1.a. **Full Title:** Determinants of Heart Rate Variability Change over 10 Years in a Population Sample: The ARIC Study

b. **Abbreviated Title (Length 26 characters):** Determinants of Heart Rate Variability Change

<table>
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<th>Writing Group</th>
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<tr>
<td>Writing group members: Lin Y. Chen, Faye Lopez, Elsayed Z. Soliman, Alvaro Alonso, and others.</td>
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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:**
4. Rationale:
Heart rate variability (HRV) is a non-invasive marker of autonomic nervous system function.\(^1\) 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-myocardial infarction (MI) patients, low HRV is associated with an increased risk of arrhythmic death\(^2\) and total mortality.\(^3\) In the general population, low HRV is associated with an increased risk of coronary heart disease (CHD)\(^4,5\) and total mortality.\(^5,6\)

Despite the prognostic significance of HRV, little is known about the determinants of HRV in the general population. Much less is known about the determinants of HRV change over time. Factors known to be associated with lower HRV include higher heart rate, older age, use of beta-blockers, history of MI, heart failure, diuretic use, diabetes mellitus, and smoking.\(^7\) Modifiable factors such as body habitus and physical activity or fitness may be associated with HRV.\(^8-14\) These associations, however, are cross-sectional and few studies have evaluated the correlates of longitudinal change in HRV over time.

We hypothesize that CHD risk factors (e.g., hypertension, diabetes) are correlated with HRV decrease over time in the general population. The overall goal of this study is to investigate the association of a comprehensive set of sociodemographic characteristics, health behaviors, and clinical characteristics with HRV decrease in a community-based sample.

5. Main Hypothesis/Study Questions:

Aim: Identify determinants of HRV decrease over time

Hypothesis: In the general population, CHD risk factors are associated with HRV decrease over time.

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

Inclusion criteria: Participants enrolled in the ARIC study at visit 1

Exclusion criteria: Missing or indeterminate HRV data at visit 1 and 4; CHD, heart failure, stroke, hypertension, and diabetes at baseline; use of beta-blockers, non-dihydropyridine calcium channel blockers, digoxin, or anti-arrhythmic drugs at baseline and during follow-up; missing risk factors; race/ethnicity other than white or black.
**Risk factors**
We will evaluate the following baseline (visit 1) risk factors: age, sex, race, educational level, income, waist circumference, body mass index (BMI), waist-hip ratio, heart rate, systolic blood pressure, diastolic blood pressure, smoking status, physical activity. We will also evaluate incident hypertension, diabetes, CHD, and heart failure.

**Outcomes measurement**
HRV data will be obtained from 2-minute beat-to-beat heart rate recordings (visit 1) and 6-minute recordings (visit 4). Change in HRV measures during follow-up will be calculated as the difference between HRV measures at visit 4 and visit 1.

**Time domain measures of HRV**
1. SDNN (ms) – standard deviation of all normal RR intervals
2. r-MSSD (ms) – root mean square successive difference, the square root of the mean of the squared differences between adjacent normal RR intervals

**Frequency domain measures of HRV**
1. LF (low frequency power) (ms$^2$) – the energy in the heart period power spectrum between 0.04 and 0.15 Hz
2. HF (high frequency power) (ms$^2$) – the energy in the heart period power spectrum between 0.15 and 0.40 Hz
3. LF/HF ratio

**Statistical analysis**
We will report means with standard deviations or medians and interquartile ranges for continuous variables, and counts with percentages for categorical variables. A natural logarithmic transformation will be used to normalize the distribution of the HRV values.

We will use multivariable general linear models to assess the association between baseline risk factors and decrease in HRV over time. Separate models will be run for each HRV measure. We will use stepwise selection methods to construct the most parsimonious model for the prediction of HRV decrease over time.

Participants with cardiovascular risk factors or who developed cardiovascular disease during follow-up may be less likely to participate in visit 4 due to death or lost to follow-up. If change in HRV is also associated with death or lost to follow-up, selection bias might occur. We will address the potential for selection bias by determining whether baseline cardiovascular risk factors and baseline HRV are associated with visit 4 participation. If so, we will use ‘inverse probability weighting’ to control for selection bias.

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 ___ 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
couraged to contact lead authors of these proposals for comments on the new
proposal or collaboration)?
   - MS #301: Dekker – Low HRV and mortality
   - MS #277: Liao – HRV and Incident CHD

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