1.a. Full Title: Prognosis of unrecognized (silent) myocardial infarction diagnosed by electrocardiogram in the ARIC Study.

b. Abbreviated Title (Length 26 characters): Prognosis of Silent MI

2. Writing Group:
   Writing group members: E. Matthew Quin, Ervin Fox, Tom Mosley, Kenneth Butler, Alan Penman, Herman Taylor, Tandaw Samdarshi, Wayne Rosamond, Richard Crow

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. EMQ

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3. Timeline:
   Complete Analysis: November 2007
   Submit first draft to publications committee: January 2007
4. **Rationale:**

The prevalence of unrecognized (silent) myocardial infarction (MI) ranges from 25-44%.(1-5) The risk associated with unrecognized MI in African Americans and how that risk compares to non-Hispanic whites is poorly described. The literature is well-established on risk factors for clinically evident MI and the long term prognosis in subjects suffering clinically evident MI. However, the population with unrecognized MI has been less well studied.

Long term follow-up and outcome data is available in few ethnic groups. In the Framingham report mentioned above, consisting of a primarily European American cohort, outcomes following unrecognized MI were similar to that of participants with recognized MI; recurrent infarctions were less likely in women with unrecognized MI as compared to those with recognized MI, although this difference was not seen in men.(2) In this group, the prognosis associated with unrecognized MI was comparable to that seen in the Bronx Aging Study; the rates of mortality due to unrecognized MI for both studies were twice that of the control population.(2,3) Another study in a group of Japanese-American men aged 45 to 68 years old also found similar outcomes in those with recognized and unrecognized MI.(5)

To our knowledge, there are no studies looking at the prognosis of unrecognized MI in a large biracial cohort. **We hypothesize that unrecognized MI will be associated with significant morbidity and mortality, comparable to that of recognized MI and that the outcomes will be similar between African American and white American participants of the ARIC Study.** Findings from this study will improve guidance for risk-guided therapy in secondary prevention of cardiovascular disease.
REFERENCES


5. Main Hypothesis/Study Questions:
What is the association between unrecognized MI and clinical outcomes (specifically hospitalized MI, incident CHD, coronary revascularization procedures, cardiovascular mortality, and all-cause mortality) in the whole cohort and by race group?
How do the outcome rates in persons with unrecognized MI differ from participants with recognized MI and participants without MI (recognized or unrecognized)?

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).

We will follow the variable definitions used in the ARIC Defined Variables Dictionaries and in Boland et al (2002). The variable for MI detected by ECG serial changes is SMI_BY04, with date SMIDATE. The ECG definition of MI is defined according to the Minnesota Code as the appearance between the baseline exam and a subsequent ARIC exam of a major Q wave or a minor Q wave with ischemic ST-T changes or an MI by computerized NOVACODE criteria confirmed by side-by-side visual comparison of electrocardiograms. SMIDATE is the estimated date of MI based on ECG evidence. It assigns the middle date of visit 1 and visit 2 if MI was detected by ECG in visit 2, and similarly for visit 2 - visit 4. Hospitalized MI (MI04, with date DATEMI) is defined as persons detected by hospital surveillance showing definite or probable MI according to ARIC classifications, or an ICD-9 410 code found anywhere among hospital discharge codes.

We will exclude persons with prevalent CHD or Rose angina at baseline (V1) (or whose CHD / Rose angina status at baseline (V1) could not be determined) and persons who did not attend for exam at V2 (as required by the definition of the SMI_BY04 variable). Additionally, persons of race group not white or AA will be excluded. Then, using the date of the V4 exam as a reference point (because V4 was the last routine exam with ECG), we will define 3 MI groups for the analysis:
a. **unrecognized MI group**: persons with ECG serial changes (SMI_BY04=1) which are not preceded by a hospitalized MI (MI04=1) post-V1 and prior to the date of the V4;

b. **recognized MI group**: persons with a hospitalized MI prior to the date of the V4 exam and either no other serial ECG changes or other serial ECG changes recorded after the date of the hospitalized MI;

c. **reference group**: persons with no unrecognized or recognized MI prior to the date of the V4 exam.

The follow-up period will be from the time of the unrecognized or recognized MI to the time of the event/outcome or the date of censoring. Outcomes will include hospitalized MI, incident CHD, coronary revascularization procedures (PTCA / CABG), and both cardiovascular and all-cause mortality. We will calculate, by MI group, crude and age/sex-adjusted event/outcome rates per 100 (or 1,000) person-years using Poisson regression. We will also conduct, by MI group, Kaplan-Meier survival analysis and Cox proportional hazard (PH) regression analysis to determine event/outcome hazard ratios. Clinical variables that will be considered for adjustment in the Cox PH models include age, sex, race-center, total, HDL, and LDL cholesterol, smoking status, systolic and diastolic blood pressures, diabetes status, BMI, physical activity, and hypertensive medications. Interaction terms for age group, sex, and race will be tested, and appropriate sub-group analyses done as required; in particular, we will be interested in analysis by race group.

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  ____ 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)?

Boland LL, Folsom AR, Sorlie PD, Taylor HA, Rosamond WD, Chambless LE, Cooper LS. Occurrence of unrecognized myocardial infarction in subjects aged 45 to 65 years (the ARIC Study). Am J Cardiol 2002;90:927-931.


11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  ____ Yes  ____ No

11.b. If yes, is the proposal  
\[\text{A. primarily the result of an ancillary study (list number)*}\]
\[\text{B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)*}\]

*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.