1.a. Full Title:
ECG Abnormalities Preceding Heart Failure: Estimation and Prediction in the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters):
ECG Predictors of HF

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

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3. Timeline:
Analyses to begin in Spring 2007. Draft of manuscript is expected during Spring 2008.

5. Rationale:

Heart failure (HF) poses a major burden on the public health systems of industrialized countries. In 1979, 399,000 individuals in the United States were discharged from a hospital with HF compared to 1,099,000 in 2004, an increase of 175%\textsuperscript{1}. The prognosis of HF is poor; 70% of women and 85% of men under age 65 will die within eight years\textsuperscript{1}. Furthermore, most persons are identified with HF in the latter stages; after hospitalization with HF at New York Heart Association classification stages III and IV\textsuperscript{2}. 
Identification of factors that increase a person's risk for HF may be important to ameliorating the burden of this disease. Various risk factors for the incidence of HF have been identified, such as cigarette smoking, hypertension, diabetes, being overweight, obesity, coronary heart disease (CHD), valvular heart disease, and left ventricular hypertrophy. Use of angiotensin-converting enzyme inhibitors, aspirin and beta blockers, treatment of dyslipidemia, and myocardial revascularization have been shown to delay the onset of HF in persons at high risk. Electrocardiographic (ECG) abnormalities are potentially useful predictors of incident HF events that are attracting renewed attention at this time.

Longer ECG QRS intervals were associated with an increased risk of incident HF, in the Framingham Study. HF diagnoses were based on Framingham Heart Study criteria. Of the 1759 participants eligible for the study, 324 developed HF over 22.3 years of follow-up (mean of 12.7 years). QRS duration was measured as both a categorical and continuous variable. QRS duration categories for complete and incomplete bundle branch blocks were defined as < 100 ms (referent), 100-119 ms (incomplete) and >=120 ms (complete). In multivariable time-dependent Cox models, incomplete and complete bundle branch blocks were associated with incident HF, hazard ratios = 1.43 (95% CI: 1.05, 1.96) and 1.74 (95% CI: 1.28, 2.35), respectively. In analyses with QRS duration as a continuous variable, HF incidence increased with longer QRS duration in age- and sex-specific models, hazard ratio = 1.27 (95% CI: 1.14, 1.41).

Recently, Rautaharju and colleagues examined ECG abnormalities and incident HF and all-cause mortality using data from the Women's Health Initiative. HF was defined as hospitalization for and treatment of HF, and a review of the medical records by a non-centralized source. Wide QRS/T angle (>=97 degrees) was associated with 3 times the risk of incident HF when compared to a QRS/T angle between 0 to 56 degrees, hazard ratio = 2.73 (95% CI:2.06, 3.60). Further, STV-5 depression, high TV-1 amplitude, and QRS non-dipolar voltage were associated with 2 times the risk of incident HF when compared to referent groups, hazard ratios = 2.11 (95% CI: 1.62,2.52), 2.16 (95% CI: 1.68, 2.78) and 2.00 (95% CI: 1.51,2.65), respectively.

Rautaharju and colleagues also identified several ECG abnormalities as manifestations of evolving HF in men and women free of CHD in the ARIC study (ARIC Ms 1145, unpublished). In men, large left ventricular mass by ECG, QT prolongation and increased heart rate were the strongest independent predictors of new-onset HF. Other independent predictors in men were ST depression in V5, wide QRS/T angle, and old (silent) myocardial infarction. In women, QRS non-dipolar voltage was associated with an increased risk of incident HF; as in men, other independent predictors were wide QRS/T angle and increased heart rate.

A potential improvement to the above studies is the consideration of repeat measurements of ECG abnormalities. It would similarly be pertinent to evaluate whether various ECG abnormalities improve risk prediction of HF, in the context of well-established risk factors for HF. Risk scores have been developed for CHD, ischemic stroke and diabetes in the ARIC cohort. Additionally, Lloyd-Jones and colleagues developed a risk score to predict lifetime risk for CHD in the Framingham Study. Further, Wang and colleagues evaluated the incremental usefulness of multiple biomarkers for predicting the risk of cardiovascular events in the Framingham Study.
To our knowledge, only one risk score has been developed for HF\textsuperscript{16}. Kannel and colleagues developed a risk appraisal function to assess the hazard of HF in 8,931 person-examinations in women and 6,354 person-examinations in men, aged 45 to 94 years. Inclusion criteria included participants with CHD, hypertension and valvular disease. Participants with HF were excluded at baseline. Risk factors included in this risk factor score were age, left ventricular hypertrophy, cardiomegaly, heart rate, systolic blood pressure, vital capacity, diabetes mellitus, evidence of myocardial infarction and valvular disease or hypertension. The logistic model was used to predict the probability of developing HF within 4 years based on the presence of the risk factors mentioned previously.

The goal of this proposal is to extend previous studies by evaluating ECG abnormalities longitudinally, using the ARIC study, a biracial cohort of 15,762 men and women. A potentially important application of the proposed risk factor score for incident HF would be the identification of groups and individuals, free of CHD, for more intensive preventive efforts. However, in order to generate valid inferences from our analyses, the short-term reliability of ECG abnormalities must first be determined. We plan to evaluate short-term reliability of available ECG abnormalities using data from the ECG Reliability Study, an ARIC ancillary study that examined 63 participants with characteristics similar to those of the ARIC cohort at its baseline visit (Vaidean et al., 2005; Whitsel et al., 2004). Participants had three ECGs recorded at each of two visits, one to two weeks apart. The short interval posed less opportunity for intermittent (ECG-altering and therefore reliability reducing) health events to occur. Previous studies have estimated the short-term error in measurement of spatial T-wave axis, QT interval, and heart rate in the ECG Repeatability Study, (Vaidean et al., 2005). These ECG abnormalities had intraclass correlation coefficients of 0.87, 0.86 and 0.82, respectively. Other ECG predictors of incident HF have yet to be evaluated for short-term reliability in the ECG Reliability Study.

