ARIC Manuscript Proposal # 1557

PC Reviewed: 10/13/09	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Electrocardiogram Predictors of Sudden Cardiac Death and Non-Sudden Incident Coronary Heart Disease (CHD) Among 19,160 Men and Women Free of CHD in the Combined Cohorts of the Atherosclerosis Risk in Communities Study (ARIC) and the Cardiovascular Health Study (CHS).

b. Abbreviated Title (Length 26 characters): ECG Predictors of SCD and Non-Sudden CHD

2. Writing Group:

Writing group members: Ronald J. Prineas, Douglas Case, Gregory Burke, Gregory Russell, Elsayed Soliman, Bruce M. Psaty, Wayne Rosamond, Thomas Rea, Nona Sotoodehnia, Wendy Post, and David Siscovick.

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

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3. Timeline: Fall, 2009

Rationale:

Sudden cardiac death (SCD) is a significant burden to the health of the US population. It is estimated that there are between 250,000 and 400,000 sudden cardiac deaths in the US each year, and SCD has few early specific warning signs distinct from those of non-SCD/coronary heart disease deaths. Nearly half of all coronary heart disease (CHD) deaths are sudden and approximately one third of these deaths are the first clinical manifestation of disease. Thus, it is important to identify risk factors, both genetic, and environmental, for SCD. Because out of hospital SCD is mostly not amenable to any treatment opportunities, it would be highly desirable to be able to identify persons at greatest risk of such an event before any clinical manifestation of CHD. A few attempts have been made to differentiate the predictability of ECG abnormality for SCD from other CHD events, but there are no definitive studies of competing risk analysis of specific ECG variables for the prediction of SCD vs. CHD. The proposed manuscript will address that deficit, and add a greater range of digital ECG parameters than have been tested in the past

5. Main Hypothesis/Study Questions:

The main purpose of this proposed manuscript is to distinguish separate electrocardiographic (ECG) and clinical algorithms for SCD and incident CHD in the combined cohorts of the Atherosclerosis Risk in Communities (ARIC), and the Cardiovascular Health Study (CHS).

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).

The proposed manuscript will use data from the combined cohorts of the Atherosclerosis Risk In Communities Study (ARIC), and the Cardiovascular Health Study (CHS).

Participants with prevalent CHD at baseline, poor quality ECG data, or missing SCD data will be excluded. Variables required for the proposed paper include:

1) Incident MI/CHD/ECG MI/or coronary artery revascularization by the end of follow-up).
2) Incident sudden death. This is currently available from Reynolds Sudden Death ancillary study. Participants were coded as to whether or not they experienced a sudden death (SCD: 0=No Cardiac Death, 1=Definite Sudden Death, 2=Possible Sudden Death, 3=Non-sudden Death, and 5=Not classifiable).
3) ECG data including Minnesota codes, continuous measures of all ECG waveforms
4) Baseline demographic and clinical variables (all compared and selected for matched definitions in both studies completed in the Reynolds approved ancillary study) including CHD risk factors: Sex, race, BMI, education, family history of stroke, family history of CHD, smoking status, alcohol use, asthma, cancer, diabetes, hypertension, Rose angina, Rose intermittent claudication, sport index (sport during leisure time), FEV1 (forced expiratory volume), HDL cholesterol, LDL cholesterol, total triglycerides, total cholesterol, SBP, DBP, hematocrit, white blood cell, total calories, dietary cholesterol, ankle brachial index, baseline fasting blood glucose, insulin, creatinine, fibrinogen, and uric acid.

Analysis:

For descriptive purposes, the rates of SCD and CHD will be calculated as the number of events divided by the person years of exposure. In addition to crude rates, SCD and CHD rates will be calculated separately by age group, sex, and race, and these rates will be weighted by the age, race, and sex Census 2000 distribution to obtain standardized rates.

Cox's proportional hazards regression models will be used to determine which demographic and clinical variables were associated with the risk of definite SCD and incident CHD events (exclusive of definite or possible SCD) and to assess the effects of ECG variables on these risks after adjustment for the demographic and clinical characteristics of the participants. Age will be used as the timescale and birth cohort (<1920, 1920-1929, 1930-1939, and 1940+) will be used as a stratification factor in all analyses. The participant's age at first visit will be considered the entry age and the age at the event will be the participant's age at which the first event occurred (i.e. the CHD event if one occurred before a sudden death). For each outcome, a backward stepping algorithm will be used initially to determine the demographic and clinical characteristics that were significantly associated with that outcome. From those, a set of covariates will be selected that are associated with either SCD or CHD and these will be the ones used in the multivariate models which assessed the effect of the ECG variables. Inherently continuous ECG variables will be considered both continuously and categorically in separate Cox models. The functional form of each continuous ECG variable will be assessed using martingale residuals as suggested by Therneau et al. Hazard ratios will be presented for a one standard deviation change in the ECG variable. In addition, for ease of interpretation, each continuous ECG variable will be also categorized into quartiles For the categorical ECG variables, hazard ratios will be presented relative to the normal category. For the categorized continuous variables, the hazard ratios will be presented relative to the 4^{th} quartile.

A proportional hazards competing risk analysis will be then done to determine if the ECG predictors for the risk of incident CHD differed from those for the risk of definite SCD. Two additional strata will be specified, one for each event type (CHD vs. SCD), and all of the participants appear in each stratum. The clinical and demographic characteristics that are significantly associated with the risk of either CHD or SCD will be included in the model. The ECG variables will be then included one at a time in the multivariable models which included the clinical and demographic covariates. The interaction between the ECG variable and event type

will be assessed to determine if the effect of the ECG variable differed by outcome, adjusting for common covariates.

All analyses will be performed with the SAS system for Windows and UNIX, version 9.1. (SAS Institute, Inc, Cary, NC)

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

8.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 __x__ 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)?

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
_x__ A. primarily the result of an ancillary study (list number* _2004.03__)
___ 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.