ARIC Manuscript Proposal #3783

1.a. Full Title: Heterogeneity of Coronary Artery Calcium Scores among Older Adults with Diabetes: The Atherosclerosis Risk in Communities Study

  b. Abbreviated Title (Length 26 characters): Diabetes and the CAC score

2.   Writing Group:

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

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3.   Timeline: Since this analysis will use existing ARIC data, analyses and manuscript preparation will be completed over the next 1 year.

4.   Rationale:

Diabetes currently affects 463 million adults worldwide, and is projected to affect 700 million individuals by year 2045.[1] In the U.S., diabetes currently affects 34.2 million Americans, costing approximately \$327 billion in healthcare costs and lost productivity annually.[2,3] Among individuals with diabetes, cardiovascular disease is the most common cause of morbidity and mortality, costing approximately \$37.3 billion annually.[4] Compared to individuals without diabetes, individuals with the disease are more likely to have coronary artery disease and are more likely to have silent myocardial ischemia and infarction,[5,6] thus, predicting and preventing cardiovascular disease among individuals with diabetes is highly important.

Coronary Artery Calcium (CAC) is a marker of systemic atherosclerosis that is strongly predictive of cardiovascular disease events and all-cause mortality.[7,8] Individuals with diabetes typically have higher CAC scores than individuals without diabetes and increasing CAC scores have been associated with higher rates of all-cause mortality and cardiovascular events among individuals with diabetes.[9,10] Within this population, a wide range of CAC scores has been observed, and importantly, individuals with diabetes and CAC scores of 0 have been found to have low short-term risk of all-cause mortality.[7,9]

Factors associated with increased risk of cardiovascular events among individuals with diabetes include duration of diabetes, insulin use, poor glycemic control, age, ethnicity, lower socioeconomic status and traditional cardiovascular risk factors such as hypertension and elevated CAC.[11,12] While hyperglycemia and elevated glycation end-products have been largely implicated in the extensive formation and progression of CAC among individuals with diabetes, it is recognized that the etiology of this is likely multi-factorial, with many unknown mechanistic pathways.[5,9]

Although current guidelines do not recommend the use of CAC for risk stratification among individuals with diabetes,[4,6] the discriminatory power of CAC for identifying individuals at high risk, and more importantly, individuals with low risk for future cardiovascular events could further guide the physician-patient discussion when outlining the management therapy for individuals with diabetes.[5,10] It could also further refine the "statin for all" approach that has been associated with higher healthcare costs and increased risk for adverse effects.[5,7,10] Additionally, it could be useful in identifying asymptomatic individuals with diabetes who are at increased risk of cardiovascular events and thus would require more aggressive therapy earlier.[10,13]

Additionally, measures of extra-coronary calcification such as aortic valve calcification(AVC) and thoracic aortic calcification(TAC) have been found to occur increasingly among individuals with diabetes.[14,15] As these measures can usually be evaluated on the same scans used to measure CAC, they can potentially increase the precision of cardiovascular disease risk prediction at no additional cost burden or exposure to radiation.[16,17]

The Atherosclerosis Risk in Communities (ARIC) study contains detailed descriptive information about individuals with diabetes of widely varying duration and severity, enabling a unique perspective for exploring the spectrum of CAC scores among older adults with diabetes. Furthermore, identifying the factors influencing the heterogeneity of CAC scores among individuals with diabetes could be beneficial for identifying individualized therapy targets in the prevention of cardiovascular disease. In this study, we hypothesize that CAC scores among older

adults with diabetes will vary widely, i.e., a substantial fraction of the population will have low scores and a substantial fraction will have very high scores. Thus, we intend to use the ARIC dataset to examine the heterogeneity of CAC scores among older adults with diabetes and the factors associated with increasing CAC scores in this population. We also plan to assess the range of extra-coronary calcification measures present in this population, and the factors influencing these values.

5. Main Hypothesis/Study Questions:

Hypotheses:
- CAC scores among older adults with diabetes will vary widely
- The heterogeneity of CAC scores will be directly reflective of diabetes specific risk-enhancing factors (as listed in the ACC/AHA guidelines)[6] and cardiometabolic risk factors.
- Similar heterogeneity will be seen with extra-coronary calcification, in particular- Aortic valve calcification(AVC) and Thoracic Aortic Calcification(TAC)

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 will be a cross-sectional analysis of already collected data from visit 7.

Inclusion criteria: All ARIC participants with diabetes (history of clinical diagnosis of diabetes, use of medication for diabetes, **HbA1c value≥6.5% or Fasting blood glucose(FBG)≥126mg/dl**) who underwent coronary artery calcium scan at visit 7.

Exclusion criteria:
- Individuals who do not meet the criteria for diabetes
- Individuals with prevalent coronary heart disease at visit 7 (by design of the ARIC CAC ancillary study)
- Individuals with missing variables of interest

Exposure variables
- Self-reported history of clinical diagnosis, Duration of diagnosis (dichotomized about the median duration of 10 years), Family history of diabetes(categorized as yes/no)
- HbA1c/FBG (modeled as a continuous variable)
- Use of diabetes medication(modeled as number of medication used), Use of insulin(categorized as yes/no)
- Diabetic kidney disease (estimated glomerular filtration rate modeled as a continuous variable, urine albumin categorized as present/not present)

Outcome variable
- CAC score
  - Secondary outcome: TAC, AVC

Other variables of interest:
- Cardiometabolic risk factors:
  - Body mass index (BMI)
  - History of dyslipidemia or medication use for cholesterol lowering or laboratory values (triglycerides, high density lipoproteins)
  - History of hypertension or medication use for hypertension
  - High-sensitivity C-reactive protein
- Additional potential confounders: Age, Sex, Race, Education level, Income, Physical activity (Physical activity during leisure time excluding sport), Smoking history, Alcohol use history, Family history of coronary heart disease, Low density lipoprotein cholesterol

Data analysis plan
- Baseline characteristics will be summarized in a table. Means and proportions will be reported for continuous and categorical values respectively.
- CAC score categories of 0, 1-99, 100-299, 300-1000, >1000 will be defined, and the heterogeneity of CAC scores among individuals with diabetes will be explored using descriptive analyses.
- CAC will be dichotomized about a clinically actionable cut-point of 100, and the association between each exposure of interest and elevated CAC (<100 vs $\geq$100) will be explored using logistic regression using the following models:
  - Model 1: will be a base model including baseline risk factors (the confounders listed above).
  - Model 2: Each exposure of interest will then be added into the model to assess how it influences CAC score beyond baseline risk factors.
  - Model 3: Number of cardiometabolic factors will be adjusted for in addition to the variables in Model 2 to assess how they further influence the relationship between the exposures of interest and CAC score category.
- The association between each exposure of interest and the secondary outcomes of TAC and AVC will be explored using the same models outlined above.
- For sensitivity analyses, we will explore the association between each exposure of interest and increasing CAC category using ordinal logistic regression in the same models outlined above.
- We will dichotomize our sample into 2 groups based on an extended list of diabetes specific risk enhancing factors: duration of diabetes, insulin therapy, HbA1c level and presence of diabetic kidney disease.
  - One group will be comprised of individuals with no diabetes specific risk-enhancing factors i.e., Individuals with diabetes duration <10 years, not on insulin therapy, HbA1C<7% and with no microalbuminuria and eGFR $\geq$60ml/min/1.73m^2
  - The second group will be comprised of individuals with $\geq$1 diabetes specific risk enhancing factors i.e., diabetes duration $\geq$10years, on insulin therapy, HbA1C>9%, microalbuminuria or eGFR<60ml/min/1.73m^2
  - The average CAC score of each group will be estimated using descriptive analyses.

- o Ordinal regression will then be used to assess the association between the 2 groups and CAC score groups adjusted for confounders and cardiometabolic factors.

Limitations: As this is an observational study, there could be potential residual confounding. Also**,** this study does not allow for longitudinal assessment of CAC incidence or progression.

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)?
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

Proposal # 3649 - Mid-life, late-life, and 30-year cumulative exposure to traditional cardiovascular risk factors and zero coronary artery calcium: The Atherosclerosis Risk in Communities (ARIC) Study

Proposal # 3628 - Estimated glomerular filtration and albuminuria and calcification of coronary arteries, aorta, and cardiac valves in older adults

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
  ___ **A. primarily the result of an ancillary study (list number* <u>2016.06</u>)**
  ___ **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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