ARIC Manuscript Proposal #2250

PC Reviewed: 11/12/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Heart Rate Variability and Incident Stroke: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): HRV & Stroke

2. Writing Group: Amber Fyfe-Johnson, Clemma Muller, Alvaro Alonso, Aaron Folsom, Eric Whitsel, Sunil Agarwal, Rebecca Gottesman, Wayne Rosamond, Richard MacLehose. Other interested investigators welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _AFJ_ **[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: Data analysis to begin immediately: 3 months.
Manuscript preparation: 3 months.

4. Rationale:

Stroke is the most severe form of cerebrovascular disease, with 795,000 cases in the U.S. each year; ischemic strokes account for approximately 85% of all strokes and

hemorrhagic strokes explain the remaining 15%[1]. Stroke is the 4th leading cause of death in the United States[2,3], and is a major cause of disability[4,5]. Population-based cohort studies such as the Atherosclerosis Risk in Communities Study (ARIC) have identified many risk factors for incident stroke[6–8]. Chief among these are older age, male sex and African American vs. white race. Modifiable or preventable risk factors include hypertension, diabetes, obesity, poor diet, and smoking[9,10]. Other pathologies identified as strong predictors of stroke onset and mortality include atrial fibrillation, increased carotid intima-media thickness (cIMT), and markers of autonomic nervous system dysfunction such as orthostatic hypotension[11].

Heart rate is a function of the baseline autonomic nervous system, whereas heart rate variability (HRV) is known to be an indirect measure of general autonomic nervous system activity[12]. Sympathetic activity decreases HRV and parasympathetic activity increases HRV[13]. Furthermore, stroke survivors have impaired HRV in addition to autonomic nervous system dysfunction[14–16]. The relationship of reduced HRV and autonomic dysfunction with all-cause and cardiovascular mortality has also been established[17–22], yet it is unclear whether reduced autonomic activity is responsible for these increases in mortality[23,24]. Although scarce, existing literature is suggestive of a positive association between reduced heart rate variability and incident stroke[25]. Current evidence is also limited by small sample sizes and therefore low statistical power.

To date, the association between HRV and incident stroke has been minimally examined. No studies have explored the association of HRV with incidence of hemorrhagic stroke. Therefore, we aim to explore the association between HRV and incident stroke in the ARIC cohort.

5. Main Hypothesis:

- Low HRV will be positively associated with risk of incident stroke.
- Lower pre-stroke HRV will predict poorer survival among individuals with incident stroke.

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 methodological limitations or challenges if present).

Study Design

Prospective cohort study from ARIC visits 1 (1987-89) and 4 (1996-98), when ECG data were measured, to the development of incident stroke by the end of 2010. The **primary analysis** will investigate the association of HRV at visit 1 with incident stroke in 2010; the **secondary analysis** will examine the association of HRV at visit 4 with incident stroke in 2010.

Inclusion/Exclusion

Participants with prevalent stroke (according to ARIC criteria) will be excluded at baseline. Subjects with missing or inconclusive HRV data will also be excluded at

baseline. Additionally, individuals who are neither African American nor white, and African Americans from the MN and MD centers will be excluded at baseline. Individuals with fatal stroke will be excluded in the analysis examining the association between HRV and stroke survival in individuals surviving an ischemic/hemorrhagic stroke.

Variables

Exposures: HRV data will be obtained using a 2 and 6-minute beat-to-beat heart rate from an electrocardiogram (ECG) recording at visits 1 and 4 respectively.

Time domain measures of HRV (**primary**)

1. SDNN (total power) (ms) – standard deviation of all normal RR intervals; *estimate of overall variability in measurement period.*
2. r-MSSD (ms) – root mean square successive difference, the square root of the mean of the squared differences between adjacent normal RR intervals; *estimate of short term components of variability in the measurement period.*

Frequency domain measures of HRV (**secondary**)

1. HF (high frequency power) (ms2) □ the energy in the heart period power spectrum between 0.15 and 0.40 Hz; *linked to parasympathetic nervous system activity.*
2. LF (low frequency power) (ms2) □ the energy in the heart period power spectrum between 0.04 and 0.15 Hz; *less known, may reflect sympathetic nervous system activity, likely reflects general autonomic nervous system activity.*
3. LF/HF ratio; *less known, may reflect sympathetic nervous system activity.*

Outcome:

- **Primary**: Incident stroke as defined by ARIC criteria; stratified by ischemic and hemorrhagic stroke in the analysis.
- **Secondary**: All-cause mortality among individuals with incident stroke (fatal strokes excluded); may stratify by stroke type in analysis.

Potential effect modifiers: Age, sex, and race.

Other confounders:

Demographics: age, sex, ARIC field center, and education.

Behavioral: physical activity, smoking status and amount, alcohol intake, dietary intake, and mental stress.

Physical/medical: systolic blood pressure, diabetes mellitus, prevalent CVD (CHD/HF), Charlson comorbidity index, BMI, orthostatic hypotension, atrial fibrillation, and cIMT.

Biomarkers: total cholesterol, high-density lipoprotein (HDL), glucose, hemoglobin A1c (HbA1c), high sensitivity C-reactive protein (hsCRP), N-terminal pro-B-type natriuretic peptide (NT-proBNP), troponin T, and lipoprotein-associated phospholipase A_2 (Lp-LPA_2).

Medication use: anticoagulant, antihypertensive, and lipid medication medication use.

Data analysis:

Baseline characteristics of participants will be described using means and proportions stratified by HRV tertiles. We will use Cox proportional hazards regression to model the relationship between HRV and stroke incidence or survival. Results will be presented for all strokes combined, and separately by stroke type (ischemic and hemorrhagic). Cubic splines may be used to visually depict the associations, and aid in selecting the most appropriate representation. HRV will be modeled continuously with time domain measures as the primary exposures: (i) $mean_{NN}$: the mean value for time between normal QRS complexes as measured during the ARIC study visits 1 and 4, and (ii) $mean_{RMS}$: the square root of the mean of the squared differences between adjacent normal RR intervals during the ARIC study visits 1 and 4. HRV will be modeled continuously with frequency domain measures (HF, LF, and LF/HF ratio) as secondary exposures.

The analysis of incident stroke will include all ARIC participants who were: (i) stroke-free at visit 1 (primary), and (ii) stroke-free at visit 4 (secondary); the analysis of post-stroke survival will be restricted to cohort members who experience incident stroke, with date of stroke marking the beginning of time at risk for the Cox regression model. This analysis will exclude individuals with fatal stroke. Stroke severity will be considered using the Charlson comorbidity index as a covariate in models for post-stroke survival. Models will be performed with and without covariate adjustment. We will perform standard Frequentist statistical analyses, as well as a Bayesian analysis using previously published findings[25] to inform the prior distribution for stroke incidence and post-stroke survival. For the latter we will use approximate Bayes methods as described by Greenland[26–28]. All analyses will be performed with Stata version 12.0 or later; inferential results will be presented as point estimates with 95% confidence intervals (Frequentist) and 95% credible intervals (Bayesian).

Limitations to the proposed analyses include: (i) limited power for the study of survival among stroke patients, (ii) limited power for exploratory analyses stratified by stroke subtype (hemorrhagic stroke in particular), and (iii) survival may be difficult to interpret as HRV measures are collected at various intervals prior to incident stroke.

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.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)?

#1998 *Determinants of Heart Rate Variability Change over 10 Years in a Population Sample: The ARIC Study*. Lin Y. Chen, Faye Lopez, Elsayed Z. Soliman, Alvaro Alonso, and others.

#1913 *Heart Rate Variability and the Risk of Sudden Cardiac Death: The ARIC Study*. Lin Y. Chen, Faye Lopez, Selcuk Adabag, Elsayed Z. Soliman, Aaron R. Folsom, Alvaro Alonso, and others.

#2100 Heart Rate Variability and Heart Failure Incidence : the Atherosclerosis Risks in Communities study. Justin B. Echouffo-Tcheugui, Sunil K. Agarwal, Stuart D. Russell, Eric A. Whitsel, Elsayed Z. Soliman, Laura R. Loehr , Saman Nazarian, Alvaro Alonso, Lin Chen, Wayne D. Rosamond, Gerardo Heiss, Josef Coresh.

#2141 *Bradycardia and risk of incident cardiovascular disease: The Atherosclerosis Risk in Communities Study*. Michael W. Cammarata, Alain G. Bertoni, Elsayed Soliman, Patricia Chang.

1459 *Cardiac autonomic imbalance and incident atrial fibrillation: the Atherosclerosis Risks in Communities study*. Sunil K. Agarwal MD MPH , Alvaro Alonso, MD PhD , Elsayed Z. Soliman MD MSc MS, Alanna Chamberlain MPH, Marietta Ambrose MD, Ross J. Simpson MD PhD, Gerardo Heiss MD PhD.

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)* _____ _____ _____)

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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