**ARIC Manuscript Proposal #3537**

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| **PC Reviewed: 1/14/20** | **Status: _____** | **Priority: 2** |
| **SC Reviewed: _____** | **Status: _____** | **Priority: ____** |

**1.a. Full Title**:
Association of Glycemic Status and Progression of Cardiac Dysfunction among Older Adults: The Atherosclerosis Risk in Communities Study

**b. Abbreviated Title (Length 26 characters)**:
Hyperglycemia and Progression of Cardiac Dysfunction

**2. Writing Group**:
Writing group members: Justin B. Echouffo-Tcheugui, Elizabeth Selvin, Natalie Daya, Chiadi E. Ndumele, Kuni Matsushita, Josef Coresh, Hicham Skali, Amil Shah; others welcome

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


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**3. Timeline**:
Analysis to begin immediately after the approval of the proposal, and submission of a draft of the manuscript for review to ARIC for review within 6 months.

**4. Rationale**:

Type 2 diabetes and heart failure (HF) are important and commonly co-occurring conditions.[1,2] Diabetes confers a 2- to 4-fold higher risk of HF.[3,4] Although several studies have described cardiac dysfunction in the context of diabetes,[5,6] the mechanisms of cardiac dysfunction are not well-defined and incompletely understood. Studies of the influence of diabetes on cardiac structure and function have mainly been cross-sectional.[7–11] These studies lack longitudinal data and have not provided a complete picture of the natural history of diabetes-related cardiac dysfunction.[7–10] Moreover, the influence of hyperglycemia on the progression across HF stages (A, B, C or D, as defined by the American College of Cardiology [ACC] and American Heart Association (AHA] [12]) has seldom been examined.[13] Whether and how diabetes accelerates the transition across HF stages remains unclear. This question is important as a large proportion of individuals have asymptomatic cardiac dysfunction predisposing to significant risk for developing clinical HF (stages C and D); the absolute number of people in stage B is 3 to 4 times higher than those with clinical overt HF.[14,15] Understanding the contribution of hyperglycemia to the transition across HF stages using longitudinal data can help to demonstrate the intrinsic effect of diabetes on the myocardium, possibly separating it from the effects of antecedent CAD and/or hypertension.
Using echocardiographic data from visits 5 &7 of the Atherosclerosis Risk in Communities (ARIC) study, we aim to assess the association of hyperglycemia (prediabetes and diabetes) with 1) longitudinal changes in cardiac structure and function, and 2) changes in HF stage over 7 years (from visit 5 [2011–2013] to visit 7 [2018-present]) in the ARIC study.

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

a) Prevalent and worsening hyperglycemia are positively associated with worsening in measures of cardiac structure and function over time in older adults.

` b) Prevalent and worsening hyperglycemia are positively associated with accelerated progression to more advanced HF stages 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).**

**Inclusion/Exclusion criteria**

Individuals included will be ARIC study participants who attended visits 5 [2011-2013] and 7 [2018–2019] including those with prevalent heart failure, underwent echocardiography and have data on glycemic markers including glycosylated hemoglobin ($HbA_{1C}$) and fasting plasma glucose (FPG).

**Exposure**

Our exposure will be hyperglycemia defined based on glycosylated hemoglobin [$HbA_{1C}$]), fasting plasma glucose (FPG), history of diagnosed diabetes, and the use of diabetes medications. The different stages of hyperglycemia will be the following:

- Diabetes mellitus: self-reported history of physician diagnosed diabetes mellitus or use of anti–diabetes mellitus medications, or visit 5-$HbA_{1C} \geq 6.5\%$ or visit 5-FPG≥126 mg/dL or non-fasting glucose>200 mg/dL;
- Prediabetes mellitus: no known diabetes mellitus, but visit 5- $HbA_{1C}$ between 5.7% and 6.4% or visit 5-FPG 100 to 125 mg/dL;

- Normal glucose regulation: no known diabetes mellitus visit 5, and visit 5- $HbA_{1C}$ < 5.7%, and visit 5-FPG level <100 mg/mL

**Outcomes**

We will have two set of outcomes

***a) Echocardiographic measures left ventricular (LV) structure and function (systolic and diastolic)***

- LV ejection fraction (LVEF),
- LV end diastolic volume (LVEDV),
- Regional wall motion abnormality (RWMA),
- LV mass indexed to $height^{2.7}$,
- Longitudinal strain (LS),
- Tissue Doppler imaging (TDI) $e'_{septal}$ ;
- $E/e'_{septal}$;
- LA volume indexed to BSA (LAVi)

***b) Stages of HF:***

- For the stages of HF, we will use measures of LV structure and function to categorize individuals into HF stages at both visits 5 &7 as described in the table below.

Table: Definition of ACC/AHA heart failure stages and classification criteria to be used. [12,15]

| HF Stage | ACC/AHA Guideline Definition | Operational Definition |
|---|---|---|
| Stage 0 | Not meeting criteria for HF Stages A, B, C, or D | *None of the following clinical risk factors*: prevalent cardiovascular disease (coronary artery disease, stroke, or peripheral arterial disease), hypertension, diabetes, obesity, metabolic syndrome, or chronic kidney disease<br>*None of the following cardiac structural or functional abnormalities:* Abnormal LVEF, regional wall motion abnormality, LV enlargement based on LVEDV indexed to BSA, left ventricular hypertrophy based on LV mass indexed to $height^{2.7}$, moderate or greater aortic stenosis, aortic regurgitation, mitral regurgitation, or mitral stenosis. |
| Stage A | At high risk for HF but without structural heart disease or symptoms of HF | At least one of the following clinical risk factors: prevalent CVD (coronary artery disease, stroke, or peripheral arterial disease), hypertension, diabetes, obesity, metabolic syndrome, or chronic kidney disease<br>*None of the following cardiac structural or functional abnormalities:* Abnormal LVEF, regional wall motion abnormality, LV enlargement based on LVEDV indexed to BSA, left ventricular hypertrophy based on LV mass indexed to $height^{2.7}$, moderate or greater aortic stenosis, aortic regurgitation, mitral regurgitation, or mitral stenosis |
| Stage B | Structural heart disease but without signs or symptoms of HF | *At least one of the following cardiac structural or functional abnormalities:* Abnormal LVEF, regional wall motion abnormality, LV enlargement based on LVEDV indexed to BSA, left ventricular hypertrophy based on LV mass indexed to $height^{2.7}$ |
| Stage C | Structural heart disease with prior or current symptoms of HF | Prevalent HF identified through a previous hospitalization based on (1) committee adjudicated HF hospitalization since 2005,or (2) hospitalization with an ICD code 428 prior to 2005Prevalent HF not identified through a previous hospitalization, and instead based on self-report of HF or treatment for HF with at least one of the following: (1) subsequent confirmation of self-report by treating physician or the participant, or (2) an NT-proBNP at ARIC Visit 4 or 5 of at least 125 pg/ml |

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| Stage D | Refractory HF requiring specialized interventions | Left ventricular assist device or chronic inotropic therapy |

- Based on the change in HF stages from visit 5 to 7, we will define progression of HF stage as transitioning from the initial HF stage (at visit 5) to a more advanced HF stage (visit 7), and we will categorize individuals into progression of HF stage vs. non-progression

**Covariates**

Covariates will include age, sex, race-center, alcohol use, smoking status, estimated glomerular filtration rate (eGFR), body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), use of hypertension medications, total cholesterol, LDL-cholesterol, HDL-cholesterol, use of cholesterol-lowering medication, history of coronary artery disease, and history of atrial fibrillation.

**Statistical analysis**

We will conduct a prospective cohort analysis of ARIC study participants who attended visits 5 (2011-2013) and 7 (2018–2019). We will present the baseline characteristics of the participants at visit 5 by glycemic status (diabetes, prediabetes and normal glucose regulation).

We will use multivariable linear regression to relate the glycemic status categories at visit 5 to longitudinal changes (absolute and percent change from baseline) in quantitative echocardiographic indices of LV structure and function from visit 5 to visit 7. The echocardiographic indices will be LVEF, LVEDV, RWMA, LV mass indexed to height$^{2.7}$, LS, TDI $e'_{septal,}$ $E/e'_{septal}$ and LAVi.

We will use logistic regression to evaluate the association of glycemic status at visit 5 with an abnormal index of systolic function or diastolic dysfunction at exam 7 ("incident dysfunction") among those with normal indices at exam 5. Incident dysfunction includes any abnormality in one of the following: LVEF, LVEDV, RWMA, LV mass indexed to height$^{2.7}$, LS, TDI $e'_{septal,}$ $E/e'_{septal}$, or LAVi.

We will then use logistic regression to examine the association between glycemic status (at visit 5) and progression of one HF stage (at visit 5) to a more advanced HF stage (at visit 7), in other words we will assess the association of glycemic and progression of HF stage (progression vs. non-progression of HF stage). In addition, among those in stage C HF at visit 5, we will examine progression from stage C to mortality prior to visit 7.

Among individuals with diagnosed diabetes at baseline, we will assessed the association between the duration of diabetes (taken as a continuous variable) and HF progression using logistic regression models.

Among individuals without diabetes, we will repeat the aforementioned analyses using the quantitative changes in glycemic markers ($HbA_{1C}$ and FPG, separately) from visit 5 to 7 as the exposure instead of glycemic status, in the models that explore the associations with HF stage progression.

Among all eligible individuals, we will construct splines to more flexibly model the associations of glycemic markers ($HbA_{1C}$, FPG) and progression of HF stage, accounting for the use of diabetes medications (among those who have diabetes). For each of the models will adjust for the following variables: age, sex, race-center, alcohol use, smoking status, eGFR, BMI, SBP, use of hypertension medication, cholesterol-lowering medication use, and history of atrial fibrillation. In subsequent models, we will additionally adjust for prevalent coronary heart disease, and also consider time-

varying CHD as a covariate. We will also conduct spline analyses linking glycemic measures to changes in echocardiographic parameters from visit 5 to visit 7, stratified by diabetes status. Given the potential for survival bias, as individuals would have to survive to visit 7 to have that echocardiographic measures, we will conduct sensitivity analyses to address this issue. Indeed, to account for death, we will perform analyses using the inverse probability of attrition weighting (IPAW) models.[16,17] The IPAW model weights study participants by the inverse of the probability that they will die, to compensate for underrepresentation of persons with characteristics associated with death. The individual probabilities will be calculated from separate logistic models (using in information from visits and annual telephone calls), and allow the derivation of weights (as the inverse of the product of these probabilities), which will then be stabilized, and applied to our outcomes models.[18]

**Limitations**

Limitations of our study will include potentially limited power, especially for subgroup analyses. Because this is an observational study, we cannot rule out the possibility of residual confounding. Further, we only have echo measures at two visits, 7 years apart, limiting our ability to characterize the continuous trajectory of change over time.

**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 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 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/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)?**

- ARIC 1164: HbA1c as a risk factor for heart failure in persons with diabetes: the Atherosclerosis Risk in Communities (ARIC) study.

- ARIC 1488: The association of hemoglobin a1c with incident heart failure among people without diabetes: the atherosclerosis risk in communities study.
- ARIC 2119: Cardiac structure and function across the glycemic spectrum in elderly men and women free of prevalent heart disease: the Atherosclerosis Risk In the Community study.

**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 (*Study #2009.16 - PI: Selvin; Study # 2015.34 - PI Amil Shah*)**

**___ 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 https://www2.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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