**ARIC Manuscript Proposal # 3820**

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| **PC Reviewed: 4/13/21** | **Status: _____** | **Priority: 2** |
| **SC Reviewed: _____** | **Status: _____** | **Priority: ____** |

**1.a. Full Title**: Diabetes Duration and Subclinical Myocardial Injury: The Atherosclerosis Risk in Communities Study (ARIC)

**b. Abbreviated Title (Length 26 characters)**: Diabetes Duration and Myocardial Injury

**2. Writing Group**: Carine E. Hamo, Justin Echouffo-Tcheugui, Sui Zhang, Roberta Florido, James Pankow, Erin D. Michos, Ronald Goldberg, Vijay Nambi, Gary Gerstenblith, Wendy S. Post, Roger S. Blumenthal, Christie Ballantyne, Joe Coresh, Elizabeth Selvin, Chiadi E. Ndumele; *others welcome*

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


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**3. Timeline**: We aim to submit this manuscript to the ARIC publications committee 1 year from the date of approval of this manuscript proposal.

4. **Rationale**:

Diabetes mellitus has a prevalence of 26 million among U.S. adults and is a major risk factor for cardiovascular disease including coronary heart disease (CHD) and heart failure (HF).[1] Among individuals younger than age 20, the incidence of diabetes is expected to rise over the upcoming decades.[1] An earlier onset of diabetes, and a longer duration of diabetes have been independently associated with subclinical atherosclerosis and cardiac dysfunction.[2] We recently conducted an analysis among participants in the Atherosclerosis Risk in Communities (ARIC) Study, finding that a longer duration and earlier onset of diabetes were associated with a higher risk of HF.[3] However, the biological mechanisms by which diabetes duration contribute to increased HF risk are not fully understood.

Cardiac troponin is a biomarker of myocardial injury traditionally used to diagnose myocardial infarction. High-sensitivity cardiac troponin T (hs-cTnT) assays enable the measurement of troponin at much lower limits of detection as compared to earlier generation assays.[4] Among participants in the ARIC Study, diabetes was independently associated with elevated hs-cTnT and this is turn was associated with higher risk for clinical events including HF, CHD, and death.[5] Among older ARIC participants (67 years-89 years) with diabetes, hs-troponin elevations were associated with a higher comorbidity burden as well as a mortality risk independent of other comorbidities.[6] However, the degree to which the duration of diabetes is associated with subclinical myocardial injury remains unknown. The ARIC study, which includes serial characterization of diabetes status as well as measurements of hs-cTnT, serves as an ideal cohort for characterizing the association of diabetes duration with markers of myocardial injury.

The current proposed study aims to determine the association between the duration of diabetes and subclinical myocardial injury, as reflected by hs-cTnT, using data from visits 1-4 in ARIC. We hypothesize that longer duration of diabetes will be associated with a higher likelihood of hs-cTnT elevation. As there are known demographic differences in the association between diabetes and HF, we will also aim to determine whether these associations vary by age, sex, race, and glycemic control.

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

**Aim/Hypothesis**:

To determine whether longer duration of diabetes is associated with higher levels of hs-cTnT, a marker of subclinical myocardial injury.

To determine whether the association with diabetes duration and hs-cTnT varies by age, sex, and race demographics, as well as by degree of glycemic control.

**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**: Cross-sectional study of ARIC Visit 4 participants, examining the association of diabetes duration from Visit 1 through Visit 4 (based on assessment of diabetes status at each visit, as well as data on self-reported age of diabetes diagnosis collected at Visit 3) with measures of hs-cTnT at Visit 4. Individuals without diabetes will serve as the reference group.

**Exposures**: The primary exposure will be diabetes duration. Diabetes will be defined as prevalent diabetes per ARIC, which is defined as fasting blood glucose ≥ 126 mg/dl, non-fasting blood glucose ≥ 200 mg/dl, self-reported physician diagnosis of diabetes, or self-reported use of diabetes medications.

In order to account for glycemic control as a potential effect modifier, we will utilize hemoglobin A1C (A1C) data from Visits 2 and 4. A1C was not directly measured at Visit 4; therefore, we will use measures of fructosamine to calculate A1C at Visit 4.

Diabetes duration will be calculated based on diabetes status at each visit from Visit 1 to Visit 4. For the purpose of this analysis, we will assume that once diabetes is diagnosed, it will persist. Data on self-reported age of diabetes diagnosis (from Visit 3) will be used to determine the duration of diabetes among individuals with a prior physician diagnosis or use of hypoglycemic medications at Visit 1. Diabetes duration will be modeled categorically (0-<5 years, 5-<10 years, 10-<15 years, and ≥15 years), as well as continuously (per 5 years of diabetes duration).

**Outcomes**: The primary outcome is elevated hs-cTnT, defined as ≥ 14ng/L, a cut- point that was shown previously to relate to cardiovascular endpoints and mortality.[7,8] The secondary outcome is measurable troponin (≥6 ng/L). We will also model hs-cTnT continuously, imputing a value of 1.5 ng/L for those with undetectable hs-cTnT as has been done in prior analyses. When modeled continuously, hs-cTnT will be log transformed to account for its skewed distribution.

**Exclusions**: We will exclude participants with a history of HF or coronary heart disease at or before Visit 4 (self-reported HF or CHD at visit 1 or HF-related hospitalization or death, adjudicated nonfatal myocardial infarction or coronary revascularization event, or silent myocardial infarction by electrocardiographic criteria at or before Visit 4), those missing data on diabetes status at any of the first 4 visits and the small number of individuals not of black or white race.

**Covariates**: Age, sex, race-center, smoking status, alcohol use, body mass index, LDL-cholesterol, HDL-cholesterol, systolic blood pressure, triglycerides, and estimated glomerular filtration rate (eGFR) at Visit 4.

**Main Analyses**:

We will compare characteristics of Visit 4 participants based on the presence of diabetes and diabetes duration at V4 (no diabetes at Visit 4; diabetes duration 0-<5 years, 5-<10 years, 10-<15 years, ≥15 years). The chi-square test will used for comparison of categorical variables and ANOVA will be used for continuous variables.

Logistic regression will be used to determine the association of diabetes duration with elevated and measurable hs-cTnT levels at Visit 4. We will model diabetes duration categorically as described above (visit of diabetes onset; categories of years of diabetes duration). We will also model diabetes duration continuously (per 5 years of diabetes duration) and will construct restricted cubic splines in order to allow for deviations from linearity in assessing the continuous association between diabetes duration and the odds of elevated hs-cTnT. We will additionally consider linear regression analyses examining the association between diabetes duration and ln hs-cTnT modeled continuously. We will use 2 levels of adjustment, to order to assess the degree to which associations are independent of traditional risk factors:

- Model 1: adjusted for age, sex, race-center, smoking status and alcohol use
- Model 2: Model 1 variables + body mass index, LDL-cholesterol, HDL-cholesterol, systolic blood pressure, triglycerides, and estimated glomerular filtration rate (eGFR)

We will also perform analyses stratified by age (<65 or ≥65 years) in an effort to distinguish between duration of diabetes and participants' age, as well as analyses stratified by sex and race. To examine the associations of duration of diabetes across levels of diabetes severity, we will perform an analysis that stratifies based on glycemic control (A1C <7% at both V2 and V4, or greater than 7% at either visit). We will test for multiplicative interactions of glycemic control, age, sex, and race with diabetes duration on the outcomes of elevated and measurable hs-cTnT.

We will consider an analysis in which we examine the association between cumulative exposure to hyperglycemia from Visit 1 to Visit 4, calculated in "excess A1C years" and hs-cTnT levels at Visit 4. This will require imputation of A1C at Visits 1 and 3 where it is currently unmeasured, using multiple imputation chained equations (MICE) which is currently being explored for other ARIC analyses. "Excess A1C years" will be calculated by centering the A1C variables at each of the first 4 ARIC visits at 7% and multiplying the average A1C by the interval of monitoring (from Visit 1 to Visit 4, approximately 9 years).

**Secondary Analyses**:

We will consider generating distinct categories for diabetes at Visit 1 diagnosed by glucose at the study visit only compared to diabetes diagnosed previously by a physician or by the use of hypoglycemic medications.

**Limitations**:

1. Survival bias inherent in studying Visit 4 participants, who were healthy enough to survive to that time point. Importantly, it is likely that those with elevated hs-cTnT at prior visits and long duration of diabetes are less likely to survive to Visit 4 without CVD events.
2. Residual confounding due to the observational nature of the study.
3. Lack of clarity regarding the exact timing of diabetes onset between 3-year visits from visits 1 to 4.

