# ARIC Manuscript Proposal Form

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Publication Committee Review Date: **02/13/24**
ARIC Manuscript Proposal Number: **#4405**

**1.a. Full Title**: Diffusivity of Coronary Calcification and Subsequent Risk of Incident Cardiovascular Disease in Adults Aged 75 and Older: The Atherosclerosis Risk in Communities (ARIC) Study

**b. Abbreviated Title (Length 26 characters)**: Calcification diffusivity & CVD

**2. Writing Group [please provide a middle initial if available; EX: Adam L Williams]:**
Writing group members: Siyu Zou, Hairong Liu, Yejin Mok, Abhishek Gami, Lin Yee Chen, Matthew Budoff, Michael J. Blaha, Kunihiro Matsushita; others are welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. SZ **[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 (The ARIC author should be involved enough in ARIC to be able to point the lead author to appropriate ancillary study PIs and to be able to search ARIC manuscript proposals if the lead author doesn't have the access needed to do such a search).


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**3. Timeline**:

Analysis will commence after the proposal is approved and data collection is complete. We aim to complete the manuscript within 6 months of receiving the necessary data for this proposal.

**4. Rationale**:

Coronary heart disease (CHD) is a leading subtype of cardiovascular disease, affecting 20.1 million adults in the US [1]. Coronary atherosclerosis may manifest as a focal lesion or diffuse lesions, although these different lesion types are usually not distinguished in most epidemiological and clinical studies. Importantly, a number of studies have reported that these lesion types have prognostic implications [2–4]. In general, diffuse lesions have been linked to increased risk of adverse outcomes [5–19].

However, there are a few important caveats in those studies. First, several studies only focus on the number of coronary vessels with plaque as a measure of diffusivity whereas the total number of plaques or the location of plaques (i.e., proximal or distal) may confer unique prognostic value [5–12]. Second, many studies explored only CHD and mortality as outcomes, although diffusivity may be associated with other cardiovascular disease (CVD) outcomes such as stroke, heart failure (HF), and atrial fibrillation (Afib) [6,9,13–16,20–23]. Third, some studies investigated selected populations (e.g., patients with CHD [17] or only White individuals [8,12–14,18,24]), potentially limiting their generalizability. Fourth, few studies reported results of older adults aged 75 years and older, the fastest-growing population in the US [8,11,12,18]. Finally, several studies were conducted a few decades ago when the clinical environment was quite different [5,10,12,14–17,24].

The Atherosclerotic Risk Communities (ARIC) Study conducted non-contrast cardiac-gated chest computed tomography (CT) among ~2,300 White and Black participants aged 75+ in 2018-2019, which will allow us to address those caveats. We will explore the association of coronary atherosclerosis diffusivity with subsequent risk of myocardial infarction (MI), stroke, HF, and Afib. Specifically, we will primarily explore the number of coronary arteries (i.e., right coronary, left main, left anterior descending, and left circumflex) with calcification and the number of total calcified plaques as measures of diffusivity. We will also explore whether these diffusivity measures in proximal and distal lesions have different prognostic implications. Secondarily, we will investigate the number of vascular beds and cardiac valves with calcification although some of extra-coronary calcification (ECC) (e.g., aortic valve) may involve non-atherosclerotic pathophysiology.

**5. Main Hypothesis/Study Aims:**

Hypothesis: Greater calcification diffusivity will be associated with an increased risk for CVD (especially MI) independently of potential confounders.

**6. Design and analysis - please address the following aspects:**

**a) study design:**

Prospective cohort study. We will use cardiac CT data at visit 7 to define diffusivity, as detailed below.

**b) inclusion/exclusion**

Inclusion

- Participants from the ARIC study who underwent ECG-gated CT scans at visit 7 and have comprehensive measurements of both CAC and ECC, including the Agatston score, the number of calcified vascular/valvular beds, the number of calcified coronary arteries, and the number of calcified plaques.

Exclusion

- Individuals with a history of coronary heart disease (CHD) by design of ARIC CAC ancillary
- Participants with relevant CVD at baseline according to the outcome of analysis (e.g., we will exclude participants with prior stroke when we analyze stroke as the outcome, and we will do the same for HF and Afib).
- Races other than Black or White due to small sample size
- Participants with missing data on covariates or outcomes of interest

**c) outcome and other variables of interest with specific reference to the time of their collection**

Exposures: Diffusivity of Vascular Calcification

Based on the non-contrast cardiac-gated CT scans from visit 7, we will evaluate the following measures of CAC and ECC:

- Number of Calcified Coronary Arteries: This will be an ordinal variable ranging from 0 to 4, representing the involvement of main coronary arteries (left main, left anterior descending, left circumflex, and right coronary arteries) in CAC [10].
- Number of Calcified Plaques Within Coronary Arteries: Quantified for each coronary artery and totaled for each participant.
- We will also define the number of calcified coronary arteries and the total number of calcified plaques separately for proximal (before the first major branch) and distal (after the first major branch) lesions.
- Extent of Calcification in Vascular/Valvular Beds: A combined measure of CAC and four sites of ECC, scored from 0 to 6. ECC sites include aortic valve calcification (AVC), aortic valve ring calcification (AVRC), mitral valve calcification (MVC), and ascending aorta calcification (AAC), and descending aorta calcification (DAC) [25].

