

ARIC Manuscript Proposal # 3580

PC Reviewed: 3/10/20
SC Reviewed: _____

Status: _____
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Characterizing the distribution of coronary artery and extra-coronary artery calcification in the 75-and-older population: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): CAC and ECC distribution in older adults

2. Writing Group

Writing group members: Frances Wang, Miguel Caínzos Achirica, Shoshana H. Ballew, Aaron Folsom, Lynne Wagenknecht, Thomas Mosley, Josef Coresh, Michael Blaha, Kunihiro Matsushita

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. **FW [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: These analyses will use existing ARIC data; thus, manuscript preparation will be conducted over the next 12 months.

4. Rationale:

As a pathophysiological manifestation of atherosclerosis, coronary artery calcium (CAC) is one of the strongest predictors of atherosclerotic cardiovascular disease (ASCVD) events, such as myocardial infarction and stroke. The AHA/ACC/Multi-Society 2018 Guideline on the Management of Blood Cholesterol emphasized the value of CAC for refining ASCVD risk prediction among individuals age 45-75 and guiding primary prevention therapies. The guideline defined a CAC score ≥ 100 and/or $\geq 75^{\text{th}}$ age-, sex-, and race- specific percentile as a marker of high ASCVD risk.¹ In current clinical practice, CAC is commonly reported as both an absolute CAC score as well as a demographic-specific percentile based on data from the Multi-Ethnic Study of Atherosclerosis (MESA).^{2,3}

While the value of cardiovascular risk prediction with traditional atherosclerotic risk factors in the 75-and-older population is controversial, some experts suggest CAC may be a useful risk predictor in this specific population,⁴⁻⁶ since CAC can reflect both cumulative exposure of atherosclerotic risk factors and individual susceptibility to those risk factors.⁷⁻¹⁰ Indeed, current clinical guidelines recommend assessing CAC for refining risk assessment of older adults with low risk factor burden.¹ However, since MESA percentiles for the 75+ age group are lacking due to limited data availability, knowledge regarding the population-based distribution of CAC in the 75-and-older population is minimal, precluding reporting of CAC percentiles and limiting our ability to interpret absolute CAC scores in this population.

To fill this knowledge gap, using new CAC data available in ARIC Visit 7, we aim to characterize the distribution of CAC and determine percentiles in the 75-and-older population. This analysis will also allow us to quantify the prevalence of zero and low CAC in the older adult population. This quantification is important since the concept of “de-risking” (i.e., identifying lower risk individuals in whom preventive pharmacotherapies could be safely avoided) according to zero and low CAC is promising.^{10,11} On the other hand, for the older adult population there is also a perception that the prevalence of CAC ($\text{CAC} > 0$) is very high and thus CAC may not be very useful for de-risking those 75-and-older;^{12,13} therefore, the present study will provide important answers to these questions. Additionally, we will repeat the investigation for extra-coronary calcification (ECC) since ECC has been shown to provide additional prognostic information beyond CAC and may be used clinically in the future.¹⁴⁻¹⁷

5. Main Hypothesis/Study Questions:

Aim 1: To characterize the distribution of CAC in the 75-and-older population

Aim 1a: To determine age, sex, and race-specific CAC percentiles for the 75-and-older population

Aim 1b: To quantify the prevalence of zero CAC in the 75-and-older population

Aim 2: To explore the distribution of ECC in the 75-and-older population

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study Design: Cross-sectional study

Inclusion Criteria:

- Black and white ARIC participants who underwent CAC scan at Visit 7
- Age 75+

Exclusion Criteria:

- Prevalent coronary heart disease (by design of the ARIC CAC ancillary study)

Covariates:

From Visit 7 data, we will consider:

- Sociodemographics: age, race, sex, education, income
- Physical information: body mass index
- Lifestyle: smoking status
- Comorbidities: dyslipidemia, hypertension, diabetes, obesity, use of antihypertensive and cholesterol lowering medication
- Laboratory examinations: NT-proB-type Natriuretic Peptide (BNP), troponin T

Statistical analysis plan:

Baseline characteristics of the participants will be summarized by sex and race. Participants will be stratified by sex and race to examine the distribution of CAC by age for each of the sex-race subgroups. Since the distributions of CAC are expected to be skewed with ~10% of individuals with CAC 0, we will use locally weighted regression (span=0.7) to first nonparametrically model the log-transformed positive (non-zero) portion of the CAC distribution for each subgroup. We will use ranked pool residuals from the local regression to calculate percentiles of the residuals. The residuals for each percentile will be added back to the age-specific fitted values and then exponentiated to yield CAC corresponding to each percentile in the non-zero portion of the distribution over age. To estimate percentiles for the overall CAC distribution, the j th percentile will be calculated with the equation $CAC_j = 100 * (p + [(1 - p)j]/100)$ where p is the proportion of individuals, within the given age, sex, and race with CAC 0. Further details and strengths of this method for estimating nonparametric percentiles have been previously published.^{3,18} Prevalence and median CAC score by subgroups over age will also be analyzed and compared. Additionally, associations between CAC percentiles/scores and surrogate markers of cardiovascular health, NT-proBNP, and troponin T, will be assessed using multivariable linear regression. The same analyses will be conducted on ECC parameters (valvular and aortic calcification). Associations between CAC values and ECC findings will also be examined using linear regression and concordance of 0 calcification findings will be assessed using Kappa statistics. Sensitivity analyses will include restricting analyses to non-diabetics, stratifying analyses by statin usage, and excluding those with a history of stroke to determine whether

estimated percentile values are drastically affected. Additionally, percentile findings for CAC and ECC may be validated and enriched using the MESA database.

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

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)?

There are no existing ARIC manuscript proposals on the cross sectional distribution of CAC in older adults or on related topics.

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* 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 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 shows you which journals automatically upload articles to Pubmed central.

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