ARIC Manuscript Proposal #4352

PC Reviewed: 11/21/23	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Predictors of coronary artery calcium distribution: the Atherosclerosis Risk in Communities (ARIC) study

b. Abbreviated Title (Length 26 characters): CAC distribution prediction

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3. Timeline: Since data is available, manuscript preparation is expected to be complete within 12 months after approval.

4. Rationale:

Coronary artery calcium (CAC) provides a reproducible, highly personalized, and actionable assessment of an individual's risk of coronary heart disease (CHD) and cardiovascular disease (CVD).[1] CAC is quantified using the Agatston score, which sums the score of all unique coronary calcified lesions (each individual lesion is scored using measurement of the lesion's area multiplied by a density weighting factor based on the CT attenuation within the lesion).[2] CAC scoring using the Agatston score has been incorporated in clinical primary prevention and cholesterol guidelines to inform decision-making and risk prediction.[3,4] However, traditional CAC scoring using the Agatston score has limitations – for example, it does not consider other characteristics of CAC such as the identity and number of the vessels involved and does not capture the distribution of calcification. Therefore, 2 patients with the same CAC score may have significantly different patterns of CAC involvement in the coronary vessels.[5] Emerging data has demonstrated that diffuse non-obstructive atherosclerotic burden, rather than localized stenotic CHD, is superior in predicting CVD risk.[6] Given this shift in understanding of CVD risk, there has been interest in incorporating advanced CAC phenotypes, such as the distribution of CAC, to enhance CVD risk assessment using the CAC score.[7]

The distribution of CAC can be captured using the number of coronary arteries with CAC (scored 1 – 4 based on CAC in the left main, left circumflex, left anterior descending, and right coronary artery) or based on the "diffusivity index" of CAC. The diffusivity index represents the dispersion of CAC across coronary vessels and is calculated by dividing the CAC score of the vessel with the highest CAC score by the total Agatston CAC score and subtracting this value from 1 (1- CAC in most affected vessel/total CAC score). Individuals with higher diffusivity index therefore have a more diffuse pattern of CAC. In the Multi-Ethnic Study of Atherosclerosis (MESA), there was significant heterogeneity between the number of vessels with CAC and CAC score, particular in patients with intermediate CAC score (1-300).[8] The addition of the number of vessels to the CAC score significantly improved the ability of CAC score to predict CHD and CVD events (C-statistic improvement of 0.01 to 0.033). Addition of the pattern of CAC distribution to the Agatston score and number of vessels with CAC did not improve risk prediction.[8]

Findings from the CAC Consortium have shown a graded increase in CHD and CVD-specific mortality as the number of calcified vessels increase. Further, having a diffuse CAC phenotype was associated with higher CVD-specific and trend towards CHD-specific mortality compared to a more concentrated CAC phenotype. Diabetes mellitus, hypertension, and hyperlipidemia were predictive of increased vessel involvement.[9]

Given the added prognostic value of advanced CAC measures beyond the Agatston score, the aim of this analysis is to identify long-term predictors of different CAC phenotypes, with an emphasis on diffuse CAC phenotypes, to enable earlier identification of patients at risk for CHD and CVD. Further, we aim to characterize the patterns of distribution of CAC in elderly patients (> 75 years old), a population in whom there is sparse data on CAC phenotypes beyond the Agatston score.

5. Main Hypothesis/Study Questions:

In a multi-ethnic cohort of asymptomatic adults:

1. What is the distribution by age and sex of CAC distribution patterns (concentrated, intermediate, and diffuse; and number of coronary vessels) in older adults with CAC?

2. What 30-year traditional risk factors predict patterns of diffuse vs concentrated CAC in older adults?

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: This is a prospective study that leverages advanced CAC measures.

Study population: Participants from ARIC Visit 7 (2018-2019) aged 75 and older who underwent CAC scanning will be included.

Exposure variables:
Baseline variables from Visits 1-7 will be used for analyses and include race/ethnicity, education level, tobacco use status, body mass index (kg/m^2), low-density lipoprotein cholesterol (LDL- C, mg/dL), high-density lipoprotein cholesterol (HDL-C, mg/dL), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), diabetes category (no diabetes, pre-diabetes, and diabetes [we will also explore diabetes duration as well]), and family history of myocardial infarction. We will also examine lipoprotein(a) values from ARIC Visit 4. Lipoprotein(a) values are over 90% genetically determined, and therefore change very little over life.

Outcomes:
Outcome variables will include the number of vessels with CAC (ordinal variable, ranging from 0-4) indicating incident CAC in the left main, left anterior descending, left circumflex, and right coronary artery, the diffusivity index (continuous variable), and the identity of the vessel with CAC (categorical variable).

The diffusivity index will be calculated for all participants. The diffusivity index represents the dispersion of CAC across coronary vessels and is calculated by dividing the CAC score of the vessel with the highest CAC score by the total Agatston CAC score and subtracting this value from 1 in accordance with prior work.[8,9] For those with only 1-vessel involvement, the diffusivity index will be 0, and for those with 0-vessel involvement, the diffusivity index will be set at -0.1. The 25^{th} and 75^{th} percentile of diffusivity index will be calculated to assign subjects a category of CAC diffusivity (25^{th} percentile of diffusivity index defined as a "concentrated" plaque phenotype and 75^{th} percentile of diffusivity index defined as a "diffuse" plaque phenotype).

Statistical analysis plan:
Baseline demographic variables will be tabulated for the study population and stratified by number of vessels with CAC (Table 1). Ordinal regression models will be used to identify risk factors for increased vessel involvement (Table 2). We will conduct analysis accounting for

values for exposure variables from Visit 1 and 7. In addition, we will also examine 32-year trajectories in the exposure variables by time averaging their values, as we have done in prior ARIC papers. To calculate time-weighted averages for risk factors, the weighted average of risk factor values will be used for all ARIC visits (1987-2019), accounting for time between measurements. Linear regression and multivariable logistic regression models will be used to identify risk factors for increased diffusivity index and as diffuse vs. concentrated plaque phenotype (Table 3). The number of vessels with CAC and identity of the coronary artery involved within CAC score categories (e.g. CAC 1-100, 101-300, >300) will be graphically represented to identify heterogeneity between CAC score and number of vessels with CAC/identity of coronary artery (Figure 1 and 2).

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* 2022.11**)**

___ 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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