ARIC Manuscript Proposal #1350

PC Reviewed: 03/18/08 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:

Comparative value of current ECG codes for myocardial infarction / Ischemia in predicting incident fatal and nonfatal cardiac events and total mortality in the Atherosclerosis Risk in Communities Study (ARIC)

b. Abbreviated Title (Length 26 characters):
ECG MI Criteria and Mortality

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. ZMZ **[please confirm with your initials electronically or in writing]**

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3. Timeline:

Start analyses: upon receipt of data from the coordinating centre
Submission for publication: March 2009

4. Rationale:

The leading cause of mortality in the United States is cardiovascular disease (CVD). It was responsible for approximately 872,000 of 2.4 million deaths or approximately 36% in 2004.[1] Over the past decades, the electrocardiogram (ECG) has been a key diagnostic tool for myocardial infarction or ischemia. The criteria for MI and ischemia have been used as evidence for coronary heart disease (CHD) in epidemiological studies and clinical trial. The ECG is not only a simple, noninvasive, inexpensive, and most widely used CVD test when dynamic changes are expected as in patients with chest pain, but also static findings on the routine ECG are a simple way of stratifying patients' risk for CVD mortality.[2-6]

Among the coding systems for classification of ECG abnormalities, the Minnesota Code (MC), [7] developed in the early 1960s, is the most widely used in epidemiological studies and clinical trials. MC code was an important step toward standardization of measurement and classification of morphologic ECG features. The Novacode (NC) [8] system is an extension of the MC. It was developed initially in the late 1980s and further refined in 1998 and still evolving. NC is a hierarchic coding scheme for prevalent ECG abnormalities, and it incorporated from the beginning coding criteria for clinically significant incident ECG alterations both in terms of deterioration as well as resolving abnormalities. Criteria for significant ECG changes were also incorporated in the newer version of the MC, for the categories used for MI classification stratified into three specific locations (anterolateral, inferior/posterior and anterior).

There are only limited data available with comparative evaluation of the predictive value of the MC and NC coding of incident MI/Ischemia for adverse fatal and nonfatal cardiac events and total mortality.

EPICARE in Wake Forest University, School of Medicine is an ECG center that has been responsible for a number of studies incorporating electronic ECG data processing and reporting for either research or services for NIH, university and pharmaceutical company based studies, nationally and internationally for almost half of a century.

In this study we propose to compare the value of current ECG classification systems (Minnesota code and Novacode) for myocardial infarction/Ischemia in predicting incident fatal and nonfatal cardiac events and total mortality.

References:

1- Heart Disease and stroke statistics – 2007 Update. From the AHA statistics Committee and Stroke Statistics Subcommittee. Circulation 2007; 115:e69-e98

2- Engel G, Beckerman JG, Froelicher VF, Yamazaki T, Chen HA, Richardson K, McAuley RJ, Ashley EA, Chun S, Wang PJ. Electrocardiographic arrhythmia risk testing. Current Problems in Cardiology. July 2004;29:365-384

3- Rautaharju PM, Rautaharju F. Investigative electrocardiography in epidemiological studies and clinical trials. Published by Springer-Verlag London, 2007; 166

4- Rautaharju PM, Kooperberg C, Larson JC, LaCroix A. Electrocardiographic Abnormalities that predict Coronary Heart Disease events and mortality

5- Zhang ZM, Prineas RJ, Case D, Soliman EZ, Rautaharju PM for the ARIC Research Group: Comparison of the prognostic significance of the electrocardiographic QRS/Tangles in predicting incident coronary heart disease and total mortality (from the atherosclerosis risk in communities study). Accepted for publication: *The American J of Cardiology* 2007; 100:844-849

6- Tervahauta M, Pekkanen J, Punsar S, Nissinen A. Resting electrocardiogram abnormalities as predictors of coronary events and mortality among elderly men. Am J Med 1996;100:641-645

7- Prineas RJ, Crow RS, Blackburn H. The Minnesota Code Manual of Electrocardiographic Findings. Boston: John Wright PSB, 1982;203

8- Rautaharju PM, Park LP, Chaitman BR, Rautaharju F, Zhang ZM. The Novacode criteria for classification of ECG abnormalities and their clinically significant progression and regression. *J Electrocardiol* 1998;31(3):157-187

5. Main Hypothesis/Study Questions:

This study aims to:

(1) To compare the relative risk of the MC and NC coding of incident MI/Ischemia for incident fatal and nonfatal events combined and for total mortality in the population of the Atherosclerosis Risk in Communities Study (ARIC)

(2) To evaluate if the predictive value for incident MI /Ischemia and total mortality can be improved by more refined stratification of Q wave amplitudes (50, 75 and 100 microvolts) in the population of the Atherosclerosis Risk in Communities Study (ARIC)

(3) To compare the Minnesota Codes 1, 4, 5, and 92 for Q/QS wave and ST-T change by leads and by sites in baseline CHD group, and the predictive value for total mortality in the population of the Atherosclerosis Risk in Communities Study (ARIC)

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).

