ARIC Manuscript Proposal #3891

PC Reviewed: 7/13/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1. a. Full Title: Sex and Race Specific Burden of Aortic Valve Calcification among Adults ≥75 years: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): AVC Among Older Adults

2. Writing Group:
Writing group members: Ellen Boakye, Olufunmilayo H. Obisesan, Omar Dzaye, Albert D. Osei, Zeina Dardari, Frances M. Wang, John Jeffery Carr, Yasuyuki Honda, Candace M. Howard-Claudio, Lynne Wagenknecht, Kuma Konety, Josef Coresh, Kunihiro Matsushita, Michael J. Blaha*, Seamus P. Whelton*

*Co-senior authors

I, the first author, confirm that all the co-authors have given their approval for this manuscript proposal. E.B **[please confirm with your initials electronically or in writing]**

First author: Ellen Boakye
Address: Johns Hopkins School of Medicine
733 N. Broadway Street, Baltimore, MD, 21201
Phone: 443-453-4349
E-mail: eboakye2@jhmi.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: Kunihiro Matsushita, MD, PhD
Address: 2024 E. Monument Street, Suite 2-600
Baltimore, MD 21287
Phone: 443-287-8766 Fax: 443-683-8358
E-mail: kmatsus5@jhmi.edu

3. Timeline: Analyses and manuscript preparation will be completed over the next 1 year.

4. Rationale:
Aortic stenosis (AS) is among the most prevalent valvular pathologies in the U.S. and is associated with significant morbidity, mortality, and healthcare costs.[1–3] The prevalence of calcific aortic valve disease, the most common etiology of AS, increases greatly after the age of 75 years, and among older adults in the U.S. its prevalence is projected to more than double by 2050.[4,5]

Aortic valve calcification (AVC), which is the underlying pathophysiologic process of calcific AS, is a slowly progressive process that can be easily visualized via a non-contrast cardiac computed tomography (CT) scan and reliably quantified using the Agatston score.[6,7] AVC measured from cardiac CT is reproducible, independent of valvular gradients or hemodynamics, and has a high sensitivity for the detection of small amounts of AVC.[8,9] The burden of AVC measured by cardiac CT scan is also associated with AS severity and disease progression, and is an independent predictor of adverse clinical outcomes among patients with AS.[10,11]

Racial differences in the prevalence of AS have been observed with White persons having a greater prevalence than Black individuals.[12,13] Similarly, among middle-aged asymptomatic adults, White persons have been shown to have a higher risk of AVC compared to Black individuals, independent of traditional cardiovascular disease (CVD) risk factors.[14] AVC prevalence has also been demonstrated to be higher in men than in women, and, among persons with AS, men have been shown to have a higher AVC burden than women for the same degree of AS.[11,15] However, among older adults (age ≥75 years), the group most affected by calcific AS, there are limited data describing the differential prevalence and severity of AVC by sex and race.

Additionally, while traditional CVD risk factors are generally associated with an increased prevalence of AVC among middle-aged adults,[14,16,17] studies assessing these associations among older adults are limited. We, therefore, propose to describe the sex and race-specific prevalence and severity of AVC, as well as the association of traditional CVD risk factors with AVC prevalence among adults aged ≥75 years without coronary heart disease (CHD) using the Atherosclerosis Risk in Communities (ARIC) Study.

5. Main Hypotheses/Study Questions:
Hypotheses:

- AVC prevalence and severity will be lower among older Black compared to older White individuals.
- AVC prevalence and severity will be higher in older men than in older women.

- CVD risk factors will only be moderately associated with AVC in this cohort of older adults.
- Despite older persons being the age group most affected by calcific AS, there will still be a significant proportion of older adults with no detectable AVC.

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 Design: Cross-sectional

Inclusion Criteria: ARIC participants aged ≥75 years with AVC assessed at visit 7.

Exclusion Criteria: Participants 1) with missing information on AVC, 2) with prevalent CHD (by the design of the ARIC CAC ancillary study), and 3) of a race other than Black or White.

Dependent Variable: AVC at visit 7 modeled as:

- Absent vs present
- Categorical (0, 1-99, ≥100 Agatston score)
- </≥75th percentile
- Continuous by the Agatston score

Independent Variables: Assessed at the time of AVC assessment (visit 7)

- Age
- Sex
- Race
- Education
- Body Mass Index (BMI: kg/m^2)
- Smoking (never, former, current)
- Systolic blood pressure (SPB)
- Diastolic blood pressure (DBP)
- Antihypertensive medication use (including diuretics)
- Diabetes (fasting glucose level ≥126 mg/dL, non-fasting glucose level ≥200 mg/dL, self-reported physician diagnosis or use of antidiabetic medications)
- Total cholesterol (TC: mg/dL)
- HDL cholesterol (HDL-C: mg/dL)
- Triglycerides (TG: mg/dL)
- Lipoprotein (a) (Lp(a): mg/dL; measured at visit 4)

- Use of lipid-lowering medications

Data analysis plan:

