# ARIC Manuscript Proposal #3837

**PC Reviewed: 5/11/21**      **Status: _____**      **Priority: 2**
**SC Reviewed: _____**      **Status: _____**      **Priority: ____**


**1.a. Full Title**: Short-term prognosis according to calcification of coronary arteries, aorta, and cardiac valves in the 75-and-older population

  **b. Abbreviated Title (Length 26 characters)**: Calcifications and cardiovascular disease in older adults

**2. Writing Group**:
Writing group members: Yejin Mok, Yasuyuki Honda, Frances M. Wang, Candace M. Howard-Claudio, Aaron Folsom, Josef Coresh, Matthew Budoff, Michael Blaha, Kunihiro Matsushita


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

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**3. Timeline**: Analyses and manuscript preparation will be performed over the next 6 months


**4. Rationale**:

Coronary artery calcification (CAC) is one of the most potent predictors of atherosclerotic cardiovascular disease (ASCVD). Therefore, the American Heart Association/American College of Cardiology (AHA/ACC) Cholesterol guideline recommends considering CAC measurement if the decision of statin therapy is uncertain.[1] Also, this guideline lists several groups that may particularly benefit from CAC assessment, including older adults (i.e., men 55-80 years and women 60-80 years).

However, data on CAC as a predictor of adverse outcomes are limited in individuals aged ≥75 years. A few studies explored CAC in this specific population but only investigated mortality as an outcome[2, 3] or only tested the improvement of ASCVD risk prediction beyond age without accounting for other traditional risk factors.[4] In addition, extra-coronary calcification (ECC) (e.g., calcification in aortic valve, mitral valve, and aorta) has been shown to provide additional prognostic information beyond CAC,[5-12] but, to our knowledge, no studies have investigated the association of ECC with adverse cardiovascular outcomes in individuals aged ≥75 years.

The guideline recommends clinician-patient discussions based on 10-year ASCVD predicted risk. Indeed, several landmark studies of CAC and ECC utilized this time frame of 10 years.[13-16] However, this time frame may not be ideal for older adults with somewhat limited life expectancy. Thus, the short-term prognostic value of CAC and ECC beyond traditional risk factors should be investigated.

Therefore, we aim to comprehensively explore the associations of CAC and ECC (i.e., calcification in the ascending aorta, aortic valve ring, aortic valve, descending aorta, and mitral valve) with short-term risk (e.g., less than 2-3 years) of mortality and cardiovascular events, including coronary heart disease (CHD), stroke, and heart failure in older adults aged ≥75 years using data from the Atherosclerosis Risk in Communities (ARIC) study. The ARIC study has one of the largest existing datasets of CAC and ECC measurements in individuals aged ≥75 years and can provide unique opportunities to study the associations.

5. **Main Hypothesis/Study Questions**:
- Is a higher CAC score independently associated with a higher risk of mortality and CVD in older adults aged ≥75 years?
- Is higher ECC (i.e., ascending aorta, aortic valve ring, aortic valve calcification, descending aorta, and mitral valve calcifications) associated with a higher risk of mortality and CVD independently of CAC in older adults aged ≥75 years?

**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: Prospective cohort study**

**Inclusion:**
- All ARIC participants aged ≥75 years who have information on CAC and ECC will be included in the analyses.

**Exclusion:**

- Individuals with prevalent CHD at visit 7 (2018-2019) (study design of ARIC CAC ancillary)
- Missing CAC or ECC data
- Missing data on covariates of interest
- Non-Black and non-White

**Exposures:**
- **Calcification of coronary artery and vascular beds other than coronary arteries**
  - CAC measured by non-contrast CTs were calculated using the Agatston method. CAC will be modeled as a categorical variable (e.g., 0 vs. 1-99, 100-299, 300-999, and 1000+ [we will explore a few categorization approaches]) and continuous variable (ln[CAC+1]) to include participants with CAC=0.
  - ECC includes calcification at five sites: aortic valve, aortic valve ring, mitral valve, ascending aorta, and descending aorta. ECC variables will also be modeled as categorical and continuous variables.
  - We will also explore the total number of vascular beds (0-6 including CAC and all ECC sites) with calcification as an independent variable.

**Covariates of interest:** socio-demographic characteristics (age, race, gender, education), alcohol intake, smoking status, body mass index, history of stroke, history of heart failure, hypertension (systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of antihypertensive medication), diabetes (fasting blood glucose ≥126 mg/dl, non-fasting glucose ≥200 mg/dl, reported a history of diabetes, or use of diabetes medication), use of anti-diabetes medications, lipid parameters (total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride), and lipid-lowering therapy.

**Outcomes:**
- Composite and individual adverse outcomes of mortality, CHD (myocardial infarction+fatal CHD), stroke and heart failure
  - CHD, stroke, and heart failure will be based on cases adjudicated by ARIC physician panels.

**Statistical Analysis:**
1. We will summarize baseline characteristics according to the presence and absence of CAC and ECC.
2. Cumulative incidence of adverse outcomes will be estimated by the presence and absence of CAC and ECC using the Kaplan-Meier method.
3. Subsequently, we will examine the association of CAC and ECC with the risk of adverse outcomes using Cox proportional hazards models.
4. We will repeat the Cox analysis for the number of vascular beds with calcification.
5. We will perform subgroup analysis according to age, gender, race, and clinical conditions (diabetes, hypertension, smoking status, statin use, and history of stroke and heart failure).
6. We will exploratorily evaluate c-statistics and net reclassification index after adding CAC or ECC to traditional CVD risk factors.

**Limitations**
- Limited number of events
  - We will have limited power for some analyses such as the subgroup analysis.
  - Unlikely to have adequate power for prediction statistics, as noted above.

**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 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/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)?**

**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.

## References

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