

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.

First author: Riccardo M. Inciardi

Address: Brigham and Women's Hospital
Cardiovascular Division
75 Francis Street, PBB-116
Boston, MA 02115

Phone: 617-525-6-790 Fax: 617-582-6027

E-mail: rinciardi@bwh.harvard.edu

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).

Name: **Hicham Skali, MD**
Address: Brigham and Women's Hospital
Cardiovascular Division
75 Francis Street
Boston, MA 02115

Phone: 857-307-1988 Fax: 617-582-6027

E-mail: hskali@post.harvard.edu

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 glyceemic 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 glyceemic 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 glyceemic 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 glyceemic 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 glyceemic 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 glyceemic 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 \geq 6.5%, or fasting glucose \geq 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 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 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.csc.unc.edu/ARIC/search.php>

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 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.csc.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.csc.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:

1. Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. *Lancet* 2014; 383: 1068-83.
2. Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Res Clin Pract* 2011; 94: 311-21.
3. Rawshani A, Rawshani A, Franzen S, Eliasson B, Svensson AM, Miftaraj M et al., Mortality and cardiovascular disease in type 1 and type 2 diabetes. *N Engl J Med* 2017; 376: 1407-18.
4. Warren B, Pankow JS, Matsushita K, Punjabi NM, Daya NR, Grams M, Woodward M, Selvin E. Comparative prognostic performance of definitions of prediabetes: a prospective cohort analysis of the Atherosclerosis Risk in Communities (ARIC) study. *Lancet Diabetes Endocrinol.* 2017 Jan;5(1):34-42.
5. Selvin E., Steffes M.W., Zhu H., Matsushita K, Wagenknecht L, Pankow J et al., Glycated Hemoglobin, diabetes, and Cardiovascular Risk in Nondiabetic Adults. *N Engl J Med* 2010;362:800-11.
6. Matsushita K., Blecker S., Pazin-Filho A., Bertoni A, Chang PP, Coresh J et al., The Association of Hemoglobin A1c With Incident Heart Failure Among People Without Diabetes: The Atherosclerosis Risk in Communities Study. *Diabetes* 59:2020–2026, 2010
7. Skali H, Shah A, Gupta DK, Cheng S, Claggett B, Liu j et al., 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. *Circ Heart Fail.* 2015;8:448-454

8. White A, Folsom A, Chambless L, Sharret R, Yang K, Conwill D et al., ARIC investigators. ScienceDirect-Journal of Clinical Epidemiology: community surveillance of coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) study: methods and initial two years' experience. Journal of Clinical Epidemiology 1996;49:223–233
9. Shah A, Claggett B, Loehr LR, Chang PP, Matsushita K, Kitzman D et al., Heart Failure Stages Among Older Adults in the Community The Atherosclerosis Risk in Communities Study. Circulation. 2017;135:224–240.
10. Rosamond WD, Folsom AR, Chambless LE, Wang CH, McGovern PG, Howard G et al., Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. Stroke. 1999;30:736 –743
11. White AD, Folsom AR, Chambless LE, Sharrett AR, Yang K, Conwill D, et al., Community surveillance of coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) study: methods and initial two years' experience. J Clin Epidemiol. 1996;49:223–233