone: 601-984-4190 Fax: 601-984-5638
E-mail: tsuzuki@umc.edu

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).

Name: **Thomas H. Mosley, Jr., PhD**
Address: Department of Medicine-Geriatrics
2500 N State
Jackson, MS 39216
Phone: 601.984.2763 Fax: 601.815.3422
E-mail: tmosley@umc.edu

3. Timeline:
Data to be used in this proposal are currently available. Analyses and manuscript preparation will be performed over the next 6 months

4. Rationale:
Sudden cardiac death (SCD), defined as a sudden and unexpected pulseless condition with cardiac etiology, has remained a public health issue in the U.S. and globally.[1] It has been estimated that 210,000 – 330,000 people experienced SCD annually in the U.S.[2], accounting for 15 percent of annual mortality.[3] SCD could occur out-of-hospital as well as in-house. There is a decrease in frequency of ventricular fibrillation as an initial rhythm at the time of SCD. However, the incidence of SCD is not decreasing. There is a need to investigate on risk factors for SCD and to improve risk stratification.[1]

Atherosclerosis has been shown to be associated with coronary heart disease (CHD) and stroke.[4, 5] Carotid intima-media thickness (C-IMT) is a known surrogate marker for atherosclerosis and has been shown to be associated with cardiovascular disease.[6, 7] Early identification of subclinical atherosclerosis could lead to more aggressive lifestyle modifications and medical treatment.[2] While SCD and CHD share many of the risk factors,[8] whether subclinical atherosclerosis is associated with incidence of SCD remains unknown.

5. Main Hypothesis/Study Questions:

Hypothesis: Subclinical atherosclerosis detected by carotid intima-media thickness 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).

Inclusions:
All ARIC subjects with data of carotid intima-media thickness (IMT) at Visit 1

All CHS subjects with data of carotid intima-media thickness (IMT) at the baseline clinic visit

Exclusions:
Subjects with CHD or heart failure (HF) at baseline
Subjects without data of IMT at Visit 1 in ARIC or at the baseline clinic visit in CHS.
Non-black and non-white participants in ARIC

Exposures of interest:

Carotid atherosclerosis by ultrasound (IMT) at baseline. Several C-IMT variables will be used for analyses: mean IMT, common carotid artery-IMT (CCA-IMT), maximum C-IMT, maximum CCA-IMT, and presence or absence of plaque. Details of C-IMT were documented in previous ARIC publications[6, 7, 9] and CHS publications.[5, 10, 11]

Briefly, in ARIC, IMT was measured in 6 carotid sites: common carotid artery (1 cm proximal to the dilatation of the carotid bulb), the carotid bifurcation (1cm proximal to the flow divider), and the internal carotid artery (1cm distal to the flow divider). C-IMT was defined as mean of the 6 measurements. The presence of atherosclerotic plaque at any of the 6 segments was defined as wall thickness in excess of 1.5 mm or the presence of lumen encroachment or irregular intimal surface and/or image characteristics indicative of structural heterogeneity of the arterial wall.[9]

In CHS, mean and maximum IMT were measured. The maximal IMT was defined as the mean of the maximal IMT of the near and far wall on both the left and right sides. Maximum C-IMT and CCA-IMT will be used for analysis. Absence of plaque was defined as a smooth intimal surface with no regional discrete plaque.[12] Intermediate- risk plaque were hyperdense, calcified, or homogeneous plaque or those with a mildly irregular surface. High-risk plaques had an irregular or ulcerated surface or were hypodense or heterogeneous plaque occupying >50% of the total plaque volume. Intermediate-risk and high-risk plaques were grouped and compared with no plaque.

Maximum common carotid IMT will be used in order to meta-analyze ARIC and CHS together.

Outcome:
Primary Outcome: incident SCD
In ARIC, all events classified as having fatal coronary heart disease (CHD) were reviewed. SCD is defined as a sudden pulseless condition presumed to be due to a ventricular tachyarrhythmia in a previously stable individual without evidence of a noncardiac cause of cardiac arrest. After review of data available, cases were classified as definite sudden arrhythmic death, possible sudden arrhythmic death, not sudden arrhythmic death, or unclassifiable. For this analysis, SCD was defined as definite or possible sudden arrhythmic deaths.

In CHS, all CHS deaths were reviewed to classify SCD cases. CHD deaths were classified as defintite, possible, or not SCD. CHS SCD included definite and possible SCD.

Secondary Outcome: non-SCD (NSCD), defined as CHD death not meeting SCD criteria

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), presence/absence of left ventricular hypertrophy by electrocardiogram
Lifestyle: smoking status and alcohol consumption

Comorbidities: hypertension, diabetes mellitus (DM), dyslipidemia
Medications: beta blockers, anti-arrhythmic drugs
Time-dependent variable: interval CHD and HF

Statistical Analysis Plan:
Cox proportional hazards models will be used to evaluate associations of incident SCD with baseline C-IMT. C-IMT will be treated as continuous variables with potential nonlinearities evaluated using smoothers such as fractional polynomials (study-specific quartiles or continuous). Categorical variables such as presence versus absence of plaque for C-IMT will also be examined. Sensitivity to adjustment models will be examined using a number of adjustment models including: (M1) age, sex, and race-by-center terms; (M2) M1 + education, hypertension, diabetes mellitus, Cornell voltage, BMI, HDL and LDL cholesterols, current drinking, and current smoking; (M3) M2 + time-varying adjustors from M2.

Sub-analyses will be performed stratified by age-group, sex, race, DM, hypertension, obesity (defined as BMI$\geq$30 kg/m^2). Stratified analysis and interaction term will be used to evaluate for possible interactions. Secondary analyses will be performed for the secondary endpoint of (NSCD).

The above analyses will be performed in both ARIC and CHS.

Meta-analysis will be performed to combine ARIC and CHS results using fixed effect analysis. The meta-analysis results will be considered as primary results of the study.

Limitations:
First, our definition of SCD was based on adjudicated fatal CHD. Other etiologies of SCD such as inherited rhythm disorders might not have been detected by our SCD definition. Second, we will use single measurements of C-IMT at visit 1. There may be changes over time. However, our focus is to see if these subclinical atherosclerosis measures are associated with incident SCD and not on serial changes of these variables over time. Lastly, there will remain a possibility of residual confounding although we adjust for variables that are known to be associated with SCD.

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)?

- MS#781: Subclinical atherosclerosis measures and incident CVD in diabetics. A Folsom
- MS#1086r: Epidemiologic Implications of the Cardiac Arrest Case Definition. Thomas Rea
- MS#1188: Carotid Wall Thickness and Risk of Ischemic Stroke Subtypes. The Atherosclerosis Risk in Communities (ARIC) Study. Tetsuya Ohira
- MS#1213: The clinical utility of carotid intimal medial thickness in reclassifying risk for incident CHD and stroke in the ARIC study. Vijay Nambi MD
- MS#1214: Diabetes, inflammation and sudden coronary death in the ARIC study cohort. A. Newton
- MS#1333: Socioeconomic indicators and the risk of sudden cardiac death. Anna Kucharska-Newton
- MS#1378: Ventricular premature contractions and risk of incident stroke and sudden cardiac death. S. K. Agarwal
- MS#1888: Assessment of Conventional Cardiovascular Risk Factors and Multiple Biomarkers for the Prediction of Sudden Cardiac Death. R. Deo

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*AS#2013.01; AS#2013.12)

___ 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.

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