- The characteristics of the study sample will be presented and stratified by AVC status (0, 1-99, ≥100 Agatston score). Means and proportions will be reported for continuous and categorical values respectively. Differences will be tested using ANOVA and χ^2 for continuous and categorical variables respectively.
- The prevalence (>0 Agatston score) and severity of AVC (0, 1-99, ≥100 Agatston score) stratified by race and sex will be reported.
- The proportion of participants with AVC >0 Agatston score and AVC ≥100 Agatston score by age (continuous) stratified by sex and race will also be reported.
- Logistic regression models (or log-binomial depending on the prevalence of AVC) will be used to assess the association of the above listed independent variables with AVC prevalence as follows:
    - Model 1: Crude
    - Model 2: Adjusted for age, sex, race, education
    - Model 3: Model 2 + All other independent variables listed above.
    - We will also perform subgroup analyses by sex and race.
- Similarly, logistic regression models will be used to examine the association of the listed independent variables with a high AVC burden (AVC ≥100 Agatston score and AVC ≥75^{th} percentile).
- Ordinal logistic regression models will be also used to examine the association of the listed independent variables with AVC severity (0, 1-99, ≥100 Agatston score), modeled as above.
- For sensitivity analyses:
    - Subgroup analyses by statin use
    - Linear regression models will be used to examine the association of the listed independent variables with AVC as a log-transformed continuous variable (log (AVC+1)).

Limitations:

Due to the cross-sectional nature of this study, we are not able to assess the temporal relationship between AVC development and the risk factors assessed. However, this is a descriptive study and not one to establish causality.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __X__ No

b. If yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit"? ____ Yes ____ No

(The 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 current derived consent file ICTDER05 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 inactive status. ARIC Investigators have access to the publications lists under the Study Members Area of the website at: http://www.cscc.unc.edu/aric/mantrack/maintain/search/dtSearch.html

___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)?

ARIC Manuscript Proposal #3580: Characterizing the distribution of coronary artery and extra-coronary artery calcification in the 75-and-older population: The Atherosclerosis Risk in Communities (ARIC) Study

ARIC Manuscript Proposal #3566: Association of coronary artery and extra-coronary calcification with reduced physical function and frailty in older adults: The Atherosclerosis Risk in Communities Study

ARIC Manuscript Proposal #3781: Association of cigarette smoking and coronary artery and extra-coronary calcification in older adults: The Atherosclerosis Risk in Communities Study

ARIC Manuscript Proposal #3570: Psychosocial factors and calcification of coronary arteries, aorta, and cardiac valves at older age: the Atherosclerosis Risk in Communities (ARIC) Study

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* 2016.06)

___ 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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

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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Tables:

Table 1: Characteristics of participants by AVC status

Characteristics	Overall (n=)	Aortic valve calcification (Agatston score)			p-value
		0 (n=)	1-99 (n=)	≥100 (n=)	
Age (±SD), years					
Female, %					
Black, %					
Education level, %					
<High school (<12)					
<College (12-16)					
>College (>16)					
Body mass index (kg/m^2)					
Hypertension					
SBP, mmHg					
DBP, mmHg					
Antihypertensive medication use					

Smoking status					
Never smoker					
Former smoker					
Current smoker					
Diabetes					
Total cholesterol, mg/dL					
HDL-C, mg/dL					
Triglycerides, mg/dL					
*Lp (a), md/dL					
Lipid-lowering medication					

Figure 1: Estimated prevalence of AVC by sex and race

AVC, Agatston score	Total	Whites		Blacks	
		Men (n=)	Women (n=)	Men (n=)	Women (n=)
Prevalence >0					
Distribution/severity 0 1-99 ≥100					

Table 2: Association of key CVD risk factors with AVC prevalence

Risk Factors	Model 1		Model 2		Model 3	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Body mass index (kg/m^2)						
SBP, mmHg						
DBP, mmHg						
Antihypertensive medication use						
Smoking status						
Former smoker vs never						
Current smoker vs never						
Diabetes						
Total cholesterol, mg/dL						

HDL-C, mg/dL						
Triglycerides, mg/dL						
Lp (a), mg/dL						
Lipid-lowering medication						
Model 1: Unadjusted Model 2: Adjusted for age, sex, race, and education Model 3: Model 2 + all other variables						

Table 3: Association of key CVD risk factors with AVC severity (0, 1-100, >100 Agatston score)

Risk Factors	Model 1		Model 2		Model 3	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Body mass index (kg/m^2)						
SBP, mmHg						
DBP, mmHg						
Antihypertensive medication use						
Smoking status						
Former smoker vs never						
Current smoker vs never						
Diabetes						
Total cholesterol, mg/dL						
HDL-C, mg/dL						
Triglycerides, mg/dL						
Lp (a), mg/dL						
Lipid-lowering medication						
Model 1: Unadjusted Model 2: Adjusted for age, sex, race, education, and study site Model 3: Model 2 + all other variables						

Supplementary Table 1: Association of key CVD risk factors with AVC prevalence stratified by sex and race.

Supplementary Table 2: Association of key CVD risk factors with AVC (continuous variable).