ARIC Manuscript Proposal 

PC Reviewed: 3/12/13  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: Heart Rate Variability and Heart Failure Incidence: the Atherosclerosis Risks in Communities study

b. Abbreviated Title: HRV and HF


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

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3. Timeline: Within 12 months following proposal’s acceptance.

4. Rationale:
Heart failure (HF) is common in clinical practice, and associated with a substantial burden of complications, mortality and societal costs related to hospitalizations. An improved understanding of the complex relationship between cardiac autonomic system and occurrence of HF may be useful to reduce its risk.

Low heart rate variability (HRV), a marker of autonomic dysfunction, is associated with increased risk of all-cause mortality, and has been proposed as a marker for cardiovascular disease. HRV has been studied within the framework of HF, but mainly as a prognostic factor in those with HF. Although autonomic perturbations are common before the initiation of HF, it is unclear whether, in the general population, low HRV is a
marker of increased risk of HF. Existing evidence points to a few potential pathways linking HRV to HF.

Low HRV in the settings of autonomic neuropathy, such as in the context of diabetes or end stage renal disease, can be conceived of as a risk factor for HF. Depressed HRV can be on the pathway between behavioral risk factors (low physical activity, high emotional stress, diet, alcohol consumption and smoking) and the occurrence of HF.4, 5 Also, studies have shown a longitudinal association of low HRV with precursors of HF, such as hypertension,6 and clinical diabetes7, 8 and glycemic control 9, CAD 10, and AF11. Depressed HRV may have a more direct effect on cardiac remodeling, as in normal asymptomatic individuals, it was found to be associated with impaired ventricular diastolic filling (evaluated by Doppler-derived indices), independent of other risk factors.12 On the other extreme, low HRV is noticed during severe and transient cardiomyopathy, - Takotsubo cardiomyopathy13, where an excessive release of catecholamines plays a pivotal role.

Furthermore, beta blockers improve morbidity and mortality post MI and reduce HF risk; they also simultaneously reverse autonomic imbalance through an increase in HRV3. Given the limitations of beta blockers, other interventions targeting autonomic imbalance in HF patients have been investigated. These interventions, mostly still under experimentation, include of sympathetic denervation (cardiac or renal) 14, 15 or vagal stimulation. 16 17 Such denervation may also positively affect elevated blood pressure, a strong risk factor for HF. Indeed, ablation of sympathetic innervation has gained popularity as a therapy for refractory hypertension.18

All these observations indicate the central role of the autonomic system in the pathogenesis of HF, with low HRV potentially being strong marker of physiological autonomic imbalance. Hence, understanding the complex relationship between HRV and HF may add clarification, and offer important opportunities for improving HF risk assessment and potentially modification. Indeed, numerous studies indicate the possibility of restoration of HRV to prevent HF, using interventions that include beta blockers, lifestyle changes (physical activity, relaxation training- yoga/meditation; and dietary changes), 5, 19, 20 and possibly autonomic modulation through sympathetic denervation or vagal stimulation as already mentioned. Thus, there is a potential for tailoring these interventions to those identified as being most at risk, defined as having a low HRV. We therefore intend to study HRV in relation to incident HF in ARIC.

5. Main Hypothesis/Study Questions
- Hypothesis: Decreased short term HRV, a measure of poor parasympathetic modulation of heart rate or increased sympathetic tone, will be associated with a higher incidence of heart failure independent of several confounders in particular diabetes, chronic kidney disease, hypertension.

- Study question: To examine the association of short term HRV measures and incidence of heart failure in a population based study, by race and gender.
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 analysis

**Inclusions and Exclusions:** Middle aged adults (45-65 years at enrollment in 1987) from four US communities. Those with poor quality HRV data or with ECG findings suppressing HRV analysis, or missing data on important covariates, and prevalent atrial fibrillation will be excluded. Participants with either missing or poor heart rate variability measures at baseline, and prevalent HF (identified using Gothenburg criteria at baseline), other electrical abnormalities in heart rhythm (such as atrial fibrillation, advanced AV blocks, pacemakers, wandering atrial beats, supra-ventricular or ventricular tachycardia) or missing other important covariates, as well as those taking drugs such as β-blockers, antiarrhythmics, antianginals, peripheral vasodilators, or digoxin.

