ARIC Manuscript Proposal # 3320

PC Reviewed: 1/8/19  Status: _____  Priority: 2
SC Reviewed: _________  Status: ____  Priority: ____

1.a. Full Title:
Death or Heart Failure Risk and Echocardiography across the Glycemic Spectrum in Older Adults.

b. Abbreviated Title (Length 26 characters): Echo and outcomes across dysglycemia spectrum.

2. Writing Group:
Writing group members: Riccardo M. Inciardi, Brian Claggett, Deepak K. Gupta, Susan Cheng, Jiankang Liu, Justin Echouffo Tcheugui, Kunihiro Matsushita, Elizabeth Selvin, Scott Solomon, Amil Shah, Hicham Skali

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal.

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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 (this must be an ARIC investigator).

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3. Timeline:

Echo and Outcomes across dysglycemia spectrum
Data collection is already completed. Analysis will begin following proposal approval. Manuscript will follow analysis (~3-6 months).

4. **Rationale:**

Diabetes Mellitus (DM), a highly prevalent metabolic disorder in the community, is associated with a heightened risk of death or heart failure (HF) (1-4). Dysglycemia without overt diabetes is also associated with an increased risk of death (5) and HF (6). Based on ARIC Visit 5 Echocardiographic data, we have shown that dysglycemia was associated with subtle alterations in cardiac structure and function in older adults without prevalent heart disease (7). The prognostic risk related to cardiac structure and function across the glycemic spectrum remains unclear. The Atherosclerosis Risk in Communities (ARIC) study is well suited to investigate the relationships between cardiac structure and function and risk of cardiovascular (CV) outcomes across the glycemic spectrum in older adults.

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

The primary objective of this study is to assess the relationship between cardiac structure and function and the risk of death, HF and CV events across the glycemic spectrum. We hypothesize that worse alterations in cardiac structure and function (i.e. LV remodeling, impaired diastolic function, and subclinical reduction in left ventricular systolic function) portend a higher risk of death or HF in patients with and without diabetes. We will assess if there is effect modification by glycemic status on the association between echocardiographic measures of cardiac structure and function variables and CV outcomes.

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 using glycemic status and assessment of cardiac structure and function from ARIC visit 5, and death or incident HF. Patients will be stratified by prevalent heart disease. All analyses will be performed in these 2 groups.

**Exclusion Criteria:**
Subjects with incomplete echocardiographic data or glycemic ascertainment at visit 5 will be excluded.

**Variables:**

**Outcomes**

- Primary Outcome: Composite of All cause Death/Incident Heart Failure

Secondary Outcomes:

- All cause death: Deaths were ascertained using the National Death Index and via annual phone calls or through a search of health department death certificate files (8).
- Incident Heart Failure: For incident HF after visit 5, incident HF was based on HF hospitalization or HF death according to ICD codes (code 410 in any position) obtained by ARIC surveillance of hospital discharges (9).

- Major CV events: all cause death, Incident heart failure, Stroke and coronary heart disease event (CHD). [Stroke: a hospitalization is considered eligible for possible validation as a stroke if it contained a discharge diagnosis code indicative of cerebrovascular disease (International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes 430 to 438 (10). A CHD event is defined as a validated definite or probable hospitalized MI or a definite CHD death. The criteria for definite or probable MI are based on combinations of chest pain symptoms, ECG changes, and cardiac enzyme levels (11)].

**Exposure variables**

**Echocardiographic Variables**
- LV dimensions, volumes and ejection fraction
- Global LV systolic strain (longitudinal, circumferential, radial)
- LV mass and geometry
- LV diastolic function
- LA size

**Dysglycemia categories:**
We have used these categories in a previously published manuscript (6).
Dysglycemia spectrum categories will be defined according to levels of fasting plasma glucose (FPG), HbA1c; history of DM, self reported use of hypoglycemic medications (oral or insulin).

Subjects will be categorized into one of 3 groups:
- Normal: no known diabetes mellitus at visits 1 to 5 and annual follow-up data, and visit 5 HbA1c < 5.7% and fasting glucose level <100 mg/mL;
- Pre-diabetes: no known diabetes mellitus, but visit 5 HbA1c between 5.7% and 6.4%, or fasting glucose 100 to 126 mg/dL;
- Diabetes mellitus: known diabetes mellitus or on anti–diabetes mellitus medications, visit 5-HbA1c ≥ 6.5%, or fasting glucose ≥126 mg/dL or nonfasting glucose>200 mg/dL.

We will also evaluate fasting glucose and HbA1c as continuous variables (in fasting participants)

**Analysis:**
The association between echocardiographic measures and clinical outcomes will be assessed by Cox Proportional Hazards models stratified across the dysglycemic spectrum. Effect modification will be also be evaluated.
The association between echocardiographic measures and clinical outcomes will also be assessed over HbA1c as a continuous variable, adjusting for diabetes status.

**Planned multivariable-adjusted models:**
Model 1: age, gender, race/center

*Echo and Outcomes across dysglycemia spectrum*
Model 2: model 1 + total cholesterol, LDL, triglycerides, HDL, history of hypertension, CV medication (beta-blockers, ACEi/ARBs), systolic blood pressure, diastolic blood pressure, heart rate, eGFR, BMI, smoking status.
Model 3: model 2 + NTproBNP and high sensitivity Troponin-T (hs-cTnT)

A two-sided p-value of <0.05 will be considered statistically significant.

Limitations
- Residual confounding remains a possibility.
- Power might be limited, given multiple stratification steps.

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.cscce.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)?

MP 2129

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _____ Yes  _X___ No

11.b. If yes, is the proposal
____  A. primarily the result of an ancillary study (list number* _________)
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/

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:


