ARIC Manuscript Proposal #2119

PC Reviewed: 4/9/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Cardiac structure and function across the dysglycemia spectrum in a bi-ethnic older population: the ARIC study

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

2. Writing Group:
Writing group members:
Hicham Skali, Amil Shah, Deepak Gupta, Susan Cheng, Brian Claggett, David Aguilar, Natalie Bello, Kunihiro Matsushita, Orly Vardeny, Elizabeth Selvin, Scott Solomon, Others welcome

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

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3. Timeline:

Analysis will begin following proposal approval and availability of the visit 5 data. Anticipating completion of echocardiography of the ARIC Visit 5 cohort in Fall 2013, a manuscript will be completed within 6 months of that date.

4. Rationale:

The worldwide prevalence of diabetes mellitus (DM) and heart failure (HF) is reaching parallel epidemic proportions[1] suggesting a possible interaction between the two[2]. The dysglycemia spectrum includes prediabetes and overt diabetes mellitus, and has been associated with a heightened risk of death, cardiovascular morbidity and HF [3-8]. Several epidemiological studies have shown an association between insulin resistance and DM and increased LV mass[9,10], LV hypertrophy, LV remodeling[11] and LV diastolic dysfunction[12]. However, these studies have not always yielded consistent and reproducible results, have often focused only on a portion of the dysglycemia spectrum, and/or have not extensively studied multiple parameters of cardiac structure and function.

In a Framingham Heart Study report of 2623 subjects (79.8% normal glucose tolerance), increased LV mass was associated with worsening glucose intolerance, while insulin resistance was associated with increased LV mass in women only[13]. The Jackson Heart Study studied 2399 African-Americans[14] (74% normal FBG, 13% impaired fasting glucose and 13% DM) and showed a similar association of higher LV mass and more prevalent concentric remodeling and LV hypertrophy, mostly in women.

The ARIC study offers a unique opportunity to comprehensively analyze the associations between the entire spectrum of dysglycemia and a broad range of phenotypes of cardiac structure and function in a large bi-ethnic community-based cohort. By incorporating conventional measures of cardiac structure and function and novel deformational imaging techniques[3,15] this study will answer whether the dysglycemia spectrum is associated with subclinical markers of cardiac dysfunction and eventually correlate with subclinical myocardial injury[6].

5. Main Hypothesis/Study Questions:

The primary objective of this study is to describe the impact of dysglycemia on cardiac structure and function in a large bi-ethnic elderly cohort.

We hypothesize that dysglycemia, defined as pre-diabetes or DM, will be related to abnormalities of cardiac structure including increased LV mass and hypertrophy and remodeling; in addition to decreased LV diastolic and systolic function assessed by conventional and novel echocardiographic techniques. We further hypothesize that obesity and gender may modify these relationships such that they may be accentuated in women but attenuated amongst obese participants.

Specific Aims:

1. Describe markers of cardiac structure and function across four predefined categories of the dysglycemia spectrum: Normal, Pre-diabetes, Newly diagnosed DM, Known DM (table below). We hypothesize that LV structure (higher LV mass)

and function (worse systolic and diastolic function) will be associated with worse glucose intolerance.

2. Assess the relationship between HbA1c and measures of cardiac structure and function across the categories of the dysglycemia spectrum. We hypothesize that within each category, higher HbA1c will be associated with worse diastolic function, increased LVmass and LA size, and decreased systolic function by speckle tracking echocardiography.

3. Assess the effect of dysglycemia spectrum category on the relationship between measures of cardiac structure and function and markers of subclinical myocardial injury (hs-TnT and NT-proBNP).

6. Data (variables, time window, source, inclusions/exclusions):

Eligible subjects are those who participated in the ARIC visit 5 echocardiography study (2011-2013) and have images of acceptable quality for analyses. Subjects with prevalent HF or coronary heart disease (MI, CABG) will be excluded.

Primary exposure variable:

Dysglycemia spectrum category: based on 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 four groups:

1. Normal glucose tolerance	FPG <100 mg/dL and HbA1c <5.7%
2. Pre-diabetes	FPG 100–125 mg/dL or HbA1c 5.7-6.4%
3. Newly diagnosed DM	FPG ≥126 mg/dL or HbA1c≥6.5% and not known to have DM or on DM therapy
4. Known DM	Previously known DM (abnormal HbA1c or FPB on prior ARIC visits), or on DM therapy

Secondary exposure variable to be considered and analyzed in each group is:

- HbA1c as marker of long-term glucose regulation

Primary outcome: Cardiac structure and function

The primary analysis will be to assess the impact of diabetes status on the following parameters of cardiac structure and function:

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

Clinical characteristics, echocardiographic cardiac structure and function, and biomarkers will be compared between groups of dysglycemia spectrum. In particular, clinical variables to be evaluated include: age, gender, CVD risk factors, such as hypertension, dyslipidemia, smoking, BMI/obesity, stroke/TIA, peripheral arterial disease, atrial fibrillation/flutter, chronic kidney disease, anemia, COPD & asthma, and alcohol use; ECG left ventricular hypertrophy and QRS duration; heart rate, blood pressure indices,

height, weight, body surface area, WBC count, hemoglobin, red cell distribution width, fasting plasma glucose, HgbA1c, lipids, BNP, hsTnT; vascular stiffness by pulse wave velocity; and pulmonary function tests.
Echocardiographic variables to be evaluated include those related to *cardiac structure*: LV size, LV wall thickness, LV mass, LV geometry, left atrial size and volumes, aortic root dimension, valvular disease, regional wall motion abnormalities, and right ventricular size. Parameters of *cardiac function* including LV ejection fraction, right ventricular fractional area change, Doppler mitral inflow E and A wave peak velocities, E/A ratio, deceleration time, tissue Doppler systolic and diastolic indices at both the mitral and tricuspid annulus, as well as LV myocardial mechanics from speckle tracking imaging will be assessed. Noninvasive hemodynamic parameters including stroke volume, cardiac output, LV filling pressures, pulmonary vascular resistance, and pulmonary artery pressures will also be analyzed.
Categorical variables will be compared via $\chi 2$ or Fischer exact test, while continuous data will be compared between groups via Wilcoxon rank sum test or nonparametric trend tests as appropriate. P values < 0.05 will be considered significant.
Univariate and multivariable regression analyses and analysis of variance will be used to assess associations between categories of the dysglycemia spectrum (independent) and echocardiographic characteristics (dependent) at visit 5. Adjustments for differences in clinical characteristics (based upon $P < 0.05$ and/or clinically important covariates) will be performed.
Subsequently, HbA1c will be entered in the stratified univariate and multivariate linear regression analysis models. Interaction will be assessed for gender, BMI, race and CKD.

Limitations:

- Classification in one of the groups of the dysglycemia spectrum is based on a single assessment at visit 5. There is no OGTT performed to assess true glucose intolerance.
- In general, misreporting of DM diagnosis and/or DM therapies is a possibility and can lead to misclassification of cases of diet controlled DM. In ARIC, however, selfr-reported DM appears to be reliable[16].
- Residual confounding remains a possibility.

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 ICTDER02 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

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 ICTDER02 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)?

MP1883, MP2054

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

___ 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.

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