ECG Variables:

- Used identical electrocardiographs
- Recorded standard 12-lead ECGs
- Processed the ECGs by the GE Marquette 12-SL program
- Analyzed by the Minnesota Code and Novacode

A new ARIC ECG database file will be prepared for the study excluding:

- ECGs with Minnesota codes that suppress Minnesota codes 4 or 5. Specifically, ECGs with:
  - Complete heart block
  - Wolf Parkinson White Syndrome (WPW)
  - Artificial pacemaker
  - Left bundle branch block- persistent and intermittent
  - Complete right bundle branch block
  - Intraventricular conduction delay, QRS $\geq$ 120ms
  - Ventricular fibrillation, ventricular asystole and persistent ventricular tachycardia (if any)
  - Ectopic atrial rhythm with heart rate over 140 beat per minute
  - Poor quality ECG i.e. quality control grade 5 ECGs

ECG variables needed to fulfill the aim of the study will be:

- ECG-MI data (Minnesota code and Novacode)
- Q/QS wave (Minnesota code 1 and Novacode 5)
- ST segment (Minnesota code 4 and Novacode 5)
- T wave amplitude (Minnesota code 5 and Novacode 5)

It is expected to have an ECG file that contains 15,582 baseline ECGs of ARIC subjects with complete ECG and clinical data available.

Non-ECG variables:

Non-ECG variables include demographic data, outcome measures, medical history and haemostatic measure. These variables are summarized in below:

(1) The key demographic and clinical variables will include gender, race, age, 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, FEV1 (forced expiratory volume), HDL cholesterol, LDL cholesterol, total triglycerides, total cholesterol, systolic blood pressure, diastolic blood pressure, hematocrit, white blood cell, total calories, dietary cholesterol,

ankle brachial index, baseline fasting blood glucose, insulin, creatinine, fibrinogen, and uric acid.

(2) The analysis variable will include the participant's medical history in baseline, and outcome measurement with updated fatal CHD and nonfatal CHD, total mortality.

Non-ECG variables quoted from the list of variables of ARIC population

Demos/descriptives		
V1AGE01	AGE AT VISIT 1	
V1DATE01	VISIT 1 DATE	
RACEGRP	RACE	FORMAT is $RACE
BMI01	BODY MASS INDEX IN KG/(M*M)	
BIRTHDAT	DATE OF BIRTH OF SUBJECT	
GENDER	SEX	
Outcome measures		
SUDDEN_DEATH	Definite/Possible/No for sudden death	FORMAT is SUDDEN
CENSDAT5	Censoring date by 2002 for all events	
DEATHCODE	Underlying Cause of death code	ICD9/10 for sudden deaths
DTH18	Underlying cause of death from DTHA18	ICD9/10 for all deaths
DTHDATE2	Death Date for a Person	
FATCHD3	Fatal CHD (Classified by ARIC)	FORMAT is YN
INC_BY02	Incident MI/CHD by end of 2002	FORMAT is YN
IN_BY02P	Incident MI/CHD/Procedure by end of 2002	FORMAT is YN
IN_02S	Incident MI/CHD/ECG MI by end of 2002	FORMAT is YN
IN_02SP	Incident MI/CHD/ECG MI/Procedure by end of 2002	FORMAT is YN
CARDPROC	Incident cardiac procedure by end of year 2002	FORMAT is YN
SMI_BY02	Incident ECG MI by end of year 2002	FORMAT is YN
MI02	Incident MI be end of year 2002	FORMAT is YN
FATCHD02	Fatal CHD by end of year 2002	FORMAT is YN
SMIDATE	End date for SMI_BY02	For calculation of "time-to-event"
DATEMI	End date for MI02	For calculation of "time-to-event"
DEAD02	Dead by end of year 2002	FORMAT is YN
MI3	Definite/probable MI	FORMAT is YN
POSDIA3	MI or FATCHD ((def/prob MI or def fatal CHD/MI)	FORMAT is YN
PREVMI05	prevalent MI (composite ECG OR MED HIST)	FORMAT is YN
PRVCHD05	PREVALENT CORONARY HEART DISEASE	FORMAT is YN
Medical History		
HXOFMI02	HISTORY OF MYOCARDIAL INFARCTION	FORMAT is YN
DIABTS02	DIABETES (cut point of 140)	FORMAT is YN
DIABTS03	DIABETES (cut point of 126)	FORMAT is YN
MDDXMI02	MD DIAGNOSED MYOCARDIAL INFARCTION	FORMAT is YN
HYPERT05	HYPERTENSION, DEFINITION 5	
Lipids/haemostatic		

Data analysis:

The study endpoints will be combined fatal and nonfatal CHD, CHD death and total mortality. The study will have a CHD group which had an ECG evidence or history of MI, coronary bypass surgery, or angioplasty at baseline, and another CHD-free group.

First, frequency distributions of all ECG and Non-ECG variables will be inspected to rule out anomalies and outliers possibly due to measurement artifacts.
To test the MI/ischemia code by MC or NC as predictors of CHD morbidity and mortality and total mortality, Cox regression analysis and Kaplan-Meier survival curves will be used.

The codes from MC and NC for MI / ischemia will be analyzed by lead and by site. The QRS-ST-T measurements will also be tested as continuous variables as well as dichotomized variables at different selected cut points.

For the purpose of comparison, MI /ischemia by MC and NC will undergo the same statistical tests. Also for the same purpose of comparison, correlation analysis will be done between QRS-ST-T abnormalities detected by Minnesota coding system and Novacode system.

There is a possible interaction between the baseline CHD status and the ECG exposure variables. To account for such potential differences between the baseline CVD and CVD-free groups on the effect of the ECG markers under question on the outcomes, a series of single ECG variable proportional hazards models will be evaluated. Each model will be stratified by baseline CVD status and will include the ECG variable of interest (as an explanatory variable), an interaction term between the ECG variable and baseline CVD status, and any adjustment variables.

All risk models will be first adjusted for age alone and subsequently for age and other demographic and clinical variables mentioned before under non-ECG variables.

The proportional hazards assumption of the Cox model will be checked graphically for each of the candidate variables. All analyses will be performed with the SAS system for Windows, version 9.1.

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 ____ 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 _ZMZ_____ 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)?

Combined ARIC/CHS ancillary study

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.