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]**

First author:

Address: Ronald J. Prineas
Department of Epidemiology, and Prevention
Division of Public Health Sciences
Wake Forest University School of Medicine
2000 W. First Street, Suite 505
Winston Salem, NC 27104

Phone: 336.716.7441 Fax: 336.716.0834
E-mail: rprineas@wfubmc.edu

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).

Name: Wayne D. Rosamond
Address: UNC Chapel Hill
Department of Biostatistics
Bank of America Center
137 E. Franklin Street, Suite 203
Mail Station 8030
Chapel Hill, NC 27514-4145

Phone: 919.962.3230 Fax: 919.962.3265
E-mail: uccwdr@mail.cscc.unc.edu

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.

5. Main Hypothesis/Study Questions:

Attempts to differentiate the predictability of ECG abnormality for SCD from other CHD events, as there are no definitive studies of competing risk analysis of specific ECG variables for the prediction of SCD vs. CHD. This paper addresses that deficit. We propose to distinguish separate electrocardiographic (ECG) and clinical algorithms for SCD and incident CHD. The data from 2 long-term longitudinal, cardiovascular epidemiologic studies (the Atherosclerosis Risk in Communities (ARIC), and the Cardiovascular Health Study (CHS) were combined, and all cardiovascular heart disease deaths were reviewed by trained physicians to classify SCD and non-SCD/CHD deaths according to common protocol.

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 data for the present study were in part from the Atherosclerosis Risk In Communities Study (ARIC), a population-based, multicenter prospective study designed to investigate the natural history and etiology of atherosclerotic and cardiovascular disease events from 4 U.S. communities in Maryland, Minnesota,

Mississippi, and North Carolina. Eligible participants were interviewed at home and then invited to a baseline clinical examination (1987–1989). They attended three further clinical examinations at approximately three-year intervals and received a follow-up telephone call yearly.

The rest of the present cohort derived from the Cardiovascular Health Study (CHS) which was designed to assess cardiovascular disease, its outcome and risk factors in older individuals. CHS participants were identified from the Health Care Financing Administration Medicare enrollment lists in four widely separated U.S. communities, along with other household members over the age of 65 years at enrollment. Recruitment centers were located in Washington County, Maryland; Forsyth County, North Carolina; Sacramento County, California; and Allegheny County, Pennsylvania. Exclusion criteria for the Cardiovascular Health Study included active treatment for cancer, being wheelchair-bound or institutionalized, or being unable to participate in the examination. Prevalent coronary artery disease, stroke and heart failure did not exclude participants from study enrollment. Details of the design, sampling, and recruitment, as well as the interview and examination, have been published previously (11). The CHS cohort included 5201 participants recruited in 1989-1990 and 687 additional subjects recruited in 1992-1993 to enhance the racial/ethnic diversity of the cohort (11). All participants were > 65 years of age. Annual clinic exams were conducted between 1989-1999, and included recording of medical history, blood pressure, heart rate, electrocardiography and less frequently anthropometric measurements, fasting blood chemistries, echocardiography, carotid ultrasonography and other objective measurements. Self-report of cardiovascular diseases at baseline was validated according to standardized criteria through assessment of medications, medical records, and/or by relevant information obtained during the initial examination.

Of the 21042 participants (15469 ARIC and 5573 CHS) with good quality ECG data included in our original dataset, 1815 (745 ARIC and 1070 CHS) had prevalent CHD when they entered the study and were deleted from the analysis of incident

events. Participants were coded according to whether or not they had an incident CHD event during follow-up (CHD: 1=Yes and 0=No). Events include incident MI/CHD/ECG MI/or coronary artery revascularization by the end of follow-up). Additionally, 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). Most (N=16475) participants had no event or a non-CHD death (13805 and 2670, respectively), and these are considered censored in the analysis at their date of last contact or death. Two hundred fifty-one (251) participants experienced a definite sudden death as their first event. Nonfatal CHD events occurred in 2233 participants. Of these, 39 subsequently experienced a definite sudden death, but for purposes of the incidence analysis, they are coded as having a CHD event. We just analyzed the first event for each participant. An additional 201participants experienced incident CHD deaths that were not considered sudden. The remaining 67 participants died, but their CHD/SD status could not be determined (57 considered possible sudden death and 10 unclassifiable), and are excluded from the analysis, leaving 19160 evaluable participants. We also identified the following outliers: 54 HDL values (those < 20, >140), 68 LDL values< 40, > 400), 6 total cholesterol values (< 70, > 500), 4 hematocrit values (< 20, > 73.7), 144 insulin values (> 100.8), 144 C-reactive protein values (> 30.4), 236 fibrinogen values (< 109.2, > 508.8), 303 triglyceride values (> 395.3), 130 uric acid values (< 1.2, > 10.8), 180 WBC values (> 12.2), and 57 total calories values (< 500, > 6000). The data of the participants with these values remain in the study, but their "out-of-range" values are replaced by a missing value.

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

Cox's proportional hazards regression models were 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 was used as the timescale and birth cohort (<1920, 1920-1929, 1930-1939, and 1940+) was used as a stratification factor in all analyses (25). The participant's age at first visit was considered the entry age and the age at the event was the participant's age at which the first event occurred (i.e. the CHD event if one occurred before a sudden death). The demographic and clinical variables included gender, 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 (all variables from baseline data). For each outcome, a backward stepping algorithm was used initially to determine the demographic and clinical characteristics that were significantly associated with that outcome. From those, a set of covariates (shown in Table 2) was selected that were associated with either SCD or CHD and these were the ones used in the multivariate models which assessed the effect of the ECG variables. Inherently continuous ECG variables were considered both continuously and categorically in separate Cox models. The functional form of each continuous ECG variable was assessed using martingale residuals as suggested by Therneau et al (26). Hazard ratios are presented for a one standard deviation change in the ECG variable. In addition, for ease of interpretation, each continuous ECG variable was also categorized into quartiles For the categorical ECG variables, hazard ratios are presented relative to the normal category. For the categorized continuous variables, the hazard ratios are presented relative to the 4^{th} quartile.

A proportional hazards competing risk analysis (26) was 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 were specified, one for each event type (CHD vs. SCD), and all 19160 participants appear in each stratum. The clinical and demographic characteristics that were significantly associated with the risk of either CHD or SCD were included in the model. The ECG variables were 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 was assessed to determine if the effect of the ECG variable differed by outcome, adjusting for common covariates.

All analyses were 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.