ARIC Manuscript Proposal #3719

PC Reviewed: 10/13/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Duration of diabetes, glucose excursions and control, and low heart rate variability: The ARIC Study

b. Abbreviated Title (Length 26 characters): **Diabetes duration & HRV**

2. Writing Group:

Writing group members: Mary R. Rooney, Justin B. Echouffo-Tcheugui, Faye L. Norby, Elsayed Z. Soliman, Lin Yee Chen, Elizabeth Selvin (order TBD; others welcome)

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

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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: We anticipate manuscript completion within a year of acceptance.

4. Rationale:

Cardiovascular autonomic neuropathy is a serious but often commonly overlooked complication of diabetes. Heart rate variability (HRV) is a measure of variation in time between heartbeats and is a marker of autonomic dysfunction. Individuals with diabetes tend to have lower HRV compared to their non-diabetic counterparts.[1] Low HRV is associated with risk of cardiovascular disease, particularly among individuals with diabetes.[2-4] Prior studies have suggested that hyperglycemia[5-8] and hypoglycemia[9-11] may contribute directly to low HRV, and possibly explaining some of the excess risk of cardiovascular disease in diabetes.[11-13]

Duration of diabetes, glucose excursions, and poor glycemic control may be associated with lower HRV. Poor glycemic control and frequent glucose excursions are often intertwined and are strongly related to duration of diabetes; however, little has been published specifically on how diabetes duration (and presumably greater organ damage from long-standing diabetes) relates to HRV,[14] which may indicate autonomic dysfunction. It is also plausible that, in diabetes, the association of long-standing diabetes, glucose excursions, and poor glycemic control with cardiovascular outcomes is mediated by lower HRV.

5. Main Hypothesis/Study Questions:

Aim 1: To evaluate the associations of diabetes status, duration of diabetes, and biomarkers of glucose excursions (1,5-anhydroglucitol [1,5-AG]—a measure of glycosuria) and glycemic control with HRV.

Hypothesis 1: We hypothesize that a longer duration of diabetes will be associated with lower HRV measures compared to those with shorter durations of diabetes and particularly compared to those without diabetes. In individuals with diabetes, we hypothesize that glucose excursions, and poor glycemic control will be cross-sectionally associated with low HRV measures.

Aim 2: To quantify the degree to which the association of longer diabetes duration, glucose excursions, and poor glycemic control, with cardiovascular outcomes is mediated by low HRV.

Hypothesis 2: We hypothesize that the association of longer diabetes duration, glucose excursions, and poor glycemic control with cardiovascular outcomes is partially mediated by low HRV.

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

Aim 1: Cross-sectional at visit 4. We chose this visit for two reasons: 1) HRV is available at visit 1 and visit 4; and 2) diabetes duration is unknown at visit 1.

Aim 2: Prospective after visit 4.

Exclusions

Aims 1 & 2: We will exclude participants who meet any one of the following criteria:
1) missing or poor quality HRV data,
2) missing information on diabetes or information needed to estimate diabetes duration at visit 4,
3) blacks at the Maryland and Minnesota centers and those who report their race as neither black nor white.

Aim 2: In addition to the above exclusions, we will further exclude those with prevalent CVD at baseline or missing follow-up information.

Variables

Diabetes duration (Exposures in Aims 1 & 2): Diabetes duration at visit 4 will be estimated based on self-report diagnosed diabetes or glucose-lowering medication use at visits 1-4 or reported during AFU calls. We will categorize our exposure as follows: no diabetes (referent), diabetes >0-<5 years, diabetes ≥5 years.

Glucose excursions (Exposures in Aims 1 & 2) will be assessed using the biomarker serum 1,5-anhydroglucitol, a marker of glycosuria, where low serum 1,5-AG indicates that the individual has had glucose excursions. We will categorize as 1,5-AG ≥6 μg/mL (referent) vs <6 μg/mL.

Glucose control (Exposures in Aims 1 & 2) will be estimated using serum fructosamine. Fructosamine is another biomarker reflective of glucose control and is highly correlated with

hemoglobin A1C (Pearson's r~0.8 at ARIC visit 2).[15] We will categorize estimated A1C as <7% vs ≥7%.

HRV parameters (Outcomes in Aim 1 & Potential Mediators in Aim 2): We will examine the following HRV parameters.
- Standard deviation of normal-to-normal R-R intervals (SDNN)
- Root mean square of successive differences in normal-to-normal R-R intervals (RMSSD)
- Low frequency (LF) power
- High frequency (HF) power
- LF/HF ratio

Incident cardiovascular events (Outcomes in Aim 2):
- Incident CVD (heart failure, coronary heart disease, ischemic stroke, atrial fibrillation, CVD mortality) will be reported as a composite and in supplemental analyses as individual endpoints

Other variables of interest: age, sex, race-center, smoking status, drinking status, body mass index, systolic blood pressure, blood pressure-lowering medication use, total cholesterol, HDL cholesterol, lipid-lowering medication use, eGFR, 1,5-anhydroglucitol, fructosamine, medication use (beta-blockers, calcium-channel blockers, digoxin, antiarrhythmics)

Analysis

Aim 1: We will report baseline characteristics including mean (SD) for HRV measures according to the following categories for diabetes duration: no diabetes, diabetes >0-<5 years, diabetes ≥5 years. We will log transform HRV measures, depending on the shape of the distribution, and categorize HRV measures (e.g., $<25^{th}$ vs $\geq 25^{th}$ percentile). We will use ANOVA to test whether associations between categories of diabetes duration differ overall.

In the subset with diabetes, we will describe the mean HRV measures according to duration of diabetes (<5 vs ≥5 years) categories of 1,5-AG and estimated A1C. We will use linear regression to compare age- and sex-adjusted means (95% CIs) for HRV according to diabetes duration, 1,5-AG, and estimated A1C categories. We may explore whether these associations differ by age, sex, and prevalent CVD.

Aim 2: Among individuals with diabetes, we will use Cox regression to analyze the association between diabetes duration, glucose excursions and control with incident cardiovascular events. We will use a counterfactual model to estimate indirect and direct effects and the percent of the association between diabetes duration, glucose excursions and control and incident cardiovascular events that is mediated by low HRV.[16]
Model 1 = age, sex, race-center
Model 2 = Model 1 + current smoking, systolic blood pressure, blood pressure-lowering medication use, total cholesterol, HDL cholesterol, lipid-lowering medication use, eGFR

In a sensitivity analysis, we will exclude individuals using medications which affect HRV, including betablockers, calcium channel blockers, digoxin, and other antiarrythmics such as amiodarone, procainamide.

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/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)?

- MS 3047 (Poon) IR indexes and HRV
- MS 2100 (Echouffo- Tcheugui) HRV and HF
- "Diabetes, glucose, insulin, and heart rate variability: the Atherosclerosis Risk in Communities (ARIC) Study" by Schroeder et al. (2005)

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* _____)
_x_ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _2009.16___ _____ _____)

*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.

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