**7.a. Will the data be used for non-CVD analysis in this manuscript?**
**____ Yes __X__ 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 ICTDER03 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 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.cscc.unc.edu/ARIC/search.php

___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)?**

ARIC Manuscript Proposal #1596. Hyperglycemia and risk of subsequent elevation of NT-proBNP and hs-cTnT. Jonathan Rubin; Kunihiro Matsushita; Christie M. Ballantyne; Ron Hoogeveen; Josef Coresh; Elizabeth Selvin

ARIC Manuscript Proposal #1759. Associations of traditional cardiovascular risk factors and high-sensitivity cardiac troponin T. Jonathan Rubin; Kunihiro Matsushita; Christie M. Ballantyne.; Vijay Nambi; Ron Hoogeveen; A. Richey Sharrett; Roger S. Blumenthal; Josef Coresh; Elizabeth Selvin

ARIC Manuscript Proposal #2352. Weight History, Subclinical Myocardial Injury and Incident HF: The Atherosclerosis Risk in Communities (ARIC) Study. Chiadi E. Ndumele; Laura K. Cobb; Mariana Lazo; Natalie Bello; Amil Shah; Vijay Nambi; Scott Solomon; Roger S. Blumenthal; Christie M. Ballantyne; Elizabeth Selvin; Josef Coresh

ARIC Manuscript Proposal #3719. Duration of diabetes, glucose excursions and control, and low heart rate variability: The ARIC Study. Mary R. Rooney, Justin B. Echouffo-Tcheugui, Faye L. Norby, Elsayed Z. Soliman, Lin Yee Chen, Elizabeth Selvin

ARIC Manuscript Proposal #3274. High-sensitivity cardiac troponin-T and I for cardiovascular risk characterization in middle-aged adults with diabetes. Olive Tang; Kunihiro Matsushita; Josef Coresh; John W (Bill) McEvoy; A. Richey Sharrett; Christie Ballantyne; Ron Hoogeveen; Elizabeth Selvin

ARIC Manuscript Proposal #2129. Diabetes and prediabetes and the incidence and progression of subclinical myocardial injury. Elizabeth Selvin; Andreea M. Rawlings; Mariana Lazo; Jonathan Rubin; Ron C. Hoogeveen; Christie M. Ballantyne; Josef Coresh.

ARIC Manuscript Proposal #1968. The association of cardiac troponin T measured by a highly sensitive assay and incident diabetes. Seamus P. Whelton, Mariana Lazo, Eun Jung Park, Josef Coresh, J. Hunter Young, Frederick L. Brancati, Ron C. Hoogeveen, Christie M. Ballantyne, Elizabeth Selvin

ARIC Manuscript Proposal #3122. Sex Differences in The Interrelationship Among Obesity, Diabetes and Subclinical Myocardial Damage: The Atherosclerosis Risk in Communities (ARIC) Study. Rachit M. Vakil; Lucia Kwak; Roberta Florido; John W. McEvoy; Vijay Nambi; Erin D. Michos; Rita Kalyani; Roger S. Blumenthal; Christie M. Ballantyne; Josef Coresh; Elizabeth Selvin; Chiadi E. Ndumele

ARIC Manuscript Proposal #2707. Hypoglycemia and Subclinical Myocardial Damage in Older Adults with Diabetes. Alexandra K. Lee, John W. McEvoy, Ron C. Hoogeveen, Christie M. Ballantyne, Elizabeth Selvin.

**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* _**#2008.10 #2006.15**)**

**___ 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.cscc.unc.edu/aric/forms/

**12. 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.**

**References:**


1. Virani SS, Alonso A, Benjamin EJ, et al. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. *Circulation.* 2020;141(9):e139-e596.
2. Reis JP, Allen NB, Bancks MP, et al. Duration of Diabetes and Prediabetes During Adulthood and Subclinical Atherosclerosis and Cardiac Dysfunction in Middle Age: The CARDIA Study. *Diabetes Care.* 2018;41(4):731-738.
3. Echouffo-Tcheugui J ZS, Florido R, Hamo C, Pankow J, Michos E, Goldberg R, Nambi V, Gerstenblith G, Post W, Blumenthal R, Ballantyne C, Coresh J, Selvin E, Ndumele C. Diabetes history and incident heart failure: the atherosclerosis risk in communities (ARIC) study. Abstract Submitted to ACC 2021.
4. Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high-sensitivity cardiac troponin T assay. *Clin Chem.* 2010;56(2):254-261.
5. Selvin E, Lazo M, Chen Y, et al. Diabetes mellitus, prediabetes, and incidence of subclinical myocardial damage. *Circulation.* 2014;130(16):1374-1382.
6. Tang O, Daya N, Matsushita K, et al. Performance of High-Sensitivity Cardiac Troponin Assays to Reflect Comorbidity Burden and Improve Mortality Risk Stratification in Older Adults With Diabetes. *Diabetes Care.* 2020;43(6):1200-1208.
7. deFilippi CR, de Lemos JA, Christenson RH, et al. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. *Jama.* 2010;304(22):2494-2502.
8. Ndumele CE, Cobb L, Lazo M, et al. Weight History and Subclinical Myocardial Damage. *Clin Chem.* 2018;64(1):201-209.