ARIC Manuscript Proposal #1913

PC Reviewed: 3/20/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Heart Rate Variability and the Risk of Sudden Cardiac Death: The ARIC Study

b. Abbreviated Title (Length 26 characters): Heart Rate Variability and Sudden Cardiac Death

2. Writing Group:

Writing group members: Lin Y. Chen, Faye Lopez, Selcuk Adabag, Elsayed Z. Soliman, Aaron R. Folsom, Eric Whitsel, Alvaro Alonso, and others

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

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3. Timeline:

Statistical Analysis: 3 months
Manuscript preparation: 3 months

4. Rationale:

Sudden cardiac death (SCD) is a major public health problem claiming up to 300,000 lives annually in the US.[1] Individuals who are at risk for SCD include patients with coronary heart disease (CHD), previous myocardial infarction (MI), left ventricular systolic dysfunction, chronic heart failure, left ventricular hypertrophy, and inherited channelopathies and cardiomyopathies.[2] However, the overwhelming majority of SCDs occurs in the general population,[3, 4] and approximately 55% of men and at least 68% of women have no clinically overt heart disease prior to SCD.[5, 6]

Heart rate variability (HRV) is a non-invasive marker of autonomic nervous system function.[7] Sympathetic stimulation decreases HRV, whereas parasympathetic stimulation increases HRV. Cardiac arrhythmias are often initiated by or occur in patients with enhanced sympathetic and diminished parasympathetic tone. In post-MI patients, low HRV is associated with an increased risk of arrhythmic death[8] and total mortality.[9] In the general population, low HRV is associated with an increased risk of CHD[10, 11] and total mortality.[11, 12] However, it is unknown whether low HRV is associated with an increased risk of SCD in the general population.

Recently, we found that atrial fibrillation (AF) increases the risk of SCD in the general population (publication pending). It is unknown whether low HRV is associated with an increased risk of SCD in patients with AF.

5. Main Hypothesis/Study Questions:

Aim #1: Evaluate the association between HRV and risk of SCD

Hypothesis #1: In the general population, low HRV is associated with an increased risk of SCD, independent of other risk factors for SCD.

Aim #2: Evaluate the association between HRV and risk of SCD in participants with incident AF

Hypothesis #2: In participants with incident AF, low HRV is predictive of SCD, independent of other risk factors for SCD.

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 population

Aim #1

Inclusion criteria: Participants enrolled in the ARIC study at Visit 1
Exclusion criteria: Missing or indeterminate HRV data at Visit 1 and missing covariates.

Aim #2

Inclusion criteria: ARIC participants diagnosed with incident AF after Visit 1
Exclusion criteria: Prevalent AF at baseline, missing or indeterminate HRV data at Visit 1, and missing covariates.

AF
AF cases will be identified from:
1) Hospital discharge records (ICD-9 code 427.31 – Atrial fibrillation)
2) ECGs performed during study visits 1 – 4

Exposures measurement
HRV data will be obtained from 2-minute beat-to-beat heart rate recordings (Visit 1) and 6-minute recordings (Visit 4):

Time domain measures of HRV (Visit 1 and Visit 4)
1. RR interval (ms)
2. SDNN (ms) – standard deviation of all normal RR intervals
3. r-MSSD (ms) – root mean square successive difference, the square root of the mean of the squared differences between adjacent normal RR intervals
4. SDSD (ms) – the standard deviation of absolute differences between successive normal RR intervals
5. pNN50 (%) – percentage of adjacent normal RR intervals that are greater than 50 ms

Frequency domain measures of HRV (Visit 4)
1. Total power (ms^2) – the energy in the heart period power spectrum up to 0.40 Hz
2. VLF (very low frequency power) (ms^2) – the energy in the heart period power spectrum between 0.0033 and 0.04 Hz
3. LF (low frequency power) (ms^2) – the energy in the heart period power spectrum between 0.04 and 0.15 Hz
4. HF (high frequency power) (ms^2) – the energy in the heart period power spectrum between 0.15 and 0.40 Hz

Outcomes measurement
SCD
All events classified as fatal coronary heart disease (CHD) (definite MI, definite fatal CHD, or possible fatal CHD, in and out of hospital) through 2001 were reviewed and adjudicated by a committee of physicians. SCD was defined as a sudden pulseless condition from a cardiac origin in a previously stable individual. Case data were sent separately to pairs of physician adjudicators for classification. After an extensive event review, which included abstraction of data from death certificates, informant interviews, physician questionnaires, coroner reports, and hospital discharge summaries, reviewers classified each CHD death as definite sudden arrhythmic death, possible arrhythmic death, not sudden arrhythmic death, or unclassifiable. SCD will be defined as the first 2 categories.

Covariates

Age, sex, race, field center, smoking status, body mass index, hypertension, diabetes, CHD, heart failure, ECG-based left ventricular hypertrophy, use of β-blockers, use of digoxin, and use of anti-arrhythmics.

Statistical analysis

Aim #1

We will estimate the survival of participants according to baseline HRV tertiles by the Kaplan-Meier method. We will use Cox proportional hazards models to estimate hazard ratio (HR) and 95% confidence interval (CI) for SCD according to baseline HRV tertiles. Model 1 will be adjusted for age, sex, race, and field center. Model 2 will additionally be adjusted for baseline smoking status, body mass index, hypertension, diabetes, ECG-based left ventricular hypertrophy, use of β-blockers, use of digoxin, and use of anti-arrhythmics. Model 3 will additionally be adjusted for incident CHD and heart failure as time-dependent covariates.

In addition, we will test for interactions between race and sex with HRV in relation to SCD by including an interaction term in the models.

For sensitivity analysis, we will repeat the analysis using HRV data obtained at Visit 4, using that visit as baseline.

Aim #2

For participants with incident AF, we will use Cox proportional hazards models to estimate HR and 95% CI for SCD according to baseline HRV tertiles. Model 1 will be adjusted for age, sex, race, and field center. Model 2 will additionally be adjusted for baseline CHD, diabetes, and heart failure. This reduced model (compared with Aim #1) is due to the relatively low number of SCD events (n=33) in 802 incident AF cases.

In addition, we will test for interactions between race and sex with HRV in relation to SCD by including an interaction term in the models.

For sensitivity analysis, we will repeat the analysis using HRV data obtained at Visit 4, using that visit as baseline.

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

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
____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 #301: Dekker – Low HRV and mortality
- MS #1557: Prineas – ECG predictors of SCD
- MS #1737: Chen – AF and SCD

We will include some authors above as co-authors in the manuscript.

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

_x_ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* ___2004.03, 1996.03_____ _____ _____)

*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.

References

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