ARIC Manuscript Proposal # 2294

PC Reviewed: 1/14/14  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: _____

1a. Full Title: Changes in heart rate over time and its relation to cardiac structure and function and prognosis in ARIC study

b. Abbreviated Title (Length 26 characters): Heart rate and echocardiography

2. Writing Group:
   Writing group members: Ali Vazir, Amil Shah, Hicham Skali, Susan Cheng, Brian Claggett, Scott Solomon, OTHERS.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. AV [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:

Analysis will begin immediately following proposal approval with the aim of completing analyses and submitting an abstract to the AHA meeting (May 2014). The subsequent aim will be to complete a manuscript within 6 months of proposal approval.
4. **Rationale:**

Resting heart rate (HR) is a risk factor of adverse outcomes in individuals with and without known cardiovascular disease\(^1\)-\(^5\). Higher resting HR have been associated with the greatest risk\(^2\)-\(^6\). A Norwegian epidemiological study has suggested that temporal changes in resting HR in subjects without known cardiovascular disease are associated with adverse outcomes, such that a rise in HR between two visits over 10-years was associated with increased mortality\(^1\). The reasons for this finding are unclear, but a possible explanation may be due to an elevation in sympathetic tone that may be associated with underlying cardiovascular disease or subclinical cardiac dysfunction. A reduction in resting HR on the other hand, may be beneficial, particularly in patients with heart failure, as observed in a trial in which initiation of an \(I_f\) inhibitor solely targeting HR reduction in patients with HF with reduced ejection fraction, was associated with lower events and improved prognosis\(^7\),\(^8\). Whether temporal changes in HR are associated with underlying subclinical abnormalities of cardiac structure and function is unknown. Furthermore the prognostic importance of temporal changes in HR within the ARIC cohort, compromising of multi-ethnic participants with and without known cardiovascular disease has not been studied.

5. **Main Hypothesis/Study Questions:**

We hypothesize that changes in resting HR from the preceding visit are associated with adverse outcome, such that a rise HR is associated with increased risk of adverse events and a fall in HR may be beneficial. Furthermore we hypothesize that changes in HR, and in particular a rise in HR, from the preceding visit may predict subclinical left ventricular disease.

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, Inclusion/Exclusion Criteria:**

This will be a retrospective and cross-sectional analysis of observational data of the ARIC cohort participants.

**Predictor variables:**

Resting HR data from participants enrolled in the ARIC cohort study at their initial visit and subsequent visits will be converted to time-updated covariate. Subsequently changes in HR from the preceding visit can be calculated by subtracting the visit HR value from the value from the preceding visit. Change from preceding visit will first be defined at the time of visit 2, and will subsequently be updated at visits 3, 4, and 5.

Changes in HR from the preceding visit will be categorized into 5 arbitrary groups: >10bpm decrease, 5-10 bpm decrease, “no change” in HR (<5 bpm change), 5-10 bpm increase in HR and
>10 bpm increase, based on the rationale that a >5 bpm change in HR may be clinically important.

Changes in resting HR will be assessed as a continuous covariate and also categorical.

**Outcome variables:**

The association between changes in resting HR from the preceding visit and following adverse outcomes will be made:

1. All-cause mortality
2. Composite of cardiovascular death and hospitalization for worsening HF, stroke or myocardial infarction.

In order to assess the association between changes in HR from the preceding visit and abnormalities of cardiac structure and function, Information on cardiac structure and function from echocardiographic measurements taken at the ARIC cohort visit 5 (2011-2013) will be compared across the categories of changes in HR that occur between visit 4 and 5. These echocardiographic measurements of cardiac structure and function include:

- Indexed LV mass
- Index LV end diastolic volume
- Index LA volume
- LVEF<50\% and LVEF <40\%
- Global longitudinal strain
- Lateral E’
- E:E’
- RV dilatation
- RV Fractional area change
- S’ on RV free wall
- Pulmonary arterial hypertension

**Statistical Analysis:**

The first part of the analysis is focused on assessing the prognostic importance of changes in HR from the preceding visit, using time-updated HR values. The descriptive statistics of this study sample will be presented for participants from visit 1. The association between changes in HR from the preceding visit and adverse outcome will be assessed using multivariate Cox proportional hazard models, adjusted for established predictors of adverse outcome such as age, established cardiovascular disease and also medications that can influence heart rate.

The second part of the analysis will assess the relationship between HR changes occurring between visit 4 and 5 and measurements of cardiac structure and function, the descriptive statistics will be presented on participants with data from visit 4 and 5.
Univariate and multivariate linear regression analysis will be used to examine the cross-sectional associations of HR change occurring between visit 4 and 5 as a continuous covariate and echocardiographic characteristics at visit 5. Adjustments for age, sex as well as key socio-demographic and clinical characteristics will be performed. We will assess for differences in the values of the parameters of cardiac structure and function across the 5 categories of HR change occurring between visit 4 and 5.

A two-sided p-value of <0.05 will be considered statistically significant.

All analysis will be performed using STATA version 12 (StataCorp, College Station, Texas).

Limitations:
A limitation of this study is the cross-sectional design, which precludes the ability make any inferences regarding causality.

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

   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.cscce.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)?

There are currently no manuscripts that are looking at changes in HR over time and their association with cardiac structure and function and prognosis.
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
   ___ B. primarily based on ARIC data with ancillary data playing a minor role
       (usually control variables; list number(s)* ____________ ____________ ____________)

   *ancillary studies are listed by number at http://www.csc.c.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.csc.c.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.
References


