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.
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 ≥ 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

<table>
<thead>
<tr>
<th>Demos/descriptives</th>
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<tbody>
<tr>
<td>V1AGE01</td>
<td>AGE AT VISIT 1</td>
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<tr>
<td>V1DATE01</td>
<td>VISIT 1 DATE</td>
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<tr>
<td>RACEGRP</td>
<td>RACE</td>
</tr>
<tr>
<td>BMI01</td>
<td>BODY MASS INDEX IN KG/(M*M)</td>
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<tr>
<td>BIRTHDAT</td>
<td>DATE OF BIRTH OF SUBJECT</td>
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<td>GENDER</td>
<td>SEX</td>
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<th>Outcome measures</th>
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<tr>
<td>SUDDEN DEATH</td>
<td>Definite/Possible/No for sudden death</td>
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<tr>
<td>CENSDAT5</td>
<td>Censoring date by 2002 for all events</td>
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<tr>
<td>DEATHCODE</td>
<td>Underlying Cause of death code</td>
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<tr>
<td>DTH18</td>
<td>Underlying cause of death from DTHA18</td>
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<tr>
<td>DTHDATE2</td>
<td>Death Date for a Person</td>
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<tr>
<td>FATCHD3</td>
<td>Fatal CHD (Classified by ARIC)</td>
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<tr>
<td>INC_BY02</td>
<td>Incident MI/CHD by end of 2002</td>
</tr>
<tr>
<td>INC_BY02P</td>
<td>Incident MI/CHD/Procedure by end of 2002</td>
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<tr>
<td>IN_02S</td>
<td>Incident MI/CHD/ECG MI by end of 2002</td>
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<td>IN_02SP</td>
<td>Incident MI/CHD/ECG MI/Procedure by end of 2002</td>
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<td>CARDPROC</td>
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<td>SMII_BY02</td>
<td>Incident ECG MI by end of year 2002</td>
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<tr>
<td>MIO2</td>
<td>Incident MI be end of year 2002</td>
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<tr>
<td>FATCHD02</td>
<td>Fatal CHD by end of year 2002</td>
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<tr>
<td>SMIDATE</td>
<td>End date for SMII_BY02</td>
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<tr>
<td>DATEMI</td>
<td>End date for MIO2</td>
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<tr>
<td>DEAD02</td>
<td>Dead by end of year 2002</td>
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<td>MI3</td>
<td>Deinite/probable MI</td>
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<td>POSDIA3</td>
<td>MI or FATCHD ((def/prob MI or def fatal CHD/MI)</td>
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<tr>
<td>PREVMI05</td>
<td>prevalent MI (composite ECG OR MED HIST)</td>
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<td>PRVCHD05</td>
<td>PREVALENT CORONARY HEART DISEASE</td>
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<tr>
<td>HXOFMI02</td>
<td>HISTORY OF MYOCARDIAL INFARCTION</td>
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<td>DIABTS02</td>
<td>DIABETES (cut point of 140)</td>
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<td>DIABTS03</td>
<td>DIABETES (cut point of 126)</td>
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<td>MDDXM102</td>
<td>MD DIAGNOSED MYOCARDIAL INFARCTION</td>
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<td>HYPERT05</td>
<td>HYPERTENSION, DEFINITION 5</td>
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<th>Lipids/haemostatic</th>
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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 __ 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.cscg.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.cscg.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.