1. **Full Title:** Bradycardia and risk of incident cardiovascular disease: The Atherosclerosis Risk in Communities Study

   **b. Abbreviated Title (Length 26 characters):** Bradycardia and CVD

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

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3. **Timeline:** Analyses will begin as soon as this manuscript proposal is approved.

4. **Rationale:**
High heart rates (HR) have predicted poor outcomes in multiple studies. Increased HR on serial ECGs has been associated with a greater likelihood of subsequent cardiovascular disease (CVD) or all-cause mortality. Once time measurement of a heart rate in clinic of 80 or greater is a predictor of all-cause, cardiovascular, and non-cardiovascular mortality and has been shown to be a better predictor than ambulatory heart. However, very few studies have examined the effect of low heart rate (<55) on cardiovascular disease and mortality.

It is well known that highly competitive athletes have lower resting heart rates, however, conflicting evidence exists regarding the prevalence of baseline ecg abnormalities and recent studies have shown both a higher rate of baseline ECG abnormalities in this population and a standard rate of ECG abnormalities. Little is known about future event rates in this population. Asymptomatic bradycardia in patients >60 years of age has been shown with multivariate analysis to have a detrimental effect (increased rate) on pacemaker implantation, but a protective effect (lower rate) on mortality. An similar effect has been shown in otherwise healthy middle-aged men (age 42-53) where bradycardia was found to have a protective effect on CVD and mortality.

In 2010, Paul et al demonstrated a linear relationship between resting HR and mortality in normotensive and untreated hypertensive individuals. Baseline HR, final HR, and HR change was analyzed during follow-up in patients attending the Glasgow Blood Pressure Clinic. Patients were classified using a threshold of 80 bpm into those who had a consistently high (high-high) or low (low-low) HR or patients whose HR increased (low-high) or decreased (high-low) over time. Interestingly, for each beat of HR change there was a 1% change in mortality risk. The highest risk of an all-cause event was associated with patients who had increased their HR by >=5. Compared with low-low patients, high-high patients had a 78% increase in the risk of all-cause mortality. Cardiovascular mortality showed a similar pattern of results.

Very little data has been reported on very low heart rate and its effect on cardiovascular disease and mortality. Some preliminary data from MESA cohort study suggest that very low heart rate (<55 resting) may be associated with increased rate of events. ARIC data would be a robust dataset worth investigating the association of very low resting heart rate and cardiovascular events and mortality.

5. Main Hypothesis/Study Questions:
1. Is there an association with resting bradycardia (with various degrees of severity) at baseline and cardiovascular events?

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: we will perform a longitudinal analysis of data.

Study Questions:
1. What are the characteristics of participants with bradycardia at exam 1?
2. What is the association between baseline bradycardia and incident CVD?
3. Is there a relationship between change in heart rate over time and incident CVD?

**Main exposure:** baseline EKG data will be used to determine resting heart rate at time of study entry.

**Main outcome:** our primary outcome will be incident cardiovascular disease to include incident CHF, myocardial infarction, stroke, and cardiovascular mortality. We will consider all adjudicated data which is currently available to determine this. Secondary endpoints will be the individual endpoints of myocardial infarction, incident CHF, Stroke, and both CV and all-cause mortality. Carotid IMT will be used as a secondary endpoint as a marker of subclinical CVD.

**Covariates:** additional variables required for analysis will include demographic factors (age, gender, race, study center, level of education), anthropometric data (height, weight, blood pressure), comorbid conditions (type 2 diabetes, hypertension, hyperlipidemia), physical activity, smoking status (current, former or never), alcohol consumption status (current, former or never), presence of atrial fibrillation or other rhythm disturbance, heart rate at all five visits and medication use (anti-hypertensive, lipid-lowering, aspirin, antiarrhythmic). Within the categories of anti-HTN drugs we will also look at drug categories, in particular beta-blockers. Finally, we will also use baseline lab values (glucose, lipids).

**Inclusion/Exclusion:**

**Inclusion:**
- All participants with baseline EKG.
- Free of major EKG abnormalities

**Exclusion:**
- Missing or Poor Quality EKG
- Major EKG abnormalities (e.g. AV-block)
- missing follow-up for CV events (should be very small number of folks)

**Data analysis:** Descriptive statistics will be initially utilized to compare participants with and without bradycardia based on their baseline characteristics (chi squared and t-tests for categorical and continuous variables, respectively). Of particular interest is the comparison of those with vs. without bradycardia with respect to age, gender, race, ECG abnormalities, and CVD risk factors. We will then determine, among those with bradycardia, what proportion of participants may have bradycardia potentially associated with drug treatment (i.e. beta blockers).

To determine association between the exposure and incident disease and mortality, we will initially model heart rate as a continuous variable while adjusting for the above mentioned covariates in a logistic regression model. Once, we have determined if a relationship exists we will subdivide the population into groups consisting of very low (<50), low (50-59), normal (60-79), and high (≥80) resting heart rates. We will calculate incidence rates of the primary outcome (per 1000 person years) in each
category and compare these using the log-rank test. We will then use Cox proportional hazards model to calculate the hazard ratios for the 4 groups. We will first adjust for drugs that might affect heart rate, and consider also stratification of analyses by beta blocker /AV nodal blocking medication use. One analysis will be performed for incident CVD as defined above, including fatal events. Secondary analyses will be performed using endpoints of incident CHF, myocardial infarction, stroke, cardiovascular mortality, and total mortality individually. We will also perform a secondary analysis using carotid IMT as an endpoint and an analysis using a time dependent heart rate variable as an exploratory analysis. Another analysis to address aim 3 will be performed using trajectory analysis, using the heart rate at the first 2 visits to group each participant into one of four groups and will be analyze the data using cox proportional hazards modeling adjusting for all of the above covariates. For each endpoint we will utilize sequential modeling to adjust for demographic factors, and potential confounders/ mediators, including medication use, exercise, blood pressure and BMI and the other above covariates. We will assess for interactions between heart rate and both gender and race/ethnicity.

Limitations: The main limitation of this proposed study would be a predicted low exposure rate, while this cannot be said for sure, even if the exposure rate is low (<10%), given there are many events in the ARIC cohort there should be enough power to detect a difference. Other limitations include possible primarily misclassification of some important exposures such as physical activity, due to the nature of the methods used to assess (survey). Also, presence of atrial fibrillation (one of the covariates) will likely underestimate the prevalence given its paroxysmal nature.

7.a. Will the data be used for non-CVD analysis in this manuscript? No  
   b. N/A

8.a. Will the DNA data be used in this manuscript? No  
8.b. N/A

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.cscce.unc.edu/ARIC/search.php

There are no existing manuscript proposals that overlap

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 #131: Population based study of heart rate variability and prevalent myocardial infarction
MS#258: Vagal tone measured by heart rate variability (HRV) is associated with serum insulin and diabetes - the ARIC Study
MS#577: Shift in autonomic balance with an active postural change, measured by heart rate variability: The ARIC Study
MS#605: Association between lower heart rate variability and the difference in hypertension prevalence in two populations from the U.S. and Poland
MS#669: Heart rate variability and hypertension.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  No
11.b. N/A

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.

The authors understand and will comply.

REFERENCES


