ARIC Manuscript Proposal # 1145

PC Reviewed: 04_/_18_/06	**Status: __A__**	**Priority: __2_**
SC Reviewed: _4/20/06_	**Status: __A__**	**Priority: __2_**

1.a. Full Title: Electrocardiographic Predictors of Incident Heart Failure

b. Abbreviated Title (Length 26 characters): ECG and Heart Failure

2. Writing Group:

Writing group members: Rautaharju PM, Prineas RJ, Chambless LE, Crow R, Heiss G

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

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(as above)

3. Timeline: Start analyses: upon approval
First draft: June 1, 2006
Submission for publication: August 1, 2006

4. Rationale:

Heart failure (HF) is associated with a grave prognosis. It is surprising, therefore, that there is a scarcity of information about electrocardiographic predictors of incident HF. ECG-LVH was associated with the risk of heart failure in the Framingham study (1). ECG strain pattern (high-amplitude QRS and downsloping ST segment with asymmetric negative T wave) was recently reported to be associated with new-onset congestive HF in hypertensive patients with ECG-LVH chosen to hypertension intervention trial (2). Cardiac resynchronization therapy has improved clinical management of HF in its chronic congestive phase. Shortening of QRS prolongation as a response to biventricular stimulation has been reported to be the only significant among clinical and ECG variables as a predictor of a positive response to resynchronization therapy (3). However, the value of QRS duration as a predictor of incident HF is unknown. A recent report from WHI on incident HF found a number of ECG variables to be significant predictors of HF in women (4). Dominant among these ECG variables was spatial QRS/T angle and

repolarization abnormalities associated with it (T wave abnormalities, ST depression). Other significant ECG predictors of HF included old myocardial infarction by ECG criteria (ECG-MI), an increased ultra-short heart rate variability and nondipolar QRS voltage. This latter novel ECG variable may reflect sequels of old MI or evolving left ventricular hypertrophy (LVH). The above new findings in women need to be re-evaluated in an independent study. ARIC follow-up has documented approximately 1,200 incident hospitalized HF in ARIC participants since the baseline, making this population-based cohort eminently suitable for the assessment of potential ECG predictors of incident heart failure.

5. Main Hypothesis/Study Questions: The hypotheses to be tested: 1) Delayed ventricular conduction is associated with increased risk of incident HF in men and in women; and 2), ECG patterns reflecting abnormal sequence of ventricular repolarization, left ventricular hypertrophy and old myocardial infarction are associated with incident HF in men and in women.

6. Data (variables, time window, source, inclusions/exclusions): A new ARIC ECG base data file has been prepared for the study by the principal author. The selection of the ECG variables was done on the basis of pathophysiological considerations and previously found association between them and HF. Because many ECG variables used in the WHI report were derived from more advanced methodology (waveform vector analysis and singular value decomposition) and were unfamiliar to clinicians, there have been many requests for a simple set of ECG variables for clinical use. Therefore, a special effort was made to derive a simplified set of ECG variables suitable for computer as well as visual ECG analysis.
ECG variables for testing of hypothesis 1: Various categories of prolonged ventricular conduction according to Novacode classification (Novacode 3). These categories include 1) left bundle branch block (n = 136); 2) right bundle branch block (n = 164); 3) indeterminate type ventricular conduction delay (n = 276); 4) borderline delay in ventricular conduction (n = 123); and 5), normal ventricular conduction (n = 14,833).
ECG variables for testing hypothesis 2: 1) ECG-MI by the Novacode criteria (prominent Q waves of smaller Q waves with T wave abnormalities); 2) QRS/T angle (spatial angle between QRS and T) calculated using standard chest lead ECG measurements; 3) ST60V5, ST depression in lead V5 at 60 ms time point following the J point; 4) STV5 slope; 5TnetV5; 6) TnetV1 (net T amplitudes calculated from (signed) peak positive and negative portions of the T wave; 7) QTrr, QT adjusted to heart rate by a simple formula as a linear function of RR; 8) HRVnn (ultrashort heart rate variability, i.e. RR interval variability (SD) of normally conducted ventricular complexes); 9) Cornell product ((RaVL + SV3)*QRSdur); 10) QRSndpv (nondipolar voltage of the QRS complex). This last novel variable is the only more complex ECG parameter. It was included here because of its consistent association with HF in WHI women.
Exclusions: ECG file 1. This file contains ECGs of 15,571 ARIC subjects with ECG data available, without any ECG exclusion, including all ECGs with prolonged ventricular conduction. Exclusions from file 2: 570 ECGs with QRS duration 120 ms or longer; 47 other ECGs with some missing ECG measurements, or a total of 617 exclusions. Thus,

14,881 ECGs remain for risk analyses. Additional exclusions: subjects with HF at the baseline of the study.

Data analysis:
Endpoint**s:** There will be only one study endpoint: incident hospitalized HF
Discretization thresholds: All data in file 1 and ECG-MI in data file 2 are dichotomized. Discretization thresholds for the other variables in data file 2 will be selected at gender-specific upper decile limits of each variable for the comparison group for risk evaluation, with deciles 1 to 9 as the reference group. For HRVnn, both the highest and the lowest deciles will be selected and deciles 2 through 8 will be used as the reference group. The rationale for using dichotomized rather than continuous exposure variables is that the results from this approach can more readily be translated for clinical use and for other future HF risk evaluation studies.
Interactions: Possible interaction between baseline CHD status and the ECG exposure variables will be evaluated for gender and ethnicity. Subsequently, the decision will be made about stratification for the risk models.
Adjustment of the risk models: All risk models will be first adjusted for age alone and subsequently for age and other demographic and clinical variables as ordinarily done in ARIC. For the latter "fully adjusted" models, each ECG variable will be first evaluated separately (single ECG variable models) without considering the other ECG variables and subsequently all ECG variables with a significant association with the risk of HF (backwards selection procedure) will be entered simultaneously into the risk mode (multiple ECG variable models).

References
1. Kannel WB, Levy D, Cupples IA. Left ventricular hypertrophy and risk of cardiac failure: insights from the Framingham Study. J Cardiovasc Pharmacol 1987;10(suppl 6):S135-S140.
2. Okin PM, Devereux RB, Nieminen MS et al. Electrocardiographic strain pattern and prediction of new-onset congestive heart failure in hypertensive patients: the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study. Circulation 2006;113:67-73.
3. Lecoq G, Leereq C, leray E et al. Clinical and electrocardiographic predictors of a positive response to cardiac resynchronisation therapy in advanced heart failure. Eur Heart J 2005;26:1094-1100.
4. Rautaharju, PM, Kooperberg C, Larson JC, LaCroix, A. Electrocardiographic Predictors of Incident Congestive Heart Failure and All-cause Mortality in Postmenopausal Women. The Women's Health Initiative. Circulation 2006;113:481-489.

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 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?
___ Yes ____ 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?
____ Yes __X__ 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"?
____ 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 encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?
A local paper using pooled CHS and ARIC data is evaluating the association of ECG variables and sudden versus non-sudden death (Prineas et al.). With this manuscript proposal limited to ECG predictors of incident HF, there is no overlap. Rather than overlapping projects, the present proposal can be considered as a prelude to the massive sudden death project.

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 (list number* _____)
___ 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.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.