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


   
   a. Adjust the estimated association of electrocardiographic abnormalities with incident heart failure for measurement error in the exposure variable(s).

   b. Estimate the degree to which these associations between electrocardiographic abnormalities at baseline, and their temporal changes and the risk of incidence of heart failure is modified by gender, race, diabetes and hypertension.

3. Assess the predictive performance of a parsimonious risk factor score based on well-established risk factors for heart failure (such as age, hypertension, diabetes, smoking, and obesity) and whether prediction is improved by inclusion of electrocardiographic abnormalities to this risk factor score.
6. Data (variables, time window, source, inclusions/exclusions):

Data:

ECG variables from ARIC visits 1, 2, 3 and 4 and from the ECG Reliability Study (AS 2002.05). Incident HF events assessed by ongoing surveillance of community hospital discharges, and by surveying death certificates from state vital statistics. HF events are defined as a hospital discharge diagnosis code of HF (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] code 428 or 518.4) or death certificates with an underlying cause of death coded as HF (ICD-9-CM code 428 or ICD-10 code I50).

The following covariates from Visit 1, 2, 3 and 4: age, smoking status / cigarette years of smoking, alcohol intake, heart rate, hypertension, body mass index, angina pectoris, myocardial infarction, peripheral vascular disease, cerebrovascular disease, history of coronary artery bypass surgery or coronary angioplasty, systolic blood pressure, hormone therapy use, self reported use of cholesterol lowering drugs, self-reported physician diagnosed diabetes or the use of hypoglycemic medications, the use of cardioactive drugs (antiarrhythmics, calcium channel blockers, beta blockers, diuretics, antidepressants, psychotherapeutic drugs), center, gender, and race.

Exclusions:
The ECG source data for the present investigation will be derived from participants with demographic and clinical laboratory data and a complete set of ECG variables merged from various ECG programs and special algorithms. Excluded from the source population will be participants with complete bundle branch block or Wolf-Parkinson-White pattern identified on the ECG (QRS duration 120 ms or longer), HF at the baseline examination, and participants with coronary heart disease status not known. Participants with missing ECG information for any of the 4 visits will be excluded from analyses used in estimation of ECG abnormalities and incident HF.

Analyses:
Estimates of reliability will be calculated for ECG predictors of interest on records collected by the ECG Reliability Study). We plan to use a nested random-effects model to partition measurement variability into the following components: between-participant, between-visit, and within-visit variance. 95% confidence intervals will be based on the F test statistic.

We plan to analyze changes in ECG variables over a 9-year period (from Visit 1 in 1987 through 1989 to Visit 4 in 1996 through 1998) in relation to incident HF. The association of changes in ECG variables with incident HF will be investigated using two different approaches. One approach, as described by Iribarren and colleagues, will evaluate continuous and categorical changes in ECG variables with incident HF using standard survival analysis techniques. The second approach, hierarchical regression models, will quantify the incidence of HF for each of the ECG variables. Although effect estimates in the evaluation of multiple exposures, are usually calculated by including each exposure in a separate model (along with any potential confounders), this method does not account for probable correlation between exposures. Added to this, the precision varies
considerably by exposure variable. Thus, in order to improve accuracy of effect estimates, hierarchical regression models will be used\textsuperscript{18,19}. Effect measure modification of the observed associations by race, gender and other covariates will be evaluated. Comparison of effect estimates will be made between models including participants with CHD with models excluding participants with CHD.

Receiver Operating Characteristic curves will be used to generate a summary statistic from the coefficients of a proportional hazards model of time to incident HF event. Separate models will be specified for the inclusion of ECG variables and the exclusion of ECG variables. Covariate information, as components of the predicted risk score will include age, left ventricular hypertrophy, cardiomegaly, systolic blood pressure, vital capacity, diabetes mellitus, hypertension, being overweight, obesity, cigarette smoking and alcohol use. Based on earlier work\textsuperscript{10,12}, a HF risk score will be calculated by multiplying each previously mentioned parameter coefficient by the individual’s value for that coefficient and summing these products. HF risk scores will be converted into a predicted probability of having an incident HF event within a specified time using Kaplan-Meier like methods and previously specified values for baseline predicted risk.

7.a. Will the data be used for non-CVD analysis in this manuscript? \underline{____ Yes}  \underline{____ No}

b. If Yes, is the author aware that the file ICTDER02 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? \underline{____ Yes}  \underline{____ No}

(This file ICTDER02 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? \underline{____ Yes}  \underline{____ No}

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 must be used to exclude those with value RES\_DNA = “No use/storage DNA”? \underline{n/a}

\underline{____ Yes}  \underline{____ 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: \url{http://www.cscc.unc.edu/ARIC/search.php}

\underline{____ X____ Yes}  \underline{____ 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 855 (Wong)
MS 922 (Henderson, Rosamond)
MS 927 (Rosamond)
MS 1118 (Kottgen)
MS 1145 (Rautaharju)

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 (list number*)

   _X_   B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s))* __AS 2002.05_____

*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

17. Iribarren C, Reed DM, Chen R, Yano K, Dwyer JH. Low serum cholesterol and mortality. Which is the cause and which is the effect? Circulation 1995;92(9):2396-403.