Outcomes: MI, stroke, HF, and Afib

- MI: We will define MI [26] as definite or probable MI or definite coronary death
- Stroke: We will define stroke [27] as adjudicated definite or probable stroke.
- Atherosclerotic CVD (ASCVD): We will also explore ASCVD as a composite of MI and stroke.
- HF: We will define HF as adjudicated definite and probable acute decompensated HF.
- Afib: Afib cases will be ascertained by examining discharge summaries for the International Classification of Diseases, Ninth Revision (ICD-9) code 427.31 or Tenth Revision (ICD-10) code I48.91 [28–30].

- CVD: We will also explore CVD as a composite of MI, stroke, HF, and Afib.

Other variables of interest and covariates

- Sociodemographic factors: Age, sex, education level, race, income
- Physical information: Body mass index, blood pressure, medication use (i.e., antihypertensive, antidiabetic and antidyslipidemic medications)
- Lifestyle: Smoking status, alcohol use, physical activity
- Metabolic factors: Blood glucose, lipids (total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides), estimated glomerular filtration rate (eGFR)
- CAC Agatston score: Measured using the Agatston scoring method [31]. Agatston score is routinely reported when CAC scan is done. Thus, for diffusivity to be clinically valuable, the diffusivity measures should show additional prognostic value beyond Agatston score. Therefore, we will treat the Agatston score as a covariate in this project. Agatston score will be treated both as a natural-log-transformed continuous and categorical variable. Categorical CAC groups will be defined as CAC=0 (reference group), CAC=1–99, CAC=100–399, and CAC≥400.

**d) summary of data analysis**

- Based on the distribution of diffusivity of vascular calcification (number of coronary arteries, number of calcified coronary plaques, and number of calcified vascular/valvular beds), the ARIC participants will be divided into categories (e.g., quartiles).
- Correlation Analysis: Spearman correlation coefficients will be used to assess the degree of association between variables including the Agatston score, number of calcified coronary arteries, number of calcified coronary plaques, and number of calcified vascular/valvular beds.
- Baseline Characteristics Comparison: Baseline characteristics across different levels of diffuse calcification (number of calcified vascular/valvular beds, calcified coronary arteries, and calcified plaques) will be compared using chi-square tests for categorical variables and analysis of variance for continuous variables, as appropriate.
- Cumulative Incidence Analysis: The Kaplan-Meier method will be employed to evaluate the cumulative incidence of CVD events over time, across different diffusivity of vascular calcification measures.
- Cox Proportional Hazards Regression: We will explore a few models to adjust for potential confounders:
    - Model 1: Unadjusted.
    - Model 2: Adjusted for demographic variables (age, sex, race, center, education).
    - Model 3: Further adjustment for traditional CVD risk factors (systolic blood pressure, antihypertensive medications, total cholesterol, HDL cholesterol, lipid-lowering medications, diabetes, eGFR, smoking status, alcohol consumption).
    - Model 4: Additional adjustment for CAC Agatston score.
- Predictive Value Analysis: This part of the analysis will include C statistics accounting for censoring and categorical net reclassification index and will evaluate whether the addition of diffusivity measures can improve ASCVD, HF, and Afib risk prediction beyond traditional predictors (listed as covariates above).

Sensitivity analyses

- We will conduct subgroup analysis by baseline age (above vs below the median), sex, race, or some clinical conditions (e.g., the use of statin therapy). We will test for interaction using the likelihood ratio test.
- To account for potential of attrition bias, we will apply inverse probability weighting approach using variables at prior visits (e.g., visits 1-4).
- We will also run Fine and Gray models to account for the competing risk of mortality [32].

**e) Any anticipated methodologic limitations or challenges if present**

Due to the study's observational design, we cannot entirely rule out the potential for remaining confounding factors. Also, since ARIC includes predominantly White and Black participants, we should be careful to generalize our findings to other racial/ethnic groups.

**f) Will the author need Limited data to complete the proposed manuscript? ☐ Yes, Limited data is needed (Provide a brief (2-3 sentences) justification for requesting PHI data) . ☒ No, De-identified data will be sufficient.**

*Please note, Limited dataset access is strict and rarely provided. Limited data includes identifiable information such as dates (birthdays, visit dates, etc.). CMS, Genomic, Geocoded, Proteomics/Somalogic, and other -omic data all fall under the limited data category. De-identified data does not include dates. All dates are date adjusted to "Days since Visit 1".

**7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? (Non-ARIC analysis means that the authors are not regarded as ARIC investigators and the "ARIC author" is essentially just a facilitator rather than an integral part of the writing group.) ☐ Yes ☒ 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 is distributed to ARIC PIs annually, 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 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 or the "sponsoring" ARIC 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 website at: https://aric.cscc.unc.edu/aric9/proposalsearch [ARIC Website Publications Proposal Search]

☒ 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)?**

**To the best of our knowledge, there are no proposals exploring calcification diffusivity measures as predictors of incident CVD in ARIC.**

**11.a. Is this manuscript proposal associated with any ARIC ancillary studies or does it use current [or ongoing] ancillary study data (this includes ACHIEVE)? ☒ Yes ☐ No → Skip to question 12**

**11.b. If yes to 11.a., is the proposal**

☒ **A. primarily the result of an ancillary study**

☐ **B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables)**

**11.c. If yes to 11.a., list number* _2016.06_**

*ancillary studies are listed by number https://aric.cscc.unc.edu/aric9/researchers/ancillary_studies/approved_ancillary_studies [ARIC Website Ancillary Studies 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 https://aric.cscc.unc.edu/aric9/publications/policies_forms_and_guidelines [ARIC Website Publications Publication Policies, Forms, and Guidelines]. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

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