**Outcome:** Incident cases of HF, identified from hospitalization records as the first HF hospitalization with an HF discharge code, or HF as the underlying cause of death on a death certificate, through 2009.

**Primary exposure:** Cardiac autonomic dysfunction will be estimated from heart rate variability measures collected with longer recordings (visit 1, and visit 4) as well as 12 lead ECG at each of the visits (visit 4), as described in previous ARIC publications, specifically, we will use:
- Mean normal-to-normal R-R interval length (RR)
- Standard deviation of normal-to-normal R-R intervals (SDNN)
- Root mean square of successive differences in normal-to-normal R-R intervals (RMSSD)
- High frequency (HF power) power

We will use few strategies with differing strengths and weaknesses: Use baseline long ECG (lots of exclusions due to poor recording quality) vs. visit 4 long recording that provides 6 minute of ECG with validated outcome post 2005. We will also consider taking averages of visit1 through visit4 10-second ECG and use visit 4 as baseline.

**Covariates:** Previously identified risk factors for HF that also influence HRV: age, sex, race-center, body mass index, physical activity, diabetes, hypertension, ECG-defined left ventricular hypertrophy, LDL cholesterol, HDL cholesterol, smoking, prevalent MI. Other covariates are education and/or income, as measures of socioeconomic status, and medications such as beta blockers, calcium channel blockers etc.

**Summary of data analysis:**
HRV measures will be natural log transformed were necessary to make their distribution normal.
Baseline characteristics of the cohort will be compared across HF status, and quartiles of HRV using appropriate tests. Crude incidence HF rates and their 95% confidence intervals for the time to development of HF will be computed assuming constant rate over time and Poisson distribution.

Modeling HRV – HF relationship:

Firstly, we will use restricted cubic splines to regress HRV measures using Cox models to examine the shape of the relationship. Based on the shape of relationship, we will decide on using alternative parametric functions or few categories which can provide good fit.

Secondly the HF events have accrued over 20 years of follow-up, given the possibility that effect of HRV may be heterogeneous by time-to-event. If proportional hazards assumption is violated, quantile regression may provide a more thorough view on the HRV effect on the occurrence of HF than mean-conditional regression. If we don’t find heterogeneity by quartiles, we will see if there is one when using median quintile regression and report estimates of association by quartile or median of time-to-event.

Hazard ratios for HF will be estimated after stratifying/adjustment for the aforementioned covariates. We will start with a model that adjusts for age, race, gender, and heart rate only. Subsequently model will additional adjust for prevalent CHD, smoking, and cholesterol. The other traditional risk factors of heart failure such as diabetes, hypertension, and chronic kidney disease may act as intermediaries – our subsequent models will adjust for these with an understanding that this may be etiological over-adjustment. Test alpha level will be set at 0.05 for main analysis and 0.1 for the interaction terms in stratified analysis.

Methodological limitations:
The quality of HRV data may be poor in a substantial proportion of cohort at baseline (>25%), thus leading to many exclusions. We do not have reasons to assume that exclusion is differential in terms of study outcome, and also similar exclusions have been used in previous studies using this data. We will additionally use HRV data obtained at visit 4 (6 min) and incident HF subsequent to visit to examine the consistency of observed results. Also, we will explore the association of time domains obtained from average of four 12 lead ECGs and incident HF post visit 4. Heart failure events are not adjudicated prior to visit 5. Multiple hypothesis testing may be of concern because of various measures of HRV. HRV measures are highly correlated thus a conservative correction such as Benferroni’s is not required. We will however consider this limitation while interpreting the results.
7.a. Will the data be used for non-CVD analysis in this manuscript?  
   | b. **No**

8.a. Will the DNA data be used in this manuscript? **No**

8.b. and 8.c **NA**

9. The ARIC 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.  **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 # 577: HRV, CHD, and mortality
   MS # 1459: HRV and AF
   MS # 1913: HRV and SCD

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  **No**

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 writing team is aware of